TABLE OF CONTENTS

SUMMARY FOR BASIS OF APPROVAL

Reference No. 85-053

Drug Licensed Name: **Hepatitis B Vaccine (Recombinant)**

Mfr: **Merck Sharp & Dohme (MSD)**

Drug Trade Name: **RECOMBIVAX HB®**

Hepatitis B Vaccine (Recombinant), RECOMBIVAX HB, is a non-infectious subunit viral vaccine derived from synthetic hepatitis B surface antigen (HBsAg) produced in yeast cells. A plasmid containing a portion of hepatitis B virus gene coding for HBsAg is cloned into yeast, and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain.

I. INDICATIONS FOR USE:

RECOMBIVAX HB is indicated for immunization against infection caused by all known subtypes of hepatitis B virus (HBV). The vaccine has been shown to be effective in inducing an immune response (anti-HBs) in initially seronegative adults and children. It has been shown to be effective in preventing chronic hepatitis B infection among infants of carrier mothers when used in conjunction with one dose of hepatitis B immune globulin.

RECOMBIVAX HB will not prevent hepatitis caused by other agents such as hepatitis A virus, non-A, non-B hepatitis viruses or other viruses known to infect the liver.

Vaccination is recommended for those persons who are or will be at increased risk of infection with all known subtypes of hepatitis B virus, including persons employed in a variety of health care occupations, patients requiring frequent and/or large volume blood transfusions or clotting factor concentrates, residents and staff of institutions for the mentally handicapped, intimate contacts of persons with persistent hepatitis B antigenemia, infants born to HBsAg positive mothers, persons at increased risk due to their sexual practices, and users of illicit injectable drugs. Additional studies are in progress in dialysis patients.

Studies are ongoing to determine the need and timing for revaccination.

II. DOSAGE AND ADMINISTRATION:

RECOMBIVAX HB consists of hepatitis B surface antigen which is produced in yeast cells. The isolated and purified antigen is adsorbed onto aluminum hydroxide as an adjuvant, and thimerosal is added as a preservative. A 1.0 ml dose of the adult formulation of the vaccine

contains 10 mcg of hepatitis B surface antigen adsorbed onto 0.5 mg of aluminum hydroxide; a 0.5 ml dose of the pediatric formulation contains 5 mcg of hepatitis B surface antigen adsorbed onto 0.25 mg of aluminum hydroxide. All formulations of vaccine contain 1:20,000 thimerosal as preservative. The vaccine has been treated with formaldehyde prior to adsorption onto alum.

Primary vaccination consists of three injections of vaccine, with the second and third injections given 1 and 6 months, respectively, after the first. Adults and children above 10 years of age are given 10 mcg (1.0 ml) of hepatitis B surface antigen per injection, while children from birth to 10 years of age receive 5 mcg (0.5 ml) of hepatitis B surface antigen per injection. Infants born to HBsAg positive mothers should receive at birth Hepatitis B Immune Globulin in conjunction with the first dose of RECOMBIVAX HB in different sites. All injections are given intramuscularly in the deltoid muscle in adults and children or in the anterolateral thigh muscle in infants and neonates, except those given to persons with hemophilia or similar disorders which are given subcutaneously. Data suggest that injections given in the buttocks are less effective in producing an immune response, perhaps since injections in the buttocks may frequently be given into fatty tissue instead of into muscle.

III. MANUFACTURING AND CONTROLS:

A. MANUFACTURING AND CONTROLS

The organism, Saccharomyces cerevisiae, strain (b)(4) (b)(4), which is utilized for the production of HBsAg, contains a plasmid containing a gene for the adw subtype of HBsAg. The culture is grown in a Yeast Extract/Soy Peptone/Dextrose (YEHD) medium at (b)(4) The fermentations are (b)(4)

(b)(4)

(b)(4)

(b)(4)

The final container is tested for sterility, general safety, (b)(4) thimerosal, (b)(4) aluminum (b)(4) and potency in mice (b)(4) (b)(4)

The manufacturer submitted for evaluation samples and protocols of five final container lots of vaccine derived from five different bulk lots produced initially at production scale. These lots met the release specifications listed at the time of their manufacture. Subsequently, modifications to the release specifications have been incorporated into the license application. These include a (b)(4) yeast impurity specification from (b)(4) to (b)(4) and a change in the (b)(4) specification for the mouse potency test from 3.0 mcg/ml to 1.5 mcg/ml. The specification requires that (b)(4) (b)(4) Additional lots have been submitted for release which when tested by the manufacturer meet all of the current release specifications.

B. STABILITY STUDIES

The recommended storage temperature of the vaccine, adsorbed onto alum is 2-8°C. Stability of the vaccine was monitored by the demonstration of potency in an in vivo mouse model and by (b)(4) (b)(4) (b)(4) of the vaccine was studied through (b)(4) (b)(4) at 2-8°C. and (b)(4) to 24 months at 2-8°C. No significant differences in potency which would indicate a loss in the immunizing potential of the product were observed throughout the period. Other studies are in process. Accelerated stability studies at (b)(4) were carried out. By the mouse potency assay, statistically significant degradation was noted only at (b)(4) By (b)(4) measurable loss of antigen occurred at temperatures (b)(4) (b)(4)

The product will have an expiration dating of twenty-four months at 2-8°C. The package insert recommends storage at 2-8°C. which is supported by the stability studies. Merck has committed to conduct ongoing stability studies.

C. VALIDATION

The major equipment used in the manufacture and filling of the vaccine has been validated at the Merck & Co., Inc., West Point, PA, facilities. In addition, appropriate specifications have been established for monitoring environmental conditions for critical work areas in this facility by the Environmental Control Department, MSD. Validation analyses for product potency and purity are performed at MSD. The test methods were found to be suitable for control and regulatory purposes.

D. LABELING

The labeling, including the package insert, has been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, 201.56 and 201.57 and found satisfactory. The container label includes a warning statement indicating "Do Not Inject Intravenously", a caution statement that federal law prohibits dispensing without prescription, a statement to "Shake Well Before Using", a statement to store at 2-8°C. (35.6 - 46.4°F) and a warning statement "Do Not Freeze." A statement to see the accompanying circular for dosage instructions is also included.

The package insert (copy attached) contains appropriate statements concerning product description, clinical pharmacology, indications and use, contraindications, warnings, precautions, adverse reactions, how supplied, dosage and administration and information on the storage of the vaccine.

E. ESTABLISHMENT INSPECTION

A pre-license inspection of the MSD biological production facilities in West Point, PA, was conducted May 12-14, 1986. No objectionable practices or exceptions to the regulations were observed.

F. ENVIRONMENTAL IMPACT ANALYSIS REPORT

An environmental assessment for the manufacture and use of RECOMBIVAX HB was completed to address the environmental impact considerations of 21 CFR, Part 25. The information provided for this environmental assessment supports the finding of no significant environmental impact. (Exhibit 2)

IV. PHARMACOLOGY, BIOCHEMISTRY AND SEROLOGY:

RECOMBIVAX HB is composed of HBsAg which is the product of a plasmid containing a portion of the hepatitis B virus gene that codes for HBsAg and which was derived from plasma of a donor infected with hepatitis B virus, subtype adw. This plasmid has been cloned into yeast. (b)(4)

(b)(4)

Serological studies have been performed to evaluate the anti-HBs antibodies raised in recipients of yeast-derived vaccine. Cross-adsorption studies were performed on anti-HBs in five recipients of yeast-derived vaccine four months post-vaccination and in six recipients of plasma-derived vaccine three months post-vaccination. In all five samples from yeast vaccine recipients 99-100% of the anti-HBs antibodies were adsorbed by both yeast-derived and plasma-derived antigen. In the six samples from plasma-derived vaccine recipients, 99-100% of the anti-HBs antibodies were adsorbed by plasma-derived HBsAg and 87-99% by yeast-derived antigen. The mean affinity constants obtained against a synthetic cyclic peptide derived from the HBsAg sequence were 4×10^7 for antibodies from both plasma-derived vaccine recipients and yeast-derived vaccine recipients.

An inhibition assay using a monoclonal antibody that had been shown to protect chimpanzees from hepatitis B infection showed 38% inhibition (10-69%) of the monoclonal antibody by samples from 10 yeast-derived vaccinees and 54% inhibition (18-99%) by samples from 10 plasma-derived vaccinees.

Avidity constants against entire HBsAg ranged from 4 to 8×10^{10} in six samples at 3 months post-vaccination from plasma-derived vaccinees and 1 to 16×10^{10} in six samples from yeast-derived vaccinees.

Comparison of the proportions of the anti-a and anti-d components of the anti-HBs response showed that at 7 months post-vaccination 95% of the anti-HBs was anti-a and 5% anti-d in 27 samples of yeast vaccine recipients and 93% anti-a and 7% anti-d in 8 samples from plasma-derived vaccine recipients.

These serological studies show that although the antibodies induced by yeast-derived and plasma-derived antigen are comparable, 1) yeast-derived antigen is slightly less capable of adsorbing antibody induced by plasma-derived antigen, 2) the antibody induced by yeast-derived antigen is somewhat less reactive in a cross inhibition assay with a protective monoclonal antibody and 3) the antibodies induced by yeast-derived antigen show greater variability in their avidity constants.

V. MEDICAL:

A. GENERAL INFORMATION

Hepatitis B virus is one of several viruses (hepatitis A, hepatitis B and several non-A, non-B hepatitis) causing a systemic infection with pathologic changes in the liver. It is a major cause of acute and chronic hepatitis and cirrhosis and has been implicated in the etiology of primary hepatocellular carcinoma worldwide. There is no effective treatment for hepatitis B infection. Six to 10% of young adults infected with hepatitis B in the United States fail to eliminate the virus and become persistently infected (chronic HBsAg carriers). It is estimated that there are 0.7 to 1.0 million chronic carriers of hepatitis B virus in the United States and more than 170 million in the world.

In the United States and Northern Europe, hepatitis B virus infects mainly adults, while children are most affected in developing areas of the world. In both cases, the virus is maintained in populations primarily by transfer of infection from chronic carriers. Such spread is effected through blood transfusion, exposure to contaminated needles or instruments, through sexual contact and by spread from carrier mother to infant in the perinatal period.

Hepatitis B surface antigen is the main component of the outer envelope of the 42 nm hepatitis B virus. Excess HBsAg is also produced in particles that are 18-22 nm in diameter. HBsAg has been found in the blood and other clinical specimens including saliva, urine, bile and feces of infected persons.

Antibodies to HBsAg (anti-HBs) have been shown to be protective against infection with HBV. A safe and effective hepatitis B vaccine comprised of hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of the virus is commercially available. An attractive alternative to human plasma as a source of HBsAg is the use of recombinant DNA technology to effect synthesis of HBsAg by a culture of microorganisms. Vaccine prepared from yeast by recombinant DNA technology was shown to be safe and antigenic in monkeys and chimpanzees and also protective in chimpanzees subsequently challenged with infectious hepatitis B virus.

B. CLINICAL STUDIES

From July 1983 to January 1986 RECOMBIVAX HB was administered to approximately 3800 participants enrolled in 50 clinical studies to assess immunogenicity and safety. The populations included in the studies are summarized in Table 1. In addition, the four studies in infants born to carrier mothers were designed to assess protection from chronic infection.

The vaccine was administered as a series of three intramuscular injections. The first two injections were given one month apart followed by a third or booster injection given six months after the first dose.

Vaccine recipients were asked to report their temperature and any injection site or systemic sequelae that occurred within a five day period following each injection of vaccine.

Post-vaccination blood samples were obtained for the determination of antibody to hepatitis B surface antigen (anti-HBs), other hepatitis B virus serologic markers (HBsAg, anti-HBc), serum alanine aminotransferase (ALT) activity, and in some instances, antibody to yeast antigens.

1. SAFETY

The vaccine was proven non-infectious for man in a human safety test in which a single 1.0 ml dose of vaccine containing 10 mcg of HBsAg was administered to each of five initially seronegative persons who were followed serologically for 6 months for appearance of markers of hepatitis B infection. No markers were detected.

RECOMBIVAX HB has been well tolerated. There have been no serious or alarming reactions directly attributable to vaccine reported among subjects who participated in the clinical studies. The types and incidence of complaints which were reported within five days following administration of 3258 injections of vaccine to 1252 healthy adults who participated in clinical studies for which analysis has been completed are summarized in Table 2. Injection site and systemic complaints were reported following 17% and 15% of the injections, respectively. Comparable rates of systemic reactions were observed in controlled clinical studies using plasma-derived vaccine in both the immunized and placebo groups. The most frequent specific injection site reactions were soreness, pain and tenderness. The most frequent systemic complaints were fatigue/weakness and headache.

In the clinical trials, no cases of anaphylaxis, severe bronchospasm or laryngeal edema were reported. There were 3 reports of urticaria, one of facial edema and 16 reports of "rash". Antibodies to yeast have been observed both pre- and post-immunization. Testing for serum IgG and IgE antibodies to yeast proteins in individuals with allergic reactions indicated no correlation between antibody responses to yeast antigens and allergic reactions.

The frequency of clinical complaints reported within five days following administration of 231 injections of vaccine to 80 healthy children (3 months to 11 years) for which analysis has been completed are summarized in Table 3. Systemic complaints including fatigue, weakness, diarrhea and irritability were reported following 14% of the injections. Injection site complaints consisting principally of soreness were reported following 2% of the injection.

2. IMMUNOGENICITY

Clinical studies have demonstrated that Hepatitis B Vaccine (Recombinant) induces protective levels of antibody in greater than 90% of healthy individuals who received the recommended three-injection regimen. A protective antibody level has been defined as 10 or more milli-International Units/ml (mIU/ml) as determined by (b)(4).

Anti-HBs responses of 511 healthy adults 20-69 years of age, 83 healthy children, and 53 dialysis patients are summarized in Table 4. The doses used were 3 x 10 mcg for adults, 3 x 5 mcg for children and 3 x 40 mcg for dialysis patients.

Antibody response to the vaccine is age dependent. The younger the vaccinee, the greater the likelihood of an immune response developing. Antibody seroconversion rates for children 1 to 10 years of age were 100% with Geometric Mean Titer (GMT) of 15,966 mIU/ml. Seroconversion rates for adults ranged from 95% to 99% for those 20 to 39 years of age and 91% for those 40 years of age or older. The Geometric Mean Titers (GMT) were 1707 mIU/ml for the 20-29 year age group and 484 mIU/ml for the 40-49 year age group. Immunocompromised persons respond less well to the vaccine than do healthy individuals. Sixty-eight percent of predialysis and dialysis patients who received three 40 mcg doses of vaccine developed protective level of anti-HBs and had a GMT of 178 mIU/ml.

Preliminary data from a double-blind, randomised, controlled study in healthy adults comparing this product and the currently licensed plasma-derived vaccine show at nine months comparable seroconversion rates of 91% (40/44) for the

recombinant vaccine and 93% (38/41) for the plasma-derived one. The GMT (402 mIU/ml) seen in these recipients of the recombinant vaccine was less than half that seen in the recipients of the plasma-derived vaccine (1676 mIU/ml).

3. EFFICACY

The protective efficacy of RECOMBIVAX HB has been demonstrated in neonates born to mothers positive for both HBsAg and HBeAg. In two clinical studies of infants who received the recommended one injection of hepatitis B immune globulin at birth followed by a three injection regimen of vaccine, efficacy in prevention of chronic hepatitis B infection was 93% in 40 infants at 6 months in one study and 93% in 57 infants at nine months in the other study.

VI. ADVISORY PANEL CONSIDERATION.

Data concerning the manufacture, safety and efficacy of Hepatitis B Vaccine (Recombinant) for the prevention of hepatitis B were discussed at the Vaccines and Related Biological Products Advisory Committee meeting on June 7, 1984, October 4, 1984 and April 3, 1986.

VII. APPROVED PACKAGE INSERT

A copy of the approved package insert is attached. (Exhibit 1)

Daljit K. Gill

Daljit K. Gill, M.D.
Chairman

Ira Berkower

Ira Berkower, M.D.

Neil Goldman

Neil Goldman, Ph.D.

Barbara C. Meyer

Barbara C. Meyer

Elizabeth B. Paul

Elizabeth B. Paul

Linda A. Smallwood

Linda A. Smallwood, Ph.D.

TABLE 1

PERSONS INCLUDED IN CLINICAL STUDIES OF HEPATITIS B VACCINE (RECOMBINANT) BETWEEN JULY 1983 AND JANUARY 1986

Populations	No. Vaccinated (≥1 Injection)
Health Care Personnel/ Other Healthy Adults	2414
Healthy Teenagers	165
Healthy Infants/Children	258
Dialysis/Predialysis Patients	288
Infants of Carrier Mothers	289
Other Groups	447
Mentally retarded institutionalized patients	
Patients with thalassemia, hemophilia, or sickle cell anemia	
Hyporesponders or nonresponders to plasma-derived vaccine	
Preimmune adults	
Chronic carriers of HBsAg	

TABLE 2

FREQUENCY OF CLINICAL COMPLAINTS WITHIN 5 DAYS FOLLOWING ADMINISTRATION OF 3255 INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) TO 1252 HEALTHY ADULTS

Clinical Complaint	% of Injections With Complaint
INJECTION SITE	
Injection site reactions consisting principally of soreness, and including pain, tenderness, pruritis, erythema, ecchymoses, swelling, warmth, and nodule formation.	16.7
BODY AS A WHOLE	
Fatigue/weakness	4.2
Headache	4.1
Fever (≥100°F)	3.2
Malaise	1.2
Sweating	0.5
Achiness	0.4
Sensation of warmth	0.4
Lightheadedness	0.3
Chills	0.2
Flushing	0.2
DIGESTIVE SYSTEM	
Nausea	1.8
Diarrhea	1.1
Vomiting	0.3
Abdominal pains/cramps	0.3
Dyspepsia	0.2
Diminished appetite	0.1
RESPIRATORY SYSTEM	
Pharyngitis	1.2
Upper respiratory infection	1.0
Rhinitis	0.8
Influenza	0.3
Cough	0.2

TABLE 2
(Continued)

FREQUENCY OF CLINICAL COMPLAINTS WITHIN 5 DAYS FOLLOWING ADMINISTRATION OF 3255 INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) TO 1252 HEALTHY ADULTS

Clinical Complaint	% of Injections With Complaint
NERVOUS SYSTEM	
Vertigo/dizziness	0.5
Paresthesia	0.1
INTEGUMENTARY SYSTEM	
Pruritis	0.3
Rash (non-specified)	0.2
Urticaria	0.1
MUSCULOSKELETAL SYSTEM	
Arthralgia including monoarticular	0.5
Myalgia	0.4
Back pain	0.2
Neck pain	0.2
Shoulder pain	0.2
Neck stiffness	0.2
HEMIC/LYMPHATIC SYSTEM	
Lymphadenopathy	0.2
UROGENITAL SYSTEM	0.2
CARDIOVASCULAR SYSTEM	0.2
PSYCHIATRIC/BEHAVIORAL	
Insomnia/Disturbed Sleep	0.1
SPECIAL SENSES	
Earache	0.2

TABLE 3

FREQUENCY OF CLINICAL COMPLAINTS WITHIN 5 DAYS FOLLOWING ADMINISTRATION OF 231 INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) TO 80 HEALTHY CHILDREN

Clinical Complaint	% of Injections With Complaint
INJECTION SITE	
Injection site reactions consisting principally of soreness	2.2
BODY AS A WHOLE	
Fatigue/weakness	3.0
Headache	0.8
Sweating	0.4
Bruise from venipuncture	0.4
Illness	0.4
DIGESTIVE SYSTEM	
Diarrhea	2.0
Vomiting	1.3
Diminished appetite	0.4
Loose stool	0.4
Nausea	0.4
Teething	0.4
RESPIRATORY SYSTEM	
Upper respiratory infection	2.6
Pharyngitis	0.8
Rhinitis	0.8
Cough	0.4
Croup	0.4
INTEGUMENTARY SYSTEM	
Papular Rash	0.8
Rash (non-specified)	0.4
Urticaria	0.4

TABLE 3
(Continued)

FREQUENCY OF CLINICAL COMPLAINTS WITHIN 5 DAYS FOLLOWING ADMINISTRATION OF 231 INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) TO 80 HEALTHY CHILDREN

Clinical Complaint	% of Injections With Complaint
PSYCHIATRIC/BEHAVIORAL	
Irritability	1.7
Insomnia/Disturbed Sleep	0.4
INFECTIOUS SYNDROMES	
Viral infection	1.7
SPECIAL SENSES	
Otitis media	0.4

TABLE 4

ANTIBODY RESPONSES AT 7/8 MONTHS AMONG HEALTHY INDIVIDUALS AND DIALYSIS PATIENTS WHO RECEIVED THREE INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) AT 0, 1 AND 6 MONTHS

				% Seroconversion	GMT(mIU/ml)
Population	Age	No.	Dose	mIU/≥10	mIU/ml≥10
Healthy Individuals	1 - 11 yrs.	14	5 mcg	100	15966.0
	12 - 19 yrs.	69	10 mcg	100	2913.4
	20 - 29 yrs.	344	10 mcg	99	1737.0
	30 - 39 yrs.	111	10 mcg	95	730.0
	≥40 yrs.	56	10 mcg	91	586.5
Dialysis Patients	≥20 yrs.	53	40 mcg	68	178.1

BRIEF SUMMARY OF YEAST RECOMBINANT HEPATITIS B VACCINE CLINICAL REPORT

I. CLINICAL AND SEROLOGIC DATA

Study Population	Number Vaccinated ≥1 Injection	Number Vaccinated 3 Injections	Clinical Reports ≥1 Injection	Clinical Reports 3 Injections	Serologic Data ≥1 Injection	Serologic Data 3 Injections
Health Care Personnel/ Other Healthy Adults	2414	1442	1626	990	1616	1048
Healthy Teenagers	165	165	165	165	165	165
Healthy Infants/ Children	258	122	220	100	213	97
Dialysis/Predialysis Patients	288	196	286	184	258	166
Other Groups	736	362	581	110	633	80

II. IMMUNOGENICITY

Antibody responses across all dose levels used are summarized below:

Study Populations	% with Anti-HBs After 3 Injections Minimal Titer (S/N ≥2.1)	Fully Protective Titer (mIU/ml ≥10)
Health Care Personnel/ Other Healthy Adults	98	96
Healthy Teenagers	100	98
Healthy Infants/Children	100	100
Dialysis/Predialysis * Patients	94	88

*Figures apply to patients that received three 40 mcg doses in the deltoid. See SUMMARY - DIALYSIS AND PREDIALYSIS PATIENTS for discussion of other regimens that were less immunogenic.

3177I/4
1/12/86

III. CLINICAL REACTIONS

There have been no reports of serious adverse experiences attributable to vaccination. Clinical reactions following vaccination have been mild and transient consisting mostly of soreness at the injection site, fatigue/weakness, headache, and nausea. Complaint frequencies across all dose levels used are summarized below:

Study Populations	% of Injections Followed by Clinical Complaints			
	Local (Injection Site)	Systemic	Any Complaint	Temperature ≥100°F (Oral)
Health Care Personnel/ Other Healthy Adults	17	15	27	3
Healthy Teenagers	5	2	6	0.2
Healthy Infants/Children	2	9	11	11
Dialysis/Predialysis Patients	3	8	10	5

IV. EFFICACY

Passive-active prophylaxis consisting of hepatitis B immune globulin and yeast recombinant hepatitis B vaccine was 98% effective in preventing chronic hepatitis B infection among infants born to mothers positive for both HBsAg and HBeAg (59 infants evaluated at six months).

GENERAL SUMMARY

Clinical studies with the yeast recombinant hepatitis B vaccine were initiated in July 1983. This document includes data from studies concerned with the vaccine's safety, immunogenicity and efficacy which were generated to support a license for the vaccine in the United States. Summaries and analyses across studies of clinical complaints and serologic responses are based on data encoded within the project database by October 15, 1985. However, several individual study summaries are derived from more recent data that have not yet been entered in the database.

VACCINE

A total of 28 lots of yeast recombinant hepatitis B vaccine have been prepared by Merck and Co., Inc., according to procedures developed in the Merck, Sharp and Dohme Research Laboratories. Eighteen of the lots are in use in human clinical trials (see Appendix I). All clinical data received to date indicate that the vaccine is safe. One of the lots (C-J625) was made using (b)(4) procedure and was (b)(4) The clinical and serologic data relating to this lot will be summarized separately, because this procedure will not be used in making commercial vaccine (see section entitled (b)(4) VACCINE). The remainder of the lots were made using a (b)(4) procedure and are in clinical trials under BB IND 1925.

CLINICAL STUDIES

Table 1 lists 50 clinical studies involving the yeast recombinant hepatitis B vaccine produced by the (b)(4) procedure that are currently in progress.

In most of the studies, participants receive the vaccine as an intramuscular injection administered at 0, 1 and 6 months. However, chronic carriers of HBsAg and certain groups of dialysis patients receive a total of 6 doses of vaccine administered at monthly intervals, while persons with prior immunity and subjects in the study designed to demonstrate noninfectivity of the vaccine are given only a single dose of vaccine. Patients with hemophilia receive the vaccine as a subcutaneous injection. Each dose of vaccine (total mcg of HBsAg administered at a given time) is generally contained within a single injection. However, each 40 mcg dose given to dialysis and predialysis patients consists of a pair of 20 mcg injections.

The numbers of subjects who have received first, second and third injections of the yeast recombinant hepatitis B vaccine are shown by population in Table 2. A total of 3861 participants have received one or more injections of vaccine, while 2309 individuals have completed a 3 dose regimen of vaccination.

Vaccinees in all studies are asked to record their temperature daily and to record any local or systemic complaints that they may have for 5 days following each injection of vaccine. Table 2 also shows by population the number of subjects for whom post vaccination clinical reports are currently available. Clinical reports following the first injection have been received for 2878

vaccinees, while 1571 reports are available for subjects who have received 3 doses of vaccine.

Postvaccination blood samples are obtained for the determination of antibody to hepatitis B surface antigen (anti-HBs), other hepatitis B virus serologic markers, alanine aminotransferase (ALT), and antibody to yeast antigens. Table 2 also shows by population the number of subjects for whom postvaccination anti-HBs data are available. Anti-HBs titers are known for 1551 subjects following 3 doses of vaccine and are available for an additional 1334 individuals following only the first or second injection of vaccine.

IMMUNOGENICITY

Anti-HBs Assay

Immune responses to vaccine are measured using a radioimmunoassay (b)(4) (b)(4) to detect antibody (anti-HBs) specific for the hepatitis B virus surface antigen (HBsAg). Two different cutoff values have been utilized in determining a positive antibody response; one to indicate seroconversion, the other an attempt to define a minimum level of antibody clearly indicative of protection from clinical infection. The lower cutoff is taken as a ratio of sample counts to negative control counts (S/N) $\geq$2.1. The higher cutoff defines as positive a sample having an anti-HBs titer in milli-International Units/ml (mIU/ml) $\geq$10. Anti-HBs titers expressed as S/N ratios cannot be converted directly into units of mIU/ml. However, the two scales of measurement are fairly similar at low titers (i.e. S/N of $\leq$10 is approximately the same as an mIU/ml of $\leq$10). There is a developing concensus that views an anti-HBs titer of S/N or mIU/ml $\geq$10 as fully adequate for protection against hepatitis B. (Centers for Disease Control: Recommendations for protection against viral hepatitis. MMWR 34 (22):313-335, June 7, 1985)

Anti-HBs responses among healthy, initially seronegative persons receiving yeast recombinant hepatitis B vaccine (b)(4) procedure) at 0, 1 and 6 months, and for whom post vaccination anti-HBs are available in units of mIU/ml, are summarized in Tables 3 to 6. Additional tabulations and discussions of antibody responses for these and other groups will be found in the population-specific summaries. Very brief accounts of the immune responses of each population are given in the following paragraphs of this general summary.

Health Care Personnel/Other Healthy Adults

Thirty-six studies are in progress involving 2414 health care personnel or other healthy adults. Participants receive a dose of the recombinant vaccine (2.5, 5, 10 or 20 mcg) at 0, 1 and 6 months. Fourteen hundred and forty-two (1442) persons have completed a 3 injection regimen of vaccination. Anti-HBs responses following the third injection have been measured for 1048 subjects and responses following only one or two injections have been measured for an additional 568 vaccinees.

Tables 3 to 6 summarize the anti-HBs responses of 801 adults, 20-69 years of age, who received 2.5, 5, 10 or 20 mcg doses of vaccine, and for whom data are available reported in units of mIU/ml. At 7/8 months (1-2 months after the third injection), 97-100% of the vaccinees had an anti-HBs titer of S/N $\geq$2.1, while 89-97% achieved a protective titer of mIU/ml $\geq$10 (Table 5). At 12 months,

92-97% of the vaccinees still had an anti-HBs titer of S/N ≥2.1, while 74-90% (86-90% of those receiving doses of 10 mcg or more) had titers of mIU/ml ≥10 (Table 6).

The level of anti-HBs attained after 3 injections of vaccine does increase with dose level (Table 5). Age and sex also influence the antibody response to vaccine. Anti-HBs levels are inversely related to age, while females tend to develop higher antibody titers than males (see SUMMARY - HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS for statistical analysis of these factors).

For healthy adults as a group, a vaccination regimen consisting of three 10 mcg doses is sufficient to induce fully protective titers of antibody (mIU/ml ≥10) in 97% of the vaccinees.

Healthy Teenagers

The vaccine has been administered at 0, 1 and 6 months to 165 seronegative, healthy teenagers (all male military recruits mostly 17-19 years of age). Subjects received 2.5, 5 or 10 mcg doses. All of the vaccine recipients had anti-HBs titers of S/N >2.1 by 7 months regardless of dose level. Using a cutoff of mIU/ml >10, 100% of subjects receiving 10 or 5 mcg doses were antibody positive, while 94% of those receiving 2.5 mcg doses had antibody at that time. Response level (titer) was found to increase significantly with dose level (see SUMMARY - HEALTHY TEENAGERS for details of the statistical analysis). At each dose level, the geometric mean antibody titers attained by teenage subjects following 3 doses of vaccine were greater than those developed by young adults (Table 5). At 12 months, 100% of those who received 10 or 5 mcg doses of vaccine have antibody, while 91% of those who received 2.5 mcg doses continue to have protective levels of anti-HBs.

Healthy Infants/Children

To date, a total of 258 healthy infants and children, 3 months to 11 years of age, who were negative for hepatitis B markers, have been vaccinated with hepatitis B recombinant vaccine. Seven to 8 month serology data are available on 97 infants and children. Antibody responses to 5, 2.5 and 1.25 mcg doses of the vaccine administered at 0, 1 and 6 months were evaluated. The vaccine was very immunogenic in this population. Seroconversion (S/N ≥2.1) exceeded 94% after 2 doses regardless of dose level. Protective levels of antibody (mIU/ml >10) were induced in 100% of vaccine recipients, one month after the third injection, regardless of dose level administered. Statistical analysis of data from study 809 showed that both log dose level and the age of the child were related to antibody titer (see SUMMARY - HEALTHY CHILDREN for details of the statistical analysis). Titers increased with log dose level, and younger children had higher titers than older children. As shown in Table 5, the GMT of anti-HBs at 7/8 months in children receiving 2.5 or 5 mcg doses of vaccine (based on study 809 only) were higher than those developed by teenagers receiving comparable dosages. At 12 months, all children surveyed still had titers of mIU/ml >10.

Dialysis and Predialysis Patients

Five studies are in progress involving 288 patients with chronic renal insufficiency. Two hundred ten patients are receiving dialysis treatments (dialysis patients), while 78 are not yet receiving such treatments (predialysis

patients). Predialysis patients receive an injection of the yeast recombinant hepatitis B vaccine (10, 20, or 40 mcg dose) at 0, 1, and 6-months. Dialysis patients receive an injection of the vaccine (20, 40 or 100 mcg dose) either at 0, 1, and 6 months or according to a more intensified regimen (20 or 40 mcg dose) at 0, 1, 2, 3, 4 and 5 months. In four of the studies, patients received the vaccine as an intramuscular injection in the deltoid. However, in one study, vaccine was administered in the buttock.

One hundred forty-seven dialysis patients and 52 predialysis patients have completed a three injection regimen of vaccination, and 34 dialysis patients have completed a six injection regimen. Serologic data following the last injection of vaccine are currently available for 50 predialysis and 84 dialysis patients who received three injections of vaccine and 32 dialysis patients on the six injection regimen. Because of the multiplicity of regimens utilized, antibody responses are summarized below in tabular form:

Patient Group	Regimen (# Doses)	Dose (mcg)	Inject. Site (B/D)	% with Anti-HBs (# Evaluated) 7/8 Months S/N ≥2.1	7/8 Months mIU/ml ≥10	12 Months S/N ≥2.1	12 Months mIU/ml ≥10
Predialysis	3	10	D	15 (13)	15 (13)	8 (12)	0 (12)
		20	D	68 (19)	58 (19)	71 (14)	50 (14)
		40	D	67 (18)	61 (18)	40 (10)	40 (10)
Dialysis	3	20	D	59 (29)	48 (29)	52 (29)	41 (29)
		40	D	94 (17)	88 (17)	81 (21)	71 (21)
		40	B	64 (36)	58 (36)	65 (37)**	54 (37)**
	6	20	B	56 (16)*	44 (16)*	50 (18)**	44 (18)**
		40	B	69 (16)*	69 (16)*	67 (15)**	60 (15)**

* 6 months
** 10 months
B = buttock
D = Deltoid

Serologic data are currently available following two injections of vaccine for dialysis patients receiving 100 mcg doses. At three months, 68% (19/28) had antibody (S/N ≥2.1), while 25% had a fully protective titer (mIU/ml≥10).

In summary, predialysis and dialysis patients do not respond to the vaccine as well as healthy adults. Responses to the vaccine among patients improved with increasing dose and were better with administration in the deltoid as opposed to the buttock. Responses to the three injection and intensified six injection regimens of vaccination appear to be similar.

Mentally Retarded Institutionalized Patients

One study is in progress including 202 mentally retarded individuals. Participants receive a 10 mcg or 20 mcg dose of the recombinant vaccine at 0, 1 and 6 months. Two hundred persons have completed a three injection regimen of vaccination. Anti-HBs responses following only one injection are available for 201 vaccinees. At 1 month 19-20% had an anti-HBs titer of S/N ≥2.1, while 8-11% achieved a protective titer of mIU/ml ≥10.

Thalassemics/Hemophiliacs

Thirty-one thalassemic children (<16 years of age) have received intramuscular injections of yeast recombinant hepatitis B vaccine in a single study. Among 15 children who received three 5 mcg doses, 89% had at least minimal evidence of anti-HBs at 7 months (S/N $\geq$2.1), while 78% had fully protective titers (S/N $\geq$10). Twelve children have received three 2.5 mcg doses of vaccine. At 7 months, all had titers of S/N $\geq$10.

Fifteen patients with hemophilia have been vaccinated subcutaneously in a single study. Twelve subjects under 20 years of age who received two 5 mcg doses all had protective levels of antibody by 3 months (mIU/ml $\geq$10). Three patients $\geq$20 years of age have received 10 mcg doses of vaccine. At 3 months, 2 of these patients had seroconverted (S/N $\geq$2.1), but neither had achieved a protective level of antibody (mIU/ml $\geq$10).

Nonresponders/Hyporesponders/Transient Responders

Six studies are in progress involving 55 healthy adults and 26 dialysis patients who failed to develop detectable anti-HBs after three injections of plasma-derived hepatitis B vaccine. The studies also include five healthy adults who were hyporesponders or transient responders to the plasma-derived vaccine. Nonresponders receive an injection of the yeast recombinant vaccine (10 or 20 mcg doses for healthy individuals and 40 mcg doses for dialysis patients) at 0, 1, and 6 months. Hyporesponders and transient responders receive a single injection containing 10 mcg of the yeast recombinant hepatitis B vaccine.

Thirty nonresponders (24 healthy adults and six dialysis patients) have completed the three injection regimen of vaccination. Anti-HBs (S/N $\geq$2.1) was detectable in 79% (11/14) of the adults measured at 7-9 months, while 50% had protective titers (mIU/ml $\geq$10). Two of four dialysis patients monitored at 7-9 months developed antibody titers of mIU/ml $\geq$10.

Three of four hyporesponders/transient responders had protective titers of anti-HBs one month after receiving a dose of the yeast recombinant vaccine.

Preimmune Adults

Two studies are being conducted to examine the response of adults, who have been documented to have hepatitis B antibody at some time in the past, to a single 5 or 10 mcg booster injection of yeast recombinant hepatitis B vaccine. Sixty-three persons have received a 10 mcg dose of vaccine. Ninety-seven percent of those participants whose anti-HBs responses were measured approximately one month following the booster demonstrated a boost in titer at that time. One individual who was antibody negative just prior to the booster injection failed to develop detectable antibody. Twenty-eight individuals received a 5 mcg booster injection. All of 25 participants tested at one month after the injection demonstrated a boost in anti-HBs titer.

Chronic Carriers

One study is being conducted to determine whether vaccination can eliminate the carrier state. Eighteen adult chronic carriers (positive for HBsAg for at least one year) have been scheduled to receive six 10 mcg doses of recombinant hepatitis B vaccine at monthly intervals. Three participants have received all

six doses; eighteen have received at least four doses. Administration of the remaining doses continues in progress. To date, none of the carriers has become negative for HBsAg.

Anti-HBs Subtype Specificity

Four major subtypes of the hepatitis B virus are known with respect to the antigenic composition of HBsAg. The subtypes are designated adw, adr, ayw, and ayr. All of the subtypes have the common antigenic determinant a, and anti-HBs specific for the a determinant of HBsAg would be expected to be protective regardless of the subtype of the challenging virus.

The immunizing component of the yeast recombinant hepatitis B vaccine is HBsAg of subtype ad. Assays were performed to ascertain that anti-HBs induced by the vaccine in human subjects is largely specific for the a determinant of HBsAg. Postvaccination serum samples with anti-HBs titers of 25 mIU/ml or more from subjects in several studies were tested to determine the percentage of antibody specific for the a and d determinants of HBsAg. Table 7 shows the results of these assays. Antibody specific for the a determinant predominates. By 3 months (2 months after the second dose of vaccine) the mean percentage of anti-a in all sera tested was 90%. The percentage of anti-a continued to increase with time and reached 95% at 7/8 months (1 to 2 months after the third dose of vaccine).

SAFETY

The vaccine has been well tolerated. There have been no reports of serious or alarming reactions attributable to vaccine. To date there have been 7 reactions that are possibly related to the vaccine. Five of these reactions are described in table 8 which lists reports of experiences among vaccine recipients that have been filed with the OoBRR. The other two reactions which are not described in Table 8 are summarized below:

1. A 23 year old female developed hives within 24 hours of receiving the first injection of vaccine. The hives were described as one large 3-4 inch lesion, pruritic, with several satellite lesions on the back and several small lesions on the legs. All symptoms resolved by day 4 post vaccination. Within 24 hours of receiving the second injection of vaccine the subject developed small hives on the back, arms, and left hand. All symptoms resolved by day 4 post vaccination. The individual received her third injection of vaccine with no evidence of hives. In the past, the subject developed hives during administration of contrast dye (for CAT scan). There is no other allergic history.

2. A 40-year old female developed a few ecchymotic flat lesions on the lateral aspect of her breasts, bilaterally, four days after the first injection of vaccine. Over the following two days the lesions increased. Vomiting occurred on the third day. All symptoms disappeared over the next 36 hours, and the subject has remained well. There was no fever, and WBC, Hgb, platelets, and coagulation profile were normal. The patient has no history of allergies to exogenous substances. No further vaccine was administered to this patient.

Table 9 summarizes the most frequent injection site or systemic complaints reported by healthy adult vaccine recipients. Injection site and systemic complaints were reported with frequencies of 17% and 15%, respectively. The most frequent specific injection site reactions were soreness, pain, and tenderness. The most frequent specific systemic complaints were fatigue/weakness and headache (see SUMMARY-HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS for a more detailed listing of clinical complaints).

In addition to monitoring clinical complaints, recipients of the yeast recombinant hepatitis B vaccine were also followed for antibody to yeast antigen, elevations of alanine aminotransferase, and acquisition of the hepatitis B virus serologic markers HBsAg and anti-HBc. Since the yeast recombinant hepatitis B vaccine does not involve intact hepatitis B virus at any stage of its formulation, and it also cannot contain core antigen, post-vaccination assays for HBsAg and anti-HBc were included only to detect possible breakthrough hepatitis B infections or infections that might have been in an early stage of incubation when vaccination was initiated.

Antibody to Yeast Antigen

In order to look for antibody to components of the yeast used to prepare the vaccine, sera from vaccine recipients were tested by radioimmune assay. The yeast antigens utilized in the assay were derived from the parent strain of S. cerevisiae used for the production of HBsAg. This strain does not contain the gene for HBsAg. Sera from 133 vaccine recipients (adults and children) were tested for antibodies to yeast antigen. One hundred percent of individuals tested had anti-yeast IgG in both pre and postvaccination sera. The titers in prevaccination sera ranged from 12,000 to 104,000 antibody units. Postvaccination anti-yeast IgG titers fluctuated over time with some increasing and others decreasing. However, a statistical test failed to show any significant trend in postvaccination anti-yeast titers of antibody (Table 10) There was also no association found between changes in the titer of anti-yeast antibody and the incidence of clinical complaints following vaccination (Table 10).

The most prominent yeast antigen found in preparations of the yeast recombinant hepatitis B vaccine is designated P60. Antibody to P60 is detected and semi-quantitated using a Western blot assay. Prevaccination and 3 month postvaccination sera from 42 individuals have been assayed for antibody to P60. There were no statistically significant associations between the level of antibody to P60 and the incidence of clinical complaints following vaccination (Table 11).

Alanine Aminotransferase (ALT)

All subjects enrolled in a clinical study have pre-vaccination ALT levels determined. To date, one or more post-vaccination levels have been obtained in most individuals. Thirty-one subjects, whose pre-vaccination ALT levels were normal, had elevated levels of this enzyme (1.5 - 7.0 times the upper limit of normal) at some time during a 7-8 month period of observation following vaccination. Elevations were transient in 22 cases. For 3 subjects, transient elevations in ALT were attributed to infectious mononucleosis, cholecystitis, or non A non B hepatitis. In all other instances, a reason for the ALT elevation was not ascertained. None of the subjects has shown any clinical or serologic signs (HBsAg or anti-HBc) of hepatitis B. For the remaining 9 subjects, one

participant's follow-up serum sample showed a decreasing ALT, and the other individuals have no follow-up sera available. These 9 individuals have shown no clinical or serologic signs of hepatitis B.

Two additional subjects had fluctuations in ALT levels. In both cases the prevaccination samples were elevated (1.5 - 2 times the upper limit of normal). After vaccination, the levels returned to normal, increased, and then began to decrease. In one case, a 4.5-fold increase in ALT was noted at 2 months after vaccination. At 3 months the ALT level was 2-fold higher than normal. In the second case a 3.5-fold increase in ALT was seen at 6 months. AT 7 months it was 2-fold higher than normal. No reason for the ALT elevation could be ascertained. No follow-up sera are available. Neither participant has been reported to show any clinical or serologic signs of hepatitis B.

Sporadic transaminase elevations may result from a variety of causes including minor muscle trauma (such as that caused by exercise and by intramuscular injections), common infection (including viral and mycoplasmol infections), drugs (including aspirin), and alcoholic beverages. In a previous clinical trial of plasma-derived hepatitis B vaccine, about one percent of the vaccine and the placebo recipients had elevated ALT levels at each testing. The elevations were sporadic; those with an elevated ALT at any given time were generally not the ones with an elevation at the next testing time. Elevations among recipients of the yeast recombinant vaccine have been similarly sporadic and of low incidence. We do not believe that the transaminace elevations that have occurred are likely to have been caused by the yeast recombinant hepatitis B vaccine.

HBsAg

The Interim Submission reported 2 initially seronegative vaccine recipients for whom a single postvaccination serum sample gave a marginally positive test for HBsAg (S/N $\geq$2.1).

In one case, the 3 month postvaccination serum from a healthy teenager tested just above the cutoff for HBsAg (S/N = 2.11). However, the prevaccination, 1, 6, and 7 month postvaccination samples were negative for HBsAg. The individual had normal ALT levels and all serum samples were negative for anti-HBc. It seems likely that the low positive test was spurious.

The second case is an adult health care professional. The subject's 6 month postvaccination serum gave a low positive test for HBsAg (S/N = 2.4). However, a subsequent retest of this serum sample tested negative for HBsAg. The prevaccination sample and all other postvaccination samples through 8 months of follow-up have been negative for HBsAg and anti-HBc and all samples have had normal ALT levels.

Anti-HBc

A total of 18 participants had serum samples positive for anti-HBc at some time during the study period. Five of the individuals had prevaccination samples positive, while 13 had positive postvaccination samples. A brief description of each case follows.

Healthy Adults

Two subjects had prevaccination serum samples positive for anti-HBc. In one case, the anti-HBc was transient. In the other case, all but one serum sample taken after vaccination remained positive. Serum samples for these individuals have remained negative for HBsAg and there has been no report of clinical illness.

One healthy adult was reported in the Interim Submission to have had a 2 month postvaccination serum sample positive for anti-HBc. The same serum sample was reported negative on retest. All subsequent samples through 12 months were negative. In two additional adults, the 6 and 8 month serum samples, respectively, were borderline positive for anti-HBc. All previous serum samples were negative. Both subjects remained HBsAg negative, and there has been no report of clinical illness. Repeat testing will be done and follow-up samples are pending.

Predialysis Patients

In the Interim Submission serum samples from 6 predialysis patients were reported positive for anti-HBc at some time during the 7 month observation period. Four of the 6 were transiently positive. Of the remaining 2 patients, one was negative on retest, and one on retest was positive for anti-HBc of the IgG class but negative for anti-HBc of the IgM class.

Dialysis Patients

Three dialysis patients had prevaccination serum samples which tested positive for anti-HBc. For one patient the positive anti-HBc was transient. Anti-HBc persisted in the other two patients. None of the patients was reported to have developed clinical illness or become HBsAg positive.

Three dialysis patients were reported to have one or more serum samples positive for anti-HBc postvaccination. In one case, the positive anti-HBc was transient. In the second case, the 9 month sample was positive. In the third case, the 3 and 6 month samples were positive. Further samples were not available. None of the patients was reported to have developed clinical illness.

Other Populations

The 8 month serum sample from a patient with hemophilia was reported positive for anti-HBc. The pre, 1 and 6 month samples were negative. The patient has been anti-HBs positive since 2 months. The patient has remained HBsAg negative and there has been no report of clinical illness.

The small percentage of vaccine recipients with serum samples positive for anti-HBc may reflect both the frequency of false positives seen with this assay and the fact that predialysis, dialysis and hemophiliac patients receive transfusions of blood and blood products at varying intervals during the course of their disease. Where possible retesting will be done and follow-up samples obtained.

EFFICACY

Four studies have been initiated to evaluate the efficacy of yeast recombinant hepatitis B vaccine in preventing chronic hepatitis B antigenemia in healthy infants born to mothers who are positive for HBsAg and either positive or negative for HBeAg. Two of the studies are being conducted in China, one is in Hong Kong, and one is in the United States. In 3 of the studies, infants receive a single injection of hepatitis B immunoglobulin immediately after birth followed by injections of yeast recombinant hepatitis B vaccine (5 mcg dose) at 0, 1 and 6 months. One of these studies also includes infants that receive HBIG plus plasma-derived hepatitis B vaccine (10 mcg dose). Two of the studies being conducted in China include groups of infants that receive a three injection regimen of yeast recombinant hepatitis B vaccine alone (5 or 10 mcg dose), and one study has a group that receives plasma-derived hepatitis B vaccine (20 mcg) without any HBIG.

To date, 412 infants have been enrolled in the 4 studies, 289 of these in groups receiving the yeast recombinant hepatitis B vaccine. No serious adverse experiences related to the vaccine have been reported.

Data are currently available for 59 infants, born to mothers positive for both HBsAg and HBeAg, who receive a single dose of HBIG and three 5 mcg doses of the yeast recombinant vaccine. A single infant in this group was HBsAg positive at 6 months. This infant was already antigen positive at birth. Based on these data, the efficacy of this passive-active prophylaxis in preventing chronic hepatitis B vaccine is estimated to be 98%.

COMPARISON OF RECOMBINANT AND PLASMA DERIVED VACCINES

The only hepatitis B vaccine currently licensed in the United States (HEPTAVAX-B) is comprised of noninfectious HBsAg that has been purified from the plasma of chronically infected persons. By contrast, the investigational recombinant hepatitis B vaccine is made from HBsAg produced by a strain of baker's yeast (S. *cerevisiae*) containing that portion of the hepatitis B virus gene which codes for surface antigen. HBsAg purified from yeast is essentially the same as that from human plasma including its particle appearance. Unlike the plasma-derived HBsAg the yeast HBsAg is not glycosylated. The recombinant HBsAg vaccine is adsorbed to alum as is the plasma-derived product.

A direct comparison of the two vaccines with respect to immunogenicity and clinical complaints will be available from two studies. One is a small (56 participants) randomized study (#807). The results for this study are presented in the appropriate study summary (see SUMMARY-HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS). The other is a double blind study in which 300 healthy adult male homosexuals will receive three doses of either yeast recombinant (10 mcg dose) or plasma-derived (20 mcg dose) hepatitis B vaccine. This study was initiated recently. The first injection of vaccine has been administered to 197 subjects, while 113 have received the second of three scheduled injections. Assays for hepatitis B serologic markers will not be done on any samples until subjects have received all injections of vaccine. However, interim clinical reports submitted following the first two injections have been examined by the clinical monitor at Merck and complaints and elevated temperatures tallied according to the type of hepatitis B vaccine (recombinant or plasma-derived) that was administered.

Clinical complaints from the study involving homosexuals are summarized in Table 12. All reactions have been mild and transient. Among recipients of plasma-derived vaccine, 39% reported injection site reactions while 31% had systemic complaints within a 5 day period following vaccination. Recipients of recombinant vaccine reported injection site reactions following 32% of the injections, while 24% had systemic complaints. Local complaints consisted almost exclusively of soreness at the injection site for recipients of either vaccine. The most frequent systemic complaints following injection of recombinant vaccine were fatigue/weakness (6%), arthralgia (6%), and nausea (4%), while the most frequent systemic complaints following injection of the plasma-derived vaccine were fatigue/weakness (16%), arthralgia (7%), and headache (6%).

Further comparison of the antibody and clinical responses to the plasma-derived and yeast recombinant hepatitis B vaccine is possible using data from multiple ongoing studies involving the recombinant vaccine and historical data obtained in earlier studies with the plasma-derived vaccine. This type of comparison is described below and demonstrates that both recombinant and plasma-derived vaccines are well tolerated and highly immunogenic. Tables 13 to 17 compare the anti-HBs responses of health care personnel and other healthy adults who received 10 mcg doses of yeast recombinant hepatitis vaccine in the current clinical trials program with similar subjects who received 20 mcg doses of plasma-derived hepatitis B vaccine in earlier studies. Seroconversion rates among adults 20-49 years of age, after 3 injections of vaccine, were 94% or greater for either vaccine (Table 15). The GMTs of responders in this age range were 1554.0 mIU/ml (approximate conversion from (b)(4) units) and 1282.3 mIU/ml for recipients of plasma-derived and recombinant vaccines, respectively.

The percentages of both plasma-derived and recombinant vaccine recipients developing anti-HBs (S/N $\geq$2.1) declined with increasing age. The geometric mean titers of responders also varied inversely with age. Although 94 - 99% of the vaccinees ages 20-49 years of age had anti-HBs after 3 injections of vaccine, the frequency of seroconversion in subjects 50-59 years of age was 90% among recipients of recombinant vaccine and 85% for those who received plasma-derived vaccine. The geometric mean titers of anti-HBs at 7/8 months in persons receiving recombinant vaccine ranged from 1707 mIU/ml for the 20-29 year age group to 442 mIU/ml in the 50-59 year age group. The GMT for recipients of plasma-derived vaccine was 2830 mIU/ml for the 20-29 year age group and 306 mIU/ml for the 50-59 year age group (Table 15).

Table 16 shows the distribution of antibody titers achieved by healthy adult vaccinees of all ages following 3 injections of either yeast recombinant or plasma-derived hepatitis B vaccine. Among recipients of the recombinant vaccine, 98% had at least minimal evidence of antibody (S/N $\geq$2.1), while 97% developed fully protective levels of anti-HBs (mIU/ml $\geq$10). Eighty-nine percent of the vaccinees had a titer of mIU/ml $\geq$100, while 58% had a titer of mIU/ml $\geq$1000. A fairly similar distribution of titers was characteristic of persons receiving the plasma-derived vaccine. Ninety-five percent seroconverted for anti-HBs (S/N $\geq$2.1), while 92% developed fully protective levels of antibody (mIU/ml $\geq$10). Seventy-eight percent of the plasma-derived vaccine recipients had a titer of mIU/ml $\geq$100, while 53% had a titer of mIU/ml $\geq$1000.

Tables 17 and 18 summarize the anti-HBs status of recombinant and plasma-derived vaccine recipients at 12 months. The GMTs of responders at 12 months are 2 to 5-fold lower than those observed at 7/8 months. However, when tallied across

all age groups, 90% of the recombinant vaccinees and 92% of the recipients of plasma-derived vaccine retained fully protective titers (mIU/ml ≥10) at 12 months (Table 18). Sixty-five percent of the recombinant vaccine recipients had titers of mIU/ml ≥100 at 12 months, while 25% still had titers of mIU/ml ≥1000. Among vaccinees who received the plasma-derived vaccine, 70% had titers of mIU/ml≥100 at 12 months, while 37% retained titers of mIU/ml ≥1000.

Table 19 shows the frequencies of local injection site complaints, any type of clinical complaint, and elevated temperatures reported by health care personnel and other healthy adults following vaccination with the yeast recombinant hepatitis B vaccine in current studies compared with the frequencies of such complaints among similar subjects in earlier studies of plasma-derived hepatitis B vaccine. With either vaccine, the frequencies of complaints were somewhat lower following the second and third injections. Over all injections, the frequencies of injection site complaints and any type of complaint were 12% and 20%, respectively for plasma-derived vaccine, while the use of recombinant vaccine was followed by reports of injection site complaint or any type of complaint with frequencies of 17% and 27%, respectively. All complaints were mild, transient in nature and consisted most frequently of injection site soreness, fatigue/weakness and headache. The frequency of elevated temperature (≥100°F, oral) reported by healthy adults during a 5 day period following vaccination was approximately 3%, both for recipients of plasma-derived vaccine and of yeast recombinant vaccine (Table 19).

Clinical studies with the recombinant vaccine demonstrate its safety and immunogenicity. A comparison with historical data obtained using plasma-derived hepatitis B vaccine shows that 10 mcg doses of the recombinant vaccine and 20 mcg doses of the plasma-derived vaccine yield similar seroconversion rates and GMTs in healthy adult recipients. Using historical data from past studies involving the plasma-derived vaccine, clinical reactions appear to be somewhat more frequent following injection of the recombinant vaccine as compared to the plasma-derived vaccine. However, in one contemporary double-blind study involving both vaccines, clinical complaints were more frequent among recipients of the plasma-derived as compared to the recombinant vaccine. Both vaccines were well tolerated with postvaccination reactions being of a mild and transient nature.

Table 1

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced By the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Healthy Adults	779-1*	Bishop	Merck & Co., PA	11/16/83	In progress	C-K444	10 mcg	0,1,6 mos.	30 (26)	100 (17/17)	94 (16/17)	7/8
Healthy Adults	809-1	Plotkin, Starr	Philadelphia	6/19/84	In progress	C-K444	10 mcg	0,1,6 mos.	20 (18)	100 (11/11)	100 (11/11)	7/8
Healthy Adults	839	Bishop	Merck & Co., PA	7/31/84	In progress	C-K444	10 mcg	Day 0	10 (5)	25 (1/4)	0 (0/4)	6
Healthy Adults	882	Iino	Japan	12/84	In progress	C-L215	10 mcg	0,1,6 mos.	50 (40)	100 (40/40)	NA	7
Healthy Adults (Male Homosexuals)	894	Polk	Baltimore	4/85	In progress	C-K563	10 mcg	0,1,6 mos.	350 (87)	NA	NA	--
						H-B-Vax C-M252	20 mcg	0,1,6 mos.	(88)	NA	NA	--
Healthy Adults	898	Bishop	Merck & Co., PA	11/18/85	In progress	C-M125	20 mcg	0,1,6 mos.	20 (2)	NA	NA	--
						C-M126	10 mcg	0,1,6 mos.	20 (1)	NA	NA	--
Healthy Adults	907	Iino	Japan	5/7/85	In progress	C-L215	10 mcg/IM	0,1,6 mos.	62 (62)	98 (54/55)	NA	7
							10 mcg/SC	0,1,6 mos.	62 (62)	97 (56/58)	NA	7
Healthy Adults	904	Kessler	Chicago	10/85	In progress	C-M718	10 mcg	0,1,6 mos.	50 (50)	NA	NA	--
						C-L217	10 mcg	0,1,6 mos.	50 (50)	NA	NA	--
Healthy Adults (Male Homosexuals)	900	Zuckerman	London, UK	8/85	In progress	C-M126	10 mcg	0,1,6 mos.	200 ( )	NA	NA	--
Health Care Personnel	792-1	Dienstag	Boston	5/84	In progress	C-K564	10 mcg	0,1,6 mos.	30 (35)	96 (27/28)	93 (26/28)	9
Health Care Personnel	794	Alter	Bethesda	4/18/84	In progress	C-K444	10 mcg	0,1,6 mos.	30 (41)	97 (35/36)	94 (34/36)**	7/8

NA = Not Available
*Suffix number indicates addendum to initial study protocol.
**This percentage is that with S/N ≥10, rather than mIU/ml ≥10.

31531/1
1/9/86

Table 1 (Cont.)

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced By the (b) (4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Health Care Personnel	794-1	Alter	Bethesda	6/84	In progress	C-K444	5 mcg	0,1,6 mos.	30 (30)	84 (21/25)	76 (19/25)**	7/8
Health Care Personnel	795-2	Deinhardt	W. Germany	12/1/84	In progress	C-L215	10 mcg	0,1,6 mos.	300 (97)	99 (79/80)	99 (79/80)	7/8
						C-K564	10 mcg	0,1,6 mos.	(148)	100 (76/76)	100 (76/76)	7/8
Health Care Personnel	798	Hollinger	Houston	4/11/84	In progress	C-K446	20 mcg	0.1,6 mos.	35 (36)	100 (35/35)	91 (32/35)	7/8
							10 mcg	0,1,6 mos.	35 (37)	97 (34/35)	97 (35/36)	7/8
							5 mcg	0,1,6 mos.	35 (36)	97 (35/36)	83 (30/36)	7/8
Health Care Personnel	801	Septimus	Houston	2/16/84	In progress	C-K444	10 mcg	0,1,6 mos.	25 (22)	100 (21/21)	100 (21/21)	7/8
Health Care Personnel	803	Judson	Denver	1/16/84	In progress	C-K444	10 mcg	0,1,6 mos.	30 (31)	85 (22/26)	85 (22/26)	7/8
Health Care Personnel	807	Schalm	Netherlands	4/4/84	In progress	C-K444	10 mcg	0,1,6 mos.	30 (31)	100 (31/31)	100 (31/31)	7/8
						H-B Vax 1510J	20 mcg	0,1,6 mos.	30 (25)	100 (22/22)	100 (22/22)	7/8
Health Care Personnel	808	Sampliner	Tucson	4/3/84	In progress	C-K444	10 mcg	0,1,6 mos.	25 (25)	96 (22/23)	96 (22/23)	7/8
Health Care Personnel	811	Grob	Switzerland	4/10/84	In progress	C-K446	10 mcg	0,1,6 mos.	11 (11)	86 (6/7)	83***(5/6)	7/8
Health Care Personnel	813	Davidson	NYC	2/1/84	In progress	C-K444	10 mcg	0,1,6 mos.	50 (62)	97 (38/39)	97 (38/39)	7/8
Health Care Personnel	813-1	Davidson	NYC	2/84	In progress	C-K444	5 mcg	0,1,6 mos.	50 (60)	94 (44/47)	91 (43/47)	7/8
Health Care Personnel	813-2	Davidson	NYC	5/84	In progress	C-K444	2.5 mcg	0,1,6 mos.	50 (61)	100 (40/40)	97 (39/40)	7/8
Health Care Personnel	813-3	Davidson	NYC	1/85	In progress	C-L220	10 mcg	0,1,6 mos.	50 (62)	95 (37/39)	92 (36/39)	6
Health Care Personnel	813-4	Davidson	NYC	2/85	In progress	C-L220	5 mcg	0,1,6 mos.	50 (61)	93 (41/44)	80 (35/44)	6

**This percentage is that with S/N ≥10, rather than mIU/ml ≥10.
***Based on 6 subjects (5 responders) for whom numeric titers are available.
3153I/2
1/8/86

00016

Table 1 (Cont.)

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine
Produced By the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Health Care Personnel	813-5	Davidson	NYC	6/85	In progress	C-M125	20 mcg	0,1,6 mos.	50 (7)	NA	NA	--
						C-M126	10 mcg	0,1,6 mos.	50 (7)	NA	NA	--
Health Care Personnel	816	Plotkin, Starr	Philadelphia	5/15/84	In progress	C-K446	10 mcg	0,1,6 mos.	25 (8)	80 (4/5)	80 (4/5)	7/8
Health Care Personnel	835	Lemon	Chapel Hill	10/26/84	In progress	C-K564	10 mcg	0,1,6 mos.	30 (29)	100 (19/19)	100 (19/19)	7-9
Health Care Personnel	838	Deinhardt	W. Germany	6/7/84	In progress	C-K733	10 mcg	0,1,6 mos.	25 (22)	94 (16/17)	94 (16/17)	7/8
Health Care Personnel	859	Clumeck	Belgium	3/12/85	In progress	C-K563	10 mcg	0,1,6 mos.	50 (31)	80 (24/30)	53 (16/30)	3
Health Care Personnel	860	Laufs	W. Germany	12/28/84	In progress	C-K563	10 mcg	0,1,6 mos.	100 (60)	100 (56/56)	100 (56/56)	7/8
Health Care Personnel	869	Rankin, Coates	Canada	5/85	In progress	C-L217	10 mcg	0,1,6 mos.	150 (71)	32 (22/68)	12 (8/68)	1
Health Care Personnel	871	Oon	Singapore	1/26/85	In progress	C-K564	10 mcg	0,1,6 mos.	30 (31)	97 (28/29)	97 (28/29)	7/8
Health Care Personnel	880	Wormser	Valhalla, NY	4/1/85	In progress	C-L215	10 mcg	0,1,6 mos.	50 (50)	86 (31/36)	64 (23/36)	6
						C-L216			50 (43)	100 (20/20)	100 (20/20)	6
						C-L217			50 (54)	88 (23/26)	81 (21/26)	6
						C-L219			50 (47)	90 (19/21)	81 (17/21)	6
						C-L220			50 (43)	97 (38/39)	90 (35/39)	6
Health Care Personnel	883	Plotkin, Starr	Philadelphia	11/13/84	In progress	C-L220	10 mcg	0,1,6 mos.	25 (28)	100 (24/24)	96 (23/24)	7/8
							5 mcg	0,1,6 mos.	25 (25)	100 (20/20)	95 (19/20)	7/8
Health Care Personnel	885	Liebowitz	Miami	7/85	In progress	C-L215	10 mcg	0,1,6 mos.	50	NA	NA	--
						C-L216			50	NA	NA	--
						C-L217			50 (50)	NA	NA	--
						C-L219			50 (50)	NA	NA	--
						C-L220			50 (50)	NA	NA	--
Health Care Personnel	889	Perillo	St. Louis	6/19/85	In progress	C-K937	10 mcg	0,1,6 mos.	50 (88)	.17 (14/82)	6 (5/82)	1
Health Care Personnel	834	Rizzetto	Italy	8/85	In progress	C-K564	10 mcg	0,1,6 mos.	30 (25)	NA	NA	--

Table 1 (Cont.)

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced By the (b) (4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Health Care Personnel	841	Zuckerman	United Kingdom	5/85	In progress	C-K563	10 mcg	0,1,6 mos.	100	NA	NA	--
Health Care Personnel	891	Hu	China	12/85	In progress	C-K564	10 mcg	0,1,6 mos.	100 (25)	NA	NA	--
						H-B-Vax 0027L	20 mcg	0,1,6 mos.	100 (25)	NA	NA	--
Health Care Personnel	912	Shimizu	Japan	9/2/85	In progress	C-L220	10 mcg/IM	0,1,6 mos.	87 (87)	75 (56/75)	NA	2
							10 mcg/SC	0,1,6 mos.	88 (88)	59 (43/73)	NA	2
Health Care Personnel	914	Burette	Belgium	11/21/85	In progress	C-M126	10 mcg	0,1,6 mos.	20 (20)	NA	NA	--
Health Care Personnel	815	Schalm	Netherlands	12/85	In progress	C-K937	10 mcg	0,1,6 mos.	30	NA	NA	--
							20 mcg	0,1,6 mos.	30	NA	NA	--
						H-B-VAX 2277K	20 mcg	0,1,6 mos.	30	NA	NA	--
Health Care Personnel	867	Crovari	Italy		Planned	C-K564	10 mcg	0,1,6 mos.	30	NA	NA	--
Health Care Personnel	899	DeBac	Italy		Planned	C-K564	10 mcg	0,1,6 mos.	30	NA	NA	--

Table 1

Clinical Studies of Hemophiliacs, Thalassemic Children and Patients With Sickle Cell Anemia
Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine			# Subjects Planned (Vaccinated)	% with anti-HBs		Time (Months)
						Lot	Dose	Regimen		S/N ≥2.1	mIU/ml ≥10	
Hemophiliacs	861	Gill	Milwaukee	11/8/84	In progress	C-K564	10 mcg	0,1,6 mos.	2 (3)	100 (2/2)	0 (0/2)	3
							5 mcg	0,1,6 mos.	25 (12)	100 (8/8)	100 (8/8)	3
Thalassemic Children	799	Stevens	NYC	9/4/84	In progress	C-K444	5 mcg	0,1,6 mos.	25 (15)	89 (8/9)	78 (7/9)	7/8
							2.5 mcg	0,1,6 mos.	25 (16)	82 (9/11)	64 (7/11)	6
Patients with Sickle Cell Anemia	861-1	Gill	Milwaukee	7/85	In progress	C-K564	5 mcg	0,1,6 mos.	10 (4)	NA	NA	--

31531/5
1/8/86

Table 1

Clinical Studies of Healthy Teenagers, Children and Infants Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Healthy Teenagers	819	Papaevangelou	Greece	5/12/84	In progress	C-K564	10 mcg	0,1,6 mos.	55 (55)	100 (52/52)	100 (52/52)	7/8
						C-K732	5 mcg	0,1,6 mos.	55 (55)	100 (54/54)	100 (54/54)	7/8
						C-K732	2.5 mcg	0,1,6 mos.	55 (55)	100 (53/53)	94 (50/53)	7/8
Healthy Children	809	Plotkin, Starr	Philadelphia	2/2/84	In progress	C-K444	5 mcg	0,1,6 mos.	20 (22)	100 (14/14)	100 (14/14)	7/8
							2.5 mcg	0,1,6 mos.	20 (17)	100 (10/10)	100 (10/10)	7/8
	809-2	Plotkin, Starr	Philadelphia	6/19/84	In progress	C-K732	2.5 mcg	0,1,6 mos.	15 (15)	100 (11/11)	100 (11/11)	7/8
							1.25 mcg	0,1,6 mos.	25 (26)	100 (14/14)	100 (14/14)	7/8
Healthy Children/ Infants	865	Yeoh	Hong Kong	2/1/85	In progress	C-K734	5 mcg	0,1 mos.	100 (90)	96 (23/24)	88 (21/24)	8
							5 mcg	0,1,6 mos.	100 (88)	100 (21/21)	100 (21/21)	8
Healthy Children	891	Hu	China	12/85	In progress	C-K564	5 mcg	0,1,6 mos.	100 (25)	NA	NA	—
						H-B Vax 0027L	10 mcg	0,1,6 mos.	100 (25)	NA	NA	—
Healthy Children	843	Oon	Singapore		Planned	C-K734	5 mcg	0,1,6 mos.	30	NA	NA	—
						C-M127	2.5 mcg	0,1,6 mos.	30	NA	NA	—
						C-M128	1.25 mcg	0,1,6 mos.	30	NA	NA	—
						C-M129	0.6 mcg	0,1,6 mos.	30	NA	NA	—

00020

Table 1

Clinical Studies of Dialysis/Predialysis Patients and Mentally Retarded Patients Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Dialysis Patients	816	Plotkin, Starr	Philadelphia	5/15/84	Inprogress	C-K446	40 mcg	0,1,6 mos.	25 (36)	80 (16/20)	75 (15/20)	7/8
							20 mcg	0,1,6 mos.	25 (39)	57 (16/28)	46 (13/28)	7/8
Dialysis Patients	838	Deinhardt	W. Germany	6/7/84	Inprogress	C-K733	40 mcg	0,1,6 mos.	50 (51)	64 (23/36)	58 (21/36)	7/8
Dialysis Patients	838-1	Deinhardt	W. Germany	11/84	Inprogress	C-K733	40 mcg	0,1,2,3,4, 6 mos.	20 (20)	67 (10/15)	60 (9/15)	10
							20 mcg	0,1,2,3,4, 6 mos.	20 (20)	50 (9/18)	44 (8/18)	10
Dialysis Patients	825	Alter	Washington	4/10/85	Inprogress	C-L915	100 mcg	0,1,6 mos.	30 (44)	68 (19/28)	25 (7/28)*	3
Predialysis Patients	789	Hamilton	Durham	5/23/84	Inprogress	C-K446	40 mcg	0,1,6 mos.	20 (15)	71 (5/7)	57 (4/7)*	7/8
							20 mcg	0,1,6 mos.	20 (14)	86 (6/7)	57 (4/7)*	7/8
						H-B Vax	40 mcg	0,1,6 mos.	20 (16)	67 (4/6)	67 (4/6)*	7/8
Predialysis Patients	811	Grob	Switzerland	4/10/84	Inprogress	C-K446	40 mcg	0,1,6 mos.	20 (13)	64 (7/11)	64 (7/11)	7/8
							20 mcg	0,1,6 mos.	20 (14)	58 (7/12)	58 (7/12)	7/8
							10 mcg	0,1,6 mos.	20 (14)	15 (2/13)	15 (2/13)	7/8
						H-B Vax	40 mcg	0,1,6 mos.	20 (11)	50 (4/8)	38 (3/8)	7/8
							20 mcg	0,1,6 mos.	20 (11)	25 (2/8)	25 (2/8)	7/8
Predialysis Patients	838-3	Deinhardt	W. Germany	1/85	Inprogress	C-K733	40 mcg	0,1,6 mos.	10 (8)	13 (1/8)	0 (0/8)	1
Mentally Retarded	889	Perrillo	St. Louis	6/19/85	Inprogress	C-K937	20 mcg	0,1,6 mos.	125 (101)	20 (20/100)	11 (11/100)	1
							10 mcg	0,1,6 mos.	125 (101)	19 (19/101)	8 (8/101)	1
Mentally Retarded	815	Schalm	Netherlands	12/85	Inprogress	C-K937	10 mcg	0,1,6 mos.	30	NA	NA	--
							20 mcg	0,1,6 mos.	30	NA	NA	--
						H-B-Vax 2277K	20 mcg	0,1,6 mos.	30	NA	NA	--

*This percentage is that with S/N≥10, rather than mIU/ml ≥10.

00021

Table 1

Clinical Studies of Nonresponders and Hyporesponders, Chronic Carriers of HBsAg, and Preimmune Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Nonresponders to Plasma Vaccine (Healthy Adults)	794-2	Alter	Bethesda	6/84	In progress	C-K444	10 mcg 5 mcg	0,1,6 mos. 0,1,6 mos.	10 (11) (1)	88 (7/8) 100 (1/1)	63 (5/8) 0 (0/1)	7/8 7/8
Nonresponders to Plasma Vaccine (Dialysis Patients)	816	Plotkin, Starr	Philadelphia	5/14/84	In progress	C-K446	40 mcg 20 mcg	0,1,6 mos. 0,1,6 mos	4 (4) 5 (5)	33 (1/3) 25 (1/4)	33 (1/3) 25 (1/4)	7/8 3
Nonresponders to Plasma Vaccine (Healthy Adults)	817	Bishop	Merck & Co., PA	3/21/84	In progress	C-K444	10 mcg	0,1,6 mos.	20 (4)	0 (0/2)	0 (0/2)	7/8
Nonresponders to Plasma Vaccine (Healthy Adults)	854	Dienstag	Boston	10/4/84	In progress	C-K564	10 mcg	0,1,6 mos.	20 (14)	58 (7/12)	25 (3/12)	6
Nonresponders to Plasma Vaccine (Dialysis Patients)	875	Johnson	Duluth	7/85	In progress	C-K937 H-B Vax	40 mcg 40 mcg	0,1,6 mos. 0,1,6 mos.	20 (17) 20 (18)	38 (5/13) 47 (7/15)	15 (2/13) 47 (7/15)	2 2
Hyporesponders to Plasma Vaccine	854	Dienstag	Boston	10/4/84	In progress	C-K564	10 mcg	Day 0	20 (2)	NA	50 (1/2)	1
Chronic carriers of HBsAg	854	Dienstag	Boston	10/4/84	In progress	C-K564	10 mcg	0,1,2,3,4, 5 mos.	15 (18)	0 (0/18)**	0 (0/18)**	--

**This percentage (proportion) refers to the number of chronic carriers who became seronegative for HBsAg after vaccination with recombinant vaccine.

31531/8
1/8/86

00022

Table 1 (Cont.)

Clinical Studies of Nonresponders and Hyporesponders, Chronic Carriers of HBsAg, and Preimmune Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine			# Subjects Planned (Vaccinated)	% with anti-HBs		Time (Months)
						Lot	Dose	Regimen		S/N ≥2.1	mIU/ml ≥10	
Transient Responders	854	Dienstag	Boston	10/4/84	In progress	C-K564	10 mcg	Day 0	15 (3)	NA	67 (2/3)	1
Non-responders/ Hypo-responders	874	Tong	California	9/85	In progress	C-K563	10 mcg	0,1,6 mos.	40 (26)	36 (9/25)	NA	1
Preimmune Adults	813-6	Davidson	NYC	7/85	In progress	C-M126	10 mcg	Day 0	100 (31)	97 (29/30)*	NA	1
Preimmune Adults	813-7	Davidson	NYC	7/85	In progress	C-M126	5 mcg 10 mcg	Day 0 Day 0	25 (28) 25 (28)	NA NA	100 (28/28)* 100 (28/28)*	1/2 1/2
Preimmune Adults	817	Bishop	Merck & Co.	3/21/84	In progress	C-K444	10 mcg	Day 0	20 (5)	100 (5/5)*	100 (5/5)	1/8

*This percentage (proportion) refers to the number of preimmune subjects (naturally acquired or vaccine-induced, as indicated) who exhibited a boost in anti-HBs titer after receiving recombinant vaccine.

Table 1

Clinical Studies of Neonates Born to Carrier Mothers Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Neonates of HBeAg+ Mothers	864	Stevens	NYC/LA/SF	9/1/84	In progress	C-K732	5 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	80 (134)	100 (47/47)	NA	6
Neonates of HBeAg+ Mothers	862	Yeoh	Hong Kong	2/85	In progress	C-K734	5 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	150 (40)	NA	100 (24/24)	3
						H-B Vax 1032K 2455J 0027L 1507J	10 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	75 (28)	NA	100 (19/19)	3
Neonates of HBeAg+ Mothers	878	Sun	China	7/85	In progress	C-K564	5 mcg	0,1,6 mos. +0.5 ml HBIG at birth	30 (30)	NA	NA	--
					Planned	C-K564	5 mcg	0,1,6 mos. (No HGIB)	70			
Neonates of HBeAg+ Mothers	892	Hu	China	12/85	In Progress	C-K564	5 mcg	0,1,6 mos.	50 (5)	NA	NA	--
							10 mcg	0,1,6 mos.	50 (5)	NA	NA	--
						H-B Vax 0027L	10 mcg	0,1,6 mos.	50 (5)	NA	NA	--
							20 mcg	0,1,6 mos.	50 (5)	NA	NA	--
Neonates of HBeAg - Mothers	862	Yeoh	Hong Kong	2/85	In progress	C-K734	5 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	(75)	NA	100 (41/41)	3
						H-B-VAX 1032K 2455J 0027L 1507J	10 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	(85)	NA	100 (42/42)	3

00024

31531/10

Table 2

List of Number Vaccinated with
Yeast Recombinant Hepatitis B Vaccine, Clinical Reports, and
Post-Vaccination Anti-HBs Data by Population Group

NA = Not Applicable

Population Group	Vaccinations Injection #			Clinical Reports Injection #			Anti-HBs Data Injection		
	1	2	3	1	2	3	1	2	3
Health Care Personnel/Other Healthy Adults	2414	2286	1442	1626	1508	990	1616	1436	1048
Healthy Teenagers	165	165	165	165	165	165	165	165	165
Healthy Infants/Children	258	222	122	220	191	100	213	189	97
Dialysis/Predialysis Patients	288	287	196	286	264	184	258	230	166
Mentally Retarded Institutionalized Patients	202	201	200	202	201	--	202	--	-
Thalassemic Children	31	31	27	30	30	5	31	27	14
Hemophiliacs	15	15	6	13	10	6	15	15	6
Patients with Sickle Cell Anemia	4	4	--	--	--	--	--	--	--
Nonresponders to Plasma-Derived Vaccine									
Healthy Adults	55	54	24	30	28	24	52	25	14
Dialysis Patients	26	24	6	25	24	6	20	21	4
Hyporesponders/Transient Responders to Plasma-Derived Vaccine	5	NA	NA	5	NA	NA	4	NA	NA
Preimmune Adults	91	NA	NA	48	NA	NA	88	NA	NA
Chronic Carriers of HBsAg	18	18	18	18	18	18	18	18	18
Infants of Carrier Mothers									
$HBsAg^+/HBeAg^+$	214	157	73	135	114	43	133	110	19
$HBsAg^+/HBeAg^-$	75	73	30	75	73	30	70	41	--
T O T A L	3861	3537	2309	2878	2626	1571	2885	2277	1551

Table 3
Antibody Responses at 3 Months Among Healthy
Initially Seronegative Persons Receiving Yeast Recombinant
Hepatitis B Vaccine at 0,1 and 6 Months

Age (Years)	1.25 mcg				2.5 mcg				5 mcg				10 mcg				20 mcg			
	% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*	
	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10
1-11	100 (7/7)	86 (6/7)	52.7	77.5	100 (16/16)	81 (13/16)	77.3	130.5	100 (10/10)	100 (10/10)	189.3	189.3								
12-19					91 (49/54)	67 (36/54)	31.8	63.3	100 (54/54)	94 (51/54)	107.9	127.4	100 (56/56)	100 (54/56)	189.2	215.4				
20-29					84 (43/51)	65 (33/51)	37.6	66.1	83 (118/142)	67 (95/142)	34.0	57.5	92 (359/388)	83 (323/388)	67.9	90.9	84 (16/19)	58 (11/19)	21.5	64.9
30-39					100 (4/4)	25 (1/4)	7.5	12.7	50 (8/16)	31 (5/16)	18.4	46.7	78 (87/112)	61 (68/112)	38.7	70.7	94 (15/16)	56 (9/16)	9.5	19.9
40-49									67 (2/3)	0 (0/3)	3.6	--	75 (21/28)	54 (15/28)	47.9	126.8				
50-59					100 (1/1)	100 (1/1)	73.6	73.6					82 (14/17)	65 (11/17)	21.6	31.3				
60-69													75 (3/4)	25 (1/4)	5.9	24.2				

*Responders only.

24101/1
12/26/85

Table 4

Antibody Responses at 6 Months Among Healthy Initially Seronegative Persons Receiving Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months

Age (Years)	1.25 mcg				2.5 mcg				5 mcg				10 mcg				20 mcg			
	% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*	
	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10
1-11	100 (21/21)	90 (19/21)	75.9	100.7	96 (26/27)	93 (25/27)	145.2	163.2	100 (19/19)	100 (19/19)	308.4	308.4								
12-19					94 (48/51)	71 (36/51)	31.3	59.4	100 (54/54)	100 (54/54)	107.5	107.5	100 (74/74)	99 (73/74)	162.9	169.3				
20-29					86 (45/52)	69 (36/52)	33.4	51.4	88 (125/142)	72 (102/142)	43.3	71.2	96 (403/419)	90 (379/419)	96.4	115.8	90 (17/19)	79 (15/19)	58.1	86.8
30-39					75 (3/4)	75 (3/4)	22.9	22.9	46 (6/13)	31 (4/13)	11.4	22.9	89 (110/124)	79 (98/124)	53.4	70.7	93 (14/15)	80 (12/15)	25.8	34.5
40-49									78 (2/3)	33 (1/3)	10.5	35.5	88 (30/34)	74 (25/34)	44.6	71.2				
50-59					100 (1/1)	100 (1/1)	15.5	15.5					81 (13/16)	69 (11/16)	42.4	59.8				
60-69													100 (3/3)	33 (1/3)	13.1	112.8				

*Responders only.

2410I-3
12/26/85

00027

Table 5

Antibody Responses at 7/8 Months Among Healthy
Initially Seronegative Persons Receiving Yeast Recombinant
Hepatitis B Vaccine at 0, 1, and 6 Months*

	1.25 mcg				2.5 mcg				5 mcg				10 mcg				20 mcg			
	% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*	
Age (Years)	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10
1-11	100 (17/17)	100 (17/17)	2059.3	2059.3	100 (20/20)	100 (20/20)	5454.0	5454.0	100 (14/14)	100 (14/14)	15866.0	15866.0								
12-19					100 (53/53)	94 (50/53)	846.3	1131.8	100 (54/54)	100 (54/54)	2553.4	2553.4	100 (69/69)	100 (69/69)	2913.4	2913.4				
20-29					100 (54/54)	96 (52/54)	270.2	316.1	98 (96/98)	94 (92/98)	357.5	423.7	99 (341/344)	99 (340/344)	1707.0	1737.0	100 (19/19)	84 (16/19)	527.3	1373.7
30-39					100 (3/3)	100 (3/3)	217.0	217.0	92 (12/13)	54 (7/13)	15.1	46.6	96 (106/111)	95 (105/111)	693.5	730.0	100 (16/16)	94 (15/16)	553.2	744.7
40-49									100 (3/3)	100 (3/3)	96.5	96.5	97 (33/34)	91 (31/34)	484.5	655.9				
50-59					100 (1/1)	100 (1/1)	21.8	21.8					90 (17/19)	90 (17/19)	442.0	442.0				
60-69													100 (3/3)	100 (3/3)	919.0	919.0				

*Includes some responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

00028

24101-5
1/11/86

Table 6

Antibody Responses at 12 Months Among Healthy
Initially Seronegative Persons Receiving Yeast Recombinant
Hepatitis B Vaccine at 0, 1, and 6 Months

Age (Years)	1.25 mcg				2.5 mcg				5 mcg				10 mcg				20 mcg			
	% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*	
	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10
1-11	100 (9/9)	100 (9/9)	819.2	819.2	100 (18/18)	94 (17/18)	2808.6	3925.0	100 (13/13)	100 (13/13)	3481.8	3481.8								
12-19					92 (49/53)	91 (48/53)	498.1	541.1	100 (54/54)	100 (54/54)	498.2	498.2	100 (55/55)	100 (55/55)	560.5	560.5				
20-29					95 (40/42)	90 (38/42)	148.6	177.6	96 (77/80)	81 (65/80)	121.7	226.2	98 (115/118)	93 (110/118)	342.7	419.3	95 (18/19)	84 (16/19)	258.2	449.3
30-39					100 (4/4)	75 (3/4)	57.1	116.6	64 (7/11)	18 (2/11)	7.9	63.4	94 (74/79)	86 (68/79)	235.4	322.7	100 (16/16)	88 (14/16)	119.2	297.9
40-49									100 (2/2)	100 (2/2)	70.2	70.2	91 (21/23)	91 (21/23)	238.3	238.3				
50-59					100 (1/1)	0 (0/1)	5.5	——					88 (15/17)	82 (14/17)	150.9	202.2				
60-69													100 (2/2)	100 (2/2)	233.5	233.5				

*Responders only.

62000

24101/7
12/26/85

Table 7

Percentages of Anti-HBs Specific for a and d Determinants of HBsAg in Post-Vaccination Sera

Time (Months)	Number of Samples	% Anti-a		% Anti-d	
		Range	Mean	Range	Mean
1	26	0-100	68	0-100	31
3	97	33-100	90	0-63	10
6	44	58-100	93	0-37	7
7/8	38	81-100	95	0-19	5

Table 8

Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
779	(b) (6)	1925	C-K444	10 mcg	(b) (6) (b) (6) (b) (6)	(b) (6)	11/15/84	A forty-one year old female developed headache, swollen face and rash within several hours after receiving the third injection of vaccine. Headache and swollen face resolved in one day, and the rash faded over four days. No clinical complaints were reported by this individual following the first and second injections of vaccine. She received her first and second injection of vaccine as scheduled, while the third injection was not administered until 11 months after the first injection. The individual does have a history of allergies.	Yes
789		1925	2449H (HEPTAVAX)	40 mcg	(b) (6) (b) (6)		10/19/84	This 30-year old male subject had congenital polycystic renal and liver disease. He had a history of recurrent hemorrhaging from esophageal varices. He was admitted to hospital for hemorrhage of esophageal varices. Death was due to subsequent infection, multisystem organ failure and shock.	No
789		1925	C-K446	20 mcg	(b) (6) (b) (6)		6/19/85	This 58-year old male subject had a history of hypertension and chronic renal failure (predialysis). He died at home approximately 4 months after receiving his second injection of vaccine. The Inv. stated the patient was lost to follow-up. Cause of death is unknown.	Unlikely
798		1925	C-K446	10 mcg	(b) (6) (b) (6) (b) (6)		11/19/84	A 32-year old male subject had an elevated ALT level at the time of his 3rd injection. On (b) (6) the patient reported his urine had been dark orange in color for the previous 7-8 days. The patient became anorexic and began to vomit. Jaundice was apparent. Diagnosis: Non-A, Non-B hepatitis.	No
801		1925	C-K444	10 mcg	(b) (6)		5/29/84	This 26-year old female became aware that she was pregnant after receiving one injection of vaccine. The vaccine was administered approximately 1 month after conception. She experienced a spontaneous abortion at 18 weeks after fetal death *in utero*. No microscopic examination was completed on the fetus. The subject previously delivered two healthy infants without complication of pregnancy. She had no known allergies.	Possibly**

* Clinical investigator's assessment.
**Clinical monitor's assessment.

3018I/1

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
801	(b) (6)	1925	C-K444	10 mcg	(b) (6) (b) (6) (b) (6)	(b) (6)	3/85	A 35-year old female subject complained of headache one day after receiving the third injection of vaccine. The headache persisted for three days and was accompanied by a sore throat and swollen eyes. She was admitted to hospital on (b) (6) with a diagnosis of clinical viral meningitis. She recovered without sequelae.	Probably Not
803		1925	C-K444	10 mcg	(b) (6)		2/7/84	A 43-year old male patient experienced sudden onset of biparietal headache, upset stomach, confusion and expressive aphasia 2 days after receiving the 1st injection of vaccine. His neurologic exam and vital signs were within normal limits. A CAT scan of the head was also normal. His WBC was slightly elevated with a shift to the left. By (b) (6) symptoms resolved spontaneously. The patient has a history of multiple childhood allergies.	No
811		1925	C-K446	20 mcg	(b) (6) (2 injections)		4/22/85	This 28-year old male with underlying renal disease and recently initiated hemodialysis, died approximately one month after administration of vaccine. The investigator reported death was due to vasculitis.	
816		1925	C-K446	40 mcg	(b) (6) (b) (6) (b) (6)		5/17/85	This 57-year old female hemodialysis patient with severe diabetes mellitus, hypertriglyceridemia, hyperkalemia, atherosclerotic cardiovascular disease and anemia, expired approximately 6 months after administration of the 3rd injection of vaccine. Death was due to myocardial infarction.	No
816		1925	C-K446	20 mcg	(b) (6) (b) (6) (b) (6)		4/15/85	This 57-year old male subject had a history of coronary artery disease with angina and end-stage renal disease (3x/week hemodialysis). Death was due to myocardial infarction.	No
816		1925	C-K446	40 mcg	(b) (6) (b) (6)		2/5/85	This 49-year old male patient had end-stage renal disease (3x/week hemodialysis). Death was due to respiratory arrest, aspiration asphyxia, end-stage renal and coronary artery disease.	No

*Clinical investigator's assessment.

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
816	(b) (6)	1925	C-K446	40 mcg	(b) (6) (b) (6)	(b) (6)	2/5/85	The patient, a 79-year old male, had end-stage renal disease (3x/week hemodialysis). Death was caused by cardiac arrest, atherosclerosis, end-stage renal disease, and multiple myeloma.	No
816		1925	C-K446	20 mcg	(b) (6)		1/22/85	This 71-year old female patient had a history of chronic renal failure, Parkinson's Disease, dementia, and abdominal aneurysm. The patient received biweekly hemodialysis. Her death was due to cardiopulmonary arrest, uremia, chronic renal failure, and abdominal aortic aneurysm without rupture.	No
816		1925	C-K446	40 mcg	(b) (6) (b) (6)		1/22/85	This 49-year old male patient had a history of cardiac myopathy and chronic renal failure (3x/week hemodialysis). His death was due to cardiac arrest, pulmonary edema, and end-stage kidney disease.	No
816		1925	C-K446	20 mcg	(b) (6) (b) (6)		2/5/85	The 53-year old female subject had a history of hypertension, diabetes mellitus, cirrhosis, severe renal osteodystrophy and end-stage renal disease (3x/week hemodialysis). Death was caused by congestive heart failure, renal failure, and severe arteriosclerosis.	No
816		1925	C-K446	20 mcg	(b) (6) (b) (6) (b) (6)		1/22/85	This 63-year old male hemodialysis patient with ESRD and severe peripheral vascular disease, was hospitalized for a left femoral-popliteal bypass and lumbar sympathectomy approximately 2 months after administration of his 3rd injection of vaccine. His hospital course was complicated by postoperative blood loss, hypotension and hyperkalemia. He subsequently experienced a respiratory arrest requiring resuscitative measures. Post resuscitation, the patient was comatose and decerebrate. His condition further deteriorated and he died 4 days after admission to the hospital.	No

*Clinical investigator's assessment.

3018I-3
1/19/86

Table B (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
816	(b) (6)	1925	C-K446	40 mcg	(b) (6) (b) (6)	(b) (6)	2/5/85	This 37-year old female subject had a history of diabetes mellitus and end-stage renal disease (2x/week hemodialysis). Her death was caused by sepsis, end-stage renal disease, acute respiratory distress syndrome, infected dialysis graft, and diabetes mellitus.	No
825		1925	C-L915	100 mcg	(b) (6)		5/14/85	This 31-year old male hemodialysis patient with ESRD, diabetes mellitus and hypertension, died 18 days after administration of his first injection of vaccine. The cause of death was reported as cardiac arrhythmia secondary to end-stage renal disease.	No
825		1925	C-L915	100 mcg	(b) (6) (b) (6)		9/11/85	This 73-year old female hemodialysis patient with ESRD, diabetes mellitus, hypertension, and hypo-parathyroidism, was hospitalized 5 days after administration of her 2nd injection of vaccine for a possible CVA. On the day of admission, the patient had been receiving her schedule dialysis treatment during which she complained of left-sided weakness. Eight days after hospitalization, the patient expired. Death was reported to be due to a CVA secondary to diabetes associated vascular disease.	No
838		1925	C-K733	40 mcg	(b) (6) (b) (6) (b) (6) (b) (6) (b) (6)		4/8/85	This 70-year old male subject had a history of coronary artery disease and end-stage renal disease. His death was due to acute myocardial infarction.	No
838		1925	C-K733	40 mcg	(b) (6) (b) (6) (b) (6)		10/17/85	This 46-year old male dialysis patient with a history of diabetes mellitus and diabetic nephropathy, died 2 months after administration of his 3rd injection of vaccine. Death was due to cardiac arrest secondary to hyperkalemia.	No

*Clinical investigator's assessment.

3018I-4
1/19/86

00034

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
861	(b) (6)	1925	C-K564	10 mcg	(b) (6) (b) (6) (b) (6)	(b) (6)	10/28/85	This 42-year old male with hemophilia type A was hospitalized one day post his 3rd injection of vaccine for melena and lightheadedness. His past medical history was significant for recurrent GI bleeding, duodenal and antral gastric ulcers, and multiple hemarthroses. On admission to the hospital an endoscopy was performed which showed a hemorrhaging telangiectasic site in the distal atrum of the stomach. The patient received 4 units of whole blood and daily cryoprecipitate infusions. He was discharged after 5 days when there was no further clinical or laboratory evidence of GI bleeding.	No
864		1925	C-K732	5 mcg	(b) (6) (b) (6) (b) (6)		6/24/85	The neonatal male received HBIG and his first injection of vaccine at birth (b) (6) . On the fifth and sixth days post-vaccination, he had a temperature of 38°C. The infant received tylenol and his temperature returned to normal. He received his second and third injections of vaccine without temperature elevation.	Unlikely
864		1925	C-K732	5 mcg	(b) (6) (b) (6) (b) (6)		6/24/85	This male neonate received one dose of HBIG at birth (b) (6) . He developed physiologic jaundice on day 4 (b) (6) after birth. The jaundice resolved by day 7. The first injection of vaccine was administered on (b) (6) The infant received the second and third injections of vaccine without local or systemic complaints.	Unlikely
864		1925	C-K732	5 mcg	(b) (6) (b) (6) (b) (6)		6/24/85	On the first day of life, this female neonate had a fever of 101.7°F. The child received one dose of HBIG at birth. The following day her temperature was normal and she received her first injection of vaccine. There were no local or systemic complaints after the first, second or third injections of vaccine.	Unlikely
864		1925	C-K732	5 mcg	(b) (6) (b) (6)		6/24/85	This male neonate was reported to have developed jaundice during the post-natal period. He had received one dose of HBIG at birth (b) (6) and his first injection of vaccine three days later. His second injection of vaccine was administered on (b) (6)	Unlikely

*Clinical investigator's assessment.

30181-5
1/19/86

00035

Table B (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
864	(b) (6)	1925	C-K732	5 mcg	(b) (6)	(b) (6)	9/19/85	This one day old full-term male infant with apgar scores of 9 at both 1 and 5 minutes was entered into study 864. He received one injection of Hep-B-Gammagee on the day of birth and his 1st injection of vaccine the following day. The infant did well until two days post-delivery when poor feeding was noted. A cardiac evaluation revealed a murmur and possible atrial septal defect. His clinical condition deteriorated requiring intubation and the administration of pressor and diuretic agents. The infant died on (b) (6) after circulatory collapse and the onset of arrhythmias. An autopsy revealed intracranial, renal and hepatic hemorrhage, hypoplasia of the left auricle and ventricle, a patent foramen ovale, an atrial septal defect, and aspiration pneumonia.	No
869		1925	C-L217	10 mcg	(b) (6)		9/24/85	Nine hours after administration of vaccine, this 46-year old female health care worker experienced generalized pruritis (without rash) which increased in intensity over the subsequent 6 hours. Pruritis continued during the next 24 hours accompanied by irritability, nausea, and parathesia in the area beneath the left breast. These symptoms resolved on the 2nd and 3rd days post-vaccination. However, the participant reported that her extremities felt stiff and heavy. Her past medical history is significant for parathesias which occurred one year prior to vaccination after a mass was surgically removed from her breast. The investigator felt that the subject's reaction had an emotional component and was not related to vaccine.	No

*Clinical investigator's assessment.

30181-6
1/19/86

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
875	(b) (6)	1925	2277K Heptavax	40 mcg	(b) (6) (b) (6)	(b) (6)	9/24/85	This 53-year old female hemodialysis patient with an 18 month history of widely metastasized adenocarcinoma of the breast in addition to COPD, HTN, uremic pericarditis and renal failure, was entered into study 875 and randomized to receive plasma derived hepatitis B vaccine. Thirty-nine days after administration of the 2nd injection of vaccine the patient died of respiratory arrest.	No
875		1925	C-K937	40 mcg	(b) (6) (b) (6)		9/13/85	Forty-seven days after administration of the 2nd injection of vaccine, this 66-year old female patient was hospitalized for an infarcted bowel. Exploratory surgery was performed and the following day the patient expired.	No
875		1925	C-K937	40 mcg	(b) (6)		9/4/85	A 32-year old male hemodialysis patient received a 20 mcg intramuscular injection of vaccine into each deltoid (total dose 40 mcg). The patient's left arm subsequently became swollen, stiff and sore. These symptoms persisted for one week and then subsided. The patient did not receive any further injections.	Possible**
875		1925	C-K937	40 mcg	(b) (6)		9/4/85	Three days after administration of the first injection of vaccine, this 72-year old male hemodialysis patient developed generalized achiness and a headache. Forty-eight hours after onset of these symptoms, he developed a flu-like syndrome with a temperature of 100°F. The patient did not receive any further vaccine injections.	Possible**
875		1925	2277K Heptavax	40 mcg	(b) (6)	unk	9/4/85	A 70-year old male dialysis patient developed an unspecified illness, requiring hospitalization, following administration of the first injection of vaccine. The investigator stated the "illness" was not related to vaccine. The patient did not receive additional vaccine injections.	No

*Clinical investigator's assessment.
**Clinical monitor's assessment.

3018I-7
1/19/86

00037

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
880	(b) (6)	1925	C-L215	10 mcg	(b) (6) (b) (6)	(b) (6)	5/6/85	This 25-year old female subject recorded a temperature of 100.1°F several days after administration of a second injection of vaccine. A CBC completed at that time revealed a normal WBC with a normal differential but a platelet count greater than 1 x $10^6/mm^3$ was noted. Bone marrow examination revealed numerous megakaryocytes. A pre-existing myeloproliferative disorder is considered the most likely diagnosis	Unlikely
883		1925	C-L220	10 mcg	(b) (6) (b) (6)		4/30/85	The subject is a dental student who developed persistent cough and tiredness. He was seen by a physician approximately 139 days after his second injection of vaccine and was tentatively diagnosed as having chronic lymphatic leukemia.	No
889		1925	C-K937	10 mcg	(b) (6)		9/24/85	Fourteen hours after administration of the 1st injection of vaccine, this 37-year old female noted facial warmth and flushing lasting 45 minutes. She subsequently developed facial urticaria. The urticaria were treated with cold packs. All symptoms subsided within 12 hours. The subject received Benadryl prior to the second and third injections and had no post-vaccination reactions. She has no known known history of allergies.	Probably**

*Clinical investigator's assessment.
**Clinical monitor's assessment.

Table 9

Most Frequent Complaints (≥1.0%) Reported by 1252 Health Care Personnel and Other Healthy Adults During a Five-Day Period Following 3255 Injection of Yeast Recombinant Hepatitis B Vaccine

Type of Complaint	Frequency as %
Local (Injection Site)	
Soreness	8
Pain	5
Tenderness	3
Pruritis	1
Systemic	
Fatigue/Weakness	4
Headache	4
Nausea	2
Diarrhea	1
Malaise	1
Pharyngitis	1
Upper Respiratory Infection (Nos)	1

Table 10

Statistical Tests Regarding Anti-Yeast Antibody

1. Test for Trend in Antibody Titer (Log Titer)

	Time			
	Prevaccination	Post First Injection	Post Second Injection	Post Third Injection
Mean Log Titer	10.6	10.6	10.8	11.0
Std. Error	0.05	0.07	0.06	0.19
Number Tested	131	70	90	12

Conclusion: No significant trend in Log Titer ($p = 0.70$)

2. Test of Association between Change in Anti-Yeast Antibody (Pre vs. Postvaccination Titers) and Incidence of Clinical Complaints (Logistic Regression Model Controlled for Age and Sex)

Test	χ^2 (1 d.f.)	p
Post First Injection	0.14	0.71
Post Second Injection	0.04	0.84

Conclusion: No association between change in anti-yeast antibody and incidence of clinical complaints

Table 11

Statistical Test of Association between Antibody to a Specific Yeast Antigen (P60) and Incidence of Clinical Complaints*

Table of p Values

Level of Antibody to P60	Clinical Complaints			
	Post First Injection	Post Second Injection	Post Third Injection	Anytime
3 Months (2 Months Post First Injection)	0.49	0.60	0.95	0.76
Change in Antibody to P60 from Prevaccination to 3 Months	0.42	0.49	0.97	0.82

* Mantel Haenzel Test with Responses Corrected for Study and Prevaccination Level of Antibody to P60. Test significant for $p < 0.05$.

Table 12

Percentage (Proportion) of Healthy Adult Male Homosexuals with Clinical Complaints Following Injections of Yeast Recombinant (10 mcg Dose) or Plasma-Derived Hepatitis B Vaccine (20 mcg Dose) in Study B94

Type of Complaint	Vaccine	First Injection	Second Injection	Both Injections
Local (Injection Site)	Plasma-Derived	42 (37/88)	35 (24/67)	39 (61/155)
	Recombinant	30 (25/83)	35 (21/60)	32 (46/143)
Systemic	Plasma-Derived	35 (31/88)	25 (17/67)	31 (48/155)
	Recombinant	29 (24/83)	18 (11/60)	24 (35/143)
Any	Plasma-Derived	61 (54/88)	51 (34/67)	57 (88/155)
	Recombinant	51 (42/83)	47 (28/60)	49 (70/143)
Temperature ≥ 100°F (oral)	Plasma-Derived	2 (2/84)	0 (0/67)	2 (2/151)
	Recombinant	5 (4/83)	7 (4/57)	6 (8/140)

Table 13

Anti-HBs Responses at 3 Months Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine at 0, 1 and 6 Months

Age (Years)	Recombinant Vaccine - 10 mcg		Plasma-Derived Vaccine - 20 mcg	
	% with Anti-HBs*	GMT (mIU/ml)**	% with Anti-HBs*	GMT (mIU/ml)**
20 - 29	92 (359/388)	68	91 (436/477)	107
30 - 39	78 (87/112)	39	88 (277/315)	46
40 - 49	75 (21/28)	48	80 (124/156)	28
50 - 59	82 (14/17)	22	61 (66/108)	27

* S/N $\geq$2.1

** Responders only; titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b)(4) titer + 4.

3086I/1
1/11/86

Table 14

Anti-HBs Responses at 6 Months Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine at 0, 1 and 6 Months

Age (Years)	Recombinant Vaccine - 10 mcg		Plasma-Derived Vaccine - 20 mcg	
	% with Anti-HBs*	GMT (mIU/ml)**	% with Anti-HBs*	GMT (mIU/ml)**
20 - 29	96 (403/419)	96	95 (434/459)	148
30 - 39	89 (110/124)	53	93 (273/293)	56
40 - 49	88 (30/34)	45	88 (128/146)	40
50 - 59	81 (13/16)	42	76 (81/107)	39

* S/N $\geq$2.1

** Responders only; titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b)(4) titer + 4.

Table 15

Anti-HBs Responses at 7/8 Months Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine at 0, 1 and 6 Months+

Age (Years)	Recombinant Vaccine - 10 mcg		Plasma-Derived Vaccine - 20 mcg	
	% with Anti-HBs*	GMT (mIU/ml)**	% with Anti-HBs*	GMT (mIU/ml)**
20 - 29	99 (341/344)	1707	98 (412/421)	2830
30 - 39	96 (106/111)	694	95 (261/274)	1050
40 - 49	97 (33/34)	484	94 (134/142)	528
50 - 59	90 (17/19)	442	85 (87/102)	360

+ Includes some responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine

* S/N $\geq$2.1

** Responders only; titer in mIU/ml for recipients of plasma-derived vaccine recipients approximated as (b)(4) titer ÷ 4.

3086I/3
1/11/86

TABLE 16

Distribution of Anti-HBs Titers at 7/8 Months
Among Health Care Personnel and Other Healthy Adults
Receiving Yeast Recombinant or Plasma-Derived
Hepatitis B Vaccine at 0, 1, and 6 Months

	% (Proportion) with Titer	
Anti-HBs Titer	Recombinant Vaccine 10 mcg	Plasma-Derived Vaccine 20 mcg
S/N ≥2.1	98 (498/509)	95 (930/983)
mIU/ml ≥10	97 (494/509)	92 (900/983)
mIU/ml ≥100	89 (451/509)	78 (772/983)
mIU/ml ≥1000	58 (294/509)	53 (519/983)

* Titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b) (4) titer + 4.

wva/31221
1/11/86

Table 17

Anti-HBs Responses at 12 Months Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine at 0, 1 and 6 Months

Age (Years)	Recombinant Vaccine - 10 mcg		Plasma-Derived Vaccine - 20 mcg	
	% with Anti-HBs*	GMT (mIU/ml)**	% with Anti-HBs*	GMT (mIU/ml)**
20 - 29	98 (115/118)	343	99 (233/236)	954
30 - 39	94 (74/79)	235	97 (67/69)	441
40 - 49	91 (21/23)	238	87 (33/38)	117
50 - 59	88 (15/17)	151	87 (46/53)	116

* S/N $\geq$2.1

** Responders only; titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b)(4) titer + 4.

30861/4
1/11/86

TABLE 18

Distribution of Anti-HBs Titers at 12 Months
Among Health Care Personnel and Other Healthy
Adults Receiving Yeast Recombinant or Plasma-Derived
Hepatitis B Vaccine at 0, 1, and 6 Months

	% (Proportion) with Titer	
Anti-HBs Titer	Recombinant Vaccine 10 mcg	Plasma-Derived Vaccine 20 mcg
S/N ≥2.1	95 (225/237)	95 (400/422)
mIU/ml ≥10	90 (213/237)	92 (387/422)
mIU/ml ≥100	65 (155/237)	70 (294/422)
mIU/ml ≥1000	25 (60/237)	37 (157/422)

*Titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b)(4) titer ÷ 4.

Table 19

Percentage (Proportion) of Health Care Personnel and Other Healthy Adults With Clinical Complaints During a 5 Day Period Following Injections of Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine

Type of Complaint	Vaccine	First Injection	Second Injection	Third Injection	All Injections
Local (Injection Site)	Plasma-Derived	13 (92/687)	10 (67/650)	11 (55/480)	12 (214/1817)
	Recombinant	20 (248/1252)	14 (157/1162)	17 (139/841)	17 (544/3255)
Any Complaint	Plasma-Derived	24 (164/687)	18 (119/650)	18 (87/480)	20 (370/1817)
	Recombinant	34 (426/1252)	23 (263/1162)	23 (196/841)	27 (885/3255)
Temperature >100°F (oral)	Plasma-Derived	3 (18/681)	3 (20/640)	2 (10/467)	3 (48/1788)
	Recombinant	4 (45/1217)	3 (28/1111)	4 (27/769)	3 (100/3097)

APPENDIX I

Lot Numbers of Vaccine Used in Clinical Trials

Lots of the yeast recombinant hepatitis B vaccine used in the clinical trials summarized in this report are identified by an alpha-numeric code consisting of two or three segments. In the Interim Submission (Report #2) issued in August 1985, many lots of vaccine were identified in text and tables using either the prefix or internal segments. In the present report, all lots are identified by the 5 digit suffix segment. To facilitate cross reference between the Interim Submission and the present report, the complete lot number for each lot of vaccine in use is listed below:

934/C-J625

972/C-K444

974/C-K446

978/C-K563

979/C-K564

985/C-K732

986/C-K733

987/C-K734

993/C-K937

81990D/18066/C-L215

817668/18067/C-L216

81991D/18068/C-L217

81992A/18070/C-L219

81954I/18071/C-L220

89303/1005/C-L915

89426/22930/C-M718

85860/22123/C-M125

85861/22124/C-M126

IMMUNE AFFINITY
VACCINE

SUMMARY - IMMUNE AFFINITY VACCINE

Recombinant hepatitis B vaccine from one lot (934/C-J625) produced by an immune affinity purification procedure has been administered to 75 initially seronegative health care personnel and other healthy adults in 3 studies (Table 1), with 72 of these completing a 3 injection regimen of vaccination. The serologic and clinical data relating to this lot are summarized separately because this procedure will not be used for the commercial product.

Table 2 shows the anti-HBs responses in persons immunized at 0, 1, and 6 months with 10 mcg doses of vaccine produced by the immune affinity procedure. All vaccinees developed protective levels of anti-HBs (mIU/ml $\geq$10) 7-8 months post the first injection of vaccine. The geometric mean titer was 1607.0 mIU/ml. Twelve months after the first injection of vaccine, 96% of the vaccinees still had titers $\geq$10 mIU/ml. However, the geometric mean titer declined to 422 mIU/ml.

There have been no serious or alarming reactions attributable to the immune affinity purified vaccine. While one adverse experience report has been filed with the OoBRR (Table 3), the reaction noted did not appear to be related to the vaccine. There was also one subject whose 2, 3, and 4 month post-vaccination sera were positive for anti-HBc. His pre-vaccination blood sample and his 1, 5, 6, and 7 month blood samples tested negative for anti-HBc. The subject has been positive for anti-HBs since one month following the first injection of vaccine. None of his blood samples have been positive for HBsAg. All samples had normal levels of AST and ALT.

Table 4 shows the frequencies of clinical complaints reported following 206 injections of the vaccine. Reports of injection site discomfort and systemic complaints were made with frequencies of 50% and 15%, respectively. The frequencies of specific injection site complaints are shown in Table 5. The most frequent complaints were soreness (34%), pain (7%), and tenderness (5%). The frequencies of specific systemic complaints by body system are shown in Table 6. Complaints occurring at frequencies of $\geq$1% were fatigue/weakness (4%), headache (2%), pharyngitis (2%), malaise (1%), rhinitis (1%), upper respiratory infection (not otherwise specified) (1%), nausea (1%), and diarrhea (1%).

Table 1

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving

Yeast Recombinant Hepatitis B Vaccine Produced by An Immune Affinity Method

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine			% Subjects Planned (Vaccinated)	% with Anti-HBs		Time (Months)
						Lot	Dose	Regimen		S/N ≥2.1	mIU/ml ≥10	
Healthy Adults	779	Bishop	Merck & Co., PA	7/13/83	In progress	C-J625	10 mcg	0,1,6 mos.	15 (15)	100(14/14)	100(14/14)	12 mos.
Health Care Personnel	792	Dienstag	Boston	11/10/83	In progress	C-J625	10 mcg	0,1,6 mos.	30 (30)	96(25/26)	96(25/26)	12 mos.
Health Care Personnel	795	Deinhardt	West Germany	11/21/83	In progress	C-J625	10 mcg	0,1,6 mos.	30 (30)	96(26/27)	93(25/27)	12 mos.

Table 2

Antibody Responses Among Health Care Personnel and Other Healthy Adults Following Vaccinatio at 0, 1, and 6 Months with 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Time (Months)	% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders	
	S/N ≥2.1	mIU/ml ≥10		S/N ≥2.1	mIU/ml ≥10
1	36 (15/70)	9 (6/70)	1.0	7.0	26.5
2	79 (8/73)	63 (46/73)	16.1	38.4	64.5
3	96 (67/70)	76 (53/70)	30.8	37.4	62.7
6	97 (69/71)	89 (63/71)	52.9	67.5	79.7
7/8	100 (70/70)	100 (70/70)	1607.0	1607.0	1607.0
9	100 (60/60)	97 (58/60)	1024.5	1024.5	1228.4
12	97 (65/67)	96 (64/67)	317.9	393.8	422.0

Studies: 779, 792, 795

Table 3

Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study-Case No. No.	BB-IND	Lot of Vaccine	Dose	Date(s) Administered	Date of Event	Date Reported	Summary of Event	Vaccine Related *
(9) (9)	(9) (9)	C-J625	10 mcg	(9) (9)	(9) (9)	1/15/85	A 30 year-old male subject was noted to have a serum ALT of 170 on (9) (9) (three months after receiving the third dose of vaccine). One week later, the serum ALT was 139. The subject's pre-vaccination ALT was 47. All sera remained negative for anti-HBc and HBsAg. The subject had been taking two antimalarial drugs, Chloroquine and Fansidar, for 2 months prior to the (9) (9) bleeding. During that time, he had been visiting East Africa.	No

* Clinical investigator's assessment.

00055

wva/31311/5
1/21/85

Table 4

Percentages of Health Care Personnel and Other Healthy Adults With Clinical Complaints During a 5-Day Period Following 206 Injections of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Studies: 779, 792, 795

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Local (Injection Site)	55 (39/71)	44 (31/70)	51 (33/65)	50 (103/206)
Systemic	22 (16/71)	13 (9/70)	9 (6/65)	15 (31/206)
Any Complaint	63 (45/71)	47 (33/70)	54 (35/65)	55 (113/206)

Studies: 779, 792, 795

Table 5

Frequency of Local (Injection Site) Complaints Occurring Within 5 Days Among Health Care Personnel and Other Healthy Adults Following 206 Injections of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Number of Vaccine Recipients: 71

Studies: 779, 792, 795

Complaint	Number	Frequency as %
Soreness	71	34
Pain	15	7
Tenderness	11	5
Stiffness/Tightness	4	2
Swelling	4	2
Ecchymosis	2	1
Erythema	2	1
Pruritis	2	1
Numbness	1	0.5
Pigment Change	1	0.5
Skin Mottled/Peeling	1	0.5
Parasthesia	1	0.5
Papule	1	0.5
Warmth	1	0.5

Table 6

Frequency of Systemic Complaints by Body System Occurring Within 5 Days
Among Health Care Personnel and Other Healthy Adults Following
206 Injections of Yeast Recombinant Hepatitis B Vaccine
Lot #934/C-J625

Number of Vaccine Recipients: 71

Studies: 779, 792, 795

Body System/Complaint	Frequency as % (Number)	Body System/Complaint	Frequency as % (Number)
Whole Body/General	8 (17)	Infectious Syndromes	1 (2)
Fatigue/Weakness	4 (9)	Herpes Labialis, Recurrent	0.5 (1)
Headache	2 (5)	Viral Infection, Nos	0.5 (1)
Malaise	1 (3)		
Sensation of Warmth, General	0.5 (1)		
Respiratory	5 (11)	Hemic/Lymphatic	0.5 (1)
Pharyngitis	2 (5)	Lymphadenopathy, Cervical	0.5 (1)
Rhinitis	1 (3)		
Upper Respiratory Infection, Nos	1 (3)		
Cough	0.5 (1)	Musculoskeletal	0.5 (1)
Sinusitis	0.5 (1)		
Laryngitis	0.5 (1)	Myalgia	0.5 (1)
Digestive	2 (5)		
Nausea	1 (3)	Organs of Special Sense	0.5 (1)
Diarrhea	1 (2)		
Dyspepsia/Heartburn	0.5 (1)	Conjunctivits	0.5 (1)
Abdominal Pain/Cramps	0.5 (1)		

Table 7

Percentages of Health Care Personnel and Other Healthy Adults With Elevated Temperatures During a 5-Day Period Following 190 Injections of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Studies: 779, 792, 795

Temperature	Dose 1	Dose 2	Dose 3	All
≥ 100°F	4 (3/70)	2 (1/63)	4 (2/57)	3 (6/190)
≥ 101°F	1 (1/70)	2 (1/63)	4 (2/57)	2 (4/190)

Immune Affinity Vaccine

Study 779 - West Point, PA - Dr. R. Bishop

Healthy adults receive 10 mcg injections of vaccine from one of two lots at 0, 1, and 6 months.

Fifteen adults have received 3 injections of vaccine from lot C-J625 produced by the immune affinity method. At 7/8 months, 100% (15/15) of the participants seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for these responders was 1758.1 mIU/ml. Among the participants with serology data at 12 months, 100% (12/12) were positive for anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 402.3 mIU/ml. No serious or alarming reactions attributable to vaccine have been reported. Subjects continue to be followed for persistence of antibody.

Refer to the summary in health care personnel and other healthy adults for responses of subjects vaccinated in this study with vaccine produced using the (b) (4) method.

Study 792 - Boston, MA - Dr. J. Dienstag

Initially seronegative health care personnel receive 10 mcg injections of vaccine from one of two lots at 0, 1, and 6 months.

Thirty persons have received 2 injections of vaccine from lot C-J625 produced by the immune affinity method, and 27 of these have received the third injection. One hundred percent (26/26) of the participants seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at nine months. The GMT for these responders was 1400.1 mIU/ml. At 12 months, 96% (25/26) of the subjects were positive for anti-HBs (mIU/ml ≥10) with a GMT of 329.8 for all vaccinees. There have been no reports of serious or alarming reactions attributable to vaccine. Subjects continue to be followed for persistence of antibody.

Refer to the summary on health care personnel and other healthy adults for responses of subjects vaccinated in this study with vaccine produced using the (b) (4) method.

Study 795 - West Germany - Dr. F. Deinhardt

The study population consists of health care personnel and other healthy adults who are initially negative for hepatitis B serologic markers. Participants receive 10 mcg injections of vaccine at 0, 1, and 6 months from one of three vaccine lots.

Immune Affinity Vaccine

Study 795 - West Germany - Dr. F. Deinhardt (Contd)

Thirty persons have received 3 injections of lot C-J625 vaccine produced by the immune affinity method. At 7/8 months, 100% (29/29) of the subjects seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for these responders was 1735.7 mIU/ml. Ninety-three percent (25/27) of the participants were positive for anti-HBs (mIU/ml ≥10) at 12 months. The GMT for all vaccinees at that time was 271.5 mIU/ml.

Refer to the summary in health care personnel and other healthy adults for responses of subjects vaccinated in this study with vaccine produced using the (b)(4) method.

STUDY 779

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 779
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among healthy adults who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 934/C-J625 (10 mcg HBsAg/ml) Lot 972/C-K444 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Robert P. Bishop, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486
SECONDARY INVESTIGATORS:	E. P. Avancena, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486 Joseph C. Rogers, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486 Joseph P. Romano, M.D. Health Services Merck Sharp and Dohme Rahway, NJ 07065
STUDY LOCATION:	Merck Sharp and Dohme West Point, PA 19486
DATE INITIATED:	July 13, 1983
DATE COMPLETED:	In progress

Study 779

STUDY PROCEDURE:

The study population consists of 41 healthy adults of either sex (excluding pregnant women) employed at Merck and Co., Inc., who were initially negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

Eligible participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine produced by either the immune affinity or the (b)(4) procedure at 0, 1 and 6 months. Study participants are asked to take and record their temperatures for five days after each injection of vaccine and to record any local or systemic complaints that they may experience.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before vaccination. Post-vaccination blood samples (10-15 ml) are obtained monthly for seven months and at 9, 12 and 24 months following the first injection of vaccine. Samples are assayed for HBsAg, anti-HBc, anti-HBs and ALT, and these may be assayed for antibody to antigens in yeast extract. Samples with an anti-HBs titer $\geq$ 25 mIU/ml units are tested to determine the relative proportions of anti-a and anti-d activity.

STUDY RESULTS:

HEALTHY ADULTS (Immune Affinity Vaccine):

10 mcg Lot 934/C-J625 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
15	15	15

Study 779

RESULTS: (Cont.)

2. Serologic Results:

Serologic data are available for 15 participants at 7/8 months. One hundred percent (15/15) of the participants seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months was 1758.1 mIU/ml (all vaccinees and responders by either cutoff).

Among the participants who had serology data at 12 months, 100% (12/12) were positive for anti-HBs (mIU/ml ≥10). The GMT for these vaccinees was 402.3 mIU/ml.

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for fifteen participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	80(12/15)	73(11/15)	73(11/15)
Systemic	33(5/15)	20(3/15)	7(1/15)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming reactions attributable to vaccine.

HBV Markers (Anti-HBc)

One subject had serum samples that tested transiently positive for anti-HBc. The 2, 3, and 4 month post-vaccination sera were positive for anti-HBc. His prevaccination blood sample and his 1, 5, 6, 7, 9 and 12 month blood samples were negative for anti-HBc. None of his sera were positive for HBsAg. All samples were normal with respect to AST and ALT.

PUBLICATIONS:

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:315-17.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
POPULATION : HEALTHY ADULTS
DOSE : 10 MCG
LOT : CJ625
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	45%	(5/11)	9.1%	(1/11)	1.7	6.1	55.5
2 MONTHS	93%	(14/15)	73%	(11/15)	32.0	44.7	88.0
3 MONTHS	100%	(14/14)	86%	(12/14)	60.5	60.5	83.5
6 MONTHS	100%	(15/15)	100%	(15/15)	68.0	68.0	68.0
7/8 MONTHS	100%	(15/15)	100%	(15/15)	1758.1	1758.1	1758.1
9 MONTHS	100%	(14/14)	100%	(14/14)	1319.9	1319.9	1319.9
12 MONTHS	100%	(14/14)	100%	(14/14)	402.3	402.3	402.3

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	11 (73.3%)	5 (33.3%)	3 (20.0%)	1 (6.7%)	0 (0.0%)	1 (7.1%)		12 (80.0%)
SORENESS	10 (66.7%)	5 (33.3%)	3 (20.0%)	1 (6.7%)	0 (0.0%)	1 (7.1%)		11 (73.3%)
TENDERNESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
ERYTHEMA (REDNESS)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
STIFFNESS/TIGHTNESS	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
ECCHYMOSIS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
SYSTEMIC	4 (26.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (7.1%)		5 (33.3%)
WHOLE BODY/GENERAL	3 (20.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (7.1%)		4 (26.7%)
FATIGUE/WEAKNESS	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (7.1%)		2 (13.3%)
HEADACHE	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
RESPIRATORY	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
SINUSITIS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PHARYNGITIS (SORE THROAT)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
DIGESTIVE SYSTEM	1 (6.7%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
DYSPEPSIA/HEARTBURN	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
PERSONS WITH COMPLAINTS	11 (73.3%)	6 (40.0%)	4 (26.7%)	2 (13.3%)	1 (6.7%)	2 (14.3%)		12 (80.0%)
PERSONS WITH NO COMPLAINTS	4 (26.7%)	9 (60.0%)	11 (73.3%)	13 (86.7%)	14 (93.3%)	12 (85.7%)		3 (20.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	9 (60.0%)	6 (40.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		11 (73.3%)
SORENESS	9 (60.0%)	6 (40.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		11 (73.3%)
STIFFNESS/TIGHTNESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
SYSTEMIC	1 (6.7%)	1 (6.7%)	1 (6.7%)	2 (13.3%)	1 (6.7%)	1 (6.7%)		3 (20.0%)
WHOLE BODY/GENERAL	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
FATIGUE/WEAKNESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
RESPIRATORY	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)		1 (6.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)		1 (6.7%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
PERSONS WITH COMPLAINTS	9 (60.0%)	6 (40.0%)	3 (20.0%)	2 (13.3%)	1 (6.7%)	1 (6.7%)		11 (73.3%)

69000

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	6 (40.0%)	9 (60.0%)	12 (80.0%)	13 (86.7%)	14 (93.3%)	14 (93.3%)	4 (26.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00070

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	9 (60.0%)	3 (20.0%)	4 (26.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	11 (73.3%)
PAIN	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
SORENESS	9 (60.0%)	2 (13.3%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (60.0%)
TENDERNESS	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
STIFFNESS/TIGHTNESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
PERSONS WITH COMPLAINTS	9 (60.0%)	3 (20.0%)	4 (26.7%)	2 (13.3%)	2 (13.3%)	2 (13.3%)	11 (73.3%)
PERSONS WITH NO COMPLAINTS	6 (40.0%)	12 (80.0%)	11 (73.3%)	13 (86.7%)	13 (86.7%)	13 (86.7%)	4 (26.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00073

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
< 99	10 (66.7%)	13 (86.7%)	14 (93.3%)	13 (86.7%)	14 (100.0%)	12 (85.7%)		10 (66.7%)
99 - 99.9	3 (20.0%)	1 (6.7%)	1 (6.7%)	2 (13.3%)	0 (0.0%)	2 (14.3%)		2 (13.3%)
100 - 100.9	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
101 - 101.9	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
TEMPERATURE TAKEN	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	14 (93.3%)	14 (93.3%)		15 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)		0 (0.0%)

Table 3 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	13 (86.7%)	15 (100.0%)	14 (93.3%)	12 (92.3%)	13 (92.9%)	12 (92.3%)		11 (73.3%)
99 - 99.9	2 (13.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (7.1%)	1 (7.7%)		3 (20.0%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
TEMPERATURE TAKEN	15 (100.0%)	15 (100.0%)	15 (100.0%)	13 (86.7%)	14 (93.3%)	13 (86.7%)		15 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	1 (6.7%)	2 (13.3%)		0 (0.0%)

Table 3 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 3 — DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
NORMAL	2 (13.3%)	2 (13.3%)	2 (13.3%)	2 (13.3%)	2 (15.4%)	2 (13.3%)		2 (13.3%)
< 99	13 (86.7%)	13 (86.7%)	13 (86.7%)	13 (86.7%)	9 (69.2%)	12 (80.0%)		11 (73.3%)
99 - 99.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	1 (6.7%)		1 (6.7%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)		1 (6.7%)
TEMPERATURE TAKEN	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	13 (86.7%)	15 (100.0%)		15 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)		0 (0.0%)

Edward M. Scolnick, Arlene A. McLean,
David J. West, Jules L. Dienstag,
Eloise Watkins, Friedrich Deinhardt and Wolfgang Jilg

23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

VIRAL HEPATITIS and LIVER DISEASE
ISBN 0-8089-1678-6

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

Reprinted from the Journal of the American Medical Association
June 1, 1984, Volume 251

Original Contributions

Clinical Evaluation in Healthy Adults of a Hepatitis B Vaccine Made by Recombinant DNA

Edward M. Scolnick, MD; Arlene A. McLean, PhD; David J. West, PhD; William J. McAleer, PhD; William J. Miller, MS; Eugene B. Buynak, PhD

• A vaccine formulated from hepatitis B surface antigen (HBsAg) produced by a recombinant strain of the yeast *Saccharomyces cerevisiae* was administered to two groups of human volunteers composed of 37 healthy, low-risk adults. Each subject received a 10-µg dose of HBsAg at 0, 1, and 6 months. By one month, 27% to 40% of the vaccinees had antibody to HBsAg, and by three months 90% to 100% were antibody positive. Large boosts in titer followed the third dose at six months. The antibody formed is predominantly specific for the *a* determinant of HBsAg. There have been no serious reactions attributable to the vaccine. The most frequent complaint has been transient soreness at the injection site. As far as we know, this is the first reported use in man of a vaccine prepared by recombinant DNA technology.

(*JAMA* 1984;251:2812-2815)

WORLDWIDE, human hepatitis B infection constitutes a major public health problem. In addition to the disability associated with acute clinical disease, chronic liver disease, cirrhosis, and primary hepatocellular carcinoma are now recognized sequelae of unresolved hepatitis B infection. Indeed, in some areas of Asia and sub-Saharan Africa, primary hepatocellular carcinoma ostensibly attributable to hepatitis B infection ranks as a leading cause of cancer deaths among males.[1]

See also p 2765.

The reservoir of hepatitis B virus resides mainly in a population of chronic carriers now estimated to number more than 200 million.[1] Infection is transmitted to susceptible persons through contact with the blood, semen, or saliva of chronic carriers or persons suffering acute infection. In low-incidence countries, such as the United States, the risk of hepatitis B infection is still high among certain groups of health care personnel, patients receiving dialysis treatments or blood products made from large pools, children born to Alaskan Eskimos or to Indochinese or Haitian refugees, residents of institutions for the mentally handicapped, prisoners, users of illicit injectable drugs, and persons who are sexually very promiscuous.[1] In high-incidence areas such as Southeast Asia, transmission from mother to child in the perinatal period is the major mode of infection supplemented by horisontal transmission between other family contacts.[2]

Since there is no effective treatment for hepatitis B infection, prevention is essential. A safe, effective human hepatitis B vaccine is now available. However, it utilizes hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of hepatitis B virus infection. Consequently, the supply of vaccine is potentially limited by available sources of suitable plasma. In addition, extensive processing and safety testing have been necessary to ensure production of a vaccine antigen that is pure and free of any extraneous living agent that might have been present in the starting plasma. Even though multiple inactivation treatments used in the antigen purification process have been shown to inactivate representatives of all major groups of animal viruses,[3] concern over the theoretical possibility of a living organism such as the etiologic agent of acquired immune deficiency syndrome being present in plasma and surviving the purification and inactivation procedures has slowed acceptance of hepatitis B vaccine.

A promising alternative to infected human plasma as a source of HBsAg for vaccine is the use of recombinant DNA technology to effect synthesis of the surface antigen by a culture of microorganisms. The hepatitis B virus gene coding for HBsAg has been cloned both in *Escherichia coli* and in yeast[4-7]; however, expression of the gene in yeast has been much better than in *E coli*. Furthermore, HBsAg

From the Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, Pa.

Reprint requests to Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, PA 19486 (Dr Scolnick).

produced by recombinant yeast cells has been shown to aggregate into particles closely resembling those isolated from human plasma, and this material was shown to include antibodies in mice and guinea pigs.[15]

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for HBsAg has been formulated into a vaccine through adsorption on alum adjuvant. Electron microscopy reveals that the purified HBsAg used for this vaccine exists as aggregate particles 20 to 22 nm in diameter, a morphology also characteristic of free surface antigen in infected plasma and of the purified antigen now used in plasma-derived hepatitis B vaccine. In contrast to HBsAg from human plasma, the antigen produced by recombinant yeast is not glycosylated. Under reducing conditions, sodium dodecyl sulfate electrophoresis of the antigen purified from yeast reveals a single band of molecular weight 23,000, which corresponds to the nonglycosylated polypeptide that is the major component of the hepatitis B virus envelope. The vaccine formulated using this material has now been shown to be immunogenic for mice and for monkeys with a potency equal to or superior to that of vaccine made from plasma-derived antigen. In addition, chimpanzees immunized with this yeast recombinant hepatitis B vaccine (HBsAg subtype *adw*) were fully protected when challenged with virus of either type *adr* or *ayr*, while unimmunized animals all showed evidence of infection when challenged.[16]

In this article we describe results of the first human immunogenicity-safety trial of the yeast recombinant hepatitis B vaccine. To the best of our knowledge, this is the first time that a vaccine prepared by recombinant DNA technology has been used in man.

MATERIALS AND METHODS

Population

Participants in this study were healthy, nonpregnant adult employees of Merck and Co, Inc. Subjects had to be negative for hepatitis B serological markers and have a normal level of alanine aminotransferase and must not have received any other hepatitis B vaccine. Written consent was obtained after providing each participant with information on the source of the investigational yeast recombinant hepatitis B vaccine, animal test results obtained with the vaccine, vaccination and bleeding schedules, and the potential risks and benefits of participation in the study.

Vaccine

Hepatitis B surface antigen for the vaccine was produced in fermentation cultures of a recombinant strain of the yeast *S cerevisiae* containing a plasmid carrying the gene for the *adw* subtype of HBsAg, as described previously.[15,16]

Two methods were employed for the purification of HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends on selection of water-immiscible molecules followed by separation by molecular size. Details of the expression of HBsAg in yeast and the purification of the surface antigen will be published elsewhere. Purified HBsAg was treated with formaldehyde to stabilize the material and to kill any extraneous living agents that might be present. The antigen was then formulated into a vaccine through adsorption on alum adjuvant to give 10 μg of HBsAg and 0.5 mg of aluminum (hydroxide) per 1-mL dose. The final formulation also contained 1:20,000 thimerosal as a preservative. Vaccine was maintained at 2 to 8 °C until used.

Procedures

A blood sample was obtained from each subject approximately two weeks prior to the first vaccination and was tested for HBsAg, antibody to HBsAg (anti-HBs), antibody to core antigen (anti-HBc), alanine aminotransferase (ALT), and yeast antibody. Subjects found eligible on the basis of these assays were scheduled to receive a 1.0-mL (10-μg HBsAg) intramuscular injection of the yeast recombinant vaccine at 0, 1, and 6 months. Postvaccination blood samples for the determination of hepatitis B serological markers, ALT, and yeast antibody were scheduled monthly for seven months and at 9, 12, and 24 months following the first injection.

Vaccinees were asked to take their temperature daily for five days after each injection of vaccine and to report any local or systemic reactions that might occur during this period.

Assays

Standard radioimmunoassay test kits were used for the determination of HBsAg, anti-HBs, and anti-HBc. Titers of anti-HBs were expressed in international milliunits per milliliter using the formulation described by Hollinger et al.[17] A serum sample was considered positive for anti-HBs if the ratio of the sample counts per minute to the negative control serum counts per minute was 2.1 or greater.

Estimates of the proportion of anti-HBs in postvaccination sera specific for the *a* or *d* determinants of HBsAg were based on an assay described by Hoofnagle et al.[18] Briefly, aliquots of each serum sample are incubated with a subtype *ad* HBsAg-positive serum, with a subtype *ay* HBsAg-positive serum, and with normal human serum for two hours at room temperature, and then each mixture is carried through a standard radioimmunoassay to measure residual anti-HBs. Based on the percent of neutralization with the two HBsAg subtype sera when compared with the unneutralized normal human serum, an estimate can be made of the relative amounts of anti-*a* and anti-*d* antibodies present. Since the vaccine is a monovalent-type *adw* preparation, sera will contain either anti-*d* antibodies, anti-*a* antibodies, or a combination of both types, and the amount of neutralization with the HBsAg-*ay* serum is therefore a direct assay for the amount of anti-*a* present. Subtracting the amount of neutralization with the HBsAg-*ay* serum from that found for the HBsAg-*ad* serum then gives an estimate of the amount of anti-*d* present.

A radioimmunoassay was developed to detect yeast antibodies in the sera of vaccine recipients. For this assay, an extract of the parent strain of *S cerevisiae* lacking the plasmid containing the gene for HBsAg was prepared by disrupting a 50% suspension of the cells in a homogenizer and then clarified by centrifugation at 9,000 *g* followed by passage through a 0.45-mμm membrane filter. The clarified, filtered extract was diluted to a final protein concentration of 80 μg/mL with 0.1 M carbonate buffer and pH 9.6 and adsorbed to ¼-in polystyrene beads overnight at 4 °C. Washed, dried beads were maintained at −20 °C. Two hundred-microliter volumes of sera diluted 1:100, 1:1,000, and 1:10,000 in phosphate-buffered saline containing 0.5% bovine serum albumin and 0.5% Tween 20 were incubated with coated beads for three hours at 37 °C. Following three washes with water, the beads were incubated with 200 μL of iodine 125 protein A (specific activity, 100,000 cpm) for 1.5 hours at 37 °C. The protein A binds and labels any antiyeast antibody on the bead that is of the IgG class. After three additional water washes, the beads were counted and titers of yeast antibody were determined by interpolation from a standard curve derived using dilutions of a hyperimmune guinea pig serum having an antibody titer to parent yeast extract of 1 million.

The serum samples of vaccinees were also measured for changes in preexisting specific yeast antibodies or the appearance of new yeast antibodies using a sodium dodecyl sulfate polyacrylamide gel electrophoresis (reducing), Western blot technique. In this procedure, parent yeast extract is separated on a 12.5% polyacrylamide gel. After transfer to a nitrocellulose sheet, polypeptides from the gel are detected by incubation with a 1:50 dilution of the vaccinee's serum, followed by incubation with ^{125}I protein A and exposure to x-ray film (T. Mason, PhD, oral communication, 1982).

RESULTS

The vaccine has been well tolerated. None of the 37 subjects studied to date has experienced a serious adverse effect attributable to vaccine. There has been no evidence of hepatitis B infection among vaccinees, ie, no elevation of ALT values and no antigenemia. Mild soreness at the injection site generally lasting one to two days was reported by 73% to 80% of vaccinees who received vaccine purified by immune affinity chromatography (lot 934) but by a substantially smaller proportion—20% to 24%—of subjects who received vaccine prepared by hydrophobic interaction chromatography (lot 972) (Table 1). Infrequent systemic complaints occurring within a five-day period following vaccination have included elevated temperature (38.3 to 38.8 °C [101 to 102 °F], oral), fatigue, headache, gastrointestinal disturbance, symptoms of upper respiratory tract infection, and nosebleed.

Table 2 summarizes our observations to date on the human immunogenicity of yeast recombinant hepatitis B vaccine. Fifteen persons (ten men, five women; age range, 23 to 53 years; median age, 33 years) have received all three doses of lot 934 vaccine prepared by the immune affinity chromatography method. Forty percent had a detectable titer of anti-HBs within one month of receiving the first dose. By two months, the proportion of seroconverters rose to 93%, and at three months, all recipients of this vaccine were antibody positive. The geometric mean titer following primary immunization reached a plateau at four months, then increased more than 25-fold following the booster dose at six months.

Table 1.—Proportion (%) of Vaccinees With Clinical Complaints During a Five-Day Period Following Injection of Yeast Recombinant Hepatitis B Vaccine

Nature of Complaint	Vaccine Lot No.	Dose 1	Dose 2	Dose 3
Soreness at injection site	934	12/15 (80)	11/15 (73)	11/15 (73)
	972	5/21 (24)	3/15 (20)	...
Systemic* complaints	934	5/15 (33)	3/15 (20)	1/15 (7)
	972	1/21 (5)	2/15 (13)	...

*Included persons with one or more episodes of the following: temperature, 38.3 to 38.8 °C (101 to 102 °F) (two), fatigue (three), gastrointestinal disturbance (four), headache (five), symptoms of upper respiratory tract infection (three), and nosebleed (one).

Table 2.—Seroconversion Frequencies and Geometric Mean Titers (GMTs)* for Anti-HBs Among Initially Seronegative Healthy Adults Receiving 10-µg Doses of Yeast Recombinant Hepatitis B Vaccine†

Vaccine Lot No. (Method of Preparation)	No. of Subjects Vaccinated	Time, mo	Seroconversion Proportion (%)	GMT: All Vaccinees	GMT: Responders Only
934 (Immune affinity chromatography)	15	1	6/15 (40)	1.8	8.0
		2	14/15 (93)	31.7	44.2
		3	15/15 (100)	56.5	56.5
		4	15/15 (100)	78.2	78.2
		5	14/14 (100)	77.2	77.2
		6	15/15 (100)	97.9	97.9
		7	12/12 (100)	1,906.1	1,906.1
972 (Hydrophobic interaction chromatography)	22	1	4/15 (27)	1.4	39.6
		2	8/12 (67)	17.8	103.7
		3	6/6 (100)	59.5	219.5

*In international milliunits per milliliter.
†At 0, 1, and 6 months.
‡All serum samples with titers of less than 0.6 mIU/mL were assigned a value of 0.3 mIU/mL for calculating GMTs.

Table 3.—Percentages of Anti-HBs Specific for *a* and *d* Determinants of HBsAg in Postvaccination Sera*

Vaccine Lot No.	Time, mo	No. of Samples	% Anti-*a* Range	% Anti-*a* Mean	% Anti-*d* Range	% Anti-*d* Mean
934	1	1	...	47	...	53
	2	7	87-98	93	2-10	6
	3	10	83-98	89	2-17	10
	4	13	88-98	89	2-36	11
	5	12	90-97	92	2-20	8
	6	8	92-97	94	2-8	5
	7	12	89-100	98	0-11	2
972	1	3	56-91	74	9-44	26
	2	8	87-100	94	0-13	6

*Assay done only on serum samples having an anti-HBs titer of 25 mIU/mL or greater.

Twenty-two subjects have received vaccine from lot 972 made from HBsAg purified by the hydrophobic intraction chromatography method. These vaccinees have not been followed up for as long as the lot 934 recipients, and none has yet received a third dose. Preliminary serological results are shown in Table 2 for 15 of these volunteers (12 men, three women; age range, 24 to 63 years; median age, 40 years). The percentage of seroconverters was 27% at one month, 67% at two months, and 80% at three months. Geometric mean titers within the first three months of follow-up were similar to those observed among recipients of lot 934 vaccine.

Postvaccination serum samples with anti-HBs titers of 25 ImU/mL or greater were assayed to determine the percentage of antibody specific for the *a* and *d* determinants of HBsAg. Table 3 shows the results of these assays. Antibody specific for the *a* determinant predominates. In the interval from two to seven

months following the first dose of vaccine, anti-a antibody accounted for approximately 90% of the total anti-HBs.

Earlier studies (unpublished) showed that the yeast recombinant hepatitis B vaccine induced a predominantly anti-a form of anti-HBs in African green monkeys and that these antibodies have persisted through two years of follow-up.

Analysis of serum samples from participants in this study has revealed no significant postvaccination increases in yeast antibody titers as measured by radioimmunoassay. By Western blot analysis, each human serum sample shows a unique "fingerprint" spectrum of antibodies to yeast components. There may be only a few or as many as 20 different bands present. Analysis of monthly postvaccination serum samples from participants in this study has shown no change in the yeast antibody pattern for any person as compared with his prevaccination pattern. There has been no appearance of new antibodies in postvaccination sera and no significant increases in the intensity of existing antibody bands.

CONCLUSIONS

The results of this study indicate that an alum-adsorbed hepatitis B vaccine formulated using HBsAg of subtype *adw* synthesized by recombinant yeast cells is safe and immunogenic for man. Seroconversion rates and titers of anti-HBs obtained with the yeast recombinant vaccine in this study are comparable with those observed in earlier studies of healthy adults using vaccine derived from human plasma.[14,17]

Previous studies with hepatitis B vaccine of human plasma origin showed that protection from infection is associated with vaccine-induced anti-HBs.[15-17] Furthermore, one of these trials demonstrated that antibody formed in response to vaccine of HBsAg subtype *ad* provided cross-protection against infection caused by heterologous virus of subtype *ay*.[18] Since the antibody formed by recipients of the yeast recombinant hepatitis B vaccine is predominantly anti-a, this vaccine should be protective against all hepatitis B virus subtypes. The efficacy of the yeast vaccine against both homologous *ad* and heterologous *ay* virus challenge in chimpanzees has been demonstrated.[19]

Studies are under way to assess antibody persistence and to determine optimal doses of the yeast recombinant hepatitis B vaccine for both healthy and immunocompromised adults and children.

References

1. Francis DP: Selective primary health care: Strategies for control of disease in the developing world: III. Hepatitis B virus and its related diseases. *Rev Infect Dis* 1983;5:322-333.
2. Gust I: Comparison of the epidemiology of hepatitis A and B, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 129-143.
3. Immunization Practices Advisory Committee: Inactivated hepatitis B virus vaccine. *Ann Intern Med* 1982;97:379-383.
4. Hilleman MR, McAleer WJ, Buynak EB, et al: Quality and safety of human hepatitis B vaccine. *Dev Biol Stand* 1983;54:3-12.
5. Burrell CJ, Mackay P, Greenaway PJ, et al: Expression in *Escherichia coli* of hepatitis B virus DNA sequences cloned in plasmid pBR322. *Nature* 1979;279:43-47.
6. Valenzuela P, Gray P, Quiroga M, et al: Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen. *Nature* 1979;280:815-819.
7. Valenzuela P, Medina A, Rutter WJ, et al: Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298:347-350.
8. Hitzeman RA, Chen CY, Hagie FE, et al: Expression of hepatitis B virus surface antigen in yeast. *Nucleic Acids Res* 1983;11:2745-2763.
9. Miyanohara A, Toh-e A, Nozaki C, et al: Expression of hepatitis B surface antigen gene in yeast. *Proc Natl Acad Sci USA* 1983;80:1-5.
10. McAleer WJ, Buynak EB, Maigetter RZ, et al: Human hepatitis B vaccine from recombinant yeast. *Nature* 1984;307:178-180.
11. Hollinger FB, Adam E, Hoiberg D, et al: Response to hepatitis B vaccine in a young adult population, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 451-466.
12. Hollinger FB, Gerety RJ, Smallwood LA, et al: Subtyping of hepatitis B surface antigen and antibody by radioimmunoassay. *Gastroenterology* 1977;72:280-286.
13. Deinhardt F, Zachoval R, Frosner H, et al: Passive-active immunization against hepatitis B, in Krugman S, Sherlock S (eds): *Proceedings of the European Symposium on Hepatitis*. New York, KPR Inter/Media Corporation, 1981, pp 140-150.
14. Szmuness W, Stevens CE, Harley EJ, et al: The immune response of healthy adults to a reduced dose of hepatitis B vaccine. *J Med Virol* 1981;8:123-129.
15. Krugman S, Holley HP Jr, Davidson M, et al: Immunogenic effect of inactivated hepatitis B vaccine: Comparison of 20 microgram and 40 microgram doses. *J Med Virol* 1981;8:119-121.
16. Hilleman MR, Buynak EB, McAleer WJ, et al: Hepatitis A and hepatitis B vaccines, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 385-397.
17. Desmyter J, Colaert J, Verstraete M, et al: Hepatitis B vaccination of hemophiliacs. *Scand J Infect Dis* 1983;38(suppl):42-45.
18. Szmuness W, Stevens EC, Zang EA, et al: A controlled trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981;1:377-385.
19. Francis DP, Hadler SC, Thompson SE, et al: The prevention of hepatitis B with vaccine: Report of the Centers for Disease Control multicenter efficacy trial among homosexual men. *Ann Intern Med* 1982;97:362-366.
20. Szmuness W, Stevens CE, Harley EJ, et al: Hepatitis B vaccine in medical staff of hemodialysis units: Efficacy and subtype cross-protection. *N Engl J Med* 1982;307:1481-1486.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

Printed and Published in the United States of America

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 792
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Recombinant Hepatitis B Vaccine Lot #934/C-J625 (10 mcg HBsAg/ml) Lot #979/C-K564 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Jules L. Dienstag, M.D. Associate Professor of Medicine Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114
SECONDARY INVESTIGATOR:	Eloise Watkins, R.N., M.P.H. Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114 Lynn F. Butterly, M.D. Clinical & Research Fellow Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114
STUDY LOCATION:	Massachusetts General Hospital Fruit Street Boston, MA 02114
DATE STUDY INITIATED:	November 10, 1983.
DATE STUDY COMPLETED:	In progress.

Study 792

STUDY POPULATION: The study population consists of 65 health care personnel of either sex (excluding pregnant women), who were negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

PROCEDURE: Eligible participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine produced by the immune affinity or the (b) (4) procedure at 0, 1, and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination and on the day of the first vaccination. Post-vaccination blood samples are obtained monthly for seven months and at 9, 12, and 24 months from subjects vaccinated with lot #934/C-J625. Post-vaccination blood samples are taken at 1, 2, 3, 6, 8, 12, and 24 months from persons injected with vaccine lot #979/C-K564. The samples are assayed for HBsAg, anti-HBc, anti-HBs, yeast antibody and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml are tested for the proportions of anti-a and anti-d activity.

STUDY RESULTS: HEALTH CARE PERSONNEL (Immune Affinity Vaccine):

10 mcg lot #934/C-J625 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
30	30	27

Study 792

RESULTS: (Cont.)

2. Serologic Results:

Serologic data are available for 26 study participants at 7/8 months. One hundred percent of the participants seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months was 1400.1 mIU/ml (for all vaccinees and for responders by either cutoff).

Among subjects with serology data at 12 months, 96% (25/26) were positive for anti-HBs (mIU/ml ≥10). The GMT at that time was 329.8 mIU/ml for all vaccinees and 436.4 mIU/ml for responders with a titer of mIU/ml ≥10..

See Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for 27 participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	78(21/27)	43(13/30)	59(16/27)
Systemic	18(5/27)	13(4/30)	11(3/27)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no alarming or serious reactions attributable to vaccine.

ALT Elevations

A 30-year old male subject was noted to have a serum ALT 3-4 times the upper limit of normal 3 months after receiving the third injection of vaccine (Lot C-J625). All sera remained negative for anti-HBc and HBsAg.

Study 792

RESULTS: (Cont.) The subject had been taking two antimalarial drugs for two months prior to the observed ALT. The reaction was not felt to be related to the vaccine.

PUBLICATIONS:

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

Dienstag JL, Watkins E, Hinkle CA. Safety and immunogenicity of a recombinant hepatitis B vaccine (Abstract). In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:710.

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:315-17.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CJ625
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	40%	(12/30)	6.7%	(2/30)	1.0	6.6	20.0
2 MONTHS	79%	(23/29)	62%	(18/29)	16.7	35.8	61.2
3 MONTHS	93%	(26/28)	75%	(21/28)	29.8	41.8	65.3
6 MONTHS	96%	(26/27)	85%	(23/27)	50.5	64.2	93.4
7/8 MONTHS	100%	(26/26)	100%	(26/26)	1400.1	1400.1	1400.1
9 MONTHS	100%	(24/24)	96%	(23/24)	911.3	911.3	1145.9
12 MONTHS	96%	(25/26)	96%	(25/26)	329.8	436.4	436.4

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE I DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	19 (70.4%)	2 (7.4%)	4 (14.8%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		21 (77.8%)
SORENESS	15 (55.6%)	1 (3.7%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		16 (59.3%)
TENDERNESS	3 (11.1%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (14.8%)
SLOUGH/TISSUE NECROSIS	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
NUMBNESS	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
PIGMENT CHANGE	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
SYSTEMIC	0 (0.0%)	3 (11.1%)	1 (3.7%)	2 (7.4%)	3 (11.1%)	2 (7.4%)		5 (18.5%)
WHOLE BODY/GENERAL	0 (0.0%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)		3 (11.1%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)		1 (3.7%)
MALAISE	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)		2 (7.4%)
HEADACHE	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
RESPIRATORY	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	2 (7.4%)	2 (7.4%)		2 (7.4%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)
HEMIC AND LYMPHATIC	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
LYMPHADENOPATHY, CERVICAL	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
MYALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
PERSONS WITH COMPLAINTS	19 (70.4%)	5 (18.5%)	5 (18.5%)	3 (11.1%)	3 (11.1%)	2 (7.4%)	22 (81.5%)
PERSONS WITH NO COMPLAINTS	8 (29.6%)	22 (81.5%)	22 (81.5%)	24 (88.9%)	24 (88.9%)	25 (92.6%)	5 (18.5%)
PERSONS WITH NO DATA	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)

Table 7 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	12 (40.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (43.3%)
SORENESS	10 (33.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (36.7%)
TENDERNESS	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	2 (6.7%)	1 (3.3%)	4 (13.3%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (3.3%)	3 (10.0%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
MALAISE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)	1 (3.3%)	2 (6.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (3.3%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	2 (6.7%)
PERSONS WITH COMPLAINTS	12 (40.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	2 (6.7%)	1 (3.3%)	14 (46.7%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	18 (60.0%)	29 (96.7%)	29 (96.7%)	29 (96.7%)	28 (93.3%)	29 (96.7%)	16 (53.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

06000

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (27 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	14 (51.9%)	5 (18.5%)	5 (18.5%)	1 (3.7%)	2 (7.4%)	1 (3.7%)		16 (59.3%)
PAIN	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
SORENESS	12 (44.4%)	5 (18.5%)	5 (18.5%)	1 (3.7%)	1 (3.7%)	1 (3.7%)		13 (48.1%)
TENDERNESS	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
SWELLING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)		1 (3.7%)
PAPULE(S)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)		1 (3.7%)
SYSTEMIC	0 (0.0%)	3 (11.1%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		3 (11.1%)
WHOLE BODY/GENERAL	0 (0.0%)	2 (7.4%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		2 (7.4%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
HEADACHE	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
RESPIRATORY	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (27 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	14 (51.9%)	8 (29.6%)	5 (18.5%)	2 (7.4%)	2 (7.4%)	1 (3.7%)	17 (63.0%)
PERSONS WITH NO COMPLAINTS	13 (48.1%)	19 (70.4%)	22 (81.5%)	25 (92.6%)	25 (92.6%)	26 (96.3%)	10 (37.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	25 (83.3%)	25 (86.2%)	25 (83.3%)	23 (85.2%)	22 (78.6%)	25 (89.3%)		17 (56.7%)
99 - 99.9	5 (16.7%)	4 (13.8%)	5 (16.7%)	4 (14.8%)	6 (21.4%)	3 (10.7%)		13 (43.3%)
TEMPERATURE TAKEN	30 (100.0%)	29 (96.7%)	30 (100.0%)	27 (90.0%)	28 (93.3%)	28 (93.3%)		30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (3.3%)	0 (0.0%)	3 (10.0%)	2 (6.7%)	2 (6.7%)		0 (0.0%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	25 (83.3%)	25 (83.3%)	28 (93.3%)	25 (86.2%)	25 (83.3%)	25 (86.2%)		20 (66.7%)
99 - 99.9	5 (16.7%)	5 (16.7%)	2 (6.7%)	4 (13.8%)	5 (16.7%)	4 (13.8%)		10 (33.3%)
TEMPERATURE TAKEN	30 (100.0%)	30 (100.0%)	30 (100.0%)	29 (96.7%)	30 (100.0%)	29 (96.7%)		30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (3.3%)		0 (0.0%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (27 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	22 (81.5%)	21 (80.8%)	21 (84.0%)	19 (76.0%)	20 (80.0%)	20 (80.0%)		15 (55.6%)
99 - 99.9	5 (18.5%)	5 (19.2%)	4 (16.0%)	6 (24.0%)	5 (20.0%)	5 (20.0%)		12 (44.4%)
TEMPERATURE TAKEN	27 (100.0%)	26 (96.3%)	25 (92.6%)	25 (92.6%)	25 (92.6%)	25 (92.6%)		27 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (3.7%)	2 (7.4%)	2 (7.4%)	2 (7.4%)	2 (7.4%)		0 (0.0%)

RECOMBINANT YEAST HEPATITIS B VACCINE: IMMUNOGENICITY AND SAFETY. JL Dienstag, E Watkins, and CA Winkle. Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

Cumbersome to produce, expensive, and limited in supply, currently available human plasma-derived hepatitis B vaccines are likely to be replaced in the future by "genetically engineered" vaccines. Recently, a recombinant DNA vaccine was prepared in recombinant yeast Saccharomyces cerevisiae strain 2150-2-3 cells transformed with the plasmid pMB5 56-CAP347/33, containing the gene for hepatitis B surface antigen (HBsAg/ad) (Valenzuela et al. Nature 1982; 298:347-50). Purified by biochemical and biophysical methods from the yeast extract, the HBsAg particles synthesized by these yeast cells are not glycosylated but otherwise are indistinguishable from native 22 nm HBsAg particles. Treated with formalin and adsorbed to alum, the recombinant vaccine is immunogenic and protective in experimental animals. We administered three 10 µg doses of the recombinant hepatitis B vaccine (Merck Sharp & Dohme Research Laboratories) at time 0, 1, and 6 months to 60 seronegative adult health workers. The frequency and geometric mean titer (mIU/ml) of anti-HBs responses were as follows:

Month	1	2	3	4	5	6
Number	37	29	30	29	25	16
anti-HBs+	41%	83%	93%	97%	96%	94%
GMT ± SD	7 ± 2	33 ± 5	36 ± 6	66 ± 6	55 ± 8	79 ± 6

94 ± 9 (mean ± SD) % of the anti-HBs was specific for the a determinant of HBsAg. Changes in antibodies to yeast antigens were negligible. The most frequent adverse reaction was transient soreness at the injection site, occurring after 32% of first, 37% of second, and 55% of third injections. No serious adverse effects were encountered, and neither type B nor non-B hepatitis has occurred in any vaccinee. These preliminary results demonstrate that the recombinant yeast hepatitis B vaccine is safe and that 10 µg of the recombinant vaccine is equivalent in immunogenicity to 20 µg of the plasma-derived vaccine.

Dienstag JL, Watkins E, Winkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

SAT-LA.50

SAFETY AND IMMUNOGENICITY OF A RECOMBINANT HEPATITIS B VACCINE

J.L. Dienstag*, E. Watkins, and C.A. Hinkle

Gastrointestinal Unit (Medical Services), Massachusetts General Hospital, and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02114

Currently available, licensed hepatitis B vaccines are prepared from plasma obtained from hepatitis B surface antigen (HBsAg) carriers. Cumbersome to produce, expensive, and available in limited supply, the plasma vaccine is likely to be replaced in the future by one of a number of later generation vaccines. Recently, a recombinant DNA vaccine was prepared in recombinant yeast Saccharomyces cerevisiae strain 2150-2-3 cells transformed with plasmid pHBS56-GAP347/33, which contains the gene for HBsAg (Valenzuela et al, Nature 1982; 298:347-50). The HBsAg synthesized by these yeast cells was purified from the yeast extract by physical and chemical methods and was found to be indistinguishable from native 22 nm HBsAg particles, except that the HBsAg is not glycosylated. Treated with formalin and adsorbed to alum, the recombinant vaccine is comparable in purity to the plasma vaccine and is immunogenic and protective in experimental animals.

We studied the immunogenicity and safety of recombinant hepatitis B vaccine Lot 934, formulated to contain 10 micrograms of HBsAg per 1.0 ml dose (Merck Sharp & Dohme Research Laboratories). Thirty seronegative adult health care workers received three 1.0 ml doses of the recombinant vaccine at time 0, 1 and 6 months. Adverse effects were limited to soreness at the injection site, and immunogenicity was excellent, approximating 50% at one month. Three months of follow-up will be complete by the time of the International Meeting.

Dienstag JL, Watkins E, Hinkle CA. Safety and immunogenicity of a recombinant hepatitis B vaccine (Abstract). In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984:710.

Edward M. Scolnick, Arlene A. McLean,
David J. West, Jules L. Dienstag,
Eloise Watkins, Friedrich Deinhardt and Wolfgang Jilg

23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

VIRAL HEPATITIS and LIVER DISEASE
ISBN 0-8089-1678-5

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 795
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine by health care personnel and other healthy adults negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625 (10mcg HBsAg/ml) Lot #979/C-K564 (10mcg HBsAg/ml) Lot #81990 D/18066/C-L215 (10 mcg HBsAg/0.5 ml)
PRINCIPAL INVESTIGATOR:	Prof. Dr. Friedrich Deinhardt Max v. Pettenkofer Institut Pettenkoferstrasse 9a 8000 Muenchen 2 WEST GERMANY
SECONDARY INVESTIGATORS:	Dr. W. Jilg Dr. R. Zachoval Dr. G. Zoulek Dr. M. Kroner Dr. J. Abb Dr. B. Lorbeer The above secondary investigators have the same address as the principal investigator. Dr. U. Bienzle Landesinstitut fuer Tropenmedizin Ansbacherstr. 5 D-1000 Berlin 30 WEST GERMANY
STUDY LOCATIONS:	Max V. Pettenkofer Institut Pettenkoferstrasse 9a 8000 Muenchen 9a WEST GERMANY Landesinstitut fuer Tropenmedizin Ansbacherstr. 5 D-1000 Berlin 30 WEST GERMANY

Study 795

DATE INITIATED: November 21, 1983.

DATE COMPLETED: In progress.

STUDY POPULATION: The study population consists of approximately 300 health care personnel and other healthy adults of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

PROCEDURE: Eligible participants receive a 10 mcg injection intramuscular injection of vaccine produced by the immune affinity or (b) (4) procedure at 0, 1, and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination and on the day of the first vaccination. Post-vaccination blood samples are obtained monthly for seven months and at 9, 12, and 24 months from recipients of lot #934/C-J625 vaccine. Recipients of lots #979/C-K564 and #81990D/18066/C-L215 are bled at 1, 2, 3, 6, 8, 12, and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml are tested for the proportions of anti-a and anti-d activity. Samples may also be assayed for yeast antibody.

Study 795

RESULTS:

HEALTH CARE PERSONNEL (Immune Affinity Vaccine):

10 mcg Lot #934/C-J625 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
30	30	30

2. Serologic Results:

Serologic data are available for 29 participants at 7/8 months. One hundred percent (29/29) of the subjects seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months was 1735.7 mIU/ml (all vaccinees and responders by either cutoff).

Among participants with serology data available at 12 months, 93% (25/27) were positive for anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 271.5 mIU/ml, while it was 419.2 mIU/ml for subjects with titers of mIU/ml ≥10.

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for at least 23 participants after each injection. The overall frequencies of complaints are presented below:

Type of Complaint	Frequency in % by Injection No.		
	1	2	3
Injection Site	21(6/29)	28(7/25)	26(6/23)
Systemic	21(6/29)	8(2/25)	9(2/23)

Study 795

RESULTS (CONT.):

Refer to Table 2 for listings of specific complaints after each injection. Maximum temperature data are presented in Table 3.

There were no serious or alarming reactions attributable to vaccine.

PUBLICATIONS:

Deinhardt F, Jilg W, Zoulek G, Lorbeer B, Wilske B. Clinical evaluation of a recombinant hepatitis B vaccine. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:699.

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Dienhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2:1174-5.

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Dienhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:315-17.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CJ625
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	28%	(8/29)	10%	(3/29)	8.6	8.6	25.0
2 MONTHS	72%	(21/29)	59%	(17/29)	10.8	37.5	55.7
3 MONTHS	96%	(27/28)	71%	(20/28)	22.8	26.8	50.5
6 MONTHS	97%	(28/29)	86%	(25/29)	48.5	58.2	75.7
7/8 MONTHS	100%	(29/29)	100%	(29/29)	1735.7	1735.7	1735.7
9 MONTHS	100%	(22/22)	95%	(21/22)	990.8	990.8	1263.5
12 MONTHS	96%	(26/27)	93%	(25/27)	271.5	352.7	419.2

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	5 (17.2%)	2 (6.9%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (20.7%)
PAIN	4 (13.8%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (13.8%)
TENDERNESS	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
ERYTHEMA (REDNESS)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
ECCHYMOSIS	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
SYSTEMIC	3 (10.3%)	2 (6.9%)	4 (13.8%)	2 (6.9%)	1 (3.4%)	1 (3.4%)	6 (20.7%)
WHOLE BODY/GENERAL	1 (3.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.9%)
FATIGUE/WEAKNESS	1 (3.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.9%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
HERPES LABIALIS, RECURRENT	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
RESPIRATORY	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
RHINITIS	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (3.4%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
NAUSEA	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)
CONJUNCTIVITIS	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)
PERSONS WITH COMPLAINTS	8 (27.6%)	3 (10.3%)	5 (17.2%)	2 (6.9%)	1 (3.4%)	1 (3.4%)	11 (37.9%)
PERSONS WITH NO COMPLAINTS	21 (72.4%)	26 (89.7%)	24 (82.8%)	27 (93.1%)	28 (96.6%)	28 (96.6%)	18 (62.1%)
PERSONS WITH NO DATA	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)

00107

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	4 (16.0%)	3 (12.0%)	3 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		7 (28.0%)
PAIN	4 (16.0%)	2 (8.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (20.0%)
SWELLING	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
PARESTHESIA	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
SYSTEMIC	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (8.0%)
WHOLE BODY/GENERAL	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
FATIGUE/WEAKNESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
RESPIRATORY	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
RHINITIS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
LARYNGITIS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
COUGH	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
DIGESTIVE SYSTEM	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
NAUSEA	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
PERSONS WITH COMPLAINTS	5 (20.0%)	4 (16.0%)	3 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		8 (32.0%)
PERSONS WITH NO COMPLAINTS	20 (80.0%)	21 (84.0%)	22 (88.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)		17 (68.0%)
PERSONS WITH NO DATA	5 (16.7%)	5 (16.7%)	5 (16.7%)	5 (16.7%)	5 (16.7%)	5 (16.7%)		5 (16.7%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	5 (21.7%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (26.1%)
PAIN	4 (17.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (17.4%)
TENDERNESS	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
WARMTH	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
SWELLING	1 (4.3%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.7%)
PRURITIS (ITCHING)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
SYSTEMIC	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	2 (8.7%)
WHOLE BODY/GENERAL	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
FATIGUE/WEAKNESS	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (4.3%)
VIRAL INFECTION, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (4.3%)
PERSONS WITH COMPLAINTS	6 (26.1%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	7 (30.4%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH NO COMPLAINTS	17 (73.9%)	22 (95.7%)	23 (100.0%)	23 (100.0%)	23 (100.0%)	21 (95.5%)		16 (69.6%)
PERSONS WITH NO DATA	3 (11.5%)	3 (11.5%)	3 (11.5%)	3 (11.5%)	3 (11.5%)	3 (12.0%)		3 (11.5%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	18 (78.3%)	21 (87.5%)	20 (80.0%)	21 (84.0%)	20 (87.0%)	20 (83.3%)		16 (64.0%)
99 - 99.9	5 (21.7%)	3 (12.5%)	5 (20.0%)	4 (16.0%)	3 (13.0%)	4 (16.7%)		9 (36.0%)
TEMPERATURE TAKEN	23 (76.7%)	24 (80.0%)	25 (83.3%)	25 (83.3%)	23 (76.7%)	24 (80.0%)		25 (83.3%)
TEMPERATURE NOT TAKEN	7 (23.3%)	6 (20.0%)	5 (16.7%)	5 (16.7%)	7 (23.3%)	6 (20.0%)		5 (16.7%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	11 (64.7%)	12 (66.7%)	13 (76.5%)	11 (61.1%)	11 (64.7%)	12 (66.7%)			10 (55.6%)
99 - 99.9	6 (35.3%)	6 (33.3%)	4 (23.5%)	7 (38.9%)	6 (35.3%)	6 (33.3%)			8 (44.4%)
TEMPERATURE TAKEN	17 (56.7%)	18 (60.0%)	17 (56.7%)	18 (60.0%)	17 (56.7%)	18 (60.0%)			18 (60.0%)
TEMPERATURE NOT TAKEN	13 (43.3%)	12 (40.0%)	13 (43.3%)	12 (40.0%)	13 (43.3%)	12 (40.0%)			12 (40.0%)

Table 3 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	10 (71.4%)	11 (78.6%)	12 (85.7%)	13 (92.9%)	12 (85.7%)	10 (76.9%)			10 (66.7%)
99 - 99.9	4 (28.6%)	3 (21.4%)	2 (14.3%)	1 (7.1%)	2 (14.3%)	2 (15.4%)			4 (26.7%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)			1 (6.7%)
TEMPERATURE TAKEN	14 (46.7%)	14 (46.7%)	14 (46.7%)	14 (46.7%)	14 (46.7%)	13 (43.3%)			15 (50.0%)
TEMPERATURE NOT TAKEN	16 (53.3%)	16 (53.3%)	16 (53.3%)	16 (53.3%)	16 (53.3%)	17 (56.7%)			15 (50.0%)

SAT-LA.16

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

F. Deinhardt*, W. Jilg, G. Zoulek, B. Lorbeer, and B. Wilske
Max von Pettenkofer-Institute, 8000 Munchen 2, Western Germany

Thirty healthy, young volunteers free of any HBV markers were vaccinated with a recombinant hepatitis B vaccine prepared by Merck, Sharp & Dohme, West Point, PA. Ten µg HBsAg were administered intramuscularly at time 0, and one month later. Seroconversion rates and geometric mean concentrations after 1, 2 and 3 months were compared with an age- and sex-matched control group vaccinated with 20 µg of plasma derived vaccine (Merck Sharp & Dohme) (Table 1).

Table 1: Comparison of immune response after recombinant vaccine and plasma derived vaccine.

month	seroconversion %		anti-HBs (geom. mean) mIU	
	recombinant vaccine	plasma vaccine	recombinant vaccine	plasma vaccine
1	27	44	8.6	15.2
2	70	95	37.0	52.5
3	97	95	27.4	164.4

In the recombinant vaccine group, 38% of the total anti-HBs at month 3 was directed against the determinant a of HBsAg, compared to 30% in the control group. No increase in antibody titers against candida albicans was found in recipients of the recombinant vaccine 4 weeks after the second injection as compared to prevaccination levels. No serious side effects were observed in any of the vaccinated individuals.

Deinhardt F, Jilg W, Zoulek G, Lorbeer B, Wilske B. Clinical evaluation of a recombinant hepatitis B vaccine. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Straton, 1984:699.

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

W. JILG B. LORBEER
M. SCHMIDT B. WILSKE
G. ZOULEK F. DEINHARDT

Max von Pettenkofer-Institut, D-8000 München 2, West Germany

Summary Recombinant hepatitis B vaccine prepared from antigen expressed in yeast was given to 30 healthy young volunteers. Seroconversion rates and anti-HBs levels were compared with those in a control group matched for age and sex who had received plasma-derived hepatitis B vaccine. 4 weeks after the third immunisation results were similar in the two groups. In the recombinant vaccine group the immune response developed more slowly during the early phase and seroconversion rates and mean anti-HBs levels were slightly lower in males; this probably reflects use of a lower dose of recombinant vaccine (10 μg compared with 20 μg of the plasma vaccine). Side-effects were slight and antibody titres against *Candida albicans* were not increased in recipients of the recombinant vaccine.

Introduction

CURRENT hepatitis B vaccines are effective and safe.[1] However, because they are prepared from plasma of human hepatitis B virus carriers, supply is restricted by the amount of plasma available and by the cost of purifying the hepatitis B surface antigen (HBsAg) to render it free from hepatitis B virus and other possible infectious agents. Thus, to meet the worldwide need for hepatitis B vaccine, new means of preparation are required. Lately, vectors carrying the DNA sequence for HBsAg were prepared[2] and the antigen was expressed in the yeast *Saccharomyces cerevisiae*.[3] Yeast cells assemble the HBsAg polypeptides into particles similar to the 22 nm particles found in human plasma; yeast HBsAg, however, unlike human HBsAg is not glycosylated. A vaccine developed from yeast HBsAg stimulated antibody production in mice, grivet monkeys, and chimpanzees; and when vaccinated chimpanzees were challenged with human hepatitis B virus of different subtypes, they were completely protected.[4] We now report the immunisation of 30 healthy young volunteers with the first hepatitis B vaccine produced by recombinant DNA technology.

Subjects, Materials, and Methods

Subjects

30 healthy medical students and laboratory workers were studied (17 female, 13 male; mean age 25±3 yr, range 21–34). Subjects in the control group had been immunised with plasma-derived vaccine in an earlier study;[1] they were matched by age and sex to the study group (table I). Before vaccination, all subjects were negative for HBsAg, anti-HBs, and antibodies against hepatitis B core antigen (anti-HBc), and their gamma-glutamyltransferase levels were normal (females and aspartate aminotransferases ≤17 and ≤10 IU/l, respectively).

TABLE I—SEX AND AGE DISTRIBUTION OF THE TWO VACCINATION GROUPS*

	Total		Female		Male	
	No	Age (yr)	No	Age (yr)	No	Age (yr)
Recombinant vaccine	30	26·0±3·1 (21–34)	17	26·0±3·5 (21–34)	13	25·3±2·6 (23–32)
Plasma-derived vaccine	41	25·0±2·7 (21–33)	23	24·7±3·0 (21–32)	18	25·6±2·3 (23–33)

*Means and standard deviations (range).

Vaccines

The recombinant hepatitis B vaccine was prepared by Merck Sharp & Dohme research laboratories (lot 934/C-J 625). It consists of purified HBsAg, subtype *adw*, produced in recombinant *S cerevisiae* and absorbed on aluminium hydroxide. 1 ml of vaccine contained 10 μg of HBsAg. Plasma vaccine was also subtype *adw* (lot 773/001-2/ C-F 732-2 Merck Sharp & Dohme). Subjects in the study group received 10 μg of recombinant vaccine intramuscularly at 0, 1, and 6 months; subjects in the control group received 20 μg of plasma-derived vaccine at the same intervals. (Since the recombinant vaccine was treated with formalin only, and not with pepsin and urea, it was initially thought to be more immunogenic than the plasma vaccine.) Blood samples were taken on the day of the first vaccination and then monthly. Subjects were asked to keep daily records of body temperature and side-effects for 5 days after each injection.

Serology

HBsAg, anti-HBs, and anti-HBc were tested by radioimmunoassay with commercially available kits ('AUSRIA II', 'AUSAB', 'CORAB', Abbott Laboratories). Anti-HBs concentrations in IU/l were calculated by the method of Hollinger *et al.*,[6] the first WHO reference preparation 1977 being used in a dilution of 1:400.[7] Because *S cerevisiae* and *C albicans* have common antigenic determinants,[8] antibodies against *C albicans* were determined by passive haemagglutination in 26 subjects on day 0 and 4 weeks after the second and third injections of recombinant vaccine. Sera were examined for antibodies against the determinant *a* of HBsAg as previously described.[9]

Results

Seroconversion rates and mean anti-HBs levels during the course of immunisation are shown in table II. The immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels. These differences became non-significant after the booster dose at month 6 when 29 out of 30 subjects (97%) were anti-HBs positive (control, 41 out of 41) with a geometric mean anti-HBs level of 2135 IU/l (control, 4299 IU/l). All anti-HBs-positive individuals in the recombinant vaccine group had anti-HBs values above 10 IU/l; 2 (6·7%) were low responders (anti-HBs below 100 IU/l), 3 (10%) were intermediate responders (anti-HBs 101–1000 IU/l), and 22 (73·3%) were normal to high responders (anti-HBs greater than 1000 IU/l). Similar values

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2:1174-5.

TABLE II—IMMUNE RESPONSES AFTER VACCINATION

Month	Seroconversion (%)		Anti-HBs (IU/l)*		p†
	Recombinant vaccine (n = 30)	Plasma-derived vaccine (n = 41)	Recombinant vaccine	Plasma-derived vaccine	
1	0 (27)	10 (40)	9	15	<0·05
2	21 (70)	39 (95)	30	93	<0·05
3	23 (77)	39 (95)	39	164	<0·05
4	23 (77)	39 (95)	63	220	<0·05
5	23 (77)	39 (95)	79	273	<0·05
6	23 (77)	39 (95)	60	313	<0·05
7	29 (97)	41 (100)	2155	4200	>0·05

*Anti-HBs is given as the geometric mean in responders only.
†Wilcoxon's rank-sum test.

TABLE III—IMMUNE RESPONSES IN MALES AND FEMALES (AFTER THREE INOCULATIONS)

—	Recombinant vaccine	Plasma-derived vaccine	p*
Males			
Seroconversion (%)†	12/13 (92)	16/16 (100)	
Anti-HBs (IU/l)‡	911	3994	<0·05
Females			
Seroconversion (%)†	17/17 (100)	23/25 (100)	
Anti-HBs (IU/l)‡	3282	4640	>0·05

*Wilcoxon's rank-sum test.
†Number of anti-HBs-positive subjects divided by the total number.
‡Geometric mean.

were obtained in the control group. Although the immune responses to the two vaccines were similar after the full course of immunisation, responses of male and female subjects differed. In both groups all the women seroconverted and the geometric mean anti-HBs levels did not differ significantly (3282 IU/l vs 4640 IU/l). However, in males receiving recombinant vaccine the seroconversion rate was 92% vs 100%, and the geometric mean anti-HBs was 911 vs 3994 IU/l (table III).

Preliminary tests indicate that recombinant vaccine, like the plasma-derived vaccine, induces antibodies against both the *a* and the *d* components of HBs antigen. After month 3, about 30% of the total anti-HBs was directed against determinant *a*.

No important side-effects were observed after immunisation with the recombinant vaccine. Minor local symptoms such as transient pain, itching, burning, and slight swelling at the injection site were reported after 24 of the 90 injections. On no occasion did body temperature rise above 37·9°C.

Of 26 subjects tested, all had antibodies against *C albicans* on day 0 (titres from 1:80 to 1:320) and titres did not increase after immunisation.

Discussion

Three doses of 10 μg recombinant hepatitis B vaccine gave seroconversion rates and geometric mean anti-HBs levels similar to those induced by three doses of 20 μg plasma-derived vaccine. The results were also comparable with those obtained in large trials of conventional vaccines.[10,11]

The immune response to the recombinant vaccine, however, was less strong during the early phase (1–6 months) in all subjects, and in males mean anti-HBs values were lower in the recombinant group even after the complete course of immunisation. These results are comparable with findings in subjects immunised with a smaller dose (5 μg) of conventional vaccine (Jilg W, Zachoval R, Schmidt M, Deinhardt F, unpublished), and may reflect the use of smaller amounts of antigen. Antigen content of both recombinant vaccine and plasma-derived vaccine is determined as HBsAg protein. The vaccines are produced and treated differently, however;[4,12] therefore similar protein content does not necessarily mean similar immunogenicity. The yeast and plasma derived HBsAg differed in reactivity in radioimmunoassay tests; the reactivity of the HBsAg produced in yeast was only 20–50% of the reactivity of plasma-derived HBsAg.[4] Thus, weight-for-weight the immunogenicity of the recombinant vaccine seems to be less than that of the plasma-derived vaccine. Another explanation for the lower immune response may be that 10 μg of recombinant vaccine was given per single dose compared with 20 μg of plasma-derived vaccine. A higher dose (20 or 40 μg) of the recombinant vaccine would probably give the same results as the plasma-derived vaccine.

Despite the slightly lower immunity achieved with the recombinant vaccine, protection will probably be as good as with the conventional vaccine, in that all 29 subjects with detectable anti-HBs had values above the protection level of 10 IU/l.[13] In 73%, anti-HBs levels after the third vaccination were more than 1000 IU/l; this has been shown to guarantee persistence of anti-HBs above the protective limit for at least 3 years.[14] In addition, all subjects who seroconverted had antibodies against the common determinant *a* of HBsAg, indicating cross-protection against infections with other subtypes of HBsAg. Side-effects after the recombinant vaccine were negligible and did not differ from those observed after plasma-derived vaccine. The absence of a rise in antibodies against *C albicans* indicates that no cross-reacting yeast antigens were present in the vaccine.

We thank Mrs Liesel Sabersky for expert technical assistance.

Correspondence should be addressed to W. J., Max v. Pettenkofer-Institut, Pettenkoferstr. 9 a, 8000 München 2, West Germany.

REFERENCES

1. Deinhardt F. Control of hepatitis A and B with vaccines. *Ann Clin Res* 1982; 14: 230–44.
2. Valenzuela P, Gray P, Quiroga M, Zaldivar J, Goodman HM, Rutter WJ. Nucleotide sequence of the gene coding for the major protein of hepatitis B surface antigen. *Nature* 1979; 280: 815–19.
3. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298: 347–50.
4. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984; 307: 178–80.
5. Zachoval R, Jilg W, Lochner B, Schmidt M, Deinhardt F. Passive-active immunization against hepatitis B. *J Infect Dis* 1984; 150: 113–17.
6. Hollinger FB, Adam E, Hadlow D, Melnick JL. Response to hepatitis B vaccine in a young adult population. In: Kleinman W, Alter MJ, Maynard JE, eds. Viral hepatitis: 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 451–60.
7. World Health Organization. *WHO Tech Rep Ser* no 630; 1979: 39.
8. Tsuchiya T, Fukazawa Y, Kuroiwa S. Serological classification of the genus *Candida*. In: Tokyo Research Committee of Candidiasis. Studies of candidiasis in Japan. Tokyo: Education Ministry of Japan, 1981: 34–36.
9. Jilg W, Deinhardt C, Deinhardt F, Papaevangelou GJ, Mantzavinos HS, Orestis LB. Hepatitis B surface antigen (HBsAg) subtype-specific and shared determinants recognized by hepatitis B. *J Med Virol* 1984; 13: 171–78.
10. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981; 1: 377–85.
11. Coursaget J, Jouglard P, Coursaget AM, et al. Randomized placebo-controlled trial of hepatitis B surface antigen vaccine in French homosexual men. *J Medical staff Lancet* 1981; 1: 659–62.
12. Hilleman MR, Buynak EB, McAleer WJ, McLean AA. Human hepatitis B vaccine. In: Kreighauer K, Rowland K, eds. Proceedings of the European Symposium on Hepatitis B Antigen: March Sharp & Dohme International, 1981: 139–50.
13. Coursaget A, Coursaget P, Bocq F, et al. Prevention of hepatitis B by active and passive immunization. In: Kleinman W, Alter MJ, Maynard JE, eds. Viral hepatitis 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 389–95.
14. Jilg W, Schmidt M, Zachoval R, Deinhardt F. Persistenz von Antikörpern gegen Hepatitis B-Oberflächenantigen nach Impfung gegen Hepatitis B. *Dtsch Med Wochenschr* (in press).

Edward M. Scolnick, Arlene A. McLean,
David J. West, Jules L. Dienstag,
Eloise Watkins, Friedrich Deinhardt and Wolfgang Jilg

23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

VIRAL HEPATITIS and LIVER DISEASE
ISBN 0-8089-1678-5

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

(b) (4)

[redacted]

TEST FOR
NONINFECTIVITY

TEST FOR NONINFECTIVITY
STUDY 839

In clinical trials of the hepatitis B vaccine derived from infected human plasma, one study was specifically designated as a safety study to ascertain that hepatitis B was not transmitted via the purified vaccine. The yeast recombinant hepatitis B vaccine is not made from plasma, and intact hepatitis B virus should not be present at any stage of its formulation. However, in early discussions with the OoBRR, it was suggested that one study be conducted as a true human "safety" test.

In Study 839, a single 10 mcg dose of vaccine was administered to five healthy adult volunteers. The subjects were followed serologically for six months. During that time period, none of the participants developed any marker of hepatitis B infection (HBsAg, anti-HBc, or elevated ALT). One subject developed a low titer (6.0 mIU/ml) of anti-HBs four months after receiving the single 10 mcg injection of vaccine. There were no reports of serious or alarming adverse experiences.

STUDY 839

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 839.
PURPOSE:	To assess the lack of infectivity of the vaccine among healthy adults who are negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #972/C-K444 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Robert Bishop, M.D. Health Services WP 38-4 Merck Sharp and Dohme West Point, PA 19486
SECONDARY INVESTIGATOR:	E. P. Avancena, M.D. Health Services WP 38-4 Merck Sharp and Dohme West Point, PA 19486
STUDY LOCATION:	Merck Sharp and Dohme West Point, PA 19486
DATE INITIATED:	July 31, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 5 healthy adults of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level, have not previously received any hepatitis B vaccine and have no known risk factors for hepatitis B.
PROCEDURE:	Participants receive a single 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine. Vaccine recipients are asked to record their temperature daily for 5 days after vaccination and also to record any local or systemic complaints that they may have during this period. Unexpected or serious adverse reactions will be reported immediately to the study physician.

Study 839

PROCEDURE: (CONT.)

A blood specimen (10-15 ml) is obtained from each participant 1-2 weeks before vaccination. Post-vaccination blood samples are taken at 2, 4, and 6 months. All samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT at MSDRL. Samples may also be assayed for yeast antibody.

RESULTS:

HEALTHY ADULTS:

10 mcg Lot #972/C-K444 at time zero.

1. Number Vaccinated: 5

2. Serologic Results:

One subject developed a low titer (6.0 mIU/ml) of anti-HBs 4 months after receiving the vaccine. Refer to Table 1 for anti-HBs responses for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for all 5 participants. The overall frequencies of complaints are presented below.

Type	Frequency in %
Injection Site	20 (1/5)
Systemic	40 (2/5)

Refer to Table 2 for listings of specific clinical complaints. Maximum temperature data are provided in Table 3.

There were no serious or alarming adverse reactions attributable to vaccination.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0839
POPULATION : HEALTHY ADULTS
DOSE : 10 MCG
LOT : CK444
REGIMEN : Day 0
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	RESPONDERS	
						S/N >= 2.1	MIU/ML >= 10
2 MONTHS	0%	(0/5)	0%	(0/5)	0.3		
4 MONTHS	25%	(1/4)	0%	(0/4)	1.2	6.0	
6 MONTHS	25%	(1/4)	0%	(0/4)	0.9	6.2	

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0839
TREATMENT :
LOT NUMBER : CH444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (5 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
SORENESS	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
SYSTEMIC	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
WHOLE BODY/GENERAL	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
SWEATING	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
FATIGUE/WEAKNESS	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
INTEGUMENTARY SYSTEM	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
URTICARIA/HIVES	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
PRURITIS/ITCHING	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
NERVOUS SYSTEM	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
VERTIGO/DIZZINESS	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
PERSONS WITH COMPLAINTS	3 (60.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (60.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0839
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (5 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH NO COMPLAINTS	2 (40.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)		2 (40.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0839
TREATMENT :
LOT NUMBER : CK464
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

	TOTAL VACCINEES (5 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER
MAX TEMPERATURE (DEG F, ORAL)	0	1	2	3	4	5		WITH MAX TEMP
< 99	4 (80.0%)	5 (100.0%)	4 (80.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)		3 (60.0%)
99 - 99.9	0 (0.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (20.0%)
101 - 101.9	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (20.0%)
TEMPERATURE TAKEN	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)		5 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

IMMUNOGENICITY/
SAFETY

HEALTH CARE PERSONNEL
/HEALTHY ADULTS

SUMMARY - HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS

Persons employed in a variety of health care occupations are known to be at above-average risk for hepatitis B infection and therefore constitute a sizeable candidate population for vaccination with hepatitis B vaccine. Initially seronegative health care personnel and other healthy adults were selected as a major group in which to evaluate the immunogenicity and reactogenicity of the yeast recombinant hepatitis B vaccine. To date, 2414 individuals in 36 studies have received at least one injection of vaccine, and 1442 of these have completed a 3 dose regimen of vaccination. Anti-HBs titers following the third injection have been measured in 1048 vaccinees, while clinical reports are available for 990 of these individuals. Titers currently available in units of mIU/ml for 829 subjects show that the vaccine is highly immunogenic, with protective levels of anti-HBs (mIU/ml $\geq$10) developed by 96%. The vaccine has been well tolerated with approximately one-fourth of the vaccinees reporting minor transient complaints such as injection site soreness, fatigue, and headache.

IMMUNOGENICITY

Dose:

Table 1 summarizes the antibody responses of 1123 health care personnel and other healthy adults (excludes data from study #880 which compares consistency lots), who received injections containing 2.5, 5, 10, or 20 mcg doses of yeast recombinant hepatitis B vaccine at 0, 1, and 6 months, and for whom post-vaccination test data are currently available in units of mIU/ml. Anti-HBs responses following the third injection of vaccine are shown for 736 subjects, while responses after only one or two injections of vaccine are included for an additional 387 subjects. At 3 months (2 months following the second injection of vaccine), 80-89% of the vaccine recipients had anti-HBs based on a cutoff of S/N $\geq$2.1. By 7/8 months (1-2 months after the third injection of vaccine), the proportion of vaccinees with antibody rose to 97-100%. Slightly lower seroconversion rates were observed using a cutoff of mIU/ml $\geq$10. With this cutoff, 57-75% of the vaccine recipients had anti-HBs by 3 months, while 89-97% were antibody positive by 7-8 months.

The effect of log dose level on seroconversion for anti-HBs was analyzed statistically. The analysis was done using only data from four studies that each involved more than one dose level, although seroconversion rates in these studies (Tables 2, 3) were very similar to those observed across all studies (Table 1). Over the four studies, seroconversion rate was found to increase significantly with log dose level at 1, 3, and 6 months based on a cutoff of S/N $\geq$2.1 ($p < 0.001$ to 0.002). There was no significant trend at 7/8 months, with 95% or more of the vaccinees positive for antibody regardless of dose level. (See Appendix 1 for a description of statistical methods used.)

Using data from three of the four studies (titers not available in units of mIU/ml for study #794) seroconversion rates based on a cutoff of mIU/ml ≥10 showed a significant upward trend with increasing log dose level at 3 and 6 months ($p < 0.001$). Again, at 7/8 months there was no significant trend, with 89% or more of the vaccinees having titers of mIU/ml ≥10 at all dose levels.

A regression of log anti-HBs titers on log dose level, sex, and age, for all vaccinees with mIU/ml data (study #859 excluded because of missing sex and age data), showed all three factors to be statistically significant at each time point with the exception of log dose level at 1 month ($p = 0.001$ for sex at 1 month and $p < 0.001$ for all else). Larger doses produced higher titers.

Overall geometric mean titers (GMTs) of anti-HBs by dose level are shown in Table 1. At 7/8 months, the GMTs for responders with a titer of S/N ≥2.1 were 255.8 mIU/ml (2.5 mcg dose), 245.1 mIU/ml (5 mcg dose), 1264.3 mIU/ml (10 mcg dose), and 539.0 mIU/ml (20 mcg dose). Among responders with a titer of mIU/ml ≥10, the GMTs at 7/8 months were 295.3 mIU/ml (2.5 mcg dose), 348.7 mIU/ml (5 mcg dose), 1321.9 mIU/ml (10 mcg dose) and 1021.5 mIU/ml (20 mcg dose).

Sex:

Table 4 shows antibody responses of health care personnel and other healthy adults by sex (does not include data from the consistency lots study, #880) who received 2.5, 5, or 10 mcg doses of yeast recombinant hepatitis B vaccine, and for whom test data are currently available in units of mIU/ml. Responses for the 20 mcg dose are not shown as recipients of this dose were exclusively male. Seroconversion rates tended to be somewhat lower among males as compared to females at early post-vaccination times. By 7/8 months, 97-100% of the vaccinees had anti-HBs (S/N ≥2.1) regardless of sex, while 87-100% had titers of mIU/ml ≥10.

As noted in the earlier discussion on dose level, multiple regression analysis showed that log anti-HBs titer was also significantly related to sex at all time points ($p = 0.001$ for sex at 1 month and $p < 0.001$ at other times). Females tended to have higher titers than males when adjusted for age and dose level.

Age:

Table 5 shows antibody responses of health care personnel and other healthy adults ≥40 years of age and <40 years of age, who received 10 mcg doses of the yeast recombinant hepatitis B vaccine, and for whom test data are available in units of mIU/ml (excludes data from study #880 which compares consistency lots). The summary of antibody response by age is limited to the 10 mcg dose of vaccine since few adults ≥40 years have yet received other dosages. In general, older individuals responded less rapidly and developed lower anti-HBs titers than younger subjects. However, by 7/8 months, 91% of even the older vaccinees had titers of mIU/ml ≥10.

first and second injection of vaccine as scheduled, while the third injection was not administered until 11 months after the first injection. The individual does have a history of allergies.

2. A 26-year old female became aware that she was pregnant after receiving one injection of vaccine. The vaccine was administered approximately one month after conception. She experienced a spontaneous abortion at 18 weeks after fetal death in utero. No microscopic examination was completed on the fetus. The subject previously delivered two healthy infants without complication of pregnancy. She had no known allergies.

3. A 37 year-old female noted facial warmth and flushing 14 hours after receiving her first injection of vaccine. Within the next 3 hours she developed facial urticaria. She was treated with cold packs. The symptoms subsided and she recovered in 12 hours. The subject was treated with Benedryl prior to the second and third injection, and had no post-vaccination reactions.

4. A 23 year-old female developed hives within 24 hours of receiving the first injection of vaccine. The hives were described as one large 3-4 inch lesion, pruritic, with several satellite lesions on the back, and several small lesions on the legs. All symptoms resolved by day 4 post vaccination. Within 24 hours of receiving the second injection of vaccine, the subject developed small hives on the back, arms, and left hand. All symptoms resolved by day 4 post vaccination. The individual received her third injection of vaccine with no evidence of hives. In the past, the subject developed hives during administration of contrast dye (for CAT scan). There is no other allergic history.

5. A 40 year-old female developed a few ecchymotic flat lesions on the lateral aspect of her breasts, bilaterally, 4 days after the first injection of vaccine. Over the following 2 days the lesions increased. Vomiting occurred on the third day. All symptoms disappeared over the next 36 hours, and the subject has remained well. There was no fever, and WBC, Hgb, platelets, and coagulation profile were normal. The patient has no history of allergies to exogenous substances. No further vaccine was administered to this patient.

Mild transient injection site reactions and systemic complaints were reported following injection of vaccine at frequencies of 17% and 15%, respectively (Table 8). The frequency of complaints after the first injection was higher than after the second or third injections. Table 9 lists specific injection site reactions that occurred with a frequency of $\geq$0.1%, while Tables 10 and 11 show specific systemic complaints that occurred at frequencies of $\geq$0.1%. The most frequent injection site reactions were soreness (8%), pain (5%), tenderness (3%) and pruritis (1%). Systemic complaints that occurred at a frequency of $\geq$1% include fatigue/weakness (4%), headache (4%), nausea (2%), pharyngitis (1%), malaise (1%), diarrhea (1%) and upper respiratory infection (not otherwise specified) (1%) (Table 11). A temperature of $\geq$100°F (oral) was reported following 3% of all injections (Table 12).

A statistical analysis of seroconversion rates as a function of age was done for recipients of 10 mcg doses of vaccine using only data from studies that involved subjects <40 years of age and ≥40 years of age. These data are summarized in Table 6. Based on a cutoff of S/N ≥2.1, the seroconversion rate over studies was significantly higher in the <40 year age group than in the ≥40 year age group at 1 ($p < 0.001$), 3 ($p = 0.021$), and 6 months ($p = 0.032$). Similar differences were seen when the seroconversion rates were based on a cutoff of mIU/ml ≥10, with significance achieved at 1 ($p = 0.021$), 3 ($p = 0.022$), and 6 months ($p = 0.047$).

The multiple regression analysis mentioned previously showed that log anti-HBs titer was also significantly related to age at each time point ($p < 0.001$). The level of response was shown to decrease with age.

Persistence of Antibody:

In most of the clinical studies now in progress, antibody titers will be monitored for a period of 2 years following the initial injection of vaccine. At present, limited data are available through 12 months of follow-up. Table 1 summarizes available data at this time point for 415 health care personnel and other healthy adults whose titers have been measured in units of mIU/ml. The GMTs of responders with titers of mIU/ml ≥10 at 7/8 months declined 2 to 4-fold by 12 months. Similar declines in antibody titer over this time interval were characteristic of the subset of vaccinees consisting of all those with serologic data at both 7/8 and 12 months. Table 7 shows the distribution of titers at 7/8 months and 12 months, respectively, for health care personnel and other healthy adults who received 10 mcg doses of vaccine. Minimal evidence of antibody (S/N ≥2.1) was present in 98% of the vaccinees at 7/8 months and 95% at 12 months, while fully protective levels (mIU/ml ≥10) were present in 97% and 90% at 7/8 and 12 months, respectively. Higher titers (mIU/ml ≥100) were characteristic of 89% of the vaccinees at 7/8 months and of 65% at 12 months, while 58% and 25% of the vaccine recipients were in the highest titer category (mIU/ml ≥1000) at 7/8 and 12 months, respectively.

SAFETY

In general, the yeast recombinant hepatitis B vaccine has been well tolerated. There have been no reports of serious or alarming reactions attributable to vaccination. Tables 8-12 summarize clinical complaints and elevated temperatures reported by health care personnel and other healthy adults following injection with the yeast recombinant hepatitis B vaccine (exclude data from study #880 which compares consistency lots).

Five subjects have had reactions that possibly were related to vaccination. These reactions are summarized below:

1. A forty-one year old female developed headache, swollen face and rash within several hours after receiving the third injection of vaccine. The headache and swollen face resolved in one day, while the rash faded over 4 days. No clinical complaints were reported by this individual following the first and second injections of vaccine. She received her

COMPARISON OF CONSISTENCY LOTS

Five lots of the yeast recombinant hepatitis B vaccine were manufactured in a production setting to demonstrate consistency. Study 880 was conducted to evaluate the safety and immunogenicity of these consistency lots in seronegative health care personnel. Subjects in this study receive 10 mcg doses of vaccine from one of the consistency lots at 0, 1, and 6 months. Data from this study were excluded from the preceding across studies summary for health care personnel and other healthy adults.

A total of 233 persons have received one or more doses of vaccine in Study 880. Postvaccination clinical data are currently available for all subjects, while serologic data have been obtained for 227 of the vaccinees. These include data on clinical complaints for 99 subjects and anti-HBs response data for 139 subjects who have received all three injections of vaccine.

Table 13 shows the age and sex characteristics by lot of the subjects vaccinated in Study 880. Recipients of each lot were fairly similar except for a preponderance of males among recipients of lot C-L220.

Table 14 summarizes the antibody responses of persons who received vaccine from the 5 consistency lots. At 3 months (2 months following the second injection of vaccine), 84% (range 66-97%) of the vaccine recipients had at least minimal levels of anti-HBs (S/N $\geq$2.1), while 72% (range 59-83%) had protective levels of antibody (mIU/ml $\geq$10). By 7/8 months (1-2 months after the third injection of vaccine), 98% (range 92-100%) of the vaccinees had antibody titers of S/N $\geq$2.1, and 96% (range 91-100%) had titers of mIU/ml $\geq$10. Geometric mean titers of antibody by 7/8 months were 627.6 mIU/ml (range 332.6-1187.6 mIU/ml) for all vaccinees, 742.9 mIU/ml (range 476.4-1187.6 mIU/ml) for responders with a titer of S/N $\geq$2.1, and 830.8 mIU/ml (range 593.6-1187.6 mIU/ml) for responders with a titer of mIU/ml $\geq$10.

Clinical complaints occurring during a five-day period following injections with vaccine from the consistency lots are summarized in Table 15. There were no serious adverse experiences attributed to vaccination. All reactions were mild and transient. Local (injection site) reactions were reported following 5-12% of injections with the various consistency lots. The frequency of systemic complaints following injection from these lots ranged from 3-9%. Ten to 15% of the injections from each lot of vaccine involved some complaint. A temperature of $\geq$100°F (oral) was reported following 0-3% of injections.

This study and a second of similar design continue in progress.

A statistical analysis is now being done to evaluate differences between the 5 consistency lots of vaccine with respect to seroconversion rates and geometric mean titers of anti-HBs as well as the reported frequencies of clinical reactions. The results of the analysis will be submitted to the OoBRR as a supplement to this report by the end of March, 1986.

SUMMARY OF ADULT STUDIES

The yeast recombinant hepatitis B vaccine has been well tolerated by healthy adult recipients. A vaccination regimen consisting of three 10 mcg doses is sufficient to induce fully protective titers of antibody in 97% of the vaccinees.

Table 1

Antibody Responses Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months

Time (Months)	2.5 mcg					5 mcg *					10 mcg *					20 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders					Responders	
	S/P≥2.1	mIU/ml ≥10	All Vaccinees	S/P≥2.1	mIU/ml ≥10	S/P≥2.1	mIU/ml ≥10	All Vaccinees	S/P≥2.1	mIU/ml ≥10	S/P≥2.1	mIU/ml ≥10	All Vaccinees	S/P≥2.1	mIU/ml ≥10	S/P≥2.1	mIU/ml ≥10	All Vaccinees	S/P≥2.1	mIU/ml ≥10
1	27 (16/60)	15 (9/60)	1.0	23.6	65.9	27 (45/167)	15 (25/167)	0.9	15.7	50.7	30 (258/851)	16 (140/851)	1.0	15.1	43.0	29 (10/35)	11 (4/35)	0.7	8.7	72.9
3	85 (48/56)	62 (35/56)	17.0	33.0	63.2	80 (128/161)	62 (100/161)	12.4	31.6	55.9	89 (512/583)	75 (437/583)	31.2	55.1	89.7	89 (31/35)	57 (20/35)	10.3	16.4	38.1
6	85 (49/57)	70 (40/57)	17.7	32.1	61.0	84 (133/159)	68 (107/158)	10.7	29.9	67.8	94 (591/618)	87 (535/618)	60.2	89.2	101.0	91 (31/34)	79 (27/34)	26.2	40.3	57.6
7/8 †	100 (58/58)	91 (56/58)	255.8	255.8	295.3	97 (111/114)	90 (102/114)	205.7	245.1	340.7	98 (518/529)	97 (514/529)	1072.3	1264.3	1321.9	100 (35/35)	89 (31/35)	539.0	539.0	1021.5
12	95 (65/67)	91 (61/67)	98.1	127.0	172.3	92 (85/93)	76 (69/93	63.3	96.7	240.1	95 (228/240)	90 (216/240)	198.5	275.1	343.8	97 (34/35)	86 (30/35)	184.5	217.4	370.9

* Table does not include results for 11 subjects in Study P84 whose anti-HBs responses are available only in units of S/N.

† Table includes a number of responses measured at 8 months when that was the first blood sample obtained following the third injection of vaccine.

Table 2

Seroconversion Rates for Anti-HBs (Based on a Cutoff of S/N ≥2.1)
Among Health Care Personnel and Other Healthy Adults Receiving
Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months
(Studies Involving More Than One Dose Level)

Time (Months)	% (Proportion) with Anti-HBs			
	2.5 mcg	5 mcg	10 mcg	20 mcg
1	27 (16/60)	28 (54/196)	36 (74/205)	29 (10/35)
3	86 (48/56)	80 (151/190)	87 (167/191)	89 (31/35)
6	86 (49/57)	84 (154/184)	93 (177/190)	91 (31/34)
7/8*	100 (58/58)	95 (133/140)	98 (148/151)	100 (35/35)

* Includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

Studies: 794, 798, 813, 883

wva/31241/5
1/9/86

Table 3

Seroconversion Rates for Anti-HBs (Based on a Cutoff of mIU ≥10)
Among Health Care Personnel and Other Healthy Adults Receiving
Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months
(Studies Involving More Than One Dose Level)

Time (Months)	% (Proportion) with Anti-HBs			
	2.5 mcg	5 mcg	10 mcg	20 mcg
1	15 (9/60)	15 (25/167)	19 (31/167)	11 (4/35)
3	62 (35/56)	62 (100/161)	72 (113/158)	57 (20/35)
6	70 (40/57)	68 (107/158)	84 (130/154)	79 (27/34)
7/8*	97 (56/58)	90 (102/114)	96 (110/114)	89 (31/35)

* Includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

Studies: 798, 813, 883

Table 4

Antibody Responses by Sex Among Health Care Personnel and Other Healthy Adults Receiving Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months

Time (Months)	Sex	2.5 mcg					5 mcg *					10 mcg *				
		% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
					Responders					Responders					Responders	
		S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10	S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10	S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10
1	F	33 (7/21)	19 (4/21)	1.3	22.3	54.0	37 (16/43)	16 (7/43)	1.2	10.6	52.8	34 (140/418)	19 (78/418)	1.2	15.6	41.8
	M	23 (9/39)	13 (5/39)	0.8	24.6	77.3	23 (29/124)	14 (18/124)	0.8	19.5	49.9	26 (108/412)	14 (59/412)	0.9	15.1	45.4
3	F	90 (18/20)	60 (12/20)	18.4	29.0	61.8	93 (38/41)	80 (33/41)	35.2	49.2	69.2	88 (213/241)	81 (196/241)	44.8	80.1	100.6
	M	83 (30/36)	64 (23/36)	16.3	36.2	64.0	75 (90/120)	56 (67/120)	8.6	26.2	51.6	88 (274/311)	72 (224/311)	25.7	43.5	72.7
6	F	90 (17/19)	74 (14/19)	23.1	34.6	48.9	95 (38/40)	88 (35/40)	54.1	71.1	87.8	95 (256/269)	91 (244/269)	90.2	117.2	135.5
	M	84 (32/38)	68 (26/38)	14.8	30.9	45.9	80 (95/118)	61 (72/118)	13.1	31.7	59.8	93 (324/348)	84 (291/348)	43.8	59.2	78.6
7/8 †	F	100 (19/19)	100 (19/19)	301.5	301.5	301.5	100 (30/30)	97 (29/30)	560.3	560.3	646.1	99 (225/228)	97 (222/228)	1502.6	1675.1	1816.9
	M	100 (39/39)	95 (37/39)	236.2	236.2	292.2	96 (81/84)	87 (73/84)	144.8	180.5	272.9	97 (292/300)	97 (291/300)	829.0	1011.5	1036.9
12	F	100 (16/16)	88 (14/16)	94.9	94.9	144.4	100 (23/23)	91 (21/23)	238.5	238.5	357.3	94 (104/110)	91 (100/110)	264.9	374.5	448.6
	M	94 (29/31)	87 (27/31)	99.9	149.0	188.7	90 (63/70)	69 (48/70)	40.9	69.1	167.3	95 (124/130)	89 (116/130)	155.5	212.3	273.3

* Table does not include results for 71 subjects in Study 794 whose anti-HBs responses are available only in units of S/N.

† Table includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

uva-1/3/86-31271/1

00137

Table 5

Antibody Responses by Age Group Among Health Care Personnel and Other Healthy Adults Receiving 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months*+

Time (Months)	Age Group (Years)	% with Anti-HBs		GMT (mIU/ml)		
				All Vaccinees	Responders	
		S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1	<40	32(227/699)	18(129/699)	1.1	15.7	42.7
	≥40	16(21/130)	6(9/130)	0.6	11.9	54.5
3	<40	89(449/503)	78(394/503)	36.7	60.4	86.2
	≥40	78(38/49)	55(27/49)	11.0	30.3	67.4
6	<40	95(534/564)	88(498/564)	66.4	85.4	104.4
	≥40	87(46/53)	70(37/53)	21.6	40.6	68.4
7/8**	<40	98(464/472)	98(462/472)	1225.9	1409.4	1446.0
	≥40	95(53/56)	91(51/56)	345.7	487.8	586.5
12	<40	96(190/198)	90(179/198	225.7	293.6	375.7
	≥40	90(38/42)	88(37/42)	108.4	198.7	223.7

*Table does not include results for 71 subjects in Study 794 whose anti-HBs responses were available only in units of S/N.

+Table does not include results for 32 subjects whose ages are not presently known.

**Table includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

Table 6

Seroconversion Rates for Anti-HBs by Age Group
(Based on a Cutoff of S/N ≥2.1)
Among Health Care Personnel and Other Healthy Adults Receiving
10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine
at 0, 1, and 6 Months †

Time (Months)	Age Group (Years)	% (Proportion) with Titer	
		S/N ≥2.1 *	mIU/ml ≥10 **
1	<40	35 (131/378)	16 (57/350)
	≥40	16 (22/139)	6 (8/129)
3	<40	89 (224/253)	79 (181/230)
	≥40	73 (43/59)	55 (27/49)
6	<40	94 (250/266)	89 (212/239)
	≥40	84 (51/61)	69 (36/52)
7/8†	<40	98 (221/225)	97 (192/198)
	≥40	94 (61/65)	91 (50/55)

† Includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

* Studies: 779, 792, 794, 801, 803, 807, 809, 813, 835, 838, 869, 883, 889
** Studies: As above, but excluding study 794.

wva/3124I/8
1/9/86

Table 7

Distribution of Anti-HBs Titers at 7/8 and 12 Months
Among Health Care Personnel and Other Healthy Adults
Receiving 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine
at 0, 1, and 6 Months

Anti-HBs Titer	% (Proportion) with Titer	
	7/8 Months *	12 Months
S/N ≥2.1	98 (498/509)	95 (225/237)
mIU/ml ≥10	97 (494/509)	90 (213/237)
mIU/ml ≥100	89 (451/509)	65 (155/237)
mIU/ml ≥1000	58 (294/509)	25 (60/237)

* Includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

Table 8

Percentages of Health Care Personnel and Other Healthy
Adults with Clinical Complaints During a Five-Day Period
Following 3255 Injections of Yeast Recombinant Hepatitis B Vaccine

Type of Complaint	First Injection	Second Injection	Third Injection	All Injections
Local (Injection Site)	20 (248/1252)	14 (157/1162)	17 (139/841)	17 (544/3255)
Systemic	19 (244/1252)	13 (148/1162)	11 (90/841)	15 (482/3255)
Any Complaint	34 (426/1252)	23 (263/1162)	23 (196/841)	27 (885/3255)

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835, 838, 839, 860, 869, 883, 889

31171/1
1/2/86

Table 9

Frequency of Local (Injection Site) Complaints Occurring within 5 Days Among Health Care Personnel and Other Healthy Adults Following 3255 Injections of Yeast Recombinant Hepatitis B Vaccine

Number of Vaccine Recipients: 1252

Complaint	Number	Frequency as %
Soreness	259	8
Pain	149	5
Tenderness	98	3
Pruritis	36	1
Stiffness/Tightness	14	0.4
Erythema	14	0.4
Ecchymosis	10	0.3
Swelling	10	0.3
Pain on Injection	6	0.2
Warmth	6	0.2
Lymphadenopathy, Regional	5	0.2
Arm Feels Heavy	5	0.2
Nodule	4	0.1
Paresthesia	4	0.1
Papule	3	0.1
Inflammation	3	0.1
Numbness	3	0.1

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835, 838, 839, 860, 869, 883, 889

Table 10

Percentage (Number) of Health Care Personnel and Other Healthy Adults with Specific Systemic Complaints During a Five-Day Period Following 3255 Injections of Yeast Recombinant Hepatitis B Vaccine

Number of Vaccine Recipients: 1252

Complaint Frequency 1–4%	
Fatigue/Weakness	4 (138)
Headache	4 (135)
Nausea	2 (58)
Pharyngitis	1 (40)
Malaise	1 (38)
Diarrhea	1 (35)
Upper Respiratory Infection, NOS	1 (32)

Complaint Frequency 0.4–0.9%	
Rhinitis	0.8 (26)
Dizziness	0.5 (16)
Sweating	0.5 (15)
Achiness	0.4 (14)
Myalgia	0.4 (13)
Sensation of Warmth, General	0.4 (13)
Illness, NOS	0.4 (12)

Complaint Frequency 0.1–0.3%	
Arthralgia, Other	0.3 (11)
Influenza, NOS	0.3 (10)
Abdominal Pains/Cramps	0.3 (10)
Lightheaded	0.3 (10)
Vomiting	0.3 (10)
Pruritis/Itching	0.3 (10)
Rash	0.3 (10)
Chills	0.2 (8)
Flush	0.2 (8)
Shoulder Pain	0.2 (7)
Cough	0.2 (7)
Back Pain	0.2 (6)
Neck Pain	0.2 (6)
Dyspepsia/Heartburn	0.2 (6)
Neck Stiffness	0.2 (5)
Earache	0.2 (5)
Lymphadenopathy, Cervical	0.2 (5)
Lymphadenopathy, General	0.1 (4)
Arthralgia, Monoarticular	0.1 (4)
Diminished Appetite	0.1 (4)
Paresthesia	0.1 (4)
Urticaria/Hives	0.1 (4)
Clay Colored Stools	0.1 (3)
Insomnia/Disturbed Sleep	0.1 (3)
Sinusitis	0.1 (3)
Laryngitis	0.1 (3)

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835, 838, 839, 860, 869, 883, 889

Table 11

Frequency of Systemic Complaints by Body System Occurring Within Five Days Among Health Care Personnel and Other Healthy Adults Following 3255 Injections of Yeast Recombinant Hepatitis B Vaccine

Number of Vaccine Recipients: 1252

Body System/Complaint	Frequency as % (Number)
Whole Body/General	10 (315)
Fatigue/Weakness	4 (138)
Headache	4 (135)
Malaise	1 (38)
Sweating	0.5 (15)
Achiness	0.4 (14)
Sensation of Warmth, General	0.4 (13)
Illness, NOS	0.4 (12)
Lightheaded	0.3 (10)
Chills	0.2 (8)
Flush	0.2 (8)
Digestive	3 (103)
Nausea	2 (58)
Diarrhea	1 (35)
Abdominal Pains/ Cramps	0.3 (10)
Vomiting	0.3 (10)
Dyspepsia/ Heartburn	0.2 (6)
Diminished Appetite	0.1 (4)
Clay-colored Stools	0.1 (3)
Respiratory	3 (87)
Pharyngitis	1 (40)
Upper Respiratory Infection, NOS	1 (32)
Rhinitis	0.8 (26)
Cough	0.2 (7)
Sinusitis	0.1 (3)
Laryngitis	0.1 (3)
Musculoskeletal	2 (52)
Myalgia	0.4 (13)
Arthralgia, Other	0.3 (11)
Shoulder Pain	0.2 (7)
Back Pain	0.2 (6)
Neck Pain	0.2 (6)
Neck Stiffness	0.2 (5)
Arthralgia, Monoarticular	0.1 (4)
Nervous System	0.8 (27)
Dizziness	0.5 (16)
Paresthesias	0.1 (4)
Integumentary	0.7 (24)
Pruritis/Itching	0.3 (10)
Rash	0.3 (10)
Urticaria/Hives	0.1 (4)
Infections Syndromes	0.4 (12)
Influenza, NOS	0.3 (10)
Organs of Special Sense	0.3 (11)
Earache	0.2 (5)
Hemic/Lymphatic	0.2 (8)
Lymphadenopathy, Cervical	0.2 (5)
Lymphadenopathy, General	0.1 (4)
Urogenital	0.2 (6)
Psychiatric/Behavioral	0.2 (6)
Insomnia/Disturbed Sleep	0.1 (3)
Cardiovascular	0.2 (5)

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835, 838, 839, 860, 869, 883, 889

31021-1-12/20/85

Table 12

Percentages of Health Care Personnel and Other Healthy Adults with Elevated Temperatures During a Five-Day Period Following 3097 Injections of Yeast Recombinant Hepatitis B Vaccine*

(Oral) Temperature	First Injection	Second Injection	Third Injection	All Injections
≥100°F	4 (45/1217)	3 (28/1111)	4 (27/769)	3 (100/3097)
≥101°F	0.7 (9/1217)	0.5 (6/1111)	1 (7/769)	0.7 (22/3097)
≥102°F	0.1 (1/1217)	0.1 (1/1111)	0.4 (3/769)	0.2 (5/3097)
≥103°F	0 (0/1217)	0.1 (1/1111)	0 (0/769)	0.03 (1/3097)

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835 838, 839, 860, 869, 883, 889

* Fever, temperature not recorded, was reported in 14 cases.

3118I/1
1/2/86

Table 13

Age and Sex Characteristics of Health Care Personnel
Receiving Injections of Yeast Recombinant Hepatitis B Vaccine
from Five Consistency Lots in Study 880

Lot Number	Age (Years)		Sex (%)	
	Mean	S.D.	Male	Female
C-L215	25.6	3.6	54.2	45.8
C-L216	30.8	6.9	58.1	41.9
C-L217	32.0	10.0	56.6	43.4
C-L219	30.6	9.5	54.4	45.6
C-L220	25.6	4.3	74.4	25.6

Table 14

Antibody Responses Among Health Care Personnel Receiving 10 mcg Doses of
Yeast Recombinant Hepatitis B Vaccine (5 Consistency Lots) at 0, 1, and 6 Months in Study 880

	All Lots Combined					Lot C-L215					Lot C-L216				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Months)	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10
1	25 (56/227)	11 (26/227)	0.9	12.5	49.8	24 (11/46)	13 (64/64)	0.9	12.5	33.0	20 (8/41)	7 (3/41)	0.7	9.3	39.6
3	84 (144/171)	72 (123/171)	23.9	49.7	73.2	86 (32/37)	73 (27/37)	31.9	58.7	95.4	86 (25/29)	76 (22/29)	18.7	34.2	45.7
6	92 (143/156)	79 (124/156)	32.0	45.5	62.8	86 (31/36)	64 (23/36)	23.0	36.8	71.8	100 (22/22)	100 (22/22)	51.5	51.5	51.5
7/8	98 (136/139)	96 (133/139)	627.6	742.9	830.8	100 (33/33)	94 (31/33)	591.2	591.2	799.3	100 (24/24)	100 (24/24)	1187.6	1187.6	1187.6

	Lot C-L217					Lot C-L219					Lot C-L220				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Months)	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10
1	19 (10/52)	8 (4/52)	0.8	14.5	91.2	22 (10/45)	9 (4/45)	0.7	10.7	36.7	40 (17/43)	21 (9/43)	1.7	14.6	63.8
3	84 (32/38)	68 (26/38)	23.6	48.7	77.4	66 (21/32)	59 (19/32)	9.5	51.7	63.9	97 (34/35)	83 (29/35)	50.5	55.6	84.8
6	87 (26/30)	77 (23/30)	27.5	53.5	69.7	90 (27/30)	73 (22/30)	29.7	48.0	77.2	97 (37/38)	89 (34/38)	39.5	43.2	53.1
7/8	96 (22/23)	91 (21/23)	345.8	476.4	593.6	92 (23/25)	92 (23/25)	332.6	612.6	612.0	100 (34/34)	100 (34/34)	1012.0	1012.0	1012.0

001147

wva/31271/4
1/28/86

Table 15

Percent (Proportion) of Health Care Personnel With Clinical Complaints During a 5-Day Period Following Vaccination With Yeast Recombinant Hepatitis B Vaccine From Five Consistency Lots in Study 880*

Lot #	Type of Complaint	First Injection	Second Injection	Third Injection	Total
C-L215	Local (Injection Site)	8 (4/48)	12 (6/46)	4 (1/24)	9 (11/118)
	Systemic	2 (1/48)	2 (1/46)	4 (1/24)	3 (3/118)
	Any Local or Systemic	10 (5/48)	13 (6/46)	4 (1/24)	10 (12/118)
	Temperature ≥100°F (Oral)	2 (1/45)	0 (0/38)	0 (0/4)	1 (1/97)
C-L216	Local (Injection Site)	9 (4/43)	5 (2/43)	9 (1/11)	7 (7/97)
	Systemic	19 (8/43)	2 (1/43)	0 (0/11)	9 (9/97)
	Any Local or Systemic	21 (9/43)	5 (2/43)	9 (1/11)	12 (12/97)
	Temperature ≥100°F (Oral)	0 (0/35)	0 (0/25)	0 (0/6)	0 (0/66)
C-L217	Local (Injection Site)	11 (6/53)	4 (2/53)	0 (0/17)	7 (8/123)
	Systemic	13 (7/53)	4 (2/53)	0 (0/17)	7 (9/123)
	Any Local or Systemic	23 (12/53)	4 (2/53)	0 (0/17)	11 (14/123)
	Temperature ≥100°F (Oral)	3 (1/38)	3 (1/32)	0 (0/5)	3 (2/75)
C-L219	Local (Injection Site)	17 (8/46)	9 (4/46)	6 (1/17)	12 (13/109)
	Systemic	9 (4/46)	0 (0/46)	6 (1/17)	5 (5/109)
	Any Local or Systemic	22 (10/46)	9 (4/46)	12 (2/17)	15 (16/109)
	Temperature ≥100°F (Oral)	0 (0/38)	0 (0/26)	0 (0/12)	0 (0/76)
C-L220	Local (Injection Site)	0 (0/43)	9 (4/43)	7 (2/30)	5 (6/116)
	Systemic	7 (3/43)	5 (2/43)	3 (1/30)	5 (6/116)
	Any Local or Systemic	7 (3/43)	14 (6/43)	10 (3/30)	10 (12/116)
	Temperature ≥100°F (Oral)	0 (0/42)	0 (0/40)	0 (0/20)	0 (0/102)

*A complaint or an elevated temperature is recorded here if it occurred during any portion of a 5-day follow-up period.

APPENDIX 1

STATISTICAL METHODS

All tests of significance were two-sided at 0.05 significance level.

A. Clinical Complaints

1. The incidence of the various clinical complaints in dialysis patients on the three dose regimen, healthy teenagers and healthy children were evaluated as a function of log dose level using the Mantel-Haenszel Test[1] for trend.

2. All other differences in the incidences of the various clinical complaints in dialysis patients due to dose level or regimen and in health care personnel receiving vaccine from consistency lots were assessed by the Likelihood Ratio Chi-Square.

B. Seroconversion Rates

1. The effect of dose level on seroconversion rates in healthy adults, healthy teenagers and healthy children was analyzed over studies using the Mantel Haenszel Test[1] for trend.

2. Differences in seroconversion rates in healthy adults due to age or sex were evaluated over studies using the Mantel Haenszel Test[1] for heterogeneity.

3. Differences in seroconversion rates due to age in healthy children, dose level in dialysis patients, and vaccine lot in health care personnel were assessed by the Likelihood Ratio Chi-Square.

C. Level of Response (Titers)

The effect of age, sex, lot (consistency lots only in Study 880), or dose level (all other studies) in health care personnel and other healthy adults, of dose level in healthy teenagers, of dose level and age in healthy children, and of dose level and regimen in dialysis patients were analyzed by fitting these variables to a regression model. Subjects who were negative for antibody to hepatitis B surface antigen were assigned a titer of 0.3 mIU/ml in the analysis.

REFERENCE

1. Tarone RE, Ware J: On Distribution-Free Tests for Equality of Survival Distributions. Biometrika 64: 156-160, 1977.

HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS

Study 779 - West Point, PA - Dr. R. Bishop

Healthy adults are receiving 10 mcg injections of vaccine from one of two lots at 0, 1, and 6 months.

Twenty-six adults received two injections of vaccine from lot C-K444, and 21 of these received the third injections. Seroconversion for anti-HBs (S/N $\geq$ 2.1) at 7/8 months was 100% (17/17). Ninety-four percent (16/17) developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at 7/8 months for all vaccinees was 808.5 mIU/ml and 1124.9 for responders (mIU/ml $\geq$10). Subjects continue to be followed for persistence of antibody.

One person who received vaccine from lot C-K444 developed a frontal headache and erythematous papular rash several hours after the third injection was administered. This individual has a history of multiple allergies. The reaction was considered vaccine-related.

Refer to the summary on immune affinity vaccine for responses of subjects vaccinated in this study using vaccine produced by that method.

Study 792 - Boston, MA - Dr. J. Dienstag

Initially seronegative health care personnel are receiving 10 mcg injections of vaccine from one of two lots at 0, 1, and 6 months.

Thirty-five subjects have received two injections of vaccine from lot C-K564 and 32 of these have received the third injection. Seroconversion for anti-HBs (S/N $\geq$ 2.1) was 96% (27/28) at 9 months. Ninety-three percent (26/28) of the participants developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at 7/8 months for all vaccinees was 531.1 mIU/ml and 826.3 for responders (mIU/ml $\geq$10).

There have been no reports of serious or alarming reactions attributable to vaccine. Subjects continue to be followed for persistence of antibody.

Refer to the summary on immune affinity vaccine for responses of subjects vaccinated in this study using vaccine produced by that method.

Study 794 - Bethesda, MD - Dr. H. Alter

Health care personnel and nonresponders to plasma-derived vaccine, who are negative for hepatitis B serologic markers, are enrolled in study 794. Health care workers receive 5 mcg or 10 mcg injections and nonresponders receive 10 mcg injections of yeast recombinant vaccine from lot C-K444 vaccine at 0, 1, and 6 months. Forty-one health care workers received the initial 10 mcg injection of vaccine and forty of these participants have also received the

Study 794 - Bethesda, MD - Dr. H. Alter (Contd)

second and third injections. At seven months, 97% (35/36) of the vaccinees seroconverted for anti-HBs (S/N ≥2.1). Ninety-four percent (34/36) developed levels of anti-HBs ≥10 S/N. The GMT at seven months for all vaccinees was 160.8 S/N and 209.3 for responders (S/N ≥10).

Thirty subjects received two 5 mcg injections of vaccine. Twenty-eight of these participants received the third injection. Eighty-four percent (21/25) of the vaccinees seroconverted (S/N ≥2.1) for anti-HBs at seven months. Seventy-six percent (19/25) developed anti-HBs titers ≥10 S/N at that time. The GMT for all vaccinees was 54.0 S/N and 152.9 for responders (S/N ≥10).

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 795 - West Germany - Dr. F. Deinhardt

The study population consists of health care personnel and other healthy adults who are negative for hepatitis B serologic markers. Participants are scheduled to receive 10 mcg injections of vaccine at 0, 1, and 6 months from one of 3 vaccine lots.

One hundred forty-eight persons have received vaccine from lot C-K564. One hundred twenty-six of these participants have received all three injections. Seroconversion for anti-HBs (S/N ≥2.1) at 7/8 months was 100% (76/76). All of these vaccinees developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months for all vaccinees was 2143.1 mIU/ml.

Ninety-seven persons have received lot C-L215 vaccine. Ninety-four of those participants have received all three injections. At 7/8 months, 99% (79/80) of the vaccinees seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 7/8 months for all vaccinees was 2436.1 mIU/ml and 2655.2 for responders (mIU/ml ≥10).

No serious or alarming reactions attributable to vaccine have been reported. The study continues in progress.

Refer to the summary on immune affinity vaccine for responses of subjects vaccinated in this study using vaccine produced by that method.

Study 798 - Houston, TX - Dr. F. B. Hollinger

The study population consists of male paramedical personnel who are initially negative for hepatitis B serologic markers. Participants are assigned to receive vaccine at one of three dose levels (5 mcg, 10 mcg or 20 mcg) from lot C-K446 at 0, 1, and 6 months.

Thirty-six persons have received the initial 20 mcg injection of vaccine, and all but one of these have received the second and third injections. Sero-

Study 798 - Houston, TX - Dr. F. B. Hollinger (Cont.)

conversion for anti-HBs at 7/8 months (S/N ≥2.1) was 100% (35/35). Ninety-one percent (32/35) of the vaccine recipients had an anti-HBs titer ≥10 mIU/ml with a GMT for the responders of 1193.3 mIU/ml.

Thirty-seven participants received three 10 mcg injections of vaccine. Seroconversion (S/N ≥ 2.1) at 7/8 months was 97% (34/35). Ninety-seven percent (35/36) of the vaccine recipients had anti-HBs titers of mIU/ml ≥ 10 with a GMT for responders of 601.6 mIU/ml.

Thirty-six persons have received three 5 mcg injections of vaccine. Ninety-seven percent (35/36) of the vaccine recipients seroconverted for anti-HBs (S/N ≥ 2.1) at 7/8 months. Eighty-three percent (30/36) of the participants developed titers of mIU/ml ≥ 10. The GMT at 7/8 months was 72.9 mIU/ml for all vaccinees and 136.9 for responders (mIU/ml ≥10). Subjects continue to be followed for persistence of antibody.

No serious or alarming adverse experiences attributable to vaccine have been reported. Subjects continue to be followed for persistence of antibody.

Study 801 - Houston, TX - Dr. E. Septimus

Initially seronegative health care workers in this study are receiving 10 mcg injections of vaccine from lot C-K444 at 0, 1, and 6 months.

Twenty-two subjects have received the first injection of vaccine and twenty-one of these have also received the second and third injections. Seroconversion for anti-HBs (S/N ≥2.1) at 7 to 8 months was 100% (21/21). All of these participants developed protective levels (mIU/ml ≥10) of anti-HBs at that time. The GMT at 7/8 months for all vaccinees was 280.8 mIU/ml. Subjects continue to be followed for persistence of antibody.

One subject (26-year old female) became aware that she was pregnant after receiving one injection of vaccine. The vaccine was administered approximately one month after conception. She experienced a spontaneous abortion at 18 weeks after fetal death in utero. No microscopic examination was completed on the fetus. The subject previously delivered two healthy infants without complication of pregnancy. She had no known allergies. The experience was considered possibly related to vaccine.

Study 803 - Denver, CO - Dr. G. Judson

Health care personnel, negative for hepatitis B serologic markers, are receiving 10 mcg injections of vaccine from lot C-K444 at 0, 1, and 6 months.

Study 803 - Denver, CO - Dr. G. Judson (Cont.)

Thirty-one persons have received the initial injection. Thirty of these have also received the second and third injections. At 7/8 months, 85% (22/26) of the participants seroconverted (S/N ≥2.1) and developed protective levels (mIU/ml ≥10) of anti-HBs. The GMT at that time for all vaccinees was 584.6 mIU/ml and 2136.0 for responders (mIU/ml ≥10).

No serious or alarming reactions attributable to vaccine have been reported. Subjects continue to be followed for persistence of antibody.

Study 807 - The Netherlands - Dr. S. Schalm

Health care personnel who are negative for hepatitis B virus serologic markers, are receiving 10 mcg injections of yeast recombinant hepatitis B vaccine lot C-K444 or 20 mcg injections of licensed plasma-derived vaccine lot 1510J (HEPTAVAX-B) at 0, 1, and 6 months.

Thirty-one participants have received three 10 mcg injections of yeast recombinant vaccine. Seroconversion for anti-HBs (S/N ≥ 2.1 and mIU/ml ≥ 10) at 7/8 months was 100% (31/31) with a GMT of 885.1 mIU/ml for all vaccinees.

Twenty-five subjects have received three 20 mcg injections of licensed plasma-derived vaccine. At 7/8 months, seroconversion for anti-HBs (S/N ≥ 2.1 and mIU/ml ≥ 10) was 100% (22/22) with a GMT of 6164.4 mIU/ml for all vaccinees.

No study participant reported a serious or alarming reaction attributable to vaccine. Serologic testing continues in progress.

Study 808 - Tucson, Arizona - Dr. R. Sampliner

Health care personnel who are negative for hepatitis B virus serologic markers, are receiving 10 mcg injections of vaccine from lot C-K444 at 0, 1, and 6 months.

Twenty-five subjects have received three injections of vaccine. At 7/8 months, 96% (22/23) of the participants seroconverted (S/N ≥2.1) and developed protective levels (mIU/ml ≥10) of anti-HBs. The GMT at that time for all vaccinees was 1711.5 mIU/ml and 2535.7 for responders (mIU/ml ≥10).

The vaccine has been well tolerated with no reports of serious adverse events related to vaccine. The study continues in progress.

Study 809 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

In study 809 healthy adults and healthy children (1-11 years), initially negative for hepatitis B serologic markers, are scheduled to receive vaccine at 0, 1, and 6 months.

Study 809 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr (Cont.)

Eighteen healthy adults have received the initial 10 mcg injection of vaccine from lot C-K444. All but one of these participants received the second and third injections. At 7/8 months, 100% (11/11) of the vaccinees seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at that time for all vaccinees was 955.7 mIU/ml.

There have no reports of alarming or serious adverse experiences attributable to vaccine. Subjects continue to be followed up for persistence of anti-HBs. Refer to the summary on infants and children for responses of other subjects vaccinated in this study.

Study 811 - Switzerland - Dr. P. Grob

Health care personnel and predialysis patients, initially negative for hepatitis B virus serologic markers, are enrolled in study 811. Health care personnel receive 10 mcg injections of vaccine lot C-K446 at 0, 1, and 6 months.

Eleven health care personnel have received an initial 10 mcg injection of yeast recombinant vaccine. Eight of these have received the second and third injections. At 7/8 months, 86% (6/7) of the participants seroconverted for anti-HBs (S/N ≥2.1). Eighty-three percent (5/6) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 7/8 months for all vaccinees was 275.1 mIU/ml and 1076.6 mIU/ml for five of the responders. Among subjects with serology data available at 12 months, 83% (5/6) were positive for anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 44.1 mIU/ml.

There have been no reports of serious or alarming reactions attributable to vaccine. Subjects continue to be followed for persistence of antibody. Refer to the summary on dialysis and predialysis patients for responses of other subjects vaccinated in this study.

Study 813 - New York, NY - Dr. M. Davidson

The study enrolls health care personnel, some of whom are seronegative for hepatitis B virus markers and have never been vaccinated, and others (preimmune) who have previously been vaccinated with either yeast recombinant hepatitis B vaccine or plasma-derived hepatitis B vaccine (HEPTAVAX-B). There are five groups of initially seronegative adults, not randomized by age, who are scheduled to receive vaccine from lots C-K444 or C-L220 at 0, 1, and 6 months. These participants receive either 2.5 mcg, 5 mcg or 10 mcg injections. There is an additional group of seronegative adults, ≥40 years of age, who are scheduled to receive either 10 mcg injections of lot C-M126 or 20 mcg injections of lot C-M125 at 0, 1, and 6 months.

Sixty-one health care personnel have received two 2.5 mcg injections of vaccine and sixty of these have received the third injection. At 7/8 months,

Study 813 - New York, NY - Dr. M. Davidson (Cont.)

100% (40/40) of the subjects seroconverted for anti-HBs (S/N ≥2.1) and 97% (39/40) developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees at that time was 291.5 mIU/ml and 321.5 for responders (mIU/ml ≥10).

One-hundred-twenty-one seronegative adults have received one 5 mcg injection of vaccine. One-hundred-twenty and 115 of these have received the second and third injections, respectively. Ninety-eight percent (42/43) of the participants seroconverted for anti-HBs (S/N ≥2.1) at 7/8 months. Ninety-five percent (41/43) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at 7/8 months was 523.8 mIU/ml and 693.9 for responders (mIU/ml ≥10).

In the 10 mcg dose group, 131 health care personnel have received the first injection of vaccine. One-hundred-twenty-four and 109 of these have received the second and third injections, respectively. At 7/8 months, 100% (36/36) of the vaccinees seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 1509.3 mIU/ml.

Seven adults have received one 20 mcg injection of vaccine and four of these have received the second injection. Serologic data are not yet available for these participants.

To date, recipients of 10 mcg injections have developed higher anti-HBs titers than those receiving 2.5 mcg or 5 mcg injections of vaccine.

A 23 year-old female developed pruritic hives on her back and extremities after the first and second 10 mcg injections of lot C-L220 vaccine. All symptoms resolved within four days after each injection. The reaction is considered vaccine related. The subject has a history of allergy to contrast dye. She received the third injection of vaccine without development of hives.

No serious adverse experiences attributable to vaccine have been reported. The study continues in progress. Refer to the summary on preimmune adults for data regarding other subjects vaccinated in this study.

Study 815 - Holland - Dr. S. Schalm

The study population consists of institutionalized mentally retarded individuals and health care personnel who are seronegative for hepatitis B markers. The health care personnel will serve as controls in this study. Participants will be paired (mentally retarded and controls) and randomized to receive either 10 mcg or 20 mcg injections of yeast recombinant vaccine or 20 mcg injections of plasma-derived vaccine. All injections will be administered at 0, 1, and 6 months.

Serologic and clinical follow-up data for the health care personnel are not presently available. No serious or alarming adverse reactions attributable to vaccine have been reported. Vaccination and follow-up of all participants continues in progress.

Study 816 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

The population consists of three groups of initially seronegative adults: dialysis patients, dialysis patients who were previously vaccinated with plasma-derived hepatitis B vaccine and failed to respond, and health care personnel. All participants are receiving vaccine from lot C-K446 at 0, 1, and 6 months. Dialysis patients receive 40 mcg injections of vaccine, while health care personnel are administered 10 mcg injections.

Eight health care personnel have received two 10 mcg injections and 6 of these have received the third injection. At 7/8 months, anti-HBs (S/N $\geq$ 2.1 or mIU/ml $\geq$ 10) was present in 80% (4/5) of the subjects tested. The GMT for all vaccinees and responders (mIU/ml $\geq$10) at 7/8 months was 37.9 mIU/ml and 127.2 mIU/ml, respectively.

Refer to the summary on dialysis/predialysis patients for responses of other subjects vaccinated in this study.

Study 834 - Italy - Dr. M. Rizzetto

Initially seronegative healthy adults are receiving 10 mcg (1.0 ml) injections of vaccine lot C-K564 at 0, 1, and 6 months.

Twenty-five subjects have been enrolled in the study and have received one injection of vaccine. Serologic and clinical follow-up data are not presently available.

There has been one report of an adverse experience considered possibly related to vaccine. A 40 year-old female developed a few ecchymotic flat lesions on the lateral aspect of her breast, bilaterally, 4 days after the first injection of vaccine. Over the following 2 days the lesions increased. Vomiting occurred on the third day. All symptoms disappeared over the next 36 hours, and the subject has remained well. There was no fever, and WBC, Hgb, platelets, and coagulation profile were normal. The patient has no history of allergies to exogenous substances. No further vaccine was administered to this patient.

The study continues in progress.

Study 835 - Chapel Hill, NC - Dr. S. Lemon

Health care personnel, who are negative for hepatitis B virus serologic markers, are receiving 10 mcg injections of vaccine from lot C-K564 at 0, 1, and 6 months.

Twenty-nine subjects have received the first two injections of vaccine, and 23 of these have received the third injection. At 7/9 months, 100% (19/19) of the participants seroconverted (S/N 2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT at that time for all vaccinees was 560.9 mIU/ml.

Study participants have not reported any alarming or serious adverse events related to vaccine. The study continues in progress.

Study 838 - West Germany - Dr. F. Deinhardt

Populations vaccinated in this study include health care personnel and adult dialysis and predialysis patients. Health care personnel are receiving 10 mcg injections of vaccine from lot C-K733 at 0, 1, and 6 months.

Twenty-two health care personnel have received the first 10 mcg injection. Nineteen and 17 of these have received the second and third injections, respectively. At 7/8 months, 94% (16/17) of the participants seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT at that time for all vaccinees and responders was 284.8 mIU/ml and 437.1 mIU/ml, respectively.

There have been no reports of alarming or serious adverse experiences attributable to vaccine. The study continues in progress. Refer to the summary on dialysis and predialysis patients for responses of the other subjects vaccinated in this study.

Study 841 - London, UK - Dr. A. Zuckerman and Dr. I. Murray-Lyon

Initially seronegative health care personnel are receiving 10 mcg (1.0 ml) injections of vaccine lot C-K563 at 0, 1, and 6 months.

Serologic and clinical follow-up data are not presently available. No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress.

Study 859 - Belgium - Dr. N. Clumeck

Health care personnel are receiving 10 mcg injections of yeast recombinant vaccine from lot C-K563 at 0, 1, and 6 months.

Thirty-one persons have received the first two injections. One month after the second injection, 80% (24/30) of the vaccine recipients were positive for anti-HBs (S/N $\geq$ 2.1). Fifty-three percent (16/30) of the subjects developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at three months for all vaccinees was 11.8 mIU/ml and 60.0 for responders (mIU/ml $\geq$10).

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 860 - Hamburg, West Germany - Dr. R. Laufs

Health care personnel, initially seronegative for hepatitis B serologic markers, are receiving 10 mcg injections of vaccine from lot C-K564 at 0, 1, and 6 months.

Sixty persons have received the initial injection, and 59 of these have received the second and third injections. At 7/8 months, 100% (56/56) of the participants seroconverted (S/N $\geq$2.1) and developed protective levels (mIU/ml $\geq$10) of anti-HBs. The GMT for all vaccinees was 2421.1 mIU/ml.

Study 860 - Hamburg, West Germany - Dr. R. Laufs (Cont.)

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 869 - Toronto, Ontario - Dr. J. Rankin

The study population consists of seronegative health care personnel who are receiving 10 mcg injections of vaccine from lot C-L217 at 0, 1, and 6 months.

Seventy-one participants have received the first two injections of vaccine. At one month, 32% (22/68) of the subjects seroconverted (S/N $\geq$2.1) for anti-HBs. Twelve percent (8/68) developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at one month for all vaccinees was 1.2 mIU/ml and 44.8 for responders (mIU/ml $\geq$10).

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 877 - Republic of Singapore - Prof. Oon Chong Jin

Healthy adults, who are negative for hepatitis B virus serologic markers, are receiving 10 mcg injections of vaccine from lot C-K564 at 0, 1, and 6 months.

Thirty-one subjects have received all three injections of vaccine. At 7/8 months, 97% (28/29) of the participants seroconverted (S/N $\geq$2.1) and developed protective levels (mIU/ml $\geq$10) of anti-HBs. The GMT at that time was 508.9 mIU/ml for all vaccinees and 663.7 for responders (mIU/ml $\geq$10).

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 880 - Valhalla, NY - Dr. G. Wormser

Initially seronegative health care personnel are receiving 10 mcg injections (0.5 ml) of vaccine at 0, 1, and 6 months from one of the following consistency lots: C-L215, C-L216, C-L217, C-L219, C-L220.

Forty-eight subjects have received two injections of vaccine lot C-L215 and forty of these have received the third injection. At 7/8 months, 100% (29/29) seroconverted (S/N $\geq$2.1) for anti-HBs and 93% (27/29) developed protective levels of antibody (mIU/ml $\geq$10). The GMT for all vaccinees at that time was 602.9 mIU/ml and 853.6 for responders (mIU/ml $\geq$10).

Forty-three subjects have received two injections of vaccine lot C-L216 and eighteen of these have received the third injection. At 7/8 months, 100% (10/10) seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees was 986.9 mIU/ml.

Study 880 - Valhalla, NY - Dr. G. Wormser (Cont.)

Fifty-three participants have received two injections of vaccine lot C-L217. Twenty-six of these were administered the third injection. Ninety-one percent (10/11) seroconverted for anti-HBs (S/N ≥2.1) at 7/8 months. Eighty-two percent (9/11) developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees at 7/8 months was 331.1 mIU/ml and 1157.1 for responders (mIU/ml ≥10).

Forty-six adults have received two injections of vaccine lot C-L219 and twenty-one of these have received the third injection. At 7/8 months, 100% (11/11) seroconverted (S/N ≥2.1) and developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees at that time was 583.4 mIU/ml.

Forty-three participants have received two injections of vaccine lot C-L220. Thirty-eight of these have been administered the third injection. At 7/8 months, 100% (29/29) seroconverted for anti-HBs (S/N ≥ 2.1) and developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees at that time was 1009.9 mIU/ml.

No serious or alarming adverse experiences related to vaccine have been reported. Clinical and serologic follow-up continues in progress.

Study 882 - Tokyo, Japan - Dr. S. Iino

Healthy adults, initially negative for hepatitis B serologic markers, are receiving 10 mcg injections of vaccine from lot C-L215 at 0, 1, and 6 months.

Forty adults have received all three injections of vaccine. At 7 months, 100% (40/40) of the vaccine recipients seroconverted for anti-HBs (S/N ≥ 2.1).

No serious or alarming reactions related to vaccine have been reported. This study continues in progress.

Study 883 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

Initially seronegative health care personnel are receiving 5 mcg or 10 mcg injections of vaccine from lot C-L220 at 0, 1, and 6 months.

Twenty-five subjects have received two 5 mcg injections of vaccine, and 24 of these have received the third injection. At 7/8 months, 100% (20/20) of the participants seroconverted (S/N ≥2.1) for anti-HBs. Ninety-five percent (19/20) developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months for all vaccinees was 215.3 mIU/ml and 259.0 for responders (mIU/ml ≥10).

Twenty-eight subjects have received two 10 mcg injections of vaccine, and 27 of these have received the third injection. One hundred percent (24/24) of the participants seroconverted (S/N ≥ 2.1) for anti-HBs at 7/8 months.

Study 883 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr (Cont.)

Ninety-six percent (23/24) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 7/8 months for all vaccinees was 863.2 mIU/ml and 1084.9 for responders (mIU/ml ≥10).

There have been no reports of serious or alarming reactions to vaccine. The study continues in progress.

Study 885 - Tampa, FL - Dr. A. Leibowitz

Initially seronegative healthy adults are receiving 10 mcg doses of vaccine at 0, 1, and 6 months from one of the following consistency lots: C-L215, C-L216, C-L217, C-L219, C-L220.

One hundred fifty persons have received the first injection of vaccine. One hundred of these participants have received the second injection. No serologic results are currently available. There have been no reports of serious or alarming adverse experiences attributable to vaccine. The study continues in progress.

Study 889 - St. Louis, MO - Dr. R. Perrillo

The study population consists of two initially seronegative groups: institutionalized mentally retarded individuals and health care personnel. Mentally retarded individuals receive either 10 mcg injections or 20 mcg injections of vaccine. Health care personnel receive 10 mcg injections. All participants are receiving vaccine from lot C-K937 at 0, 1, and 6 months.

Eighty-eight health care personnel have received the first injection of vaccine and 82 of these have received the second injection. At one month, 17% (14/82) of the participants seroconverted (S/N ≥2.1) for anti-HBs with a GMT for all vaccinees of 0.5 mIU/ml.

One female subject developed facial urticaria approximately one hour after receiving the first injection of vaccine. All symptoms subsided within 12 hours after onset. The reaction was considered probably related to vaccine. The subject received Benadryl prior to the second and third injections and had no post-vaccination reactions.

There were no serious adverse experiences attributable to vaccine. The study continues in progress.

Study 894 - Baltimore, MS - Dr. B. F. Polk

The study population consists of homosexual males who are negative for all hepatitis B markers and have not previously received any hepatitis B vaccine. Participants are randomized to receive either 20 mcg infections of plasma-derived vaccine (lot C-M252) or 10 mcg injections of yeast recombinant vaccine (lot C-K563) at 0, 1, and 6 months.

Study 894 - Baltimore, MS - Dr. B. F. Polk (Cont.)

Eighty-seven participants have received one 10 mcg injection of yeast recombinant vaccine and sixty-three of these have received the second injection. One subject only has received the third injection. Serologic data are not presently available.

Eighty-eight participants have received one 20 mcg injection of plasma-derived vaccine and seventy of these have received the second injection. None have yet received the third injection. Serologic data are not presently available.

No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress.

Study 898 - West Point, PA - Dr. R. Bishop

Initially seronegative healthy adults, 40 years of age or older, are receiving either 10 mcg (1.0 ml) injections of vaccine lot C-M126 or 20 mcg (1.0 ml) injections of vaccine lot C-M125. All injections are administered at 0, 1, and 6 months.

To date, one participant has received the initial 10 mcg injection of vaccine, while two subjects have received single 20 mcg injections of vaccine. Post-vaccination serologic results are not presently available. No serious or alarming adverse reactions attributable to vaccine have been reported. The study continues in progress.

Study 900 - London, UK - Dr. A. Zuckerman and Dr. I. Murray-Lyon

Initially seronegative healthy male homosexuals are receiving 10 mcg (1.0 ml) injections of vaccine lot C-M126 at 0, 1, and 6 months.

Serologic and clinical follow-up data are currently not available. No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress.

Study 904 - Chicago, IL - Dr. H. A. Kessler

Initially seronegative healthy adults are scheduled to receive 10 mcg (0.5 ml) injections of vaccine from lot C-M178 or from lot C-L217 at 0, 1, and 6 months.

One hundred participants (50 for each lot) have received the first and second injections of vaccine. Serologic and clinical follow-up data are not presently available. No serious or alarming adverse experiences have been reported. The study continues in progress.

Study 907 - Tokyo and Osaka, Japan - Dr. S. Iino and Dr. T. Kuroki

Healthy adults are receiving 10 mcg (0.5 ml) intramuscular or subcutaneous injections of vaccine lot C-L215 at 0, 1, and 6 months.
Sixty-two participants have received the first and second injections of vaccine by the intramuscular route. Sixty-two subjects have also received the first and second injections of vaccine by the subcutaneous route. One hundred twenty-one of the participants (both routes) have received the third injection. At one month after the third injection, 98% (54/55) of the vaccinees who received intramuscular injections seroconverted for anti-HBs (S/N $\geq$2.1). Ninety-seven percent (56/58) of the participants who received subcutaneous injections seroconverted for anti-HBs (S/N $\geq$2.1) at that time.

There have been no reports of alarming or serious adverse reactions attributable to vaccine. The frequency of systemic complaints was higher in the subcutaneous injection group after the first injection and higher in the intramuscular injection group after the second injection. The frequency of injection site complaints are similar between both groups after the first and second injections. The study continues in progress.

Study 912 - Japan - Dr. T. Shimizu, Dr. M. Nakao, Dr. T. Marimo, et al

Health care personnel are receiving 10 mcg (0.5 ml) intramuscular or subcutaneous injections of vaccine lot C-L220 at 0, 1, and 6 months.

Eighty-seven participants have received the first injection of vaccine by the intramuscular route. Eighty-five of these subjects received the second injection. At one month after the second injection, 75% (56/75) of the subjects seroconverted for anti-HBs (S/N $\geq$2.1).

Eighty-eight participants have received two injections of vaccine by the subcutaneous route. At one month after the second injection, 59% (43/73) of the subjects seroconverted for anti-HBs (S/N $\geq$2.1).

There have been no reports of alarming or serious adverse experiences attributable to vaccine. The frequencies of injection site and systemic complaints, after the first and second injections, were high for vaccinees in the subcutaneous injection group. The study continues in progress.

Study 914 - Bruxelles, Belgium - Dr. A. Burette and Dr. M. Deltenre

Initially seronegative health care personnel are scheduled to receive 10 mcg (1.0 ml) injections of vaccine lot C-M126 at 0, 1, and 6 months.

Twenty participants have received the first and second injections of vaccine. Serologic and clinical follow-up data are currently not available. There have been no reports of alarming or serious adverse experiences attributable to vaccine. The study continues in progress.

STUDY 779

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 779
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among healthy adults who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 934/C-J625 (10 mcg HBsAg/ml) Lot 972/C-K444 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Robert P. Bishop, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486
SECONDARY INVESTIGATORS:	E. P. Avancena, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486 Joseph C. Rogers, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486 Joseph P. Romano, M.D. Health Services Merck Sharp and Dohme Rahway, NJ 07065
STUDY LOCATION:	Merck Sharp and Dohme West Point, PA 19486
DATE INITIATED:	July 13, 1983
DATE COMPLETED:	In progress

Study 779

STUDY PROCEDURE:

The study population consists of 41 healthy adults of either sex (excluding pregnant women) employed at Merck and Co., Inc., who were initially negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

Eligible participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine produced by either the immune affinity or the (b)(4) procedure at 0, 1 and 6 months. Study participants are asked to take and record their temperatures for five days after each injection of vaccine and to record any local or systemic complaints that they may experience.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before vaccination. Post-vaccination blood samples (10-15 ml) are obtained monthly for seven months and at 9, 12 and 24 months following the first injection of vaccine. Samples are assayed for HBsAg, anti-HBc, anti-HBs and ALT, and these may be assayed for antibody to antigens in yeast extract. Samples with an anti-HBs titer $\geq$ 25 mIU/ml units are tested to determine the relative proportions of anti-a and anti-d activity.

STUDY RESULTS:

HEALTHY ADULTS (b)(4) Vaccine):

10 mcg Lot 972/C-K444 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
26	26	21

Study 779

RESULTS (CONT.):

2. Serologic Results:

Serologic data are available for 17 participants at 7/8 months. Seroconversion (S/N ≥2.1) for anti-HBs at 7/8 months was 100% (17/17). Ninety-four percent (16/17) of the vaccinees developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months for all vaccinees was 808.5 mIU/ml and 1124.9 mIU/ml for responders with a titer of mIU/ml ≥10.

Among participants with serology data at 12 months, 100% (12/12) were positive for anti-HBs (mIU/ml ≥10). The GMT at that time was 459.4 mIU/ml (all vaccinees and responders by either cutoff).

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for at least 20 participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	23(6/26)	15(4/26)	10(2/20)
Systemic	4(1/26)	15(4/26)	5(1/20)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming reactions attributable to vaccine.

Study 779

RESULTS (CONT.):

Reactions reported to the OoBRR

A 41-year old female subject, with a history of multiple allergies, received her first and second injections of vaccine without clinical complaints.

Several hours after receiving her third injection of vaccine, she developed a frontal headache and an erythematous papular rash. One 4 mg chlortrimeton tablet was administered. The headache resolved within 24 hours and the rash faded over the next four days. The clinical investigator considered the reaction to be vaccine related.

PUBLICATIONS:

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoffnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984: 315-17.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
POPULATION : HEALTHY ADULTS
DOSE : 10 MCG
LOT : CK444
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	29%	(7/24)	17%	(4/24)	1.3	24.0	98.7
2 MONTHS	65%	(15/23)	52%	(12/23)	10.4	58.4	110.4
3 MONTHS	76%	(16/21)	62%	(13/21)	16.1	52.6	107.2
6 MONTHS	89%	(17/19)	53%	(10/19)	19.3	31.6	122.6
7/8 MONTHS	100%	(17/17)	94%	(16/17)	808.5	808.5	1124.9
9 MONTHS	100%	(11/11)	91%	(10/11)	767.2	767.2	1274.3
12 MONTHS	100%	(12/12)	100%	(12/12)	459.4	459.4	459.4

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 8779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	4 (15.4%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (23.1%)
SORENESS	4 (15.4%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (23.1%)
SYSTEMIC	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
WHOLE BODY/GENERAL	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
HEADACHE	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
PERSONS WITH COMPLAINTS	5 (19.2%)	2 (7.7%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (26.9%)
PERSONS WITH NO COMPLAINTS	21 (80.8%)	24 (92.3%)	25 (96.2%)	26 (100.0%)	26 (100.0%)	26 (100.0%)	19 (73.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK944
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.8%)	2 (7.7%)	3 (11.5%)	2 (7.7%)	1 (3.8%)	0 (0.0%)	4 (15.4%)
SORENESS	1 (3.8%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)
TENDERNESS	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
STIFFNESS/TIGHTNESS	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
SYSTEMIC	0 (0.0%)	3 (11.5%)	0 (0.0%)	1 (3.8%)	3 (11.5%)	3 (11.5%)	4 (15.4%)
WHOLE BODY/GENERAL	0 (0.0%)	2 (7.7%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	3 (11.5%)
SWEATING	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
HEADACHE	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	2 (7.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
CARDIOVASCULAR	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)

00170

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
HYPERTENSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)		1 (3.8%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)		2 (7.7%)
NAUSEA	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)		2 (7.7%)
PERSONS WITH COMPLAINTS	1 (3.8%)	5 (19.2%)	3 (11.5%)	3 (11.5%)	4 (15.4%)	3 (11.5%)		8 (30.8%)
PERSONS WITH NO COMPLAINTS	25 (96.2%)	21 (80.8%)	23 (88.5%)	23 (88.5%)	22 (84.6%)	23 (88.5%)		18 (69.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	2 (10.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (10.0%)
SORENESS	2 (10.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (10.0%)
SYSTEMIC	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)		1 (5.0%)
WHOLE BODY/GENERAL	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
EDEMA, FACE	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
HEADACHE	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)		1 (5.0%)
PRURITIS/ITCHING	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
RASH, NOS	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)		1 (5.0%)
PERSONS WITH COMPLAINTS	3 (15.0%)	3 (15.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)		3 (15.0%)
PERSONS WITH NO COMPLAINTS	17 (85.0%)	17 (85.0%)	19 (95.0%)	19 (95.0%)	19 (95.0%)	20 (100.0%)		17 (85.0%)
PERSONS WITH NO DATA	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)		1 (4.8%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (26 PATIENTS) - DOSE 1								DAYS POST VACCINATION	NUMBER WITH MAX TEMP
	0	1	2	3	4	5				
NORMAL	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (4.2%)	1 (4.2%)	1 (4.3%)				1 (3.8%)
< 99	24 (92.3%)	24 (92.3%)	24 (92.3%)	23 (95.8%)	22 (91.7%)	21 (91.3%)				21 (80.8%)
99 - 99.9	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (4.2%)	1 (4.3%)				4 (15.4%)
TEMPERATURE TAKEN	26 (100.0%)	26 (100.0%)	26 (100.0%)	24 (92.3%)	24 (92.3%)	23 (88.5%)				26 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)	2 (7.7%)	3 (11.5%)				0 (0.0%)

Table 3 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (26 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	2 (8.0%)	2 (8.0%)	2 (8.0%)	2 (8.7%)	2 (8.7%)	2 (9.1%)		2 (8.0%)
< 99	22 (88.0%)	20 (80.0%)	23 (92.0%)	21 (91.3%)	21 (91.3%)	20 (90.9%)		19 (76.0%)
99 - 99.9	1 (4.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (12.0%)
101 - 101.9	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
TEMPERATURE TAKEN	25 (96.2%)	25 (96.2%)	25 (96.2%)	23 (88.5%)	23 (88.5%)	22 (84.6%)		25 (96.2%)
TEMPERATURE NOT TAKEN	1 (3.8%)	1 (3.8%)	1 (3.8%)	3 (11.5%)	3 (11.5%)	4 (15.4%)		1 (3.8%)

Table 3 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (21 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	5 (25.0%)	5 (25.0%)	5 (25.0%)	5 (27.8%)	5 (29.4%)	5 (27.8%)			5 (25.0%)
< 99	14 (70.0%)	14 (70.0%)	15 (75.0%)	12 (66.7%)	12 (70.6%)	13 (72.2%)			14 (70.0%)
99 - 99.9	1 (5.0%)	1 (5.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)			1 (5.0%)
TEMPERATURE TAKEN	20 (95.2%)	20 (95.2%)	20 (95.2%)	18 (85.7%)	17 (81.0%)	18 (85.7%)			20 (95.2%)
TEMPERATURE NOT TAKEN	1 (4.8%)	1 (4.8%)	1 (4.8%)	3 (14.3%)	4 (19.0%)	3 (14.3%)			1 (4.8%)

Edward M. Scolnick, Arlene A. McLean,
David J. West, Jules L. Dienstag,
Eloise Watkins, Friedrich Deinhardt and Wolfgang Jilg

23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

VIRAL HEPATITIS and LIVER DISEASE
ISBN 0-8089-1678-5

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

Reprinted from the Journal of the American Medical Association
June 1, 1984, Volume 251

Original Contributions

Clinical Evaluation in Healthy Adults of a Hepatitis B Vaccine Made by Recombinant DNA

Edward M. Scolnick, MD; Arlene A. McLean, PhD; David J. West, PhD; William J. McAleer, PhD; William J. Miller, MS; Eugene B. Buynak, PhD

• A vaccine formulated from hepatitis B surface antigen (HBsAg) produced by a recombinant strain of the yeast *Saccharomyces cerevisiae* was administered to two groups of human volunteers composed of 37 healthy, low-risk adults. Each subject received a 10-μg dose of HBsAg at 0, 1, and 6 months. By one month, 27% to 40% of the vaccinees had antibody to HBsAg, and by three months 80% to 100% were antibody positive. Large boosts in titer followed the third dose at six months. The antibody formed is predominantly specific for the *a* determinant of HBsAg. There have been no serious reactions attributable to the vaccine. The most frequent complaint has been transient soreness at the injection site. As far as we know, this is the first reported use in man of a vaccine prepared by recombinant DNA technology.

(*JAMA* 1984;251:2812-2815)

WORLDWIDE, human hepatitis B infection constitutes a major public health problem. In addition to the disability associated with acute clinical disease, chronic liver disease, cirrhosis, and primary hepatocellular carcinoma are now recognized sequelae of unresolved hepatitis B infection. Indeed, in some areas of Asia and sub-Saharan Africa, primary hepatocellular carcinoma ostensibly attributable to hepatitis B infection ranks as a leading cause of cancer deaths among males.[1]

See also p 2765.

The reservoir of hepatitis B virus resides mainly in a population of chronic carriers now estimated to number more than 200 million.[2] Infection is transmitted to susceptible persons through contact with the blood, semen, or saliva of chronic carriers or persons suffering acute infection. In low-incidence countries, such as the United States, the risk of hepatitis B infection is still high among certain groups of health care personnel, patients receiving dialysis treatments or blood products made from large pools, children born to Alaskan Eskimos or to Indochinese or Haitian refugees, residents of institutions for the mentally handicapped, prisoners, users of illicit injectable drugs, and persons who are sexually very promiscuous.[1] In high-incidence areas such as Southeast Asia, transmission from mother to child in the perinatal period is the major mode of infection supplemented by horizontal transmission between other family contacts.[3]

Since there is no effective treatment for hepatitis B infection, prevention is essential. A safe, effective human hepatitis B vaccine is now available. However, it utilizes hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of hepatitis B virus infection. Consequently, the supply of vaccine is potentially limited by available sources of suitable plasma. In addition, extensive processing and safety testing have been necessary to ensure production of a vaccine antigen that is pure and free of any extraneous living agent that might have been present in the starting plasma. Even though multiple inactivation treatments used in the antigen purification process have been shown to inactivate representatives of all major groups of animal viruses,[4] concern over the theoretical possibility of a living organism such as the etiologic agent of acquired immune deficiency syndrome being present in plasma and surviving the purification and inactivation procedures has slowed acceptance of hepatitis B vaccine.

A promising alternative to infected human plasma as a source of HBsAg for vaccine is the use of recombinant DNA technology to effect synthesis of the surface antigen by a culture of microorganisms. The hepatitis B virus gene coding for HBsAg has been cloned both in *Escherichia coli* and in yeast[5,6]; however, expression of the gene in yeast has been much better than in *E coli*. Furthermore, HBsAg

From the Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, Pa.

Reprint requests to Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, PA 19486 (Dr Scolnick).

produced by recombinant yeast cells has been shown to aggregate into particles closely resembling those isolated from human plasma, and this material was shown to include antibodies in mice and guinea pigs.[9]

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for HBsAg has been formulated into a vaccine through adsorption on alum adjuvant. Electron microscopy reveals that the purified HBsAg used for this vaccine exists as aggregate particles 20 to 22 nm in diameter, a morphology also characteristic of free surface antigen in infected plasma and of the purified antigen now used in plasma-derived hepatitis B vaccine. In contrast to HBsAg from human plasma, the antigen produced by recombinant yeast is not glycosylated. Under reducing conditions, sodium dodecyl sulfate electrophoresis of the antigen purified from yeast reveals a single band of molecular weight 23,000, which corresponds to the nonglycosylated polypeptide that is the major component of the hepatitis B virus envelope. The vaccine formulated using this material has now been shown to be immunogenic for mice and for monkeys with a potency equal to or superior to that of vaccine made from plasma-derived antigen. In addition, chimpanzees immunized with this yeast recombinant hepatitis B vaccine (HBsAg subtype *adw*) were fully protected when challenged with virus of either type *adr* or *ayr*, while unimmunized animals all showed evidence of infection when challenged.[10]

In this article we describe results of the first human immunogenicity-safety trial of the yeast recombinant hepatitis B vaccine. To the best of our knowledge, this is the first time that a vaccine prepared by recombinant DNA technology has been used in man.

MATERIALS AND METHODS

Population

Participants in this study were healthy, nonpregnant adult employees of Merck and Co, Inc. Subjects had to be negative for hepatitis B serological markers and have a normal level of alanine aminotransferase and must not have received any other hepatitis B vaccine. Written consent was obtained after providing each participant with information on the source of the investigational yeast recombinant hepatitis B vaccine, animal test results obtained with the vaccine, vaccination and bleeding schedules, and the potential risks and benefits of participation in the study.

Vaccine

Hepatitis B surface antigen for the vaccine was produced in fermentation cultures of a recombinant strain of the yeast *S cerevisiae* containing a plasmid carrying the gene for the *adw* subtype of HBsAg, as described previously.[10]

Two methods were employed for the purification of HBsAg. Immuno affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends on selection of water-immiscible molecules followed by separation by molecular size. Details of the expression of HBsAg in yeast and the purification of the surface antigen will be published elsewhere. Purified HBsAg was treated with formaldehyde to stabilize the material and to kill any extraneous living agents that might be present. The antigen was then formulated into a vaccine through adsorption on alum adjuvant to give 10 μg of HBsAg and 0.5 mg of aluminum (hydroxide) per 1-mL dose. The final formulation also contained 1:20,000 thimerosal as a preservative. Vaccine was maintained at 2 to 8 °C until used.

Procedures

A blood sample was obtained from each subject approximately two weeks prior to the first vaccination and was tested for HBsAg, antibody to HBsAg (anti-HBs), antibody to core antigen (anti-HBc), alanine aminotransferase (ALT), and yeast antibody. Subjects found eligible on the basis of these assays were scheduled to receive a 1.0-mL (10-μg HBsAg) intramuscular injection of the yeast recombinant vaccine at 0, 1, and 6 months. Postvaccination blood samples for the determination of hepatitis B serological markers, ALT, and yeast antibody were scheduled monthly for seven months and at 9, 12, and 24 months following the first injection.

Vaccinees were asked to take their temperature daily for five days after each injection of vaccine and to report any local or systemic reactions that might occur during this period.

Assays

Standard radioimmunoassay test kits were used for the determination of HBsAg, anti-HBs, and anti-HBc. Titers of anti-HBs were expressed in international milliunits per milliliter using the formulation described by Hollinger et al.[11] A serum sample was considered positive for anti-HBs if the ratio of the sample counts per minute to the negative control serum counts per minute was 2.1 or greater.

Estimates of the proportion of anti-HBs in postvaccination sera specific for the *a* or *d* determinants of HBsAg were based on an assay described by Hoofnagle et al.[12] Briefly, aliquots of each serum sample are incubated with a subtype *ad* HBsAg-positive serum, with a subtype *ay* HBsAg-positive serum, and with normal human serum for two hours at room temperature, and then each mixture is carried through a standard radioimmunoassay to measure residual anti-HBs. Based on the percent of neutralization with the two HBsAg subtype sera when compared with the unneutralized normal human serum, an estimate can be made of the relative amounts of anti-*a* and anti-*d* antibodies present. Since the vaccine is a monovalent-type *adw* preparation, sera will contain either anti-*d* antibodies, anti-*a* antibodies, or a combination of both types, and the amount of neutralization with the HBsAg-*ay* serum is therefore a direct assay for the amount of anti-*a* present. Subtracting the amount of neutralization with the HBsAg-*ay* serum from that found for the HBsAg-*ad* serum then gives an estimate of the amount of anti-*d* present.

A radioimmunoassay was developed to detect yeast antibodies in the sera of vaccine recipients. For this assay, an extract of the parent strain of *S cerevisiae* lacking the plasmid containing the gene for HBsAg was prepared by disrupting a 50% suspension of the cells in a homogenizer and then clarified by centrifugation at 9,000 g followed by passage through a 0.45-μm membrane filter. The clarified, filtered extract was diluted to a final protein concentration of 80 μg/mL with 0.1 M carbonate buffer and pH 9.6 and adsorbed to ½-in polystyrene beads overnight at 4 °C. Washed, dried beads were maintained at −20 °C. Two hundred-microliter volumes of sera diluted 1:100, 1:1,000, and 1:10,000 in phosphate-buffered saline containing 0.5% bovine serum albumin and 0.5% Tween 20 were incubated with coated beads for three hours at 37 °C. Following three washes with water, the beads were incubated with 200 μL of iodine 125 protein A (specific activity, 100,000 cpm) for 1.5 hours at 37 °C. The protein A binds and labels any antiyeast antibody on the bead that is of the IgG class. After three additional water washes, the beads were counted and titers of yeast antibody were determined by interpolation from a standard curve derived using dilutions of a hyperimmune guinea pig serum having an antibody titer to parent yeast extract of 1 million.

The serum samples of vaccinees were also measured for changes in preexisting specific yeast antibodies or the appearance of new yeast antibodies using a sodium dodecyl sulfate polyacrylamide gel electrophoresis (reducing), Western blot technique. In this procedure, parent yeast extract is separated on a 12.5% polyacrylamide gel. After transfer to a nitrocellulose sheet, polypeptides from the gel are detected by incubation with a 1:50 dilution of the vaccinee's serum, followed by incubation with ^{125}I protein A and exposure to x-ray film (T. Mason, PhD, oral communication, 1982).

RESULTS

The vaccine has been well tolerated. None of the 37 subjects studied to date has experienced a serious adverse effect attributable to vaccine. There has been no evidence of hepatitis B infection among vaccinees, ie, no elevation of ALT values and no antigenemia. Mild soreness at the injection site generally lasting one to two days was reported by 73% to 80% of vaccinees who received vaccine purified by immune affinity chromatography (lot 934) but by a substantially smaller proportion—20% to 24%—of subjects who received vaccine prepared by hydrophobic interaction chromatography (lot 972) (Table 1). Infrequent systemic complaints occurring within a five-day period following vaccination have included elevated temperature (38.3 to 38.8 °C [101 to 102 °F] oral), fatigue, headache, gastrointestinal disturbance, symptoms of upper respiratory tract infection, and nosebleed.

Table 2 summarizes our observations to date on the human immunogenicity of yeast recombinant hepatitis B vaccine. Fifteen persons (ten men, five women; age range, 23 to 53 years; median age, 33 years) have received all three doses of lot 934 vaccine prepared by the immune affinity chromatography method. Forty percent had a detectable titer of anti-HBs within one month of receiving the first dose. By two months, the proportion of seroconverters rose to 93%, and at three months, all recipients of this vaccine were antibody positive. The geometric mean titer following primary immunization reached a plateau at four months, then increased more than 25-fold following the booster dose at six months.

Table 1.—Proportion (%) of Vaccinees With Clinical Complaints During a Five-Day Period Following Injection of Yeast Recombinant Hepatitis B Vaccine

Nature of Complaint	Vaccine Lot No.	Dose 1	Dose 2	Dose 3
Soreness at injection site	934	12/15 (80)	11/15 (73)	11/15 (73)
	972	5/21 (24)	3/15 (20)	...
Systemic* complaints	934	5/15 (33)	3/15 (20)	1/15 (7)
	972	1/21 (5)	2/15 (13)	...

*Includes persons with one or more episodes of the following: temperature, 38.3 to 38.8 °C (101 to 102 °F) (two), fatigue (three), gastrointestinal disturbance (four), headache (five), symptoms of upper respiratory tract infection (three), and nosebleed (one).

Table 2.—Seroconversion Frequencies and Geometric Mean Titers (GMTs)* for Anti-HBs Among Initially Seronegative Healthy Adults Receiving 10-µg Doses of Yeast Recombinant Hepatitis B Vaccine†

Vaccine Lot No. (Method of Preparation)	No. of Subjects Vaccinated	Time, mo	Seroconversion Proportion (%)	GMT: All Vaccinees‡	GMT: Responders Only
934 (Immune affinity chromatography)	15	1	6/15 (40)	1.6	3.9
		2	14/15 (93)	31.7	34.2
		3	15/15 (100)	55.5	55.5
		4	15/15 (100)	76.2	76.2
		5	14/14 (100)	77.2	77.2
		6	15/15 (100)	87.9	87.9
		7	12/12 (100)	1,905.1	1,905.1
972 (Hydrophobic interaction chromatography)	22	1	4/15 (27)	1.4	38.8
		2	8/12 (67)	17.8	106.7
		3	4/5 (80)	50.8	218.8

*In international milliunits per milliliter.
†At 0, 1, and 6 months.
‡All serum samples with titers of less than 0.6 ImU/mL were assigned a value of 0.3 ImU/mL for calculating GMTs.

Table 3.—Percentages of Anti-HBs Specific for *a* and *d* Determinants of HBsAg in Postvaccination Sera*

Vaccine Lot No.	Time, mo	No. of Samples	% Anti-*a*: Range	% Anti-*a*: Mean	% Anti-*d*: Range	% Anti-*d*: Mean
934	1	1	...	47	...	53
	2	7	87-98	93	2-10	6
	3	10	83-98	90	2-37	13
	4	12	86-99	89	2-35	11
	5	12	93-97	92	2-20	8
	6	8	93-97	94	2-6	5
	7	12	89-100	98	0-11	2
972	1	2	59-91	74	9-44	26
	2	9	87-100	94	0-13	6

*Assay done only on serum samples having an anti-HBs titer of 25 ImU/mL or greater.

Twenty-two subjects have received vaccine from lot 972 made from HBsAg purified by the hydrophobic interaction chromatography method. These vaccinees have not been followed up for as long as the lot 934 recipients, and none has yet received a third dose. Preliminary serological results are shown in Table 2 for 15 of these volunteers (12 men, three women; age range, 24 to 63 years; median age, 40 years). The percentage of seroconverters was 27% at one month, 67% at two months, and 80% at three months. Geometric mean titers within the first three months of follow-up were similar to those observed among recipients of lot 934 vaccine.

Postvaccination serum samples with anti-HBs titers of 25 ImU/mL or greater were assayed to determine the percentage of antibody specific for the *a* and *d* determinants of HBsAg. Table 3 shows the results of these assays. Antibody specific for the *a* determinant predominates. In the interval from two to seven

months following the first dose of vaccine, anti-*a* antibody accounted for approximately 90% of the total anti-HBs.

Earlier studies (unpublished) showed that the yeast recombinant hepatitis B vaccine induced a predominantly anti-a form of anti-HBs in African green monkeys and that these antibodies have persisted through two years of follow-up.

Analysis of serum samples from participants in this study has revealed no significant postvaccination increases in yeast antibody titers as measured by radioimmunoassay. By Western blot analysis, each human serum sample shows a unique "fingerprint" spectrum of antibodies to yeast components. There may be only a few or as many as 20 different bands present. Analysis of monthly postvaccination serum samples from participants in this study has shown no change in the yeast antibody pattern for any person as compared with his prevaccination pattern. There has been no appearance of new antibodies in postvaccination sera and no significant increases in the intensity of existing antibody bands.

CONCLUSIONS

The results of this study indicate that an alum-adsorbed hepatitis B vaccine formulated using HBsAg of subtype *adw* synthesized by recombinant yeast cells is safe and immunogenic for man. Seroconversion rates and titers of anti-HBs obtained with the yeast recombinant vaccine in this study are comparable with those observed in earlier studies of healthy adults using vaccine derived from human plasma.[15-17]

Previous studies with hepatitis B vaccine of human plasma origin showed that protection from infection is associated with vaccine-induced anti-HBs.[18-20] Furthermore, one of these trials demonstrated that antibody formed in response to vaccine of HBsAg subtype *ad* provided cross-protection against infection caused by heterologous virus of subtype *ay*.[20] Since the antibody formed by recipients of the yeast recombinant hepatitis B vaccine is predominantly anti-a, this vaccine should be protective against all hepatitis B virus subtypes. The efficacy of the yeast vaccine against both homologous *ad* and heterologous *ay* virus challenge in chimpanzees has been demonstrated.[18]

Studies are under way to assess antibody persistence and to determine optimal doses of the yeast recombinant hepatitis B vaccine for both healthy and immunocompromised adults and children.

References

1. Francis DP: Selective primary health care: Strategies for control of disease in the developing world: III. Hepatitis B virus and its related diseases. *Rev Infect Dis* 1983;5:332-338.
2. Gust I: Comparison of the epidemiology of hepatitis A and B, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 129-143.
3. Immunization Practices Advisory Committee: Inactivated hepatitis B virus vaccine. *Ann Intern Med* 1982;97:279-283.
4. Hilleman MR, McAleer WJ, Buynak EB, et al: Quality and safety of human hepatitis B vaccine. *Dev Biol Stand* 1983;54:3-12.
5. Burrell CJ, Mackay P, Greenaway PJ, et al: Expression in *Escherichia coli* of hepatitis B virus DNA sequences cloned in plasmid pBR322. *Nature* 1979;279:43-47.
6. Valenzuela P, Gray P, Quiroga M, et al: Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen. *Nature* 1979;280:815-819.
7. Valenzuela P, Medina A, Rutter WJ, et al: Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298:347-350.
8. Hitzeman RA, Chen CY, Hagie FE, et al: Expression of hepatitis B virus surface antigen in yeast. *Nucleic Acids Res* 1983;11:2745-2763.
9. Miyanohara A, Toh-e A, Nozaki C, et al: Expression of hepatitis B surface antigen gene in yeast. *Proc Natl Acad Sci USA* 1983;80:1-5.
10. McAleer WJ, Buynak EB, Maigetter RZ, et al: Human hepatitis B vaccine from recombinant yeast. *Nature* 1984;307:178-180.
11. Hollinger FB, Adam E, Hoiberg D, et al: Response to hepatitis B vaccine in a young adult population, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 451-465.
12. Hollinger FH, Gerety RJ, Smallwood LA, et al: Subtyping of hepatitis B surface antigen and antibody by radioimmunoassay. *Gastroenterology* 1977;72:230-234.
13. Deinhardt F, Zacheval R, Fresser H, et al: Passive-active immunization against hepatitis B, in Krugman S, Shorloch S (eds): *Proceedings of the European Symposium on Hepatitis*. New York, KPR Inter/Media Corporation, 1981, pp 160-180.
14. Szmuness W, Stevens CE, Harley EJ, et al: The immune response of healthy adults to a reduced dose of hepatitis B vaccine. *J Med Virol* 1981;8:185-189.
15. Krugman S, Holley HP Jr, Davidson M, et al: Immunogenic effect of inactivated hepatitis B vaccine: Comparison of 20 microgram and 40 microgram doses. *J Med Virol* 1981;8:119-121.
16. Hilleman MR, Buynak EB, McAleer WJ, et al: Hepatitis A and hepatitis B vaccines, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 385-397.
17. Desmyter J, Colaert J, Verstraete M, et al: Hepatitis B vaccination of hemophiliacs. *Scand J Infect Dis* 1982;33(suppl):42-45.
18. Szmuness W, Stevens CE, Zang EA, et al: A controlled trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981;1:377-385.
19. Francis DP, Hadler SC, Thompson SE, et al: The prevention of hepatitis B with vaccine: Report of the Centers for Disease Control multicenter efficacy trial among homosexual men. *Ann Intern Med* 1982;97:362-366.
20. Szmuness W, Stevens CE, Harley EJ, et al: Hepatitis B vaccine in medical staff of hemodialysis units: Efficacy and subtype cross-protection. *N Engl J Med* 1982;307:1481-1484.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

Printed and Published in the United States of America

STUDY 792

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 792
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625 (10 mcg HBsAg/ml) Lot #979/C-K564 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Jules L. Dienstag, M.D. Associate Professor of Medicine Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114
SECONDARY INVESTIGATOR:	Eloise Watkins, R.N., M.P.H. Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114 Lynn F. Butterly, M.D. Clinical & Research Fellow Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114
STUDY LOCATION:	Massachusetts General Hospital Fruit Street Boston, MA 02114
DATE INITIATED:	November 10, 1983.
DATE COMPLETED:	In progress.

25271
12/20/85

Study 792

STUDY POPULATION: The study population consists of 65 health care personnel of either sex (excluding pregnant women), who were negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

PROCEDURE: Eligible participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine produced by the immune affinity or the (b)(4) procedure at 0, 1, and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination and on the day of the first vaccination. Post-vaccination blood samples are obtained monthly for seven months and at 9, 12, and 24 months from subjects vaccinated with lot #934/C-J625. Post-vaccination blood samples are taken at 1, 2, 3, 6, 8, 12, and 24 months from persons injected with vaccine lot #979/C-K564. The samples are assayed for HBsAg, anti-HBc, anti-HBs, yeast antibody and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml are tested for the proportions of anti-a and anti-d activity.

STUDY RESULTS: HEALTH CARE PERSONNEL (b)(4) Vaccine):

10 mcg lot #979/C-K564 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
35	35	32

Study 792

RESULTS: (Cont.)

2. Serologic Results:

Serologic data are available for 28 study participants at nine months. Seroconversion (S/N ≥2.1) for anti-HBs at 9 months was 96% (27/28). Ninety-three percent (26/28) of the participants developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at nine months was 531.1 mIU/ml for all vaccinees and 826.3 mIU/ml for responders with a titer of mIU/ml ≥10.

Among participants with serology data at 12 months, 83% (20/24) were positive for anti-HBs (mIU/ml ≥10). The GMT at that time was 234.1 mIU/ml for all vaccinees and 403.0 mIU/ml for responders with a titer of mIU/ml ≥10.

See Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for all participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	20(7/35)	23(8/35)	25(8/32)
Systemic	14(5/35)	11(4/35)	9(3/32)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming reactions attributable to the vaccine.

PUBLICATION:

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK564
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	RESPONDERS	
						S/N >= 2.1	MIU/ML >= 10
1 MONTH	29%	(10/34)	5.9%	(2/34)	1.1	7.2	78.6
2 MONTHS	88%	(28/32)	75%	(24/32)	24.5	43.4	65.9
3 MONTHS	91%	(29/32)	81%	(26/32)	45.1	63.4	83.3
6 MONTHS	97%	(29/30)	97%	(29/30)	72.4	84.0	84.0
9 MONTHS	96%	(27/28)	93%	(26/28)	531.1	672.7	826.3
12 MONTHS	92%	(22/24)	83%	(20/24)	234.1	403.0	403.0

Table 2
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	6 (17.1%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		7 (20.0%)
PAIN	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
SORENESS	5 (14.3%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		6 (17.1%)
SYSTEMIC	2 (5.7%)	3 (8.6%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	1 (2.9%)		5 (14.3%)
WHOLE BODY/GENERAL	1 (2.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)		4 (11.4%)
SWEATING	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
MALAISE	0 (0.0%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (5.7%)
HEADACHE	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)		2 (5.7%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
MUSCULOSKELETAL	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
MYALGIA	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	0 (0.0%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NAUSEA	0 (0.0%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NERVOUS SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
VERTIGO/DIZZINESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	8 (22.9%)	5 (14.3%)	3 (8.6%)	2 (5.7%)	0 (0.0%)	1 (2.9%)	11 (31.4%)
PERSONS WITH NO COMPLAINTS	27 (77.1%)	30 (85.7%)	32 (91.4%)	33 (94.3%)	35 (100.0%)	34 (97.1%)	24 (68.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	7 (20.0%)	2 (5.7%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
SORENESS	7 (20.0%)	2 (5.7%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
SYSTEMIC	2 (5.7%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	4 (11.4%)
WHOLE BODY/GENERAL	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
HEADACHE	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NERVOUS SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
VERTIGO/DIZZINESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	7 (20.0%)	2 (5.7%)	3 (8.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	9 (25.7%)
PERSONS WITH NO COMPLAINTS	28 (80.0%)	33 (94.3%)	32 (91.4%)	34 (97.1%)	34 (97.1%)	35 (100.0%)	26 (74.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00189

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 3 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	6 (18.8%)	3 (9.4%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (25.0%)
PAIN	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
SORENESS	5 (15.6%)	1 (3.1%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (18.8%)
TENDERNESS	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
PRURITIS (ITCHING)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
SYSTEMIC	1 (3.1%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	3 (9.4%)
WHOLE BODY/GENERAL	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
HEADACHE	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	2 (6.3%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	1 (3.1%)
MUSCULOSKELETAL	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
MYALGIA	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
PERSONS WITH COMPLAINTS	6 (18.8%)	3 (9.4%)	3 (9.4%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	9 (28.1%)
PERSONS WITH NO COMPLAINTS	26 (81.3%)	29 (90.6%)	29 (90.6%)	31 (96.9%)	31 (96.9%)	31 (96.9%)	23 (71.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 6792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (35 PATIENTS) - DOSE 1								DAYS POST VACCINATION	NUMBER WITH MAX TEMP
	0	1	2	3	4	5				
< 99	25 (71.4%)	28 (84.8%)	31 (88.6%)	31 (91.2%)	26 (76.5%)	25 (75.8%)				15 (42.9%)
99 - 99.9	10 (28.6%)	4 (12.1%)	3 (8.6%)	3 (8.8%)	8 (23.5%)	8 (24.2%)				18 (51.4%)
100 - 100.9	0 (0.0%)	1 (3.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)				2 (5.7%)
TEMPERATURE TAKEN	35 (100.0%)	33 (94.3%)	35 (100.0%)	34 (97.1%)	34 (97.1%)	33 (94.3%)				35 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	2 (5.7%)	0 (0.0%)	1 (2.9%)	1 (2.9%)	2 (5.7%)				0 (0.0%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (35 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	27 (79.4%)	30 (85.7%)	30 (85.7%)	31 (88.6%)	26 (76.5%)	31 (91.2%)			18 (51.4%)
99 - 99.9	7 (20.6%)	5 (14.3%)	5 (14.3%)	4 (11.4%)	7 (20.6%)	3 (8.8%)			16 (45.7%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)			1 (2.9%)
TEMPERATURE TAKEN	34 (97.1%)	35 (100.0%)	35 (100.0%)	35 (100.0%)	34 (97.1%)	34 (97.1%)			35 (100.0%)
TEMPERATURE NOT TAKEN	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (2.9%)			0 (0.0%)

Table 3 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (32 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	28 (90.3%)	28 (93.3%)	28 (93.3%)	28 (93.3%)	22 (81.5%)	27 (93.1%)		21 (65.6%)
99 - 99.9	2 (6.5%)	2 (6.7%)	2 (6.7%)	2 (6.7%)	5 (18.5%)	2 (6.9%)		10 (31.3%)
100 - 100.9	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
TEMPERATURE TAKEN	31 (96.9%)	30 (93.8%)	30 (93.8%)	30 (93.8%)	27 (84.4%)	29 (90.6%)		32 (100.0%)
TEMPERATURE NOT TAKEN	1 (3.1%)	2 (6.3%)	2 (6.3%)	2 (6.3%)	5 (15.6%)	3 (9.4%)		0 (0.0%)

RECOMBINANT YEAST HEPATITIS B VACCINE: IMMUNOGENICITY AND SAFETY. JL Dienstag, E Watkins, and CA Hinkle. Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

Cumbersome to produce, expensive, and limited in supply, currently available human plasma-derived hepatitis B vaccines are likely to be replaced in the future by "genetically engineered" vaccines. Recently, a recombinant DNA vaccine was prepared in recombinant yeast Saccharomyces cerevisiae strain 2150-2-3 cells transformed with the plasmid pHBS 56-GAP 347/33, containing the gene for hepatitis B surface antigen (HBsAg/ad) (Valenzuela et al. Nature 1982; 298:347-50). Purified by biochemical and biophysical methods from the yeast extract, the HBsAg particles synthesized by these yeast cells are not glycosylated but otherwise are indistinguishable from native 22 nm HBsAg particles. Treated with formalin and adsorbed to alum, the recombinant vaccine is immunogenic and protective in experimental animals. We administered three 10 µg doses of the recombinant hepatitis B vaccine (Merck Sharp & Dohme Research Laboratories) at time 0, 1, and 6 months to 60 seronegative adult health workers. The frequency and geometric mean titer (mIU/ml) of anti-HBs responses were as follows:

Month	1	2	3	4	5	6
Number	37	29	30	29	25	16
anti-HBs+	41%	83%	93%	97%	96%	94%
GMT ± SD	7 ± 2	33 ± 5	36 ± 6	46 ± 4	55 ± 6	79 ± 4

94 ± 9 (mean ± SD) % of the anti-HBs was specific for the a determinant of HBsAg. Changes in antibodies to yeast antigens were negligible. The most frequent adverse reaction was transient soreness at the injection site, occurring after 52% of first, 37% of second, and 55% of third injections. No serious adverse effects were encountered, and neither type B nor non-B hepatitis has occurred in any vaccinee. These preliminary results demonstrate that the recombinant yeast hepatitis B vaccine is safe and that 10 µg of the recombinant vaccine is equivalent in immunogenicity to 20 µg of the plasma-derived vaccine.

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

STUDY 794

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 794
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among: 1. health care personnel who are negative for hepatitis B virus serologic markers. 2. health care personnel immunized with plasma derived vaccine who were nonresponders (anti-HBs negative)
VACCINE:	Yeast Recombinant Hepatitis B Vaccine: Lot #972/C-K444 (10 mcg/HBsAg ml)
PRIMARY INVESTIGATOR:	Harvey J. Alter, M.D. Chief, Immunology Section Clinical Center Blood Bank National Institutes of Health Bethesda, Maryland
SECONDARY INVESTIGATOR:	David Henderson, M.D. James Schmitt, M.D. Ms. Deloris Koziol Ms. Beverly Elder
STUDY LOCATION:	Clinical Center Blood Bank National Institute of Health Bethesda, Maryland 20205
DATE INITIATED:	April 12, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 71 health care personnel of either sex (excluding pregnant women) who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepalitis B vaccine. It also includes 11 nonresponders to plasma-derived vaccine.

Study 794

PROCEDURE:

Health care workers receive either 5 mcg or 10 mcg doses of vaccine at 0, 1 and 6 months. Nonresponders receive 10 mcg doses at 0, 1 and 6 months. All injections are intramuscular. Participants are asked to record their temperature for 5 days after each injection and note any local or systemic reactions.

Blood specimens are obtained prior to vaccination, and monthly for 7 months and at 9, 12 and 24 months post initial injection. All samples are assayed for anti-HBs, anti-HBc, HBsAg and ALT by Dr. Alter. Samples with anti-HBs titers $\geq$ 25 mIU/ml may be tested for anti-a and anti-d activity at MSDRL.

RESULTS:

HEALTH CARE PERSONNEL:

10 mcg Lot #972/C-K444 at 0, 1 and 6 months
5 mcg Lot #972/C-K444 at 0, 1 and 6 months

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
10 mcg	41	40	40
5 mcg	30	30	28

2. Serologic Results:

Serologic data are available for 36 study participants who received 10 mcg injections and for 25 who received 5 mcg injections at 7/8 months. Seroconversion at 7/8 months was 94% (34/36) S/N $\geq$10 among those receiving 10 mcg doses, with a GMT of 160.8 and 209.3 for all vaccinees and responders, respectively.

Among the recipients of 5 mcg doses, 76% (19/25) had seroconverted, with GMT's of 54 and 152.9 respectively. Table 1 shows seroconversion rates and GMT's for up to 12 months of follow-up.

Study 794

RESULTS: (Cont.)

3. Clinical Complaints:

Clinical follow-up data are available for 41, 40, and 40 participants following the first, second and third injections of 10 mcg doses, and for 30, 30, and 28 participants following the first, second and third injections of 5 mcg doses. Specific complaints and maximum temperatures reported during the 5 days following each injection are provided in Tables 2 through 5.

Type of Complaint	Dose Level	Frequency in % by Injection 1	2	3
Injection Site	10 mcg	25(10/42)	8(3/40)	23(9/40)
	5 mcg	13(4/30)	10(3/30)	14(4/28)
Systemic	10 mcg	18(7/41)	18(7/40)	10(4/40)
	5 mcg	17(5/30)	13(4/30)	14(4/28)

There were no serious or alarming adverse reactions attributable to vaccine.

ALT Elevations:

Two subjects who received 10 mcg doses of vaccine had transient elevation of ALT (1.5 - 4.0 times the upper limit of normal) one to two months after the second dose. Within one to two months of the elevations, the ALT levels returned to normal. A reason for the ALT elevations has not been discovered. The subjects have not shown any clinical or serologic signs (HBsAg or anti-HBc) of hepatitis B.

Table 1

Antibody Responses Among Health Care Personnel Following Vaccination
with 10 or 5 mcg Doses of Yeast Recombinant Hepatitis B Vaccine
Lots #972/C-K444 at 0, 1, and 6 Months in Study #794

	10 mcg					5 mcg				
	% with Anti-HBs		GMT (S/N)			% with Anti-HBs		GMT (S/N)		
Time (Months)	S/N ≥ 2.1	S/N ≥ 10	All Vaccinees	S/N ≥ 2.1	S/N ≥ 10	S/N ≥ 2.1	S/N ≥ 10	All Vaccinees	S/N ≥ 2.1	S/N ≥ 10
1	29(11/38)	18(7/38)	2.3	15.2	35.7	31(9/29)	14(4/29)	2.1	8.9	33.3
2	83(29/35)	54(19/35)	16.4	28.7	75.5	74(20/27)	48(13/27)	8.4	17.2	37.9
3	79(26/33)	61(20/33)	17.7	35.8	73.6	79(23/29)	59(17/29)	12.6	23.8	40.5
6	89(32/36)	69(25/36)	27.5	41.2	78.8	81(21/26)	69(18/26)	14.2	26.2	35.3
7	97(35/36)	94(34/36)	160.8	165.4	209.3	84(21/25)	76(19/25)	54.0	113.4	152.9
9	97(34/35	94(33/35)	132.7	152.8	166.5	83(19/23)	78(18/23)	44.9	98.1	119.5
12	97(33/34)	97(33/34)	99.2	113.7	113.7	83(19/23)	78(18/23)	44.5	96.9	113.5

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (41 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	7 (17.5%)	7 (17.5%)	4 (10.0%)	2 (5.0%)	2 (5.0%)	1 (2.5%)		10 (25.0%)
INFLAMMATION	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.5%)
PAIN	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.5%)
SORENESS	6 (15.0%)	5 (12.5%)	3 (7.5%)	2 (5.0%)	2 (5.0%)	1 (2.5%)		8 (20.0%)
TENDERNESS	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.5%)
PRURITIS (ITCHING)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.5%)
SYSTEMIC	3 (7.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	1 (2.5%)	2 (5.0%)		7 (17.5%)
WHOLE BODY/GENERAL	3 (7.5%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	1 (2.5%)	1 (2.5%)		5 (12.5%)
SWEATING	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.5%)
FATIGUE/WEAKNESS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.5%)
MALAISE	2 (5.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	1 (2.5%)	1 (2.5%)		4 (10.0%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.5%)

00200

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0790
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (41 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
MUSCULOSKELETAL	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	2 (5.0%)
MYALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (2.5%)
ARTHRITIS	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
CLAY-COLORED STOOLS	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PERSONS WITH COMPLAINTS	10 (25.0%)	9 (22.5%)	5 (12.5%)	2 (5.0%)	3 (7.5%)	3 (7.5%)	16 (40.0%)
PERSONS WITH NO COMPLAINTS	30 (75.0%)	31 (77.5%)	35 (87.5%)	38 (95.0%)	37 (92.5%)	37 (92.5%)	24 (60.0%)
PERSONS WITH NO DATA	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0796
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	3 (7.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.5%)
SORENESS	2 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
TENDERNESS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PRURITIS (ITCHING)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
SYSTEMIC	3 (7.5%)	2 (5.0%)	2 (5.0%)	1 (2.5%)	1 (2.6%)	2 (5.3%)	7 (17.5%)
WHOLE BODY/GENERAL	3 (7.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	1 (2.6%)	6 (15.0%)
SWEATING	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
FLUSH	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
FATIGUE/WEAKNESS	1 (2.5%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
MALAISE	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	2 (5.0%)
HEADACHE	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)

20200

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
ECCHYMOSES	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
DIGESTIVE SYSTEM	1 (2.5%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
ABDOMINAL PAINS/CRAMPS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
DIARRHEA	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
NAUSEA	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
CLAY-COLORED STOOLS	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
NERVOUS SYSTEM	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	2 (5.0%)
VERTIGO/DIZZINESS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
TREMOR	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	1 (2.5%)
PERSONS WITH COMPLAINTS	6 (15.0%)	2 (5.0%)	2 (5.0%)	1 (2.5%)	1 (2.6%)	2 (5.3%)	10 (25.0%)
PERSONS WITH NO COMPLAINTS	34 (85.0%)	38 (95.0%)	38 (95.0%)	39 (97.5%)	38 (97.4%)	36 (94.7%)	30 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (2.6%)	0 (0.0%)

00203

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK464
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	8 (20.0%)	3 (7.5%)	2 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (22.5%)
PAIN	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
SORENESS	5 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (12.5%)
TENDERNESS	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
PAPULE(S)	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PRURITIS (ITCHING)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
ECCHYMOSIS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
SYSTEMIC	2 (5.0%)	1 (2.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	4 (10.0%)
WHOLE BODY/GENERAL	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
FATIGUE/WEAKNESS	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
MALAISE	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
LOOSE STOOL	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
CLAY-COLORED STOOLS	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PERSONS WITH COMPLAINTS	9 (22.5%)	3 (7.5%)	4 (10.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	10 (25.0%)
PERSONS WITH NO COMPLAINTS	31 (77.5%)	37 (92.5%)	36 (90.0%)	39 (97.5%)	40 (100.0%)	40 (100.0%)	30 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 8794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (41 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
NORMAL	5 (12.5%)	6 (16.7%)	6 (16.2%)	6 (16.2%)	6 (16.7%)	6 (18.2%)		5 (12.5%)
< 99	30 (75.0%)	29 (80.6%)	30 (81.1%)	30 (81.1%)	29 (80.6%)	27 (81.8%)		27 (67.5%)
99 - 99.9	5 (12.5%)	1 (2.8%)	1 (2.7%)	0 (0.0%)	1 (2.8%)	0 (0.0%)		7 (17.5%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)		1 (2.5%)
TEMPERATURE TAKEN	40 (97.6%)	36 (87.8%)	37 (90.2%)	37 (90.2%)	36 (87.8%)	33 (80.5%)		40 (97.6%)
TEMPERATURE NOT TAKEN	1 (2.4%)	5 (12.2%)	4 (9.8%)	4 (9.8%)	5 (12.2%)	8 (19.5%)		1 (2.4%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (40 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	5 (12.5%)	5 (13.5%)	5 (13.9%)	5 (13.5%)	5 (15.2%)	6 (17.6%)		5 (12.5%)
< 99	32 (80.0%)	31 (83.8%)	30 (83.3%)	31 (83.8%)	26 (78.8%)	26 (76.5%)		29 (72.5%)
99 - 99.9	3 (7.5%)	1 (2.7%)	1 (2.8%)	1 (2.7%)	2 (6.1%)	2 (5.9%)		6 (15.0%)
TEMPERATURE TAKEN	40 (100.0%)	37 (92.5%)	36 (90.0%)	37 (92.5%)	33 (82.5%)	34 (85.0%)		40 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	3 (7.5%)	4 (10.0%)	3 (7.5%)	7 (17.5%)	6 (15.0%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK464
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (40 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	8 (20.0%)	8 (20.5%)	8 (21.6%)	8 (21.1%)	8 (21.1%)	8 (20.5%)		8 (20.0%)
< 99	30 (75.0%)	29 (74.4%)	26 (70.3%)	29 (76.3%)	28 (73.7%)	30 (76.9%)		26 (65.0%)
99 - 99.9	2 (5.0%)	2 (5.1%)	3 (8.1%)	1 (2.6%)	2 (5.3%)	1 (2.6%)		6 (15.0%)
TEMPERATURE TAKEN	40 (100.0%)	39 (97.5%)	37 (92.5%)	38 (95.0%)	38 (95.0%)	39 (97.5%)		40 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (2.5%)	3 (7.5%)	2 (5.0%)	2 (5.0%)	1 (2.5%)		0 (0.0%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0790
TREATMENT :
LOT NUMBER : CK440
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (13.3%)
PAIN	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
SORENESS	2 (6.7%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (10.0%)
ERYTHEMA (REDNESS)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
STIFFNESS/TIGHTNESS	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
SYSTEMIC	1 (3.3%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	3 (10.3%)	2 (6.9%)	5 (16.7%)
WHOLE BODY/GENERAL	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	3 (10.3%)	1 (3.4%)	4 (13.3%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
FATIGUE/WEAKNESS	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
MALAISE	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	2 (6.9%)	0 (0.0%)	2 (6.7%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	1 (3.3%)
SYSTEMIC INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.4%)	1 (3.3%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RESPIRATORY	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.3%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.3%)
PERSONS WITH COMPLAINTS	5 (16.7%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	3 (10.3%)	2 (6.9%)	8 (26.7%)
PERSONS WITH NO COMPLAINTS	25 (83.3%)	27 (90.0%)	28 (93.3%)	29 (100.0%)	26 (89.7%)	27 (93.1%)	22 (73.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.3%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (10.0%)
PAIN	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
SOREMESS	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
SYSTEMIC	3 (10.0%)	1 (3.3%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	4 (13.3%)
WHOLE BODY/GENERAL	3 (10.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	3 (10.0%)
CHILLS	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)
MALAISE	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
HEADACHE	2 (6.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
AXILLARY AREA SORE	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK944
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (30 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER
CLINICAL COMPLAINTS	0	1	2	3	4	5		WITH COMPLAINTS
NAUSEA	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
PERSONS WITH COMPLAINTS	3 (10.0%)	2 (6.7%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)		5 (16.7%)
PERSONS WITH NO COMPLAINTS	27 (90.0%)	28 (93.3%)	26 (86.7%)	30 (100.0%)	30 (100.0%)	29 (96.7%)		25 (83.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00212

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0796
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.6%)	3 (10.7%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (14.3%)
SORENESS	1 (3.6%)	3 (10.7%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (14.3%)
SYSTEMIC	2 (7.1%)	3 (10.7%)	1 (3.6%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	4 (14.3%)
WHOLE BODY/GENERAL	2 (7.1%)	3 (10.7%)	1 (3.6%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	4 (14.3%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (3.6%)	1 (3.6%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	1 (3.6%)
MALAISE	0 (0.0%)	2 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.1%)
HEADACHE	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
SWOLLEN ANKLES	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
NERVOUS SYSTEM	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
VERTIGO/DIZZINESS	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
PERSONS WITH COMPLAINTS	2 (7.1%)	6 (21.4%)	2 (7.1%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	7 (25.0%)
PERSONS WITH NO COMPLAINTS	26 (92.9%)	22 (78.6%)	26 (92.9%)	28 (100.0%)	27 (96.4%)	28 (100.0%)	21 (75.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0796
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE I: DAYS POST VACCINATION 0	1	2	3	4	5	6	NUMBER WITH MAX TEMP
NORMAL	1 (3.3%)	1 (3.3%)	1 (3.4%)	1 (3.6%)	1 (3.6%)	1 (3.4%)		1 (3.3%)
< 99	25 (83.3%)	24 (80.0%)	26 (89.7%)	24 (85.7%)	22 (78.6%)	24 (82.8%)		17 (56.7%)
99 - 99.9	4 (13.3%)	5 (16.7%)	2 (6.9%)	2 (7.1%)	5 (17.9%)	4 (13.8%)		11 (36.7%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
TEMPERATURE TAKEN	30 (100.0%)	30 (100.0%)	29 (96.7%)	28 (93.3%)	28 (93.3%)	29 (96.7%)		30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (3.3%)	2 (6.7%)	2 (6.7%)	1 (3.3%)		0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	2 (6.7%)	2 (6.7%)	2 (6.7%)	2 (7.1%)	2 (6.7%)	2 (6.7%)		2 (6.7%)
< 99	24 (80.0%)	24 (80.0%)	24 (80.0%)	24 (85.7%)	27 (90.0%)	26 (86.7%)		19 (63.3%)
99 - 99.9	4 (13.3%)	2 (6.7%)	4 (13.3%)	2 (7.1%)	1 (3.3%)	2 (6.7%)		7 (23.3%)
100 - 100.9	0 (0.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.7%)
TEMPERATURE TAKEN	30 (100.0%)	30 (100.0%)	30 (100.0%)	28 (93.3%)	30 (100.0%)	30 (100.0%)		30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0790
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (28 PATIENTS) - DOSE 3 DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
NORMAL	4 (14.3%)	4 (14.3%)	4 (14.8%)	4 (14.3%)	4 (14.3%)	4 (14.3%)			4 (14.3%)
< 99	20 (71.4%)	21 (75.0%)	21 (77.8%)	21 (75.0%)	21 (75.0%)	22 (78.6%)			19 (67.9%)
99 - 99.9	4 (14.3%)	3 (10.7%)	2 (7.4%)	3 (10.7%)	3 (10.7%)	2 (7.1%)			5 (17.9%)
TEMPERATURE TAKEN	28 (100.0%)	28 (100.0%)	27 (96.4%)	28 (100.0%)	28 (100.0%)	28 (100.0%)			28 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 795
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine by health care personnel and other healthy adults negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625 (10mcg HBsAg/ml) Lot #979/C-K564 (10mcg HBsAg/ml) Lot #81990 D/18066/C-L215 (10 mcg HBsAg/0.5 ml)
PRINCIPAL INVESTIGATOR:	Prof. Dr. Friedrich Deinhardt Max v. Pettenkofer Institut Pettenkoferstrasse 9a 8000 Muenchen 2 WEST GERMANY
SECONDARY INVESTIGATORS:	Dr. W. Jilg Dr. R. Zachoval Dr. G. Zoulek Dr. M. Kroner Dr. J. Abb Dr. B. Lorbeer The above secondary investigators have the same address as the principal investigator. Dr. U. Bienzle Landesinstitut fuer Tropenmedizin Ansbacherstr. 5 D-1000 Berlin 30 WEST GERMANY
STUDY LOCATIONS:	Max V. Pettenkofer Institut Pettenkoferstrasse 9a 8000 Muenchen 9a WEST GERMANY Landesinstitut fuer Tropenmedizin Ansbacherstr. 5 D-1000 Berlin 30 WEST GERMANY

2384I/1
1/3/86

Study 795

DATE INITIATED: November 21, 1983.

DATE COMPLETED: In progress.

STUDY POPULATION: The study population consists of approximately 300 health care personnel and other healthy adults of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Eligible participants receive a 10 mcg intramuscular injection of vaccine produced by the immune affinity or (b)(4) procedure at 0, 1, and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination and on the day of the first vaccination. Post-vaccination blood samples are obtained monthly for seven months and at 9, 12, and 24 months from recipients of lot #934/C-J625 vaccine. Recipients of lots #979/C-K564 and #81990D/18066/C-L215 are bled at 1, 2, 3, 6, 8, 12, and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml may be tested for the proportions of anti-a and anti-d activity. Samples may also be assayed for yeast antibody.

RESULTS: HEALTH CARE PERSONNEL/OTHER HEALTHY ADULTS (b)(4) Vaccine):

10 mcg Lot #979/C-K564 at 0, 1, and 6 months
10 mcg Lot #81990D/18066/C-L215 at 0, 1, and 6 months

Study 795

RESULTS: (Contd)

1. Number Vaccinated:

Vaccine Lot	Injection No. 1	2	3
Lot C-K564	148	146	126
Lot C-L215	97	97	94

2. Serologic Results:

Serologic data are available for 76 participants, who received vaccine from lot C-K564, at 7/8 months. At that time, 100% (76/76) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT at 7/8 months for all vaccinees and for responders (either cutoff) it was 2143.1 mIU/ml.

Seven/eight month serologic data are available for 80 participants who received vaccine from lot C-L215. Ninety-nine percent (79/80) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT was 2436.1 mIU/ml and 2655.2 mIU/ml for all vaccinees, while it was 2655.2 mIU/ml for responders (either cutoff).

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for 126, 94 and 74 participants, who received lot C-K564 vaccine, after injection number 1, 2, and 3, respectively. Follow-up data are available for 96, 83 and 57 subjects, who received lot C-L215 vaccine, after injection number 1, 2, and 3, respectively. The overall frequencies of complaints follow.

Study 795

RESULTS (CONT.):

Type of Complaint	Vaccine Lot	Frequency in % by Injection No. 1	2	3
Injection Site	C-K564	30(38/126)	29(27/94)	22(16/74)
	C-L215	16(15/96)	5(4/83)	19(11/57)
Systemic	C-K564	18(22/126)	17(16/94)	12(9/74)
	C-L215	15(14/96)	8(7/83)	9(5/57)

Refer to Tables 2 and 3 for listings of specific complaints after each injection. Maximum temperature data are presented in Tables 4 amd 5.

There were serious or alarming reactions attributable to vaccine.

HBV Markers (Anti-HBc)

One subject who was positive for anti-HBc prior to vaccination, continued to be transiently positive for anti-HBc post-vaccination. The subject was negative for HBsAg and did not seroconvert for anti-HBs as of five months after enrollment in the study.

ALT Elevations

Two subjects with normal pre-vaccination ALT levels, developed elevated ALT levels (1.5-2.0 times the upper limit of normal) one month after the first injection and one month after the third injection, respectively. Another participant with an unknown pre-vaccination ALT level, developed an elevated ALT level (2.0 times the upper limit of normal) one month after the second injection. All three subjects received vaccine lot C-L215. They were negative for anti-HBc and HBsAg and were not clinically ill.

One subject with an elevated pre-vaccination ALT level (1.5 x the upper limit of normal) continued to have a similar elevation one month after the first injection of vaccine (Lot C-L215). He was negative for anti-HBc and HBsAg and was not ill.

Table 1

Antibody Responses Among Health Care Personnel Following Vaccination with
10 mcg Injections of Yeast Recombinant Hepatitis B Vaccine
Lots #979/C-K564 and #819900/18066/C-L215 at 0, 1, and 6 Months in Study #795

	10 mcg (lot #979/C-K564)					10 mcg (lot #819900/18066/C-L215)				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders	
Time (Mos.)	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	28 (36/129)	22 (29/129)	1.1	33.2	47.4	23 (22/96)	20 (19/96)	0.8	26.1	31.1
2	83 (99/119)	66 (79/119)	20.3	41.7	66.9	71 (66/93)	58 (54/69)	8.3	32.5	44.8
3	91 (79/87)	85 (74/87)	40.2	60.6	69.2	90 (62/69)	78 (54/69)	31.8	46.0	62.1
6	95 (112/118)	92 (109/118)	71.2	87.6	93.3	94 (83/88)	88 (77/88)	47.6	62.6	73.9
7/8	100 (76/76)	100 (76/76)	2143.1	2143.1	2143.1	99 (79/80)	99 (79/80)	2436.1	2655.2	2655.2

Table 2
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (140 PATIENTS) - DOSE 1						NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION						
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	36 (28.6%)	11 (8.7%)	6 (4.8%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	38 (30.2%)
PAIN	25 (19.8%)	8 (6.3%)	4 (3.2%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	27 (21.4%)
SORENESS	7 (5.6%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (5.6%)
TENDERNESS	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)
SWELLING	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
ECCHYMOSIS	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
OTHER	3 (2.4%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.4%)
SYSTEMIC	11 (8.7%)	9 (7.1%)	7 (5.6%)	5 (4.0%)	2 (1.6%)	4 (3.2%)	22 (17.5%)
WHOLE BODY/GENERAL	8 (6.3%)	9 (7.1%)	7 (5.6%)	5 (4.0%)	2 (1.6%)	4 (3.2%)	19 (15.1%)
CHILLS	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
SWEATING	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (148 PATIENTS) - DOSE 1 DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
FATIGUE/WEAKNESS	4 (3.2%)	4 (3.2%)	3 (2.4%)	2 (1.6%)	0 (0.0%)	1 (0.8%)		10 (7.9%)
HEADACHE	3 (2.4%)	4 (3.2%)	3 (2.4%)	1 (0.8%)	1 (0.8%)	3 (2.4%)		10 (7.9%)
CHEST PAIN	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
ILLNESS, NOS	2 (1.6%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (1.6%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
MUSCULOSKELETAL	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
MYALGIA	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
DIGESTIVE SYSTEM	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)		3 (2.4%)
NAUSEA	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)		3 (2.4%)
PERSONS WITH COMPLAINTS	40 (31.7%)	18 (14.3%)	12 (9.5%)	6 (4.8%)	2 (1.6%)	4 (3.2%)		49 (38.9%)
PERSONS WITH NO COMPLAINTS	86 (68.3%)	108 (85.7%)	114 (90.5%)	120 (95.2%)	124 (98.4%)	121 (96.8%)		77 (61.1%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (148 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	21 (14.3%)	21 (14.3%)	21 (14.3%)	21 (14.3%)	21 (14.3%)	21 (14.4%)	21 (14.3%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (146 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	20 (21.3%)	17 (18.1%)	7 (7.4%)	3 (3.2%)	1 (1.1%)	0 (0.0%)		27 (28.7%)
PAIN	13 (13.8%)	8 (8.5%)	3 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		16 (17.0%)
SORENESS	2 (2.1%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (3.2%)
TENDERNESS	1 (1.1%)	1 (1.1%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
ERYTHEMA (REDNESS)	1 (1.1%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
STIFFNESS/TIGHTNESS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
PRURITIS (ITCHING)	1 (1.1%)	2 (2.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
NUMBNESS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
LYMPHADENOPATHY, REGIONAL	0 (0.0%)	2 (2.1%)	2 (2.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
ECCHYMOSIS	1 (1.1%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	0 (0.0%)		2 (2.1%)
PARESTHESIA	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
SYSTEMIC	9 (9.6%)	8 (8.5%)	4 (4.3%)	2 (2.1%)	2 (2.1%)	0 (0.0%)		16 (17.0%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (146 PATIENTS) - DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
WHOLE BODY/GENERAL	8 (5.5%)	5 (3.4%)	3 (2.1%)	1 (0.7%)	1 (0.7%)	0 (0.0%)	13 (8.9%)
FATIGUE/WEAKNESS	4 (2.7%)	5 (3.4%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (4.1%)
HEADACHE	4 (2.7%)	1 (0.7%)	2 (1.4%)	1 (0.7%)	1 (0.7%)	0 (0.0%)	8 (5.5%)
ILLNESS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
RESPIRATORY	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
UPPER RESPIRATORY INFECT., NOS	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
HEMIC AND LYMPHATIC	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
LYMPHADENOPATHY, CERVICAL	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
DIGESTIVE SYSTEM	1 (0.7%)	2 (1.4%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.1%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
NAUSEA	1 (0.7%)	2 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.1%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (146 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
VOMITING	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
NERVOUS SYSTEM	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
VERTIGO/DIZZINESS	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
PERSONS WITH COMPLAINTS	28 (29.8%)	21 (22.3%)	9 (9.6%)	5 (5.3%)	3 (3.2%)	0 (0.0%)		33 (35.1%)
PERSONS WITH NO COMPLAINTS	66 (70.2%)	73 (77.7%)	85 (90.4%)	89 (94.7%)	91 (96.8%)	94 (100.0%)		61 (64.9%)
PERSONS WITH NO DATA	35 (27.1%)	35 (27.1%)	35 (27.1%)	35 (27.1%)	35 (27.1%)	35 (27.1%)		35 (27.1%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (126 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	15 (20.3%)	9 (12.2%)	3 (4.1%)	1 (1.4%)	0 (0.0%)	0 (0.0%)		16 (21.6%)
PAIN	12 (16.2%)	5 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		12 (16.2%)
SORENESS	2 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.7%)
SWELLING	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
PRURITIS (ITCHING)	0 (0.0%)	4 (5.4%)	2 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (5.4%)
SYSTEMIC	6 (8.1%)	4 (5.4%)	5 (6.8%)	2 (2.7%)	3 (4.1%)	2 (2.7%)		9 (12.2%)
WHOLE BODY/GENERAL	3 (4.1%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)		4 (5.4%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
SENSATION OF WARMTH, GENERAL	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
FATIGUE/WEAKNESS	2 (2.7%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)		3 (4.1%)
HEADACHE	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)		2 (2.7%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)		1 (1.4%)

62200

Table 2(cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (126 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)
MUSCULOSKELETAL	2 (2.7%)	2 (2.7%)	2 (2.7%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	3 (4.1%)
ARTHRALGIA (OTHER)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
SHOULDER PAIN	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
OTHER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
DIGESTIVE SYSTEM	1 (1.4%)	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)	1 (1.4%)	3 (4.1%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	2 (2.7%)
NAUSEA	1 (1.4%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	2 (2.7%)
UROGENITAL SYSTEM	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
URINARY TRACT INFECTION	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
INSOMNIA/DISTURBED SLEEP	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (126 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	19 (25.7%)	13 (17.6%)	8 (10.8%)	3 (4.1%)	3 (4.1%)	2 (2.7%)	22 (29.7%)
PERSONS WITH NO COMPLAINTS	55 (74.3%)	61 (82.4%)	66 (89.2%)	71 (95.9%)	70 (95.9%)	71 (97.3%)	52 (70.3%)
PERSONS WITH NO DATA	19 (20.4%)	19 (20.4%)	19 (20.4%)	19 (20.4%)	20 (21.5%)	20 (21.5%)	19 (20.4%)

Table 3

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (97 PATIENTS) - DOSE I: DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	12 (12.5%)	4 (4.2%)	4 (4.2%)	2 (2.1%)	2 (2.1%)	2 (2.1%)		15 (15.6%)
PAIN	8 (8.3%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		8 (8.3%)
SORENESS	2 (2.1%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (3.1%)
ERYTHEMA (REDNESS)	0 (0.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
SWELLING	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
PAPULE(S)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)		1 (1.0%)
LYMPHADENOPATHY, REGIONAL	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)		2 (2.1%)
SYSTEMIC	5 (5.2%)	10 (10.4%)	5 (5.2%)	2 (2.1%)	1 (1.0%)	0 (0.0%)		14 (14.6%)
WHOLE BODY/GENERAL	5 (5.2%)	5 (5.2%)	3 (3.1%)	2 (2.1%)	0 (0.0%)	0 (0.0%)		10 (10.4%)
CHILLS	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
SWEATING	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (97 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH
CLINICAL COMPLAINTS	0	1	2	3	4	5	COMPLAINTS
FATIGUE/WEAKNESS	2 (2.1%)	2 (2.1%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	6 (6.3%)
HEADACHE	3 (3.1%)	2 (2.1%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	4 (4.2%)
LIGHTHEADED	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
ILLNESS, NOS	1 (1.0%)	2 (2.1%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (4.2%)
RESPIRATORY	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)
COUGH	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
ARTHRALGIA, MONOARTICULAR	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
DIGESTIVE SYSTEM	0 (0.0%)	3 (3.1%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	4 (4.2%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (97 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						
CLINICAL COMPLAINTS	0	1	2	3	4	5	NUMBER WITH COMPLAINTS
NAUSEA	0 (0.0%)	2 (2.1%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
DEPRESSION	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
PERSONS WITH COMPLAINTS	15 (15.6%)	13 (13.5%)	9 (9.4%)	4 (4.2%)	3 (3.1%)	2 (2.1%)	26 (27.1%)
PERSONS WITH NO COMPLAINTS	81 (84.4%)	83 (86.5%)	87 (90.6%)	92 (95.8%)	93 (96.9%)	94 (97.9%)	70 (72.9%)
PERSONS WITH NO DATA	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)

00234

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (97 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER
CLINICAL COMPLAINTS	0	1	2	3	4	5	WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	3 (3.6%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	4 (4.8%)
PAIN	2 (2.4%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	3 (3.6%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
OTHER	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
SYSTEMIC	3 (3.6%)	2 (2.4%)	2 (2.4%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	7 (8.4%)
WHOLE BODY/GENERAL	2 (2.4%)	2 (2.4%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	5 (6.0%)
SENSATION OF WARMTH, GENERAL	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
FATIGUE/WEAKNESS	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)
LIGHTHEADED	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
ILLNESS, NOS	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	3 (3.6%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (97 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)	1 (1.2%)		3 (3.6%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
COUGH	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
CARDIOVASCULAR	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
BRADYCARDIA/BRADYARRHYTHMIA	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
MUSCULOSKELETAL	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
ARTHRALGIA (OTHER)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
DIGESTIVE SYSTEM	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (3.6%)
DIARRHEA	1 (1.2%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.4%)
NAUSEA	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
PERSONS WITH COMPLAINTS	5 (6.0%)	3 (3.6%)	3 (3.6%)	2 (2.4%)	3 (3.6%)	1 (1.2%)		10 (12.0%)
PERSONS WITH NO COMPLAINTS	78 (94.0%)	80 (96.4%)	80 (96.4%)	81 (97.6%)	80 (96.4%)	82 (98.8%)		73 (88.0%)
PERSONS WITH NO DATA	2 (2.4%)	2 (2.4%)	2 (2.4%)	2 (2.4%)	2 (2.4%)	2 (2.4%)		2 (2.4%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (94 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	6 (10.5%)	8 (14.0%)	8 (14.0%)	6 (10.5%)	4 (7.0%)	3 (5.3%)	11 (19.3%)
PAIN	2 (3.5%)	4 (7.0%)	5 (8.8%)	4 (7.0%)	3 (5.3%)	3 (5.3%)	6 (10.5%)
TENDERNESS	3 (5.3%)	2 (3.5%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	4 (7.0%)
ERYTHEMA (REDNESS)	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
WARMTH	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
SWELLING	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
PRURITIS (ITCHING)	0 (0.0%)	1 (1.8%)	2 (3.5%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	2 (3.5%)
SYSTEMIC	3 (5.3%)	2 (3.5%)	1 (1.8%)	2 (3.5%)	2 (3.5%)	2 (3.5%)	5 (8.8%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
HEADACHE	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
INFECTIOUS SYNDROMES	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	2 (3.5%)
INFLUENZA, NOS	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	2 (3.5%)

00237

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (94 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RESPIRATORY	2 (3.5%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	3 (5.3%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	1 (1.8%)
LARYNGITIS	2 (3.5%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
DIGESTIVE SYSTEM	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
OTHER	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
NERVOUS SYSTEM	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
VERTIGO/DIZZINESS	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
PERSONS WITH COMPLAINTS	9 (15.8%)	10 (17.5%)	9 (15.8%)	8 (14.0%)	6 (10.5%)	5 (8.8%)	14 (24.6%)
PERSONS WITH NO COMPLAINTS	48 (84.2%)	47 (82.5%)	48 (84.2%)	49 (86.0%)	51 (89.5%)	52 (91.2%)	43 (75.4%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (148 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	89 (87.3%)	98 (91.6%)	98 (93.3%)	100 (96.2%)	101 (100.0%)	96 (99.0%)			88 (80.7%)
99 - 99.9	13 (12.7%)	8 (7.5%)	7 (6.7%)	3 (2.9%)	0 (0.0%)	1 (1.0%)			19 (17.4%)
100 - 100.9	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (0.9%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)			1 (0.9%)
TEMPERATURE TAKEN	102 (68.9%)	107 (72.3%)	105 (70.9%)	104 (70.3%)	101 (68.2%)	97 (65.5%)			109 (73.6%)
TEMPERATURE NOT TAKEN	46 (31.1%)	41 (27.7%)	43 (29.1%)	44 (29.7%)	47 (31.8%)	51 (34.5%)			39 (26.4%)

Table 4 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (146 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
< 99	64 (87.7%)	70 (93.3%)	71 (94.7%)	69 (94.5%)	68 (95.8%)	63 (94.0%)		60 (78.9%)
99 - 99.9	9 (12.3%)	5 (6.7%)	4 (5.3%)	4 (5.5%)	3 (4.2%)	4 (6.0%)		16 (21.1%)
TEMPERATURE TAKEN	73 (50.0%)	75 (51.4%)	75 (51.4%)	73 (50.0%)	71 (48.6%)	67 (45.9%)		76 (52.1%)
TEMPERATURE NOT TAKEN	73 (50.0%)	71 (48.6%)	71 (48.6%)	73 (50.0%)	75 (51.4%)	79 (54.1%)		70 (47.9%)

00240

Table 4 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (126 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	0 (0.0%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	1 (2.4%)	1 (2.4%)			0 (0.0%)
< 99	36 (87.8%)	37 (84.1%)	40 (90.9%)	43 (97.7%)	38 (90.5%)	39 (92.9%)			38 (79.2%)
99 - 99.9	4 (9.8%)	3 (6.8%)	2 (4.5%)	0 (0.0%)	2 (4.8%)	2 (4.8%)			6 (12.5%)
100 - 100.9	1 (2.4%)	2 (4.5%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)			3 (6.3%)
101 - 101.9	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)
102 - 102.9	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (2.1%)
TEMPERATURE TAKEN	41 (32.5%)	44 (34.9%)	44 (34.9%)	44 (34.9%)	42 (33.3%)	42 (33.3%)			48 (38.1%)
TEMPERATURE NOT TAKEN	85 (67.5%)	82 (65.1%)	82 (65.1%)	82 (65.1%)	84 (66.7%)	84 (66.7%)			78 (61.9%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (97 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	85 (92.4%)	90 (93.8%)	88 (91.7%)	90 (95.7%)	89 (95.7%)	85 (95.5%)			83 (86.5%)
99 - 99.9	6 (6.5%)	4 (4.2%)	7 (7.3%)	3 (3.2%)	4 (4.3%)	3 (3.4%)			10 (10.4%)
100 - 100.9	1 (1.1%)	2 (2.1%)	1 (1.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)			3 (3.1%)
TEMPERATURE TAKEN	92 (94.8%)	96 (99.0%)	96 (99.0%)	94 (96.9%)	93 (95.9%)	89 (91.8%)			96 (99.0%)
TEMPERATURE NOT TAKEN	5 (5.2%)	1 (1.0%)	1 (1.0%)	3 (3.1%)	4 (4.1%)	8 (8.2%)			1 (1.0%)

00242

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (97 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	71 (93.4%)	74 (92.5%)	75 (93.8%)	75 (94.9%)	73 (91.2%)	72 (91.1%)			67 (83.7%)
99 - 99.9	4 (5.3%)	5 (6.3%)	4 (5.0%)	4 (5.1%)	6 (7.5%)	6 (7.6%)			10 (12.5%)
100 - 100.9	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	1 (1.2%)	1 (1.3%)			2 (2.5%)
101 - 101.9	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (1.2%)
TEMPERATURE TAKEN	76 (78.4%)	80 (82.5%)	80 (82.5%)	79 (81.4%)	80 (82.5%)	79 (81.4%)			80 (82.5%)
TEMPERATURE NOT TAKEN	21 (21.6%)	17 (17.5%)	17 (17.5%)	18 (18.6%)	17 (17.5%)	18 (18.6%)			17 (17.5%)

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 8795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (94 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	38 (86.4%)	40 (85.1%)	41 (87.2%)	44 (95.7%)	39 (88.6%)	39 (86.7%)			38 (80.9%)
99 - 99.9	3 (7.0%)	6 (12.8%)	6 (12.8%)	1 (2.2%)	3 (6.8%)	4 (8.9%)			6 (12.8%)
100 - 100.9	2 (4.7%)	1 (2.1%)	0 (0.0%)	1 (2.2%)	2 (4.5%)	2 (4.4%)			3 (6.4%)
TEMPERATURE TAKEN	43 (45.7%)	47 (50.0%)	47 (50.0%)	46 (48.9%)	44 (46.8%)	45 (47.9%)			47 (50.0%)
TEMPERATURE NOT TAKEN	51 (54.3%)	47 (50.0%)	47 (50.0%)	48 (51.1%)	50 (53.2%)	49 (52.1%)			47 (50.0%)

SAT-LA.10

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

F. Deinhardt*, W. Jilg, G. Zoulek, B. Lorbeer, and B. Wilske
Max von Pettenkofer-Institute, 8000 Munchen 2, Western Germany

Thirty healthy, young volunteers free of any HBV markers were vaccinated with a recombinant hepatitis B vaccine prepared by Merck, Sharp & Dohme, West Point, PA. Ten µg HBsAg were administered intramuscularly at time 0, and one month later. Seroconversion rates and geometric mean concentrations after 1, 2 and 3 months were compared with an age- and sex-matched control group vaccinated with 20 µg of plasma derived vaccine (Merck Sharp & Dohme) (Table 1).

Table 1: Comparison of immune response after recombinant vaccine and plasma derived vaccine.

month	seroconversion %		anti-HBs (geom. mean) mIU	
	recombinant vaccine	plasma vaccine	recombinant vaccine	plasma vaccine
1	27	44	8.6	15.2
2	70	95	37.8	52.5
3	97	95	27.4	164.4

In the recombinant vaccine group, 38% of the total anti-HBs at month 3 was directed against the determinant a of HBsAg, compared to 30% in the control group. No increase in antibody titers against candida albicans was found in recipients of the recombinant vaccine 4 weeks after the second injection as compared to prevaccination levels. No serious side effects were observed in any of the vaccinated individuals.

Deinhardt F, Jilg W, Zoulek G, Lorbeer B, Wilske B. Clinical evaluation of a recombinant hepatitis B vaccine. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Straton, 1984:699.

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

W. JILG B. LORBEER
M. SCHMIDT B. WILSKE
G. ZOULEK F. DEINHARDT

Max von Pettenkofer-Institut, D-8000 München 2, West Germany

Summary Recombinant hepatitis B vaccine prepared from antigen expressed in yeast was given to 30 healthy young volunteers. Seroconversion rates and anti-HBs levels were compared with those in a control group matched for age and sex who had received plasma-derived hepatitis B vaccine. 4 weeks after the third immunisation results were similar in the two groups. In the recombinant vaccine group the immune response developed more slowly during the early phase and seroconversion rates and mean anti-HBs levels were slightly lower in males; this probably reflects use of a lower dose of recombinant vaccine (10 μg compared with 20 μg of the plasma vaccine). Side-effects were slight and antibody titres against *Candida albicans* were not increased in recipients of the recombinant vaccine.

Introduction

CURRENT hepatitis B vaccines are effective and safe.[1] However, because they are prepared from plasma of human hepatitis B virus carriers, supply is restricted by the amount of plasma available and by the cost of purifying the hepatitis B surface antigen (HBsAg) to render it free from hepatitis B virus and other possible infectious agents. Thus, to meet the worldwide need for hepatitis B vaccine, new means of preparation are required. Lately, vectors carrying the DNA sequence for HBsAg were prepared[2] and the antigen was expressed in the yeast *Saccharomyces cerevisiae*.[3] Yeast cells assemble the HBsAg polypeptides into particles similar to the 22 nm particles found in human plasma; yeast HBsAg, however, unlike human HBsAg is not glycosylated. A vaccine developed from yeast HBsAg stimulated antibody production in mice, grivet monkeys, and chimpanzees; and when vaccinated chimpanzees were challenged with human hepatitis B virus of different subtypes, they were completely protected.[4] We now report the immunisation of 30 healthy young volunteers with the first hepatitis B vaccine produced by recombinant DNA technology.

Subjects, Materials, and Methods

Subjects

30 healthy medical students and laboratory workers were studied (17 female, 13 male; mean age 25±3 yr, range 21–34). Subjects in the control group had been immunised with plasma-derived vaccine in an earlier study;[5] they were matched by age and sex to the study group (table I). Before vaccination, all subjects were negative for HBsAg, anti-HBs, and antibodies against hepatitis B core antigen (anti-HBc), and their aminotransferase levels were normal (alanine and aspartate aminotransferases ≤17 and ≤19 IU/l, respectively).

TABLE I—SEX AND AGE DISTRIBUTION OF THE TWO VACCINATION GROUPS*

	Total		Female		Male	
	No	Age (yr)	No	Age (yr)	No	Age (yr)
Recombinant vaccine	30	24·9±3·1 (21–34)	17	24·6±3·5 (21–34)	13	25·3±2·6 (23–32)
Plasma-derived vaccine	41	25·0±2·7 (21–32)	23	24·7±3·0 (21–32)	18	25·4±2·3 (23–32)

*Means and standard deviations (range).

Vaccines

The recombinant hepatitis B vaccine was prepared by Merck Sharp & Dohme research laboratories (lot 934/C-J 625). It consists of purified HBsAg, subtype *adw*, produced in recombinant *S cerevisiae* and absorbed on aluminium hydroxide. 1 ml of vaccine contained 10 μg of HBsAg. Plasma vaccine was also subtype *adw* (lot 773/801-2/ C-F 732-2 Merck Sharp & Dohme). Subjects in the study group received 10 μg of recombinant vaccine intramuscularly at 0, 1, and 6 months; subjects in the control group received 20 μg of plasma-derived vaccine at the same intervals. (Since the recombinant vaccine was treated with formalin only, and not with pepsin and urea, it was initially thought to be more immunogenic than the plasma vaccine.) Blood samples were taken on the day of the first vaccination and then monthly. Subjects were asked to keep daily records of body temperature and side-effects for 5 days after each injection.

Serology

HBsAg, anti-HBs, and anti-HBc were tested by radioimmunoassay with commercially available kits ('AUSRIA II', 'AUSAB', 'CORAB', Abbott Laboratories). Anti-HBs concentrations in IU/l were calculated by the method of Hollinger et al,[6] the first WHO reference preparation 1977 being used in a dilution of 1:400.[7] Because *S cerevisiae* and *C albicans* have common antigenic determinants,[8] antibodies against *C albicans* were determined by passive haemagglutination in 26 subjects on day 0 and 4 weeks after the second and third injections of recombinant vaccine. Sera were examined for antibodies against the determinant *a* of HBsAg as previously described.[9]

Results

Seroconversion rates and mean anti-HBs levels during the course of immunisation are shown in table II. The immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels. These differences became non-significant after the booster dose at month 6 when 29 out of 30 subjects (97%) were anti-HBs positive (control, 41 out of 41) with a geometric mean anti-HBs level of 2135 IU/l (control, 4299 IU/l). All anti-HBs-positive individuals in the recombinant vaccine group had anti-HBs values above 10 IU/l; 2 (6·7%) were low responders (anti-HBs below 100 IU/l), 3 (10%) were intermediate responders (anti-HBs 101–1000 IU/l), and 22 (73·3%) were normal to high responders (anti-HBs greater than 1000 IU/l). Similar values

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2:1174-5.

TABLE II—IMMUNE RESPONSES AFTER VACCINATION

Month	Seroconversion (%)		Anti-HBs (IU/l)*		p†
	Recombinant vaccine (n = 30)	Plasma-derived vaccine (n = 41)	Recombinant vaccine	Plasma-derived vaccine	
1	8 (27)	18 (44)	9	15	<0·05
2	21 (70)	39 (95)	30	53	<0·05
3	28 (93)	39 (95)	29	104	<0·05
4	28 (93)	39 (95)	63	228	<0·05
5	28 (93)	39 (95)	79	273	<0·05
6	28 (93)	39 (95)	60	263	<0·05
7	29 (97)	41 (100)	2135	4299	>0·05

*Anti-HBs is given as the geometric mean in responders only.
†Wilcoxon's rank-sum test.

TABLE III—IMMUNE RESPONSES IN MALES AND FEMALES (AFTER THREE INOCULATIONS)

—	Recombinant vaccine	Plasma-derived vaccine	p*
Males:			
Seroconversion (%)†	12/13 (92)	18/18 (100)	
Anti-HBs (IU/l)‡	911	3895	<0·05
Females:			
Seroconversion (%)†	17/17 (100)	23/23 (100)	
Anti-HBs (IU/l)‡	3282	4640	>0·05

*Wilcoxon's rank-sum test.
†Numbers of anti-HBs-positive subjects divided by the total number.
‡Geometric mean.

were obtained in the control group. Although the immune responses to the two vaccines were similar after the full course of immunisation, responses of male and female subjects differed. In both groups all the women seroconverted and the geometric mean anti-HBs levels did not differ significantly (3282 IU/l vs 4640 IU/l). However, in males receiving recombinant vaccine the seroconversion rate was 92% vs 100%, and the geometric mean anti-HBs was 911 vs 3894 IU/l (table III).

Preliminary tests indicate that recombinant vaccine, like the plasma-derived vaccine, induces antibodies against both the *a* and the *d* components of HBs antigen. After month 3, about 38% of the total anti-HBs was directed against determinant *a*.

No important side-effects were observed after immunisation with the recombinant vaccine. Minor local symptoms such as transient pain, itching, burning, and slight swelling at the injection site were reported after 24 of the 90 injections. On no occasion did body temperature rise above 37·9°C.

Of 26 subjects tested, all had antibodies against *C albicans* on day 0 (titres from 1:80 to 1:320) and titres did not increase after immunisation.

Discussion

Three doses of 10 µg recombinant hepatitis B vaccine gave seroconversion rates and geometric mean anti-HBs levels similar to those induced by three doses of 20 µg plasma-derived vaccine. The results were also comparable with those obtained in large trials of conventional vaccines.[10,11]

The immune response to the recombinant vaccine, however, was less strong during the early phase (1–6 months) in all subjects, and in males mean anti-HBs values were lower in the recombinant group even after the complete course of immunisation. These results are comparable with findings in subjects immunised with a smaller dose (5 µg) of conventional vaccine (Jilg W, Zachoval R, Schmidt M, Deinhardt F, unpublished), and may reflect the use of smaller amounts of antigen. Antigen content of both recombinant vaccine and plasma-derived vaccine is determined as HBsAg protein. The vaccines are produced and treated differently, however;[4,12] therefore similar protein content does not necessarily mean similar immunogenicity. The yeast and plasma derived HBsAg differed in reactivity in radioimmunoassay tests; the reactivity of the HBsAg produced in yeast was only 20–50% of the reactivity of plasma-derived HBsAg.[4] Thus, weight-for-weight the immunogenicity of the recombinant vaccine seems to be less than that of the plasma-derived vaccine. Another explanation for the lower immune response may be that 10 µg of recombinant vaccine was given per single dose compared with 20 µg of plasma-derived vaccine. A higher dose (20 or 40 µg) of the recombinant vaccine would probably give the same results as the plasma-derived vaccine.

Despite the slightly lower immunity achieved with the recombinant vaccine, protection will probably be as good as with the conventional vaccine, in that all 29 subjects with detectable anti-HBs had values above the protection level of 10 IU/l.[13] In 73%, anti-HBs levels after the third vaccination were more than 1000 IU/l; this has been shown to guarantee persistence of anti-HBs above the protective limit for at least 3 years.[14] In addition, all subjects who seroconverted had antibodies against the common determinant *a* of HBsAg, indicating cross-protection against infections with other subtypes of HBsAg. Side-effects after the recombinant vaccine were negligible and did not differ from those observed after plasma-derived vaccine. The absence of a rise in antibodies against *C albicans* indicates that no cross-reacting yeast antigens were present in the vaccine.

We thank Mrs Liane Sabrainis for expert technical assistance.

Correspondence should be addressed to W. J., Max v. Pettenkofer-Institut, Pettenkoferstr. 9 a, 8000 München 2, West Germany.

REFERENCES

1. Deinhardt F. Control of hepatitis A and B with vaccines. *Ann Clin Res* 1982; 14: 236–44.
2. Valenzuela P, Gray P, Quiroga M, Zaldivar J, Goodman HM, Rutter WJ. Nucleotide sequence of the gene coding for the major protein of hepatitis B surface antigen. *Nature* 1979; 280: 815–19.
3. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298: 347–50.
4. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984; 307: 178–80.
5. Zachoval R, Jilg W, Lorbeer B, Schmidt M, Deinhardt F. Passive-active immunisation against hepatitis B. *J Infect Dis* 1984; 150: 112–17.
6. Hollinger FB, Adam E, Heiberg D, Melnick JL. Response to hepatitis B vaccine in a young adult population. In: Szmuness W, Alter HJ, Maynard JE, eds. Viral hepatitis: 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 451–66.
7. World Health Organisation. *WHO Tech Rep Ser* no 638; 1979: 29.
8. Tsuchiya T, Fukazawa Y, Kawakita S. Serological classification of the genus *Candida*. In: Tokyo Research Committee of Candidiasis: Studies of candidiasis in Japan. Tokyo: Education Ministry of Japan, 1961: 34–36.
9. Jilg W, Delfmann C, Deinhardt F, Roumeliotou-Karayannis AJ, Papaevangelou GJ, Mushahwar IK, Overby LR. Hepatitis B surface antigen (HBsAg) subtype-specific antibodies in persons vaccinated against hepatitis B. *J Med Virol* 1984; 13: 171–78.
10. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial on the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981; 1: 377–85.
11. Crosnier J, Jungers P, Couroucé AM, et al. Randomised placebo-controlled trial of hepatitis B surface antigen vaccine in French haemodialysis units. I Medical staff. *Lancet* 1981; i: 455–59.
12. Hilleman MR, Buynak EB, McAleer WJ, McLean AA. Human hepatitis B vaccine. In: Krugman S, Sherlock S, eds. Proceedings of the European Symposium on Hepatitis B. Rahway: Merck Sharp & Dohme International, 1981: 120–38.
13. Goudeau A, Coursaget P, Barin F, et al. Prevention of hepatitis B by active and passive-active immunisation. In: Szmuness W, Alter HJ, Maynard JE, eds. Viral hepatitis: 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 509–25.
14. Jilg W, Schmidt M, Zachoval R, Deinhardt F. Persistenz von Antikörpern gegen Hepatitis B-Oberflächenantigen nach Impfung gegen Hepatitis B. *Dtsch Med Wschr* (in press).

Edward M. Scolnick, Arlene A. McLean,
David J. West, Jules L. Dienstag,
Eloise Watkins, Friedrich Deinhardt and Wolfgang Jilg

23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

VIRAL HEPATITIS and LIVER DISEASE
ISBN 0-8089-1678-5

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 798
PURPOSE:	To evaluate antibody and clinical responses to 5 mcg, 10 mcg, and 20 mcg doses of the vaccine among healthy adult paramedics who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #974/C-K446 (20 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	F. Blaine Hollinger, M.D. Professor of Medicine, Virology and Epidemiology Baylor College of Medicine Department of Virology and Medicine Texas Medical Center Houston, TX 77030
SECONDARY INVESTIGATORS:	Catherine Troisi, Ph.D. Baylor College of Medicine Department of Virology and Medicine Texas Medical Center Houston, TX 77030 Dorothy Heiberg, R.N. Baylor College of Medicine Department of Virology and Medicine Texas Medical Center Houston, TX 77030
STUDY LOCATION:	Baylor College of Medicine Department of Virology and Medicine Texas Medical Center Houston, TX 77030
DATE INITIATED:	April 11, 1984
DATE COMPLETED:	In progress.

Study 798

STUDY POPULATION: The study population is comprised of 109 male paramedical personnel in the Houston area who were initially negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Participants are entered into the study as members of triplets, one at each dose level, matched on body weight (within 9 lbs.).

Eligible participants receive an intramuscular injection of vaccine at 0, 1, and 6 months. The volume (dose) of the injections received by an individual is 1.0 ml (20 mcg HBsAg), 0.5 ml (10 mcg HBsAg), or 0.25 ml (5 mcg HBsAg).

Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (approximately 30 ml) is obtained from each participant approximately four weeks before vaccination and on the day of vaccination. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12, and 24 months. All samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples with an anti-HBs titer $\geq$25 mIU/ml are tested to determine the proportions of anti-a and anti-d activity. Samples may be assayed for yeast antibody as required.

RESULTS: HEALTH CARE PERSONNEL:

5 mcg Lot #974/C-K446 at 0, 1, and 6 months
10 mcg Lot #974/C-K446 at 0, 1, and 6 months
20 mcg Lot #974/C-K446 at 0, 1, and 6 months

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
5 mcg	36	36	36
10 mcg	37	37	37
20 mcg	36	35	35

Study 798

RESULTS (CONT.):

2. Serologic Results:

Serology data are available, at 7/8 months, for 36, 35, and 35 participants who received 5, 10, and 20 mcg injections of vaccine, respectively.

The seroconversion rates and GMTs at 7/8 months are presented below.

Dose Levels	% with Anti-HBs S/N ≥ 2.1	% with Anti-HBs mIU/ml ≥ 10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥ 2.1	GMT (mIU/ml) Responders mIU/ml ≥ 10
5 mcg	97(35/36)	83(30/36)	72.9	82.2	136.9
10 mcg	97(34/35)	97(35/36)	513.1	620.6	620.6
20 mcg	100(35/35)	91(32/35)	733.0	733.0	1193.3

Refer to Table 1 for anti-HBs responses and GMTs at 12 months and for other time intervals.

Two subjects were found to be anti-HBs positive on the day of the first injection of vaccine (10 mcg dose). One of these vaccinees had a 3-fold rise in anti-HBs at one month and a >4-fold rise at two months. The other participant developed a >4-fold rise in anti-HBs titer five months after the second injection of vaccine.

3. Clinical Complaints:

Clinical follow-up data after each injection are available for 33, 33, and 32 participants who received 5, 10, and 20 mcg injections of vaccine, respectively. The overall frequencies of complaints follow.

Study 798

RESULTS (CONT.):

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	5 mcg	14(5/35)	3(1/33)	9(3/34)
	10 mcg	11(4/37)	18(6/33)	19(7/36)
	20 mcg	25(9/36)	28(9/32)	21(7/34)
Systemic	5 mcg	34(12/35)	15(5/33)	18(6/34)
	10 mcg	30(11/37)	15(5/33)	28(10/36)
	20 mcg	33(12/36)	28(9/32)	21(7/34)

Refer to Tables 2 through 4 for listings of specific clinical complaints by dose level and injection number. Maximum temperature data are presented in Tables 5 through 7.

There were no serious or alarming reactions attributable to vaccine.

Reactions reported to the DoBRR

A 32-year old male subject had an elevated ALT level at the time of his third injection of vaccine. Two weeks after the third injection of vaccine, the subject was symptomatic for anorexia and vomiting. He was icteric, had dark urine and elevated bilirubin and ALT levels. He was negative for anti-HAV, HBsAg, and anti-HBc. He was diagnosed as having non A non B hepatitis. This illness was not considered related to the vaccine.

PUBLICATIONS:

Hollinger FB, Sanchez Y, Troisi C, Dreesman GR, Melnick JL. Immunogenicity and reactogenicity of new hepatitis B vaccines. Hepatology 1984; 4:1027 (Abstract).

Hollinger FB, Troisi CL, Pepe PE. Anti-HBs responses to vaccination with a human hepatitis B vaccine made by recombinant DNA technology in yeast. J Infect Dis 1986; 1:156-9.

Table 1

Antibody Responses Among Healthy Adults Following Vaccination with
5, 10, or 20 mcg Injections of Yeast Recombinant Hepatitis B Vaccine
Lot #974/C-K446 at 0, 1, and 6 Months in Study #798

	5 mcg					10 mcg					20 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Mos.)	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	11 (4/36)	6 (2/36)	0.7	6.4	27.0	29 (10/35)	8.6 (3/35)	2.2	6.1	34.0	29 (10/35)	11 (4/35)	1.5	8.7	72.9
2	22 (8/36)	14 (5/36)	1.6	18.3	60.7	74 (26/35)	40 (14/35)	8.1	14.2	63.3	83 (29/35)	34 (12/35)	10.7	14.8	94.6
3	44 (16/36)	17 (6/36)	1.9	5.8	26.0	86 (30/35)	37 (13/35)	10.1	11.9	61.6	89 (31/35)	57 (20/35)	14.3	16.4	38.1
6	61 (22/36)	28 (10/36)	2.9	7.5	21.2	94 (33/35)	63 (22/35)	16.0	18.1	38.3	91 (31/34)	79 (27/34)	30.0	40.3	57.6
7/8	97 (35/36)	78 (28/36)	51.0	57.9	113.6	97 (34/35)	97 (34/35)	381.0	475.8	475.8	100 (35/35)	89 (31/35)	539.0	539.0	1021.5
12	83 (30/36)	47 (17/36)	12.7	17.6	55.1	97 (34/35)	86 (30/35)	74.5	90.4	130.1	97 (34/35)	86 (30/35)	184.6	217.4	370.9

00255

30991/2
1/3/86

Table 2
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	4 (11.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
PAIN	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
SORENESS	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
NUMBNESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
SYSTEMIC	8 (22.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (34.3%)
WHOLE BODY/GENERAL	8 (22.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
FLUSH	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
FATIGUE/WEAKNESS	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
HEADACHE	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
INTEGUMENTARY SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
MACULAR RASH	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
DIGESTIVE SYSTEM	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (36 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER
CLINICAL COMPLAINTS	0	1	2	3	4	5	WITH COMPLAINTS
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	0 (0.0%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
DIARRHEA	0 (0.0%)	1 (2.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
NAUSEA	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NERVOUS SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
VERTIGO/DIZZINESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
ORGANS OF SPECIAL SENSE	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
EYE PAIN	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	11 (31.4%)	2 (5.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (45.7%)
PERSONS WITH NO COMPLAINTS	24 (68.6%)	33 (94.3%)	32 (91.4%)	35 (100.0%)	0 (0.0%)	0 (0.0%)	19 (54.3%)
PERSONS WITH NO DATA	1 (2.8%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
SORENESS	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
SYSTEMIC	5 (15.2%)	4 (12.1%)	2 (6.1%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	5 (15.2%)
WHOLE BODY/GENERAL	2 (6.1%)	2 (6.1%)	2 (6.1%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	4 (12.1%)
MALAISE	0 (0.0%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
HEADACHE	2 (6.1%)	2 (6.1%)	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	3 (9.1%)
RESPIRATORY	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
PHARYNGITIS (SORE THROAT)	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
UPPER RESPIRATORY INFECT., NOS	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
MUSCULOSKELETAL	2 (6.1%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.1%)
MYALGIA	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
NECK PAIN	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
ORGANS OF SPECIAL SENSE	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
EARACHE	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
PERSONS WITH COMPLAINTS	6 (18.2%)	4 (12.1%)	2 (6.1%)	1 (3.0%)	0 (0.0%)	0 (0.0%)		6 (18.2%)
PERSONS WITH NO COMPLAINTS	27 (81.8%)	29 (87.9%)	31 (93.9%)	32 (97.0%)	1 (100.0%)	0 (0.0%)		27 (81.8%)
PERSONS WITH NO DATA	3 (8.3%)	3 (8.3%)	3 (8.3%)	3 (8.3%)	0 (0.0%)	0 (0.0%)		3 (8.3%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	2 (5.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (8.8%)
PAIN ON INJECTION	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
PAIN	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
SORENESS	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
PARESTHESIA	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
SYSTEMIC	3 (8.8%)	3 (8.8%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		6 (17.6%)
WHOLE BODY/GENERAL	3 (8.8%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (11.8%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
FATIGUE/WEAKNESS	2 (5.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (5.9%)
HEADACHE	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
RESPIRATORY	0 (0.0%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
RHINITIS	0 (0.0%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
DIGESTIVE SYSTEM	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
OTHER	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
UROGENITAL SYSTEM	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
OTHER	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
PERSONS WITH COMPLAINTS	4 (11.8%)	4 (11.8%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		8 (23.5%)
PERSONS WITH NO COMPLAINTS	30 (88.2%)	30 (88.2%)	31 (91.2%)	34 (100.0%)	0 (0.0%)	0 (0.0%)		26 (76.5%)
PERSONS WITH NO DATA	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.9%)

Table 3
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	3 (8.1%)	0 (0.0%)	2 (5.4%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	4 (10.8%)
SORENESS	2 (5.4%)	0 (0.0%)	2 (5.4%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	4 (10.8%)
PRURITIS (ITCHING)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
PARESTHESIA	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
SYSTEMIC	7 (18.9%)	5 (13.5%)	3 (8.1%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	11 (29.7%)
WHOLE BODY/GENERAL	5 (13.5%)	4 (10.8%)	3 (8.1%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	8 (21.6%)
FATIGUE/WEAKNESS	3 (8.1%)	4 (10.8%)	2 (5.4%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	6 (16.2%)
MALAISE	1 (2.7%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
HEADACHE	2 (5.4%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.1%)
INTEGUMENTARY SYSTEM	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
RASH, NOS	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
RESPIRATORY	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)

00262

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
UPPER RESPIRATORY INFECT., NOS	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
MUSCULOSKELETAL	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
MYALGIA	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
INSOMNIA/DISTURBED SLEEP	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
PERSONS WITH COMPLAINTS	10 (27.0%)	5 (13.5%)	5 (13.5%)	2 (5.4%)	0 (0.0%)	0 (0.0%)		14 (37.8%)
PERSONS WITH NO COMPLAINTS	27 (73.0%)	32 (86.5%)	32 (86.5%)	35 (94.6%)	0 (0.0%)	0 (0.0%)		23 (62.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	4 (12.1%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)		6 (18.2%)
SORENESS	3 (9.1%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (12.1%)
TENDERNESS	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)		2 (6.1%)
PRURITIS (ITCHING)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
SYSTEMIC	2 (6.1%)	3 (9.1%)	2 (6.1%)	3 (9.1%)	0 (0.0%)	0 (0.0%)		5 (15.2%)
WHOLE BODY/GENERAL	1 (3.0%)	3 (9.1%)	2 (6.1%)	3 (9.1%)	0 (0.0%)	0 (0.0%)		4 (12.1%)
FATIGUE/WEAKNESS	0 (0.0%)	3 (9.1%)	2 (6.1%)	3 (9.1%)	0 (0.0%)	0 (0.0%)		4 (12.1%)
HEADACHE	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
DIGESTIVE SYSTEM	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.1%)
DIARRHEA	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
NAUSEA	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
PERSONS WITH COMPLAINTS	6 (18.2%)	3 (9.1%)	3 (9.1%)	3 (9.1%)	1 (100.0%)	0 (0.0%)		11 (33.3%)

00264

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH NO COMPLAINTS	27 (81.8%)	30 (90.9%)	30 (90.9%)	30 (90.9%)	0 (0.0%)	0 (0.0%)		22 (66.7%)
PERSONS WITH NO DATA	4 (10.8%)	4 (10.8%)	4 (10.8%)	4 (10.8%)	0 (0.0%)	0 (0.0%)		4 (10.8%)

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	5 (13.9%)	3 (8.3%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (19.4%)
PAIN ON INJECTION	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
PAIN	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
SORENESS	2 (5.6%)	3 (8.3%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
TENDERNESS	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
PARESTHESIA	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
SYSTEMIC	6 (16.7%)	5 (13.9%)	3 (8.6%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	10 (27.8%)
WHOLE BODY/GENERAL	5 (13.9%)	1 (2.8%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (16.7%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
HEADACHE	3 (8.3%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.3%)
LIGHTHEADED	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
ACHINESS	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)

00266

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
MACULAR RASH	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
PRURITIS/ITCHING	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
RESPIRATORY	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		2 (5.6%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
PHARYNGITIS (SORE THROAT)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
MUSCULOSKELETAL	0 (0.0%)	1 (2.8%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		2 (5.6%)
ARTHRALGIA (OTHER)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
BACK PAIN	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
NECK PAIN	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
SHOULDER PAIN	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
DIGESTIVE SYSTEM	1 (2.8%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (8.3%)
NAUSEA	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (5.6%)

00267

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (37 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER
CLINICAL COMPLAINTS	0	1	2	3	4	5	WITH COMPLAINTS
OTHER	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	1 (2.8%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
INSOMNIA/DISTURBED SLEEP	0 (0.0%)	1 (2.8%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
PERSONS WITH COMPLAINTS	9 (25.0%)	8 (22.2%)	4 (11.4%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	12 (33.3%)
PERSONS WITH NO COMPLAINTS	27 (75.0%)	28 (77.8%)	31 (88.6%)	33 (94.3%)	0 (0.0%)	0 (0.0%)	24 (66.7%)
PERSONS WITH NO DATA	1 (2.7%)	1 (2.7%)	2 (5.4%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	1 (2.7%)

Table 4
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	8 (22.2%)	2 (5.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (25.0%)
SORENESS	8 (22.2%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (25.0%)
STIFFNESS/TIGHTNESS	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
ECCHYMOSIS	0 (0.0%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
SYSTEMIC	5 (13.9%)	5 (13.9%)	5 (13.9%)	4 (11.1%)	0 (0.0%)	0 (0.0%)	12 (33.3%)
WHOLE BODY/GENERAL	4 (11.1%)	3 (8.3%)	2 (5.6%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	8 (22.2%)
FEVER (TEMP. NOT REPORTED)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
FATIGUE/WEAKNESS	2 (5.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.3%)
HEADACHE	1 (2.8%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	3 (8.3%)
ACHINESS	0 (0.0%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
INTEGUMENTARY SYSTEM	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
PRURITIS/ITCHING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RASH, NOS	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	2 (5.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
COUGH	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
BACK PAIN	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
DIGESTIVE SYSTEM	1 (2.8%)	2 (5.6%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
DIARRHEA	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
NAUSEA	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
NERVOUS SYSTEM	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
VERTIGO/DIZZINESS	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)

Table 4 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	10 (27.8%)	7 (19.4%)	6 (16.7%)	4 (11.1%)	0 (0.0%)	0 (0.0%)		17 (47.2%)
PERSONS WITH NO COMPLAINTS	26 (72.2%)	29 (80.6%)	30 (83.3%)	32 (88.9%)	0 (0.0%)	0 (0.0%)		19 (52.8%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	8 (25.0%)	1 (3.1%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (28.1%)
PAIN	2 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.3%)
SORENESS	6 (18.8%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (18.8%)
TENDERNESS	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
SYSTEMIC	3 (9.4%)	2 (6.3%)	3 (9.4%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	9 (28.1%)
WHOLE BODY/GENERAL	3 (9.4%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (12.5%)
FATIGUE/WEAKNESS	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
HEADACHE	2 (6.3%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (9.4%)
INTEGUMENTARY SYSTEM	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	2 (6.3%)
RASH, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
OTHER	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	2 (6.3%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
RHINITIS	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
MUSCULOSKELETAL	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
ARTHRALGIA, MONOARTICULAR	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
PERSONS WITH COMPLAINTS	9 (28.1%)	3 (9.4%)	5 (15.6%)	2 (6.3%)	0 (0.0%)	0 (0.0%)		15 (46.9%)
PERSONS WITH NO COMPLAINTS	23 (71.9%)	29 (90.6%)	27 (84.4%)	30 (93.8%)	0 (0.0%)	0 (0.0%)		17 (53.1%)
PERSONS WITH NO DATA	3 (8.6%)	3 (8.6%)	3 (8.6%)	3 (8.6%)	0 (0.0%)	0 (0.0%)		3 (8.6%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	5 (14.7%)	2 (5.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		7 (20.6%)
SORENESS	4 (11.8%)	2 (5.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		6 (17.6%)
NODULE FORMATION	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
SYSTEMIC	5 (14.7%)	4 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		7 (20.6%)
WHOLE BODY/GENERAL	3 (8.8%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		6 (17.6%)
SWEATING	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
FATIGUE/WEAKNESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
MALAISE	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
HEADACHE	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (5.9%)
ACHINESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
CHEST TIGHTNESS	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
INTEGUMENTARY SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (35 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH
CLINICAL COMPLAINTS	0	1	2	3	4	5	COMPLAINTS
URTICARIA/HIVES	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
MUSCULOSKELETAL	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NECK STIFFNESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
DIGESTIVE SYSTEM	0 (0.0%)	2 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.9%)
DIARRHEA	0 (0.0%)	2 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.9%)
NAUSEA	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
VOMITING	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	8 (23.5%)	6 (17.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	10 (29.4%)
PERSONS WITH NO COMPLAINTS	26 (76.5%)	28 (82.4%)	33 (97.1%)	33 (97.1%)	0 (0.0%)	0 (0.0%)	24 (70.6%)
PERSONS WITH NO DATA	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (36 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	30 (88.2%)	32 (91.4%)	34 (97.1%)	34 (97.1%)	0 (0.0%)	0 (0.0%)			28 (80.0%)
99 - 99.9	4 (11.8%)	3 (8.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)			7 (20.0%)
TEMPERATURE TAKEN	34 (94.4%)	35 (97.2%)	35 (97.2%)	35 (97.2%)	0 (0.0%)	0 (0.0%)			35 (97.2%)
TEMPERATURE NOT TAKEN	2 (5.6%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	36 (100.0%)	36 (100.0%)			1 (2.8%)

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (36 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (3.3%)	1 (3.2%)	1 (3.4%)	1 (3.1%)	0 (0.0%)	0 (0.0%)			1 (3.1%)
< 99	25 (83.3%)	28 (90.3%)	26 (89.7%)	27 (84.4%)	1 (100.0%)	0 (0.0%)			23 (71.9%)
99 - 99.9	2 (6.7%)	1 (3.2%)	2 (6.9%)	4 (12.5%)	0 (0.0%)	0 (0.0%)			6 (18.8%)
100 - 100.9	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (3.1%)
101 - 101.9	1 (3.3%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (3.1%)
TEMPERATURE TAKEN	30 (83.3%)	31 (86.1%)	29 (80.6%)	32 (88.9%)	1 (2.8%)	0 (0.0%)			32 (88.9%)
TEMPERATURE NOT TAKEN	6 (16.7%)	5 (13.9%)	7 (19.4%)	4 (11.1%)	35 (97.2%)	36 (100.0%)			4 (11.1%)

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (36 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	6 (18.8%)	6 (18.8%)	6 (18.2%)	6 (18.8%)	0 (0.0%)	0 (0.0%)		6 (18.2%)
< 99	23 (71.9%)	23 (71.9%)	25 (75.8%)	25 (78.1%)	0 (0.0%)	0 (0.0%)		21 (63.6%)
99 - 99.9	3 (9.4%)	2 (6.3%)	2 (6.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)		5 (15.2%)
100 - 100.9	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
TEMPERATURE TAKEN	32 (88.9%)	32 (88.9%)	33 (91.7%)	32 (88.9%)	0 (0.0%)	0 (0.0%)		33 (91.7%)
TEMPERATURE NOT TAKEN	4 (11.1%)	4 (11.1%)	3 (8.3%)	4 (11.1%)	36 (100.0%)	36 (100.0%)		3 (8.3%)

Table 6

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (37 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	28 (77.8%)	33 (91.7%)	31 (86.1%)	32 (94.1%)	0 (0.0%)	0 (0.0%)			26 (72.2%)
99 - 99.9	8 (22.2%)	3 (8.3%)	5 (13.9%)	2 (5.9%)	0 (0.0%)	0 (0.0%)			10 (27.8%)
TEMPERATURE TAKEN	36 (97.3%)	36 (97.3%)	36 (97.3%)	34 (91.9%)	0 (0.0%)	0 (0.0%)			36 (97.3%)
TEMPERATURE NOT TAKEN	1 (2.7%)	1 (2.7%)	1 (2.7%)	3 (8.1%)	37 (100.0%)	37 (100.0%)			1 (2.7%)

00276

Table 6 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (37 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	21 (80.8%)	24 (96.0%)	21 (87.5%)	24 (88.9%)	0 (0.0%)	0 (0.0%)			22 (75.9%)
99 - 99.9	5 (19.2%)	1 (4.0%)	3 (12.5%)	3 (11.1%)	0 (0.0%)	0 (0.0%)			7 (24.1%)
TEMPERATURE TAKEN	26 (70.3%)	25 (67.6%)	24 (64.9%)	27 (73.0%)	0 (0.0%)	0 (0.0%)			29 (78.4%)
TEMPERATURE NOT TAKEN	11 (29.7%)	12 (32.4%)	13 (35.1%)	10 (27.0%)	37 (100.0%)	37 (100.0%)			8 (21.6%)

00280

Table 6 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (37 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (2.9%)	1 (2.9%)	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)			1 (2.9%)
< 99	27 (79.4%)	31 (91.2%)	30 (90.9%)	28 (84.8%)	0 (0.0%)	0 (0.0%)			23 (67.6%)
99 - 99.9	5 (14.7%)	2 (5.9%)	2 (6.1%)	4 (12.1%)	0 (0.0%)	0 (0.0%)			9 (26.5%)
100 - 100.9	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (2.9%)
TEMPERATURE TAKEN	34 (91.9%)	34 (91.9%)	33 (89.2%)	33 (89.2%)	0 (0.0%)	0 (0.0%)			34 (91.9%)
TEMPERATURE NOT TAKEN	3 (8.1%)	3 (8.1%)	4 (10.8%)	4 (10.8%)	37 (100.0%)	37 (100.0%)			3 (8.1%)

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (36 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	29 (80.6%)	34 (94.4%)	33 (94.3%)	33 (94.3%)	0 (0.0%)	0 (0.0%)			28 (77.8%)
99 - 99.9	6 (16.7%)	2 (5.6%)	1 (2.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)			6 (16.7%)
100 - 100.9	1 (2.8%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			2 (5.6%)
TEMPERATURE TAKEN	36 (100.0%)	36 (100.0%)	35 (97.2%)	35 (97.2%)	0 (0.0%)	0 (0.0%)			36 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	36 (100.0%)	36 (100.0%)			0 (0.0%)

00282

Table 7 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (35 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	27 (93.1%)	27 (96.4%)	28 (93.3%)	26 (89.7%)	0 (0.0%)	0 (0.0%)			26 (83.9%)
99 - 99.9	2 (6.9%)	1 (3.6%)	1 (3.3%)	2 (6.9%)	0 (0.0%)	0 (0.0%)			4 (12.9%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.4%)	0 (0.0%)	0 (0.0%)			1 (3.2%)
TEMPERATURE TAKEN	29 (82.9%)	28 (80.0%)	30 (85.7%)	29 (82.9%)	0 (0.0%)	0 (0.0%)			31 (88.6%)
TEMPERATURE NOT TAKEN	6 (17.1%)	7 (20.0%)	5 (14.3%)	6 (17.1%)	35 (100.0%)	35 (100.0%)			4 (11.4%)

Table 7 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (35 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (3.4%)	1 (3.2%)	1 (3.2%)	1 (3.1%)	0 (0.0%)	0 (0.0%)			1 (3.1%)
< 99	24 (82.8%)	30 (96.8%)	29 (93.5%)	30 (93.8%)	0 (0.0%)	0 (0.0%)			26 (81.3%)
99 - 99.9	3 (10.3%)	0 (0.0%)	1 (3.2%)	1 (3.1%)	0 (0.0%)	0 (0.0%)			4 (12.5%)
100 - 100.9	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (3.1%)
TEMPERATURE TAKEN	29 (82.9%)	31 (88.6%)	31 (88.6%)	32 (91.4%)	0 (0.0%)	0 (0.0%)			32 (91.4%)
TEMPERATURE NOT TAKEN	6 (17.1%)	4 (11.4%)	4 (11.4%)	3 (8.6%)	35 (100.0%)	35 (100.0%)			3 (8.6%)

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 153, NO. 1 • JANUARY 1986
 0022-1899/86/5301-0026$01.00

Anti-HBs Responses to Vaccination with a Human Hepatitis B Vaccine Made by Recombinant DNA Technology in Yeast

In the United States, the currently licensed vaccine against hepatitis B virus (HEPTAVAX-B®; Merck Sharp & Dohme, West Point, Pa) consists of hepatitis B surface antigen (HBsAg) that is purified from the plasma of chronically infected humans. Antibodies to the group *a* determinant of this complex antigen effectively neutralize the various subtypes of hepatitis B virus (HBV), as shown in a number of controlled clinical trials [1–3]. Despite overwhelming evidence that documents the efficacy of this vaccine, widespread acceptance by those who are at greatest risk of contracting hepatitis B has been less than expected because of a number of unrelated factors. The plasma-derived vaccine is expensive to prepare. A number of physical and chemical inactivation steps are used in purification, and extensive safety testings are mandated by the Food and Drug Administration in laboratory animals, cell cultures, and chimpanzees before the product can be marketed. In addition, there are of necessity batch-to-batch variations in human source material. These problems would have been surmountable in the marketing of this vaccine were it not for two recent events that made potential vaccine candidates overly cautious about accepting this new product: the increased incidence of Guillain-Barré syndrome that followed administration of the swine influenza vaccine in 1976 and the emergence of AIDS in the homosexual population. The latter problem was particularly relevant because HEPTAVAX-B is a plasma-derived product obtained from HBsAg-positive individuals, some of whom are in high-risk groups for AIDS. This raised the question whether AIDS might be transmitted to recipients of this vaccine. Unfortunately, despite numerous studies [4, 5] that eventually have refuted this hypothesis (on the basis of the susceptibility of retroviruses to inactivation by the physical and chemical steps used in producing the vaccine and by the lack of cases of AIDs or antibody seroconversions to human T lymphotropic virus type III observed among vaccinees at low risk of exposure to this disease), many members of groups at risk of contracting hepatitis B have been reluctant to accept this vaccine.

Because of these problems, alternate sources of vaccine are being developed. Among the first to become available for human trials was a 25,000–30,000 molecular weight HBsAg polypeptide derived by disrupting the intact 22-nm HBsAg particle with a nonionic detergent [6]. Immunogenicity of this product was superior to that of the human HBsAg source from which it was prepared, especially during the initial stages of antibody development. More recently a number of other vaccines that do not depend on human plasma as their source of HBsAg have been produced [7]. These include chemically synthesized peptides from several antigenic domains of the HBV, products of recombinant DNA technology, and live vaccinia virus recombinants containing the HBsAg gene.

In this paper we report one-year follow-up data on the immunogenicity and reactogenicity of a nonglycosylated HBsAg hepatitis B vaccine, subtype adw, made by recombinant DNA technology (Merck). The vaccine, prepared in the yeast *Saccharomyces cerevisiae* (strain 2150-2-3) [8, 9] was administered in three different doses (5, 10, and 20 μg) to an adult at-risk population.

Subjects and Methods

After screening 359 Emergency Medical Service personnel in Houston, 105 adult men (median age, 29 years; range, 22–40), determined by RIA or enzyme immunoassay to be free of any seromarkers of hepatitis B infection (Abbott Laboratories, North Chicago, Ill), were admitted to the study. All had antibody to HBsAg (anti-HBs) sample-to-negative-mean (S/N) ratios ≤1.4, levels of antibody to hepatitis B core antigen (anti-HBc) ≤39% inhibition, and HBsAg S/N ratios ≤1.2. These values are substantially below the cutoff levels endorsed by the manufacturers. In addition, each participant was required to have serum levels of liver enzyme (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) ≤50 IU/liter, as determined by the Beckman System TR enzyme autoanalyzer (Beckman Instruments, Palo Alto, Calif). Participants were in good health at the time of enrollment, had not been previously vaccinated against hepatitis B, and had signed informed consent releases. The study was approved by the Baylor College of Medicine Human Investigations Committee.

The 105 volunteers were weight matched within 4.5 kg [9a] into three groups of 35. Each member of each group received 5, 10, or 20 μg of an alum-adsorbed, DNA recombinant hepatitis B vaccine (lot no. 974/CK-446) containing 20 μg of HBsAg/ml. The vaccine was purified from

Received for publication 21 May 1985, and in revised form 9 July 1985.

This work was supported by a grant from Merck & Company, West Point, Pennsylvania. Computational assistance was provided by the CLINFO Project, funded by grant RR-00350 from the Division of Research Resources of the National Institutes of Health.

We thank Dorothy Heiberg for her expert assistance in following the subjects and performing the analyses; the Emergency Medical Service division of the Houston Fire Department for their constructive suggestions and enthusiastic support of the project; and Esperanza Tafallo and Steven Rao for their excellent technical assistance.

Please address requests for reprints to Dr. F. B. Hollinger, Department of Virology and Epidemiology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030.

yeast extract by physical and chemical methods. Hydrophobic-interaction chromatography followed by gel-exclusion chromatography was the major procedure used to prepare the purified antigen. The removal of yeast components was demonstrated in vitro by immunologic methods and in vivo by anaphylactic testing in guinea pigs.

To deliver the inoculum, we used 0.5-ml syringes for the 5 or 10 μg doses and 1.0-ml syringes for the 20 μg dose. All doses were administered by the same person. The vaccine was thoroughly resuspended before use and inoculated im in the deltoid region with a one-inch, 23-gauge needle at months 0, 1, and 6. Blood samples were obtained at one, two, three, six, eight, and 12 months after the initial inoculation (100% participation). A prevaccination oral temperature was obtained, and participants were asked to take and record their temperature with the same calibrated thermometer 4 hr after inoculation and each morning for the next three days. They were also asked to record any local or systemic symptoms experienced during this time. Responses were received by mail from ~90% of the participants.

All blood samples were processed within 24 hr and assayed for liver enzymes. The unit of measurement for anti-HBs was mIU/ml and was determined by the method of Hollinger et al. [10]. On the basis of the statistical analysis of at least 1,000 normal human sera, a value ≥0.7 mIU/ml on replicate samples was considered evidence of the presence of anti-HBs for determination of seroconversion rates. This cutoff level was ≥5 SD above the mean value for the negative control samples. All samples taken at three and eight months were also tested for anti-HBc and HBsAg to rule out unsuspected infection with HBV that might have occurred during the course of the study.

Statistical calculations included Student's *t* test, McNemar's χ^2 test, analysis of variance, and Duncan's multiple range test [11].

Results

No local or systemic reactions of a serious nature were observed by the volunteers. After the first inoculation, 14% of the vaccinees experienced mild discomfort at the site of injection; this figure was 12% after the second and third inoculations. Temperature elevations ≥1.5 F above an individual's baseline level were recorded in 3.8%, 9.3%, and 3.4% of the participants after each of the three injections, respectively. Only four oral temperatures exceeded 100 F, the highest of which was 101.2 F. Among the systemic reactions recorded after the initial inoculation, headaches (10.5%), diarrhea or abdominal complaints (9.5%), and fatigue (7.6%) were noted most frequently. Rates declined substantially after the second and third injections. Such local and systemic reactions are similar to those observed among recipients of placebos in other studies [10].

None of the participants showed serological evidence of infection with HBV during the study. Ten (9.5%) volunteers had aminotransferase levels >50 IU/liter on one or more occasions over the one-year follow-up period. This rate is similar to that observed in a previous study [10]. Muscle trauma caused by excessive physical activity was felt to be the cause of the enzyme elevations in three of these ten participants; this hypothesis was based on an AST value that was higher than the ALT value and on creatine phosphokinase levels of 47,502, 844, and 533 IU/liter. A fourth volunteer sustained a lacerated liver following an auto accident that occurred two weeks before the blood specimen that showed elevated enzyme levels was taken, and three other men were taking medications that have been reported to cause liver damage. In the other three (2.9%) volunteers, the enzyme levels had returned to normal when their blood was retested one week later. There was nothing in their histories to explain these abnormalities.

Seroconversion rates and geometric mean antibody responses for all participants are shown by dose and time in tables 1 and 2. Seroconversion rates were significantly lower in the 5-μg dose group than in the 10- or 20-μg dose

Table 1. Seroconversion rates of anti-HBs by time and dose.

	Time (months)					
Dose	1*	2	3	6*	8	12
5 (n = 35)	8.6	34.3†	45.7†	62.9†	97.1	88.6‡
10 (n = 35)	28.6	80.0	94.3	94.3	97.1	97.1
20 (n = 35)	28.6	82.9	88.6	94.3	100.0	100.0

NOTE. Results are percentages of subjects who were positive at the noted time. Doses are in μg.

* Vaccine was administered at months 0, 1, and 6.

† $P < .002$, 5 μg compared with 10 or 20 μg.

‡ Four persons who were positive for anti-HBs at eight months became seronegative at 12 months, whereas the one person who had not responded by month 8 seroconverted.

Table 2. Geometric mean levels of anti-HBs (mIU/ml) by time and dose.

	Time (months)					
Dose	1*	2	3	6*	8	12
5 (n = 35)	0.1†	0.5‡	0.7‡	2.0‡	45.7‡	10.0‡
10 (n = 35)	0.3	5.1	6.9	14.0	388.6	76.0§
20 (n = 35)	0.4	7.3	9.4	26.4	519.5	184.6

NOTE. Doses are given in μg.

* Vaccine was administered at months 0, 1, and 6.

† $P < .02$, 5 μg compared with 10 or 20 μg.

‡ $P < .001$, 5 μg compared with 10 or 20 μg.

§ $P = .03$, 10 μg compared with 20 μg.

groups at two, three, and six months after the initial inoculation ($P < .002$). By eight months all but two of the participants had produced specific antibodies. One of these two volunteers, who received 5 μg of vaccine, did develop specific anti-HBs at a low level (1.3 mIU/ml) 12 months following his initial inoculation. Therefore, the total seroconversion rate for the 5-μg group through 12 months was 100%, even though four other vaccinees who were positive at eight months were negative at 12 months; this yielded a point prevalance rate of 88.6% (table 1).

Geometric mean concentrations of anti-HBs were considerably lower in the group receiving 5 μg of yeast-derived HBsAg than in the 10- or 20-μg dose groups after the first month ($P < .001$; table 2). Similar differences were observed when weight-matched group members were compared, most notably at six and eight months. No statistically significant differences were seen between the 10- and 20-μg groups during the first eight months in terms of seroconversion rates or geometric mean levels of antibody. At each bleeding interval, however, geometric mean levels of anti-HBs in the 10-μg group were lower than those seen in the 20-μg vaccinees, and a P value of .03 was obtained at 12 months (table 2).

Discussion

The reasons for the significantly larger differences in immune response seen between the 5-μg group and the other two groups in our study are not readily apparent. Lot-to-lot variation is not a factor since the same lot of vaccine was used to inoculate all three groups. The only known variable is the volume of inoculum administered. Thus, the lower doses of vaccine not only contained less HBsAg, but the total amount of alum administered was also reduced even though the protein-to-alum ratio remained constant among the three doses. Whether a finite amount of alum is essential for an optimal response cannot be ascertained in this study, but levels of alum should not vary significantly between batches of vaccine that use identical doses of vaccine. It is interesting that similar muted responses were not seen in another study that compared 5 μg and 10 μg of yeast-derived HBsAg, although a two-fold difference in the geometric mean levels of antibody was reported [12]. Since the RIA activity of equimolar preparations of purified yeast HBsAg has been reported to vary by as much as 2.5 times [8], this might account for the interstudy differences observed at critical threshold levels.

As expected, a decline in anti-HBs concentration was observed in 96% of the subjects between the eighth and 12th months. To examine the slope of this response more completely, we determined the natural logarithms of the differences in the anti-HBs levels after dividing by the number of months between observations for each subject in the three dose groups. Similar data were obtained for adults participating in previous vaccine studies that used 40 μg of an HBsAg plasma-derived vaccine [10] and 20 or 40 μg of HEPTAVAX-B [9a], and the results were compared by analysis of variance. No significant differences in the rate of decline were found between these four groups when equivalent levels of peak anti-HBs responses were evaluated.

When geometric mean levels of anti-HBs at eight months were compared for two different plasma-derived vaccines, values ranged from 2,980 to 3,322 mIU/ml for 40 μg of vaccine to 1,975 mIU/ml for 20 μg of HBsAg [9a, 10] vs. 46 (5 μg), 389 (10 μg), and 520 (20 μg) mIU/ml for the yeast-derived product. These findings lead us to conclude that the lower antibody levels detected in adults receiving the yeast-derived vaccine may be related to the immunogenicity of the product. It is noteworthy that Dandolos et al. [13] reported similar discrepancies in anti-HBs levels between yeast- and plasma-derived vaccines, in which equivalent doses of antigen could be compared, although immune responses were significantly lower with our lot of recombinant vaccine. Since a butyl agarose method was used to remove contaminating yeast antigens from the final product in both of these studies, it is unlikely that this could account for the reduced immunogenicity found in our study. Two other studies [12, 14] did not permit equivalent time and dose comparisons between the two types of vaccines. Variations between lots, dissimilarities in the lipid content of the antigen produced in the yeast as compared with plasma-derived antigen, reduced antigenicity when compared with human HBsAg, and the fact that the yeast-derived HBsAg is not glycosylated [7, 8] may be factors responsible for the relatively lower anti-HBs response seen with the yeast-derived product. Further field trials in different at-risk groups seem appropriate before a specific adult dose of this vaccine is recommended. Nevertheless, several small trials in humans have shown that the vaccine is safe, and we anticipate that durable levels of protection should be achieved if sufficient immunogen is incorporated in the vaccine.

F. B. Hollinger, C. L. Troisi, P. E. Pepe
Departments of Medicine, and Virology and Epidemiology, Baylor College of Medicine; and the City of Houston Emergency Medical and Trauma Services, Houston, Texas

References

1. Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszke WR, William DC, Sadorsky R, Morrison JM, Kellner A. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. N Engl J Med 1980;303:833–41
2. Francis DP, Hadler SC, Thompson SE, Maynard JE, Ostrow DG, Altman N, Braff EH, O'Malley P, Hawkins D, Judson FN, Penley K, Nylund T, Christie G, Meyers F, Moore JN Jr, Gardner A, Doto IL, Miller JH, Reynolds GH, Mur-

phy BL, Schable CA, Clark BT, Curran JW, Redeker AG. The prevention of hepatitis B with vaccine: report of the Centers for Disease Control multi-center efficacy trial among homosexual men. Ann Intern Med 1982;97:362–6
3. Purcell RH, Gerin JL. Hepatitis B vaccines: a status report. In: Vyas GN, Cohen SN, Schmid R, eds. Viral hepatitis. Philadelphia: The Franklin Institute Press, 1978;491–505
4. Stevens CE, Taylor PE, Rubinstein P, Ting RCY, Bodner AJ, Sarngadharan MG, Gallo RC. Safety of the hepatitis B vaccine. New Engl J Med 1985;312:375–6
5. Poiesz B, Tomar R, Lehr B, Moore J. Hepatitis B vaccine: evidence confirming lack of AIDS transmission. MMWR, 1984;33:685–7
6. Hollinger FB, Sanchez Y, Troisi C, Dreesman GR, Melnick JL. Response to a HBsAG/*edw* polypeptide vaccine in a young adult population [abstract no. 8A.5]. In: Vyas G, Dienstag J, Hoofnagle J, eds. Viral hepatitis and liver disease. Orlando, Fla: Grune and Stratton, 1984:656
7. Purcell RH, Gerin JL. Prospects for second and third generation hepatitis B vaccines. Hepatology 1985;5:159–63
8. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. Nature 1984;307:178–80
9. Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984;251:2812–5
9a. Troisi CL, Heiberg DA, Hollinger RB. Normal immune response to hepatitis B vaccine in patients with Down's syndrome. JAMA, 1986 (in press)
10. Hollinger FB, Adam E, Heiberg D, Melnick JL. Response to hepatitis B vaccine in a young adult population. In: Szmuness W, Alter JH, Maynard JE, eds. Viral hepatitis. Philadelphia: The Franklin Institute Press, 1981;451–66
11. Snedecor G, Cochran W. Statistical methods. Ames, Iowa: Iowa State University Press, 1967
12. Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985;1:108–9
13. Dandolos E, Roumeliotou-Karayannis A, Richardson SC, Papaevangelou G. Safety and immunogenicity of a recombinant hepatitis B vaccine. J Med Virol 1985;17:57–62
14. Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984;2:1174–5

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 153, NO. 1 • JANUARY 1986
 0022-1899/86/5301-0027$01.00

The Epidemiology of *Clostridium difficile* with Use of a Typing Scheme: Nosocomial Acquisition and Cross-Infection Among Immunocompromised Patients

Gastrointestinal disturbance, particularly diarrhea, is one of the commonest side effects of the use of antibiotics. Up to 20%–25% of antibiotic-associated diarrhea occurs in conjunction with a fecal isolate of *Clostridium difficile* [1]. This organism is the major cause of pseudomembranous colitis and antibiotic-associated colitis but is also carried in the gastrointestinal tract of 2%–4% of the normal adult population and can be isolated from the feces of 30%–75% of asymptomatic neonates [2].

Received for publication 23 April 1985, and in revised form 5 August 1985.

This work was supported by the Medical Research Council. Dr. Heard was funded by a George Alwyn Research Bursary. Dr. Holland was funded by Automated Microbiology Systems Ltd.

This study would not have been possible without the help of the Sisters and nursing staff on Annie Zunz, Dalziel, Garrod, and Stanmore wards in collecting the clinical specimens. We thank them and Drs. T. A. Lister, P. F. Wrigley, J. Galton, J. Wass, K. Britten, and E. C. Huskisson and Professors J. Malpas, M. Besser, and J. Dickinson for allowing us to study their patients.

Please address requests for reprints to Dr. S. Tabaqchali, Department of Medical Microbiology, St. Bartholomew's Hospital, West Smithfield, London, EC 1A 7BE.

Clusters of antibiotic-associated colitis have been noted [3], and early animal studies suggested that environmental contamination and cross-infection might be important in the etiology of outbreaks of antibiotic-associated diarrhea [4]. However, convincing evidence for the cross-infective potential of *C. difficile*, as well as its demonstration as a predominantly nosocomial infection, has been prevented due to lack of a reliable typing scheme for this organism [5].

Various typing schemes have been suggested [6–10]. Among these, Tabaqchali et al. [8] reported a well-defined scheme for typing this organism on the basis of the incorporation of [^{35}S]methionine into bacterial proteins and have described to date nine distinct groups within the *C. difficile* species (A-E, W-Z), as demonstrated by the radiolabeled protein profile obtained by using SDS-PAGE followed by autoradiography. We have applied this technique to isolates obtained from a prospective six-month study of immunocompromised and general medical patients in an attempt to assess the carriage and acquisition of *C. difficile* among hospital patients. The effect of isolation and containment procedures on the spread of *C. difficile* was also studied.

IMMUNOGENICITY AND REACTOGENICITY OF NEW HEPATITIS B VACCINES. FB Hollinger, Y Sanchez, C Troisi, GR Dreesman, and JL Melnick, Baylor College of Medicine, Houston, TX.

An HBsAg/gdx polypeptide (PP) vaccine and a recombinant DNA vaccine produced in yeast (rSD) are being evaluated. The PP vaccine was prepared from 22-nm HBsAg particles, packaged in a micellar form and alum-adsorbed. The starting material (NIH/40) contained 300 HBsAg RIA equivalent units (RIU) based on a HEPTAVAX-B standard of 100 HBsAg RIU. 3 lots containing 5, 1, and 0.2 HBsAg RIU were compared to 2 intact particle vaccines. Vaccine was administered at 0, 1, and 6 months to 52 weight-matched adults. RESULTS: Local and systemic reactions were insignificant. The anti-HBs seroconversion rate at 4 weeks for the 5 RIU PP vaccine group (90%) was considerably better than that seen with HEPTAVAX-B. By 12 weeks, all vaccine recipients in the 1 and 5 RIU PP vaccine groups had seroconverted versus 50% of the 0.2 RIU group ($p<0.02$) which reached 100% seroconversion by month 7. Throughout follow-up, geometric mean (GM) anti-HBs levels (mIU/ml) in the 5 RIU PP group were significantly higher than in the other PP vaccine groups. At 1 month the GM anti-HBs level for the 5 RIU PP group was 8.9, whereas the 300 RIU NIH/40 vaccine group had a GM antibody level of 5.2. By 3 months, the respective anti-HBs levels were 202 vs 90, rising to 8910 and 3450 by 7 months. The 1 RIU PP vaccine produced antiHBs responses comparable to the 100 RIU HEPTAVAX-B vaccine. Thus, the polypeptide vaccines, with substantially lower RIA HBsAg reactivity, produced superior anti-HBs responses when compared with 22-nm HBsAg vaccines. These studies confirm our previous findings in chimpanzees that critical antigenic determinants are associated with these polypetides, and they provide a link to future vaccine studies using synthetic HBsAg macromolecules. The rapid anti-HBs response that follows the initial inoculation suggests that such an immunogen may be beneficial in postexposure prophylaxis where the early development of immunity is advantageous. Preliminary data through 6 months also will be presented on the immunogenicity of 3 doses (5, 10, and 20 mcg) of an HBSAg vaccine made by recombinant DNA technology in yeast (rSD).

Hollinger FB, Sanchez Y, Troisi C, Dreesman GR, Melnick JL. Immunologenicity and reactogenicity of new hepatitis B vaccines. Hepatology 1984; 4:1027 (Abstract).

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 801
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #972/C-K444 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Edward J. Septimus, M.D. Suite 740 7777 Southwest Freeway Houston, TX 77074
STUDY LOCATION:	Suite 740 7777 Southwest Freeway Houston, TX 77074
DATE INITIATED:	February 16, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 22 health care personnel of either sex (excluding pregnant woman), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and had not previously received any hepatitis B vaccine.
PROCEDURE:	Eligible participants receive a 1.0 ml (10 mg HBsAg) intramuscular injection of vaccine at 0, 1 and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

Study 801

PROCEDURE: (Cont.) A blood specimen (10-15 ml) is obtained from each participant approximately two weeks before the first vaccination. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12 and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, yeast antibody and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml are tested for the proportions of anti-a and anti-d activity.

RESULTS:

HEALTH CARE PERSONNEL:

10 mcg Lot #972/C-K444 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
22	21	21

2. Serologic Results:

Serologic data are available for 21 participants at 7/8 months. 100% (21/21) of the vaccinees seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at 7/8 months was 280.8 mIU/ml (all vaccinees and responders by either cutoff).

Among participants with serology data at 12 months, 86% (18/21) were positive for anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees at that time was 139.7 mIU/ml, while it was 256.0 mIU/ml for those with a titer of mIU/ml $\geq$10.

See Table 1 for anti-HBs responses for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for 21 participants after each injection. The overall frequencies of complaints follow.

Study 801

RESULTS (CONT.):

Type	Frequency in % by Injection No. 1	2	3
Injection Site	14(3/22)	10(2/21)	29(6/21)
Systemic	32(7/22)	29(6/21)	43(9/21)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming adverse reactions attributable to vaccination.

ALT Elevations

ALT levels 2-7 times the upper level of normal were observed in post-vaccination blood samples taken from three subjects. All elevations were transient and returned to normal. None of those participants were seropositive for HBsAg or anti-HBC. The ALT elevations in two of the subjects were attributed to infectious mononucleosis and cholecystitis. The third case was asymptomatic.

Reactions reported to the DoBRR

A 26-year old female became aware that she was pregnant after receiving one injection of vaccine. She experienced a spontaneous abortion at 18 weeks after fetal death in utero. No microscopic examination was completed on the fetus. The investigator stated the fetal death and abortion were probably not/possibly related to vaccination.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK444
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	25%	(5/20)	10%	(2/20)	0.8	10.1	47.3
2 MONTHS	81%	(17/21)	52%	(11/21)	10.5	24.4	53.9
3 MONTHS	84%	(16/19)	63%	(12/19)	18.8	37.1	74.1
6 MONTHS	89%	(17/19)	79%	(15/19)	37.1	60.3	82.1
7/8 MONTHS	100%	(21/21)	100%	(21/21)	280.8	280.8	280.8
12 MONTHS	100%	(21/21)	86%	(18/21)	139.7	139.7	256.0

00293

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (22 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (9.1%)	2 (9.1%)	1 (4.5%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	3 (13.6%)
SORENESS	2 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)
TENDERNESS	0 (0.0%)	2 (9.1%)	1 (4.5%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	2 (9.1%)
WARMTH	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
SYSTEMIC	4 (18.2%)	2 (9.1%)	5 (22.7%)	2 (9.1%)	2 (9.1%)	2 (9.1%)	7 (31.8%)
WHOLE BODY/GENERAL	4 (18.2%)	1 (4.5%)	4 (18.2%)	2 (9.1%)	1 (4.5%)	1 (4.5%)	6 (27.3%)
FATIGUE/WEAKNESS	1 (4.5%)	0 (0.0%)	2 (9.1%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	4 (18.2%)
MALAISE	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
EDEMA, FACE	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
HEADACHE	3 (13.6%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	4 (18.2%)
ACHINESS	1 (4.5%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (4.5%)

able 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (22 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
MONONUCLEOSIS, INFECTIOUS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (4.5%)
RESPIRATORY	2 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	2 (9.1%)
RHINITIS	2 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)
DYSPNEA (SHORT OF BREATH)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (4.5%)
MUSCULOSKELETAL	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
ARTHRALGIA (OTHER)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	2 (9.1%)	2 (9.1%)	4 (18.2%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
NAUSEA	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (4.5%)	2 (9.1%)
ABDOMEN DISTENDED	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	1 (4.5%)
OTHER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (4.5%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (22 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						
CLINICAL COMPLAINTS	0	1	2	3	4	5	NUMBER WITH COMPLAINTS
EARACHE	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
HEARING IMPAIRMENT	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
PERSONS WITH COMPLAINTS	5 (22.7%)	4 (18.2%)	6 (27.3%)	3 (13.6%)	2 (9.1%)	2 (9.1%)	8 (36.4%)
PERSONS WITH NO COMPLAINTS	17 (77.3%)	18 (81.8%)	16 (72.7%)	19 (86.4%)	20 (90.9%)	20 (90.9%)	14 (63.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	2 (9.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (9.5%)
SORENESS	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.8%)
PRURITIS (ITCHING)	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.8%)
SYSTEMIC	3 (14.3%)	4 (19.0%)	3 (14.3%)	1 (4.8%)	2 (9.5%)	1 (4.8%)		6 (28.6%)
WHOLE BODY/GENERAL	2 (9.5%)	4 (19.0%)	3 (14.3%)	1 (4.8%)	1 (4.8%)	1 (4.8%)		5 (23.8%)
FATIGUE/WEAKNESS	1 (4.8%)	4 (19.0%)	3 (14.3%)	1 (4.8%)	1 (4.8%)	1 (4.8%)		5 (23.8%)
HEADACHE	2 (9.5%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	1 (4.8%)	0 (0.0%)		3 (14.3%)
RESPIRATORY	1 (4.8%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (4.8%)	0 (0.0%)		2 (9.5%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (4.8%)	0 (0.0%)		1 (4.8%)
SINUSITIS	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.8%)
MUSCULOSKELETAL	0 (0.0%)	2 (9.5%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (9.5%)
ARTHRALGIA (OTHER)	0 (0.0%)	2 (9.5%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (9.5%)

00267

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
MYALGIA	0 (0.0%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.8%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)		1 (4.8%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)		1 (4.8%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)		1 (4.8%)
PERSONS WITH COMPLAINTS	3 (14.3%)	5 (23.8%)	3 (14.3%)	1 (4.8%)	2 (9.5%)	1 (4.8%)		7 (33.3%)
PERSONS WITH NO COMPLAINTS	18 (85.7%)	16 (76.2%)	18 (85.7%)	20 (95.2%)	19 (90.5%)	20 (95.2%)		14 (66.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	3 (14.3%)	2 (9.5%)	2 (9.5%)	1 (4.8%)	1 (4.8%)	2 (9.5%)	6 (28.6%)
PAIN	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
SORENESS	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	2 (9.5%)
TENDERNESS	1 (4.8%)	1 (4.8%)	2 (9.5%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	2 (9.5%)
NODULE FORMATION	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
ECCHYMOSIS	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)
OTHER	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
SYSTEMIC	3 (14.3%)	4 (19.0%)	3 (14.3%)	1 (4.8%)	2 (9.5%)	3 (14.3%)	9 (42.9%)
WHOLE BODY/GENERAL	2 (9.5%)	4 (19.0%)	3 (14.3%)	1 (4.8%)	2 (9.5%)	2 (9.5%)	8 (38.1%)
FLUSH	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
FATIGUE/WEAKNESS	0 (0.0%)	2 (9.5%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)

00299

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
HEADACHE	0 (0.0%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	2 (9.5%)	2 (9.5%)	4 (19.0%)
ACHINESS	2 (9.5%)	2 (9.5%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (14.3%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)	1 (4.8%)	2 (9.5%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	1 (4.8%)
SINUSITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (4.8%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)	1 (4.8%)	2 (9.5%)
MUSCULOSKELETAL	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)
ARTHRALGIA (OTHER)	0 (0.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
MYALGIA	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
DIGESTIVE SYSTEM	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)
ABDOMINAL PAINS/CRAMPS	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
NAUSEA	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)
UROGENITAL SYSTEM	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (21 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						
CLINICAL COMPLAINTS	0	1	2	3	4	5	NUMBER WITH COMPLAINTS
OTHER	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	2 (9.5%)
EARACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (4.8%)
EYE PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)
PERSONS WITH COMPLAINTS	6 (28.6%)	6 (28.6%)	5 (23.8%)	2 (9.5%)	3 (14.3%)	5 (23.8%)	12 (57.1%)
PERSONS WITH NO COMPLAINTS	15 (71.4%)	15 (71.4%)	16 (76.2%)	19 (90.5%)	18 (85.7%)	16 (76.2%)	9 (42.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (22 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	21 (95.5%)	20 (90.9%)	19 (90.5%)	20 (90.9%)	19 (90.5%)	21 (95.5%)		18 (81.8%)
99 - 99.9	1 (4.5%)	2 (9.1%)	2 (9.5%)	2 (9.1%)	2 (9.5%)	0 (0.0%)		3 (13.6%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		1 (4.5%)
TEMPERATURE TAKEN	22 (100.0%)	22 (100.0%)	21 (95.5%)	22 (100.0%)	21 (95.5%)	22 (100.0%)		22 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (4.5%)	0 (0.0%)		0 (0.0%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (21 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	20 (95.2%)	20 (95.2%)	19 (90.5%)	21 (100.0%)	21 (100.0%)	20 (95.2%)			17 (81.0%)
99 - 99.9	1 (4.8%)	1 (4.8%)	2 (9.5%)	0 (0.0%)	0 (0.0%)	1 (4.8%)			4 (19.0%)
TEMPERATURE TAKEN	21 (100.0%)	21 (100.0%)	21 (100.0%)	21 (100.0%)	21 (100.0%)	21 (100.0%)			21 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0801
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (21 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	16 (76.2%)	17 (85.0%)	17 (81.0%)	16 (88.9%)	19 (95.0%)	19 (95.0%)			13 (61.9%)
99 - 99.9	4 (19.0%)	1 (5.0%)	3 (14.3%)	2 (11.1%)	1 (5.0%)	0 (0.0%)			5 (23.8%)
100 - 100.9	1 (4.8%)	1 (5.0%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (4.8%)
101 - 101.9	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)			2 (9.5%)
TEMPERATURE TAKEN	21 (100.0%)	20 (95.2%)	21 (100.0%)	18 (85.7%)	20 (95.2%)	20 (95.2%)			21 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (4.8%)	0 (0.0%)	3 (14.3%)	1 (4.8%)	1 (4.8%)			0 (0.0%)

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 803
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #972/C-K444 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Franklyn N. Judson, M.D. Denver Department of Health and Hospitals Disease Control Service 605 Bannock Street Denver, CO 80204-4507
SECONDARY INVESTIGATORS:	David Cohn, M.D. Denver Department of Health and Hospitals Disease Control Service 605 Bannock Street Denver, CO 80204-4507 Morton Davidson, M.D. New York University Medical Center University Hospital 560 First Avenue New York, NY 10016
STUDY LOCATION:	Denver Department of Health and Hospitals Disease Control Service 605 Bannock Street Denver, CO 80204-4507
DATE INITIATED:	January 16, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 31 health care personnel of either sex (excluding pregnant woman), who were negative for HBsAg, anti-HBc and anti-HBs, had normal ALT level and had not previously received any hepatitis B vaccine.

Study 803

PROCEDURE:

Eligible participants receive a 1.0 ml (10 mg HBsAg) intramuscular injection of vaccine at 0, 1 and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12 and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, yeast antibody and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml are tested for the proportions of anti-a and anti-d activity.

STUDY RESULTS:

HEALTH CARE PERSONNEL:

10 mcg Lot #972/C-K444 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
31	30	30

One person had a low titer of anti-HBs when the first dose of vaccine was given.

2. Serologic Results:

Serologic data are available for 26 study participants at 7/8 months. Eighty-five percent (22/26) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT for all vaccinees at 7/8 months was 584.6 mIU/ml, while it was 2136.0 mIU/ml for responders with titers of mIU/ml $\geq$10.

STUDY RESULTS: (Cont.)

Among participants with serology data at 12 months, 81% (22/27) were positive for anti-HBs (mIU/ml $\geq$10). At that time the GMT was 147.1 mIU/ml for all vaccinees and 513.5 mIU/ml for those with a titer of mIU/ml $\geq$10.

See Table 1 for anti-HBs responses for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for 30 participants following each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	29(9/31)	33(10/30)	30(8/27)
Systemic	36(11/31)	20(6/30)	4(1/27)

Refer to Table 2 for listings of specific complaints after each injection. Maximum temperature data are provided in Table 3.

There were no serious or alarming adverse reactions attributable to vaccine.

ALT Elevations

Four participants had transient elevations in ALT levels (1.5 times the upper limit of normal). In two individuals transient elevation occurred at one month after vaccination, in the other two individuals elevation occurred at 2 and 8 months respectively. ALT levels returned to normal in all cases. An additional individual had an elevated ALT (1.5-2.0 times the upper limit of normal) at 12 months after vaccination. A repeat serology drawn two weeks later was returning

Study 803

STUDY RESULTS (CONT.):

toward normal. In all cases the reasons for the elevations are unknown. The subjects were not ill and were negative for HBsAg and anti-HBc.

Reactions Reported to the OoBRR

One subject had onset of biparietal headache, upset stomach, confusion, and expressive aphasia two days after receiving the first injection of vaccine. Neurologic and vital signs were within normal limits. A CAT scan of the head was also normal. His WBC was slightly elevated (13,000) with a shift to the left. All symptoms resolved within 2 days. The event was not considered to be vaccine related.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK444
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	43%	(12/28)	21%	(6/28)	1.8	11.8	26.5
2 MONTHS	76%	(22/29)	62%	(18/29)	17.4	58.0	107.4
3 MONTHS	78%	(21/27)	63%	(17/27)	23.8	74.1	131.7
6 MONTHS	86%	(24/28)	79%	(22/28)	53.3	121.2	163.9
7/8 MONTHS	85%	(22/26)	85%	(22/26)	584.6	2136.0	2136.0
12 MONTHS	85%	(23/27)	81%	(22/27)	147.1	431.9	513.5

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (31 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	8 (25.8%)	3 (9.7%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (29.0%)
PAIN ON INJECTION	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
PAIN	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
SORENESS	7 (22.6%)	3 (9.7%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (25.8%)
SYSTEMIC	6 (19.4%)	4 (12.9%)	4 (12.9%)	4 (12.9%)	2 (6.5%)	3 (9.7%)	11 (35.5%)
WHOLE BODY/GENERAL	4 (12.9%)	1 (3.2%)	2 (6.5%)	2 (6.5%)	1 (3.2%)	1 (3.2%)	6 (19.4%)
CHILLS	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
FATIGUE/WEAKNESS	2 (6.5%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	2 (6.5%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
LIGHTHEADED	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
INTEGUMENTARY SYSTEM	2 (6.5%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	2 (6.5%)
PAPULAR RASH	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (31 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PRURITIS/ITCHING	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)
RESPIRATORY	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	2 (6.5%)	2 (6.5%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.2%)
UPPER RESPIRATORY INFECT., NOS	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)
MUSCULOSKELETAL	1 (3.2%)	2 (6.5%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	2 (6.5%)
ARTHRALGIA (OTHER)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)
MYALGIA	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)
OTHER	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
NERVOUS SYSTEM	0 (0.0%)	1 (3.2%)	2 (6.5%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
PARESTHESIAS	0 (0.0%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
THOUGHT IMPAIRMENT	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (31 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
OTHER	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
PERSONS WITH COMPLAINTS	13 (41.9%)	7 (22.6%)	4 (12.9%)	4 (12.9%)	2 (6.5%)	3 (9.7%)	18 (58.1%)
PERSONS WITH NO COMPLAINTS	18 (58.1%)	24 (77.4%)	27 (87.1%)	27 (87.1%)	29 (93.5%)	28 (90.3%)	13 (41.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	7 (23.3%)	8 (26.7%)	5 (16.7%)	3 (10.0%)	2 (6.7%)	1 (3.3%)	10 (33.3%)
PAIN ON INJECTION	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
PAIN	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
SORENESS	4 (13.3%)	5 (16.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (16.7%)
TENDERNESS	1 (3.3%)	2 (6.7%)	2 (6.7%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	2 (6.7%)
NODULE FORMATION	0 (0.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
LYMPHADENOPATHY, REGIONAL	0 (0.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (3.3%)
SYSTEMIC	4 (13.3%)	3 (10.0%)	5 (16.7%)	4 (13.3%)	1 (3.3%)	1 (3.3%)	6 (20.0%)
WHOLE BODY/GENERAL	2 (6.7%)	2 (6.7%)	2 (6.7%)	2 (6.7%)	1 (3.3%)	1 (3.3%)	3 (10.0%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)
LIGHTHEADED	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
ACHINESS	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
INTEGUMENTARY SYSTEM	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		2 (6.7%)
PRURITIS/ITCHING	0 (0.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
RASH, NOS	0 (0.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
OTHER	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
RESPIRATORY	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
UPPER RESPIRATORY INFECT., NOS	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		2 (6.7%)
DIARRHEA	0 (0.0%)	0 (0.0%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		2 (6.7%)
PERSONS WITH COMPLAINTS	9 (30.0%)	10 (33.3%)	8 (26.7%)	6 (20.0%)	3 (10.0%)	2 (6.7%)		12 (40.0%)
PERSONS WITH NO COMPLAINTS	21 (70.0%)	20 (66.7%)	22 (73.3%)	24 (80.0%)	27 (90.0%)	28 (93.3%)		18 (60.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	7 (25.9%)	4 (14.8%)	2 (7.4%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		8 (29.6%)
PAIN ON INJECTION	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
PAIN	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
SORENESS	5 (18.5%)	2 (7.4%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		5 (18.5%)
TENDERNESS	0 (0.0%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (7.4%)
WARMTH	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
SYSTEMIC	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
ILLNESS, NOS	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
PERSONS WITH COMPLAINTS	7 (25.9%)	4 (14.8%)	3 (11.1%)	1 (3.7%)	0 (0.0%)	0 (0.0%)		8 (29.6%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	20 (74.1%)	23 (85.2%)	24 (88.9%)	26 (96.3%)	27 (100.0%)	27 (100.0%)	19 (70.4%)
PERSONS WITH NO DATA	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.9%)	2 (6.9%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (31 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	28 (90.3%)	27 (90.0%)	27 (90.0%)	27 (87.1%)	29 (96.7%)	26 (92.9%)			24 (77.4%)
99 - 99.9	3 (9.7%)	3 (10.0%)	3 (10.0%)	4 (12.9%)	1 (3.3%)	2 (7.1%)			7 (22.6%)
TEMPERATURE TAKEN	31 (100.0%)	30 (96.8%)	30 (96.8%)	31 (100.0%)	30 (96.8%)	28 (90.3%)			31 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	1 (3.2%)	3 (9.7%)			0 (0.0%)

00317

Table 3 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 2								DAYS POST VACCINATION	NUMBER WITH MAX TEMP
	0	1	2	3	4	5				
NORMAL	1 (3.3%)	0 (0.0%)	1 (3.4%)	1 (3.6%)	1 (3.6%)	1 (3.8%)				0 (0.0%)
< 99	26 (86.7%)	26 (92.9%)	25 (86.2%)	26 (92.9%)	25 (89.3%)	23 (88.5%)				24 (80.0%)
99 - 99.9	3 (10.0%)	1 (3.6%)	3 (10.3%)	1 (3.6%)	2 (7.1%)	2 (7.7%)				5 (16.7%)
101 - 101.9	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)				1 (3.3%)
TEMPERATURE TAKEN	30 (100.0%)	28 (93.3%)	29 (96.7%)	28 (93.3%)	28 (93.3%)	26 (86.7%)				30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	2 (6.7%)	1 (3.3%)	2 (6.7%)	2 (6.7%)	4 (13.3%)				0 (0.0%)

Table 3 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0803
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	22 (91.7%)	19 (79.2%)	21 (87.5%)	24 (96.0%)	21 (91.3%)	22 (95.7%)		19 (76.0%)
99 - 99.9	2 (8.3%)	5 (20.8%)	2 (8.3%)	1 (4.0%)	1 (4.3%)	1 (4.3%)		5 (20.0%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (4.3%)	0 (0.0%)		1 (4.0%)
TEMPERATURE TAKEN	24 (80.0%)	24 (80.0%)	24 (80.0%)	25 (83.3%)	23 (76.7%)	23 (76.7%)		25 (83.3%)
TEMPERATURE NOT TAKEN	6 (20.0%)	6 (20.0%)	6 (20.0%)	5 (16.7%)	7 (23.3%)	7 (23.3%)		5 (16.7%)

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 807
PURPOSE:	To compare antibody and clinical responses to yeast recombinant and plasma-derived hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINES:	1. Yeast Recombinant Hepatitis B Vaccine Lot 972/C-K444 (10 mcg HBsAg/ml) 2. Plasma-Derived Hepatitis B Vaccine Lot 1510J (20 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Solko W. Schalm, M.D. Department of Internal Medicine and Gastroenterology University Hospital Dijkzigt Rotterdam, The Netherlands
SECONDARY INVESTIGATOR:	Dr. Rudolf A. Heytink Department of Virology Erasmus University Rotterdam, The Netherlands
STUDY LOCATION:	University Hospital Dijkzigt Rotterdam, The Netherlands
DATE STUDY INITIATED:	April 4, 1984
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 50-60 health care personnel of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.
STUDY PROCEDURE:	Eligible study participants receive a 1.0 ml intramuscular injection of yeast recombinant (10 mcg HBsAg) or plasma-derived (20 mcg HBsAg) vaccine at 0, 1, and 6 months. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

Study 807

STUDY PROCEDURE (CONT.):

A blood sample is obtained from each study participant approximately two to three weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 7, 9 and 12 months. Blood samples are obtained at 24 months from those participants who have seroconverted.

All serum samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer ≥25 mIU/ml may be tested to determine anti-a and anti-d subtype specificity.

RESULTS:

HEALTH CARE PERSONNEL

Yeast Recombinant Hepatitis B Vaccine:

10 mcg Lot 972/C-K444 at 0, 1, and 6 months

Plasma-Derived Hepatitis B Vaccine:

20 mcg Lot 1510J at 0, 1, and 6 months

1. Number Vaccinated:

	Injection No.		
Vaccine	1	2	3
Yeast Recombinant	31	31	31
Plasma-Derived	25	25	25

2. Serologic Results:

Serologic data at 7-8 months are available for 31 recipients of the yeast recombinant vaccine and 22 recipients of the plasma-derived vaccine.

At 7-8 months, 100% of recipients of both the yeast recombinant (31/31) and plasma-derived (22/22) vaccines seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees and responders

Study 807

RESULTS (CONT.):

(S/N ≥2.1 and ≥10 mIU/ml) was 885.1 mIU/ml for those persons who received the yeast recombinant vaccine, and 6164.4 mIU/ml for those who received the plasma-derived vaccine.

By 12 months 94% (29/31) of recipients of the yeast recombinant and 100% (24/24) of recipients of the plasma-derived vaccines retained on anti-HBs titer of mIU/ml ≥10. The GMTs for all vaccinees at that time was 112.4 mIU/ml (yeast recombinant vaccine) and 1029.2 mIU/ml (plasma-derived vaccine).

Anti-HBs responses at 1 through 12 months are included in Table 1.

3. Clinical Results:

Clinical follow-up data are available for 36 recipients of the yeast recombinant vaccine and 25 recipients of the plasma-derived vaccine following each injection. Clinical complaints and maximum temperatures reported following each injection are provided in Tables 2-5. In summary:

Vaccine	Clinical Complaint	% Frequency by Injection No. 1	2	3
Yeast - Recombinant	Injection Site	10(3/31)	3(1/31)	7(2/31)
	Systemic	16(5/31)	7(2/31)	10(3/31)
Plasma	Injection Site	12(3/25)	4(1/25)	8(2/25)
	Systemic	20(5/25)	12(3/25)	0(0/25)

No serious or alarming adverse reactions attributable to vaccination have been reported.

PUBLICATIONS:

Heijtink RA, Kruining J, Baker M, Schalm SW. Immune response after vaccination with recombinant hepatitis B vaccine as compared to that after plasma-derived vaccine. Antiviral Res 1985; Supplement 1:273-9.

Heijtink RA, Schalm SW. Anti-HBs/a determination after hepatitis B vaccination. Submitted for publication to Lancet.

Study 807

Table 1

Antibody Responses Among Initially Seronegative Health Care Personnel Following Vaccination with 10 mcg Doses of Recombinant Hepatitis B Vaccine Lot 972/C-K444 or 20 mcg Doses of Plasma-Derived Hepatitis B Vaccine Lot 1510J at 0, 1, and 6 Months in Study 807

Time (Months)	Yeast Recombinant Vaccine					Plasma-Derived Vaccine				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders				All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1	19 (6/31)	13 (4/31)	0.7	16.7	36.4	56 (14/25)	44 (11/25)	3.3	21.4	36.6
2	77 (24/31)	39 (12/31)	5.3	12.4	44.6	100 (22/22)	77 (17/22)	59.1	59.1	148.0
3	89 (25/28)	71 (20/28)	21.5	35.9	60.7	100 (21/21)	95 (20/21)	135.0	135.0	161.9
6	94 (29/31)	84 (26/31)	48.4	68.8	94.8	100 (25/25)	100 (25/25)	271.9	271.9	271.9
7/8	100 (31/31)	100 (31/31)	885.1	885.1	885.1	100 (22/22)	100 (22/22)	6164.4	6164.4	6164.4
9	100 (31/31)	100 (31/31)	363.1	363.1	363.1	100 (24/24)	100 (24/24)	2899.4	2899.4	2899.4
12	100 (31/31)	94 (29/31)	112.4	112.4	140.5	100 (24/24)	100 (24/24)	1029.2	1029.2	1029.2

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : CK494
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (31 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.2%)	2 (6.5%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	3 (9.7%)
PAIN	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
STIFFNESS/TIGHTNESS	1 (3.2%)	1 (3.2%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
SYSTEMIC	1 (3.2%)	1 (3.2%)	1 (3.2%)	1 (3.2%)	2 (6.5%)	1 (3.2%)	5 (16.1%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	3 (9.7%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	2 (6.5%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	1 (3.2%)
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	1 (3.2%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.2%)	2 (6.5%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.2%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	1 (3.2%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (31 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
MUSCULOSKELETAL	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.2%)
BACK PAIN	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.2%)
PERSONS WITH COMPLAINTS	1 (3.2%)	3 (9.7%)	1 (3.2%)	2 (6.5%)	2 (6.5%)	1 (3.2%)		7 (22.6%)
PERSONS WITH NO COMPLAINTS	30 (96.8%)	28 (90.3%)	30 (96.8%)	29 (93.5%)	29 (93.5%)	30 (96.8%)		24 (77.4%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (31 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
PAIN	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
SYSTEMIC	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
WHOLE BODY/GENERAL	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
FATIGUE/WEAKNESS	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
PERSONS WITH COMPLAINTS	2 (6.5%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
PERSONS WITH NO COMPLAINTS	29 (93.5%)	30 (96.8%)	31 (100.0%)	31 (100.0%)	31 (100.0%)	31 (100.0%)	29 (93.5%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (31 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.2%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
PAIN	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
STIFFNESS/TIGHTNESS	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
SYSTEMIC	1 (3.2%)	1 (3.2%)	2 (6.5%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	3 (9.7%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
HEADACHE	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.5%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
NERVOUS SYSTEM	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
VERTIGO/DIZZINESS	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)
PERSONS WITH COMPLAINTS	2 (6.5%)	2 (6.5%)	3 (9.7%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	5 (16.1%)
PERSONS WITH NO COMPLAINTS	29 (93.5%)	29 (93.5%)	28 (90.3%)	30 (96.8%)	31 (100.0%)	31 (100.0%)	26 (83.9%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0007
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (31 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0007
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (31 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (3.6%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.8%)		1 (3.2%)
< 99	23 (82.1%)	22 (81.5%)	23 (85.2%)	25 (92.6%)	24 (88.9%)	24 (92.3%)		21 (67.7%)
99 - 99.9	4 (14.3%)	3 (11.1%)	3 (11.1%)	0 (0.0%)	0 (0.0%)	1 (3.8%)		6 (19.4%)
100 - 100.9	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)		2 (6.5%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)		1 (3.2%)
TEMPERATURE TAKEN	28 (90.3%)	27 (87.1%)	27 (87.1%)	27 (87.1%)	27 (87.1%)	26 (83.9%)		31 (100.0%)
TEMPERATURE NOT TAKEN	3 (9.7%)	4 (12.9%)	4 (12.9%)	4 (12.9%)	4 (12.9%)	5 (16.1%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (31 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	22 (78.6%)	24 (85.7%)	25 (96.2%)	21 (95.8%)	23 (95.8%)	23 (100.0%)			20 (71.4%)
99 - 99.9	5 (17.9%)	4 (14.3%)	0 (0.0%)	1 (4.2%)	1 (4.2%)	0 (0.0%)			7 (25.0%)
100 - 100.9	1 (3.6%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (3.6%)
TEMPERATURE TAKEN	28 (90.3%)	28 (90.3%)	26 (83.9%)	24 (77.4%)	24 (77.4%)	23 (74.2%)			28 (90.3%)
TEMPERATURE NOT TAKEN	3 (9.7%)	3 (9.7%)	5 (16.1%)	7 (22.6%)	7 (22.6%)	8 (25.8%)			3 (9.7%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0887
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (31 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	5 (19.2%)	5 (19.2%)	5 (19.2%)	5 (19.2%)	5 (20.0%)	5 (19.2%)		5 (18.5%)
< 99	17 (65.4%)	20 (76.9%)	17 (65.4%)	19 (73.1%)	19 (76.0%)	19 (73.1%)		18 (66.7%)
99 - 99.9	4 (15.4%)	1 (3.8%)	4 (15.4%)	1 (3.8%)	1 (4.0%)	2 (7.7%)		3 (11.1%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)		1 (3.7%)
TEMPERATURE TAKEN	26 (83.9%)	26 (83.9%)	26 (83.9%)	26 (83.9%)	25 (80.6%)	26 (83.9%)		27 (87.1%)
TEMPERATURE NOT TAKEN	5 (16.1%)	5 (16.1%)	5 (16.1%)	5 (16.1%)	6 (19.4%)	5 (16.1%)		4 (12.9%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : 1510J
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	3 (12.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	3 (12.0%)
PAIN	2 (8.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	2 (8.0%)
STIFFNESS/TIGHTNESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
SYSTEMIC	1 (4.0%)	3 (12.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	5 (20.0%)
WHOLE BODY/GENERAL	1 (4.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (12.0%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
ILLNESS, NOS	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
MUSCULOSKELETAL	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
BACK PAIN	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
DIARRHEA	0 (0.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : 1510J
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE I						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	4 (16.0%)	4 (16.0%)	2 (8.0%)	2 (8.0%)	1 (4.0%)	1 (4.0%)	7 (28.0%)
PERSONS WITH NO COMPLAINTS	21 (84.0%)	21 (84.0%)	23 (92.0%)	23 (92.0%)	24 (96.0%)	24 (96.0%)	18 (72.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : 1510J
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
PAIN	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
SYSTEMIC	3 (12.0%)	2 (8.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	3 (12.0%)
WHOLE BODY/GENERAL	3 (12.0%)	2 (8.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (12.0%)
FATIGUE/WEAKNESS	3 (12.0%)	2 (8.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (12.0%)
ILLNESS, NOS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
MUSCULOSKELETAL	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
BACK PAIN	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)
STOMATITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)
NERVOUS SYSTEM	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
VERTIGO/DIZZINESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 6897
TREATMENT :
LOT NUMBER : 1510J
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	4 (16.0%)	2 (8.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	4 (16.0%)
PERSONS WITH NO COMPLAINTS	21 (84.0%)	23 (92.0%)	24 (96.0%)	25 (100.0%)	24 (96.0%)	25 (100.0%)	21 (84.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0007
TREATMENT :
LOT NUMBER : 1510J
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
PAIN	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
PERSONS WITH COMPLAINTS	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
PERSONS WITH NO COMPLAINTS	23 (92.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	23 (92.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : 1510J
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (25 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
< 99	19 (82.6%)	18 (78.3%)	20 (87.0%)	16 (80.0%)	18 (81.8%)	20 (95.2%)		14 (58.3%)
99 - 99.9	3 (13.0%)	5 (21.7%)	3 (13.0%)	4 (20.0%)	3 (13.6%)	0 (0.0%)		7 (29.2%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)		1 (4.2%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)		1 (4.2%)
102 - 102.9	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.2%)
TEMPERATURE TAKEN	23 (92.0%)	23 (92.0%)	23 (92.0%)	20 (80.0%)	22 (88.0%)	21 (84.0%)		24 (96.0%)
TEMPERATURE NOT TAKEN	2 (8.0%)	2 (8.0%)	2 (8.0%)	5 (20.0%)	3 (12.0%)	4 (16.0%)		1 (4.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : 1510J
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (25 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	5 (21.7%)	5 (20.8%)	5 (20.8%)	5 (23.8%)	5 (21.7%)	5 (22.7%)		5 (20.8%)
< 99	16 (69.6%)	17 (70.8%)	17 (70.8%)	15 (71.4%)	17 (73.9%)	16 (72.7%)		16 (66.7%)
99 - 99.9	2 (8.7%)	2 (8.3%)	1 (4.2%)	1 (4.8%)	1 (4.3%)	1 (4.5%)		2 (8.3%)
101 - 101.9	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.2%)
TEMPERATURE TAKEN	23 (92.0%)	24 (96.0%)	24 (96.0%)	21 (84.0%)	23 (92.0%)	22 (88.0%)		24 (96.0%)
TEMPERATURE NOT TAKEN	2 (8.0%)	1 (4.0%)	1 (4.0%)	4 (16.0%)	2 (8.0%)	3 (12.0%)		1 (4.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0807
TREATMENT :
LOT NUMBER : 1510J
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (25 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
MAX TEMPERATURE (DEG F, ORAL)	0	1	2	3	4	5		
NORMAL	10 (47.6%)	10 (45.5%)	10 (45.5%)	10 (45.5%)	10 (45.5%)	10 (47.6%)		10 (45.5%)
< 99	9 (42.9%)	11 (50.0%)	10 (45.5%)	12 (54.5%)	10 (45.5%)	11 (52.4%)		10 (45.5%)
99 - 99.9	2 (9.5%)	1 (4.5%)	2 (9.1%)	0 (0.0%)	2 (9.1%)	0 (0.0%)		2 (9.1%)
TEMPERATURE TAKEN	21 (84.0%)	22 (88.0%)	22 (88.0%)	22 (88.0%)	22 (88.0%)	21 (84.0%)		22 (88.0%)
TEMPERATURE NOT TAKEN	4 (16.0%)	3 (12.0%)	3 (12.0%)	3 (12.0%)	3 (12.0%)	4 (16.0%)		3 (12.0%)

Antiviral Research, Suppl. 1 (1985) 273–279
Proc. 1st Int. TNO Conf. Antiviral Res. 1985 Rotterdam
A. Billiau, E. De Clercq and H. Schellekens (eds.)

IMMUNE RESPONSE AFTER VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE AS COMPARED TO THAT AFTER PLASMA-DERIVED VACCINE

R.A.HEIJTINK, J.KRUINING, M.BAKKER, S.W.SCHALM*
Departments of Virology and Internal Medicine, Erasmus University Rotterdam, Rotterdam, The Netherlands

SUMMARY

Thirty-one individuals (health care workers) were vaccinated with recombinant hepatitis B vaccine (10 µg dose) and their immune response (anti-HBs) was compared to that of twenty-five health care workers after vaccination with plasma-derived vaccine (20 µg dose). Although the seroconversion rate and the percentage of anti-HBs/a antibodies at month 7 were comparable, the geometric mean titre of anti-HBs at month 7 was considerably lower for the recombinant vaccine group (857.4 vs. 6736.5 IU/l). However, vaccinees from the two groups showing seroconversion at month 1 had comparable titres at month 7. Raising the dose of HBsAg in the recombinant vaccine may favourably influence the seroconversion rate at month 1 and thereby the immune response after three injections.

INTRODUCTION

Only six years ago, a plasma-derived vaccine was introduced to overcome the worldwide problem of hepatitis B infections.[1] General acceptance of the vaccine, however, has been hampered by the high costs and in particular by doubts about the suitability of infectious plasma as its source. Public concern has waned considerably since the discovery of human T-cell leukaemia virus as a possible cause of the acquired immune deficiency syndrome and the possibility of investigating the efficacy of inactivation of this virus in vaccine preparation procedures.[2] Meanwhile, an alternative for the latter objective has been found in the preparation of hepatitis B surface antigen by recombinant DNA technology in the yeast *Saccharomyces cerevisiae*.[3] Although the yeast recombinant DNA produced HBsAg polypeptides, unlike the native HBsAg, are not glycosylated, the vaccine thus prepared has proven to induce protective antibodies during chimpanzee challenge studies.[4] Its safety and immunicity in man has been demonstrated by several groups of investigators.[5,6,7,8] One of these studies is presented here.

Soon after the introduction of the plasma-derived vaccine it was uncertain whether an HBsAg/adw vaccine would protect against HBsAg/ayw virus infections. Nowadays it is generally known from chimpanzee studies as well as experiments in man[3 9 10] that the antibodies directed against the main determinant a provide cross protection for infections with strains not incorporated in the vaccine.

However, in the plasma-derived vaccine studies[11 12] it was found that the relative proportion of anti-HBs antibodies is variable, which may partially account for hepatitis B infections in the first few months after vaccination. Therefore, the need to monitor the development of anti-HBs/a antibodies after vaccination is stressed.

MATERIAL AND METHODS

Population

The study population consisted of 56 health care workers. Recombinant vaccine was given to 31 individuals (17 female, 14 male; mean age 32 ± 2 yr, range 20-59); plasma-derived vaccine was given to 25 individuals (13 female, 12 male; mean age 30 ± 2 yr, range 22-53). Participants to this study were negative for HBsAg, anti-HBc, and anti-HBs and had a normal alanine transferase level at the entrance to the study.

Vaccine

Participants were vaccinated at 0, 1, and 6 months with either a 10 µg HBsAg/adw dose of the recombinant hepatitis B vaccine (Merck, Sharp and Dohme, lot 972/C-K444) or a 20 µg HBsAg/adw dose of the plasma-derived vaccine (Merck, Sharp and Dohme, lot 1510 J). Recombinant HBsAg used here was purified by hydrophobic interaction chromatography.[8 9]

Assays

HBsAg, anti-HBc, anti-HBs were measured in commercially available kits (Ausria II, Corab, and Ausab; Abbott Laboratories, North Chicago, USA). The concentration of anti-HBs was calculated by the method of Hollinger et al.[13] and expressed in IU/l after comparison with the WHO standard preparation (125 IU/l), obtained from the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands. Calculations were made for positive results in Ausab only (sample/negative control ratio ≥ 2.1). Samples containing more than 200 IU/l were diluted and retested. Dilutions were made in the negative control serum from Ausab. Estimation of the proportion of anti-HBs/a antibodies was performed according to the method of Hoofnagle et al.[14] In short, undiluted or diluted sera containing 1000-2000 cpm in Ausab were incubated for 2 h at room temperature with pooled HBsAg/ad, HBsAg/ay, and normal human serum, respectively. Pooled sera

included reference sera from Dr.A.M.Courouce-Pauty as mentioned in an earlier study.[11] Reduction of cpm after incubation with HBsAg/ay strains measured the anti-HBs/a proportion of the total amount of anti-HBs, since the vaccine consisted of HBsAg/adw only. The proportion of anti-HBs/d(w) antibodies was obtained by subtracting the reduction percentage after incubation with HBsAg/ay pooled serum from the reduction percentage after incubation with HBsAg/ad pooled serum.

RESULTS

Table I shows a delayed seroconversion rate for the recombinant vaccine group as compared to the plasma-derived vaccine group in the course of the vaccine study. Similar results were obtained for titres $\geq$ 10 IU/l, the supposed protective level of antibodies.

TABLE I

SEROCONVERSION RATE AFTER VACCINATION WITH RECOMBINANT (10 µg) AND PLASMA-DERIVED (20 µg) VACCINE IN HEALTH CARE WORKERS

Month	Recombinant vaccine	Plasma-derived vaccine	Recombinant vaccine	Plasma-derived vaccine
	Percentage seroconversion		Percentage anti-HBs $\geq$ 10 IU/l	
1	19(6/31)	56(14/25)	13(4/31)	40(10/25)
2	77(24/31)	96(22/23)	39(12/31)	74(17/23)
3	90(28/31)	100(25/25)	74(23/31)	96(24/25)
6	94(29/31)	100(25/25)	87(27/31)	100(25/25)
7	100(31/31)	100(22/22)	100(31/31)	100(22/22)

Geometric mean titres of anti-HBs were significantly lower in the recombinant vaccine group as compared to the plasma-derived vaccine group at month 2, 3, 6, and 7 (Table II).

After three injections females had significantly ($p < 0.05$) higher anti-HBs titres than males in the recombinant vaccine group (1412 vs. 468 IU/l) but not in the plasma-derived vaccine group (6036 vs. 7519 IU/l).

All vaccinees were negative for HBsAg and anti-HBc at 7 months and had normal alanine transferase levels in all sera obtained. Table III illustrates the increase of the relative proportion of anti-HBs/a antibodies from about 60% at month 1 to about 100% at month 7 following the first injection for both vaccine groups as measured by specific absorption. In any sample at

TABLE II

GEOMETRIC MEAN TITRES OF ANTI-HBs AFTER VACCINATION WITH RECOMBINANT VACCINE (10 µg) AND PLASMA-DERIVED VACCINE (20 µg)

Month	Recombinant vaccine GMT in IU/l	Plasma-derived vaccine GMT in IU/l
1	16.8(n= 6)[a]	19.7(n=14)
2	13.7(n=24)	61.8(n=22)[b]
3	34.8(n=28)	177.7(n=25)[b]
6	69.0(n=29)	291.1(n=25)[b]
7	857.4(n=31)	6736.5(n=22)[b]

[a] Responders only [b] $p < 0.05$ Wilcoxon's rank sum test

TABLE III

DETERMINATION OF SUBDETERMINANT SPECIFIC ANTIBODIES AFTER VACCINATION WITH RECOMBINANT VACCINE (10 µg) AND PLASMA-DERIVED VACCINE (20 µg) AS DETERMINED BY SPECIFIC ABSORPTION

Month	Recombinant vaccine			Plasma-derived vaccine		
	No. samples	% anti-HBs/a (range)	% anti-HBs/d	No. samples	% anti-HBs/a (range)	% anti-HBs/d
1	4	60(19- 92)[a]	39	6	57(22- 99)	42
2	9	81(40- 98)	17	15	83(25- 99)	17
3	18	95(74-100)	5	23	88(26-100)	11
6	26	99(89-100)	1	24	94(43-100)	6
7	31	99(90-100)	1	22	97(91-100)	3

[a] Determination of anti-HBs/a and anti-HBs/d was limited by the minimum amount of 25 IU/l anti-HBs.

month 7 the proportion of anti-HBs/a antibodies was at least 90%. In sera with anti-HBs $\geq$ 10 IU/l at month 1, two out of four in the recombinant vaccine group and three out of six in the plasma-derived vaccine group had less than 50% anti-HBs/a. In only two cases, one in each group, the anti-HBs/a percentage at month 1 was above 90, suggesting an anamnestic response. Geometric mean titres for those vaccinees with a positive anti-HBs response

at month 1 increased to 11158 IU/l (n=6) in sera from the recombinant vaccine group and to 13748 IU/l (n=13) in sera from the plasma-derived vaccine group, both at month 7.

DISCUSSION

Table IV compares the results of the immunicity of recombinant hepatitis B vaccine of Merck, Sharp and Dohme in our study with results of others as recently published. [5 6 7 8] Several lots of vaccine with minor differences in the purification procedure were used. Comparison is made in some studies with earlier results using plasma-derived vaccine from the same manufacturer. In our study vaccination with recombinant vaccine and plasma-derived vaccine took place simultaneously. Serum samples could therefore be handled similarly and investigated with the same batch of reagents.

We found anti-HBs development during the first six months following the first injection very similar to Scolnick et al.[5] and Jilg et al.[6]. After the booster injection at month 6 we found a lower geometric mean titre than observed by others. The proportion of anti-HBs/a antibodies, however, was very similar for the two vaccine groups and increased from 60% at month 1 to about 100% at month 7.

Interestingly, we noted high titres of anti-HBs at month 7 for those vaccinees who had already shown seroconversion at month 1. Titres in this subgroup were comparable to those in early responders in the plasma-derived vaccine group. Since we had the lowest seroconversion rate at month 1 observed so far for recombinant vaccine (19%), this may explain the low geometric mean titre at month 7. The reason for the initial low conversion rate in our study is unknown. Sex and age differences with other study groups may have contributed. Sex and age effects may have their most pronounced influence on vaccination of weak responders.[16 17] The highest seroconversion rate (67%) and the highest geometric mean titre (2749 IU/l) at month 7 were observed by Papaevangelou et al.[8] in male recruits aged 17-19 years.

If our observations can be confirmed in more extended studies, equalizing the dose of HBsAg in the recombinant vaccine preparation to that of the plasma-derived vaccine may favourably influence the seroconversion rate at month 1 and the amount of anti-HBs produced after three injections.

ACKNOWLEDGEMENT

We thank Mrs. R.S.Engels-Bakker for preparation of the manuscript.

TABLE IV

IMMUNE RESPONSE AFTER VACCINATION WITH RECOMBINANT AND PLASMA-DERIVED HEPATITIS B VACCINE AS COMPARED FROM LITERATURE

Authors	Dose	Geometric mean titres in IU/l Month 1	3	6	7	No.	Mean age	No. of men	No. of women	Lot no.
Recombinant vaccine										
Scolnick et al.[5]	10 µg	8	56	68	1905	15	33,23-53	10	5	934
Jilg et al.[6]	10 µg	9	29	68	2135	30	25,21-34	13	17	934
Papaevangelou et al.[8]	10 µg	11	198	189	2749	55	17-19	55		979
Davidson and Krugman[7]	10 µg	42	145	321	1911	51	21-30			972
Present study	10 µg	17	35	69	857	31	32,20-59	14	17	972
Plasma-derived vaccine										
Jilg et al.[6]	20 µg	15	164	263	4299	41	25,21-32	18	23	
Present study	20 µg	20	177	291	6737	25	30,22-53	12	13	
Papaevangelou et al.[8]	10 µg	4	278	492	9227	50				

REFERENCES

1. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A (1981) Hepatology 1: 377-385
2. Stevens CE, Taylor PE, Rubinstein P, Ting RCY, Bodner AJ, Sarngadharan MG, Gallo RC (1985) N Engl J Med 312: 375-376
3. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD (1982) Nature 298: 347-350
4. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR (1984) Nature 307: 178-180.
5. Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB (1984) J Am Med Ass 251: 2812-2815
6. Jilg W, Lorbeer B, Schmidt M, Wilske B, Zoulek G, Deinhardt F (1984) Lancet II: 1174-1175
7. Davidson M, Krugman S (1985) Lancet I: 108-109
8. Papaevangelou G, Dandolos E, Roumeliotou-Karayannis A, Richardson SC (1985) Lancet I: 455-456.
9. Barker LF, Maynard JE, Purcell RH, Hoofnagle JH, Berquist KR, London WT (1975) Am J Med Sci 270: 189-195
10. Szmuness W, Stevens CE, Harley EJ, Zang EA, Alter HJ, Taylor PE, De Vern A, Chen GTS, Kellner, The Dialysis Vaccine Trial Study Group (1982) N Engl J Med 307: 1481-1486
11. Legler K, Strohmeyer H, Ritter S, Gerlich WH, Thomssen R (1983) Develop Biol Standard 54: 179-189
12. Jilg W, Delhoune C, Deinhardt F, Roumeliotou-Karayannis AJ, Papaevangelou GJ, Mushahwar IK, Overby LR (1984) J Med Virol 13: 171-178
13. Hollinger FB, Adam E, Melberg D, Melnick JL (1982) In: Szmuness W, Alter HJ, Maynard JE (eds) Viral Hepatitis. Philadelphia, Franklin Institute Press, pp. 451-466
14. Hoofnagle JH, Gerety RJ, Smallwood LA, Barker LF (1977) Gastroenterology 72: 290-296
15. Heijtink RA, Van Hattum J, Schalm SW, Masurel N (1982) J Med Virol 10: 83-90
16. Heijtink RA, De Jong P, Schalm SW, Masurel N (1984) Hepatology 4: 611-614
17. Stevens CE, Szmuness W, Goodman AI, Weseley SA, Fotino M (1980) Lancet II: 1211-1213

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 808
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 972/C-K444 (10 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Richard E. Sampliner, M.D. Chief, Gastroenterology 111 G, Veterans Administration Medical Center Tucson, Arizona 85723
SECONDARY INVESTIGATOR:	Timothy R. Morgan, M.D. Chief, Gastroenterology Veterans Administration Medical Center Tucson, Arizona 85723
STUDY LOCATION:	Veterans Administration Medical Center Tucson, Arizona 85723 Arizona Health Sciences Center Tucson, Arizona 85723
DATE STUDY INITIATED:	April 3, 1984
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 25 health care personnel of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc, anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.
STUDY PROCEDURE:	Eligible study participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine at 0, 1 and 6 months. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

Study B08

STUDY PROCEDURE: (Contd)

A blood sample is obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12, and 24 months.

All samples are assayed for HBsAg, anti-HBc, anti-HBs and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer ≥25 mIU/ml may be tested for anti-a and anti-d subtype specificity.

RESULTS:

HEALTH CARE PERSONNEL

10 mcg Lot 972/C-K444 at 0, 1 and 6 months.

1. Number Vaccinated:

Injection No.		
1	2	3
25	25	25

One person who was initially anti-HBs positive received vaccine. The subject did not display a boost in titer after one injection of vaccine. A >50 fold rise in titer was seen after two injections.

One person who was anti-HBc positive prior to vaccination and 1 month post vaccination received vaccine. In all subsequent serum samples the person was anti-HBc negative. The subject remained HBsAg negative with normal ALT levels through 9 months of follow-up and became anti-HBs positive at 2 months. There has been no report of clinical illness in this individual.

2. Serologic Results:

Serologic data at 7-8 months are available for 23 study participants.

Study 808

RESULTS: (Contd)

At 7-8 months, 96% (22/23) vaccine recipients seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees was 1711.5 mIU/ml at that time. Among responders with a titer of S/N ≥2.1 and mIU/ml ≥10 the GMT was 2535.7 mIU/ml at 7-8 months.

By 12 months 95% (19/20) of the vaccinees retained an anti-HBs titer of S/N ≥2.1 and mIU/ml ≥10. The GMT for all vaccinees was 631.7 mIU/ml at that time.

Anti-HBs responses at 1 through 12 months are included in Table 1.

3. Clinical Results:

Clinical follow-up data are available for 25 study participants following the first two injections and for 24 participants following the third injection of vaccine. Clinical complaints and maximum temperatures reported following each injection are provided in Tables 2 and 3. In summary:

Clinical Complaint	% Frequency by Injection No.		
	1	2	3
Injection Site	20 (5/25)	12 (3/25)	21 (5/24)
Systemic	36 (9/25)	8 (2/25)	0 (0/24)

No serious or alarming adverse reactions attributable to vaccination have been reported.

ALT Elevations

Alanine aminotranferase levels were normal in all vaccine recipients except for elevations approximately 1.5 - 2 times normal, in three participants. Case no. (b)(6) had an ALT level of 62

Study 808

RESULTS: (Contd)

at 8 months. To date subsequent ALT levels for this individual have not been reported. Case nos. (b)(6) had transient ALT levels of 64 and 90, respectively, at 1 month. All subsequent samples through 8 months of follow-up were normal. A reason for the ALT elevations was not ascertained. None of the subjects has showed any clinical or serologic signs (HBsAg or anti-HBc)of hepatitis B.

HBV Markers (Anti-HBc)

One vaccine recipient had a 2 month post-vaccination serum sample positive for anti-HBc. The same serum sample was reported negative on retest. All subsequent samples through 12 months were negative. The subject remained HBsAg negative with normal ALT levels. There has been no report of clinical illness in this individual.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0808
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK444
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS		GMT (MIU/ML)		
				RESPONDERS	
	S/N >= 2.1	MIU/ML >= 10	ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	46% (11/24)	33% (8/24)	2.6	27.9	61.6
2 MONTHS	87% (20/23)	70% (16/23)	57.6	126.8	270.8
3 MONTHS	90% (19/21)	81% (17/21)	65.0	114.4	186.9
6 MONTHS	91% (21/23)	83% (19/23)	83.3	136.8	195.0
7/8 MONTHS	96% (22/23)	96% (22/23)	1711.5	2535.7	2535.7
12 MONTHS	95% (19/20)	95% (19/20)	631.7	945.1	945.1

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 9808
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	5 (20.0%)	3 (12.0%)	2 (8.0%)	2 (8.0%)	2 (8.0%)	1 (4.0%)	5 (20.0%)
PAIN	2 (8.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
SORENESS	3 (12.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	4 (16.0%)
TENDERNESS	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	2 (8.0%)
NODULE FORMATION	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
ECCHYMOSIS	0 (0.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
SYSTEMIC	4 (16.0%)	4 (16.0%)	2 (8.0%)	3 (12.0%)	2 (8.0%)	2 (8.0%)	9 (36.0%)
WHOLE BODY/GENERAL	3 (12.0%)	1 (4.0%)	2 (8.0%)	3 (12.0%)	1 (4.0%)	0 (0.0%)	4 (16.0%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
FATIGUE/WEAKNESS	2 (8.0%)	1 (4.0%)	2 (8.0%)	2 (8.0%)	1 (4.0%)	0 (0.0%)	2 (8.0%)
HEADACHE	2 (8.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
RESPIRATORY	0 (0.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	3 (12.0%)

00352

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0808
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SINUSITIS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)
MUSCULOSKELETAL	2 (8.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	4 (16.0%)
MYALGIA	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
NECK PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)
SHOULDER PAIN	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
NECK STIFFNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)
MYASTHENIA	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
PERSONS WITH COMPLAINTS	8 (32.0%)	5 (20.0%)	4 (16.0%)	5 (20.0%)	4 (16.0%)	3 (12.0%)	10 (40.0%)
PERSONS WITH NO COMPLAINTS	17 (68.0%)	20 (80.0%)	21 (84.0%)	20 (80.0%)	21 (84.0%)	22 (88.0%)	15 (60.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0808
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	2 (8.0%)	2 (8.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (12.0%)
SORENESS	2 (8.0%)	2 (8.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (12.0%)
SYSTEMIC	2 (8.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)		2 (8.0%)
WHOLE BODY/GENERAL	1 (4.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)		2 (8.0%)
FEVER (TEMP. NOT REPORTED)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
FATIGUE/WEAKNESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)		2 (8.0%)
HEADACHE	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
DIGESTIVE SYSTEM	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
ABDOMINAL PAINS/CRAMPS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
NERVOUS SYSTEM	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
VERTIGO/DIZZINESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
PERSONS WITH COMPLAINTS	3 (12.0%)	3 (12.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)		4 (16.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0808
TREATMENT :
LOT NUMBER : CK464
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	22 (88.0%)	22 (88.0%)	24 (96.0%)	24 (96.0%)	25 (100.0%)	25 (100.0%)	21 (84.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00355

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0606
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (25 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						
CLINICAL COMPLAINTS	0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	5 (20.8%)	1 (4.2%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (20.8%)
SORENESS	4 (16.7%)	1 (4.2%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (16.7%)
TENDERNESS	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
PERSONS WITH COMPLAINTS	5 (20.8%)	1 (4.2%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (20.8%)
PERSONS WITH NO COMPLAINTS	19 (79.2%)	23 (95.8%)	22 (91.7%)	24 (100.0%)	23 (100.0%)	24 (100.0%)	19 (79.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00356

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0808
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (25 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	20 (83.3%)	21 (84.0%)	23 (92.0%)	22 (88.0%)	20 (90.9%)	18 (85.7%)			18 (72.0%)
99 - 99.9	4 (16.7%)	4 (16.0%)	2 (8.0%)	3 (12.0%)	2 (9.1%)	2 (9.5%)			6 (24.0%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)			1 (4.0%)
TEMPERATURE TAKEN	24 (96.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	22 (88.0%)	21 (84.0%)			25 (100.0%)
TEMPERATURE NOT TAKEN	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (12.0%)	4 (16.0%)			0 (0.0%)

00357

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0808
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (25 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (5.3%)		1 (4.8%)
< 99	19 (90.5%)	19 (90.5%)	19 (90.5%)	18 (85.7%)	19 (90.5%)	17 (89.5%)		15 (71.4%)
99 - 99.9	1 (4.8%)	1 (4.8%)	1 (4.8%)	2 (9.5%)	1 (4.8%)	1 (5.3%)		5 (23.8%)
TEMPERATURE TAKEN	21 (84.0%)	21 (84.0%)	21 (84.0%)	21 (84.0%)	21 (84.0%)	19 (76.0%)		21 (84.0%)
TEMPERATURE NOT TAKEN	4 (16.0%)	4 (16.0%)	4 (16.0%)	4 (16.0%)	4 (16.0%)	6 (24.0%)		4 (16.0%)

00358

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0808
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (25 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	14 (100.0%)	13 (92.9%)	13 (100.0%)	12 (100.0%)	10 (90.9%)	13 (100.0%)		12 (85.7%)
99 - 99.9	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)		2 (14.3%)
TEMPERATURE TAKEN	14 (56.0%)	14 (56.0%)	13 (52.0%)	12 (48.0%)	11 (44.0%)	13 (52.0%)		14 (56.0%)
TEMPERATURE NOT TAKEN	11 (44.0%)	11 (44.0%)	12 (48.0%)	13 (52.0%)	14 (56.0%)	12 (48.0%)		11 (44.0%)

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 809
PURPOSE:	To evaluate antibody and clinical responses to various doses of vaccine in the following initially seronegative populations: 1. Healthy Children (1-11 years of age) 2. Healthy Adults
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot # 972/C-K444 (10 mcg HBsAg/ml) 985/C-K732 (5 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Drs. Stanley Plotkin and Stuart Starr Division of Preventive Medicine Joseph Stokes, Jr. Research Institute Children's Hospital of Philadelphia 34th Street and Civic Center Blvd. Philadelphia, PA 19104
STUDY LOCATIONS:	The Pediatric Medical Associates 420 Township Line Road Havertown, PA 19083 George A. Starkweather, M.D. 1001 Pennsylvania Avenue Havertown, PA 19083
DATE INITIATED:	February 2, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of healthy children (ages 1-11 years) and healthy adults who are negative for HBsAg, anti-HBc, and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.
PROCEDURE:	Children in the study receive a 0.5 ml (5 mcg HBsAg) or a 0.25 ml (2.5 mcg HBsAg) intramuscular injection of lot # 972/C-K444 vaccine at 0, 1 and 6 months or a 0.5 ml (2.5 mcg HBsAg) or 0.25 ml (1.25 mcg HBsAg) injection of lot # 985/C-K732 vaccine according to the

Study 809

PROCEDURE (Contd): the same time schedule. Adults receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of lot # 972/C-K444 vaccine at 0, 1 and 6 months. Vaccine recipients (or the parent or guardian in the case of a minor) are asked to record their temperature daily for five days after each injection of vaccine and to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) is obtained from each prospective vaccine recipient one to two weeks before the first vaccination. Post-vaccination bleedings are obtained at 1, 3, 7 and 12 months from some of the children and at 2, 6, 8 and 12 months from others. Post-vaccination bleedings are obtained from adult vaccine recipients at 1, 2, 3, 6, 8, 12 and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples may also be tested for yeast antibody and those with an anti-HBs titer $\geq$ 25 mIU/ml may be tested for the proportions of anti-a and anti-d activity.

RESULTS:

HEALTHY ADULTS:

10 mcg Lot # 972/C-K444 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
18	17	17

2. Serologic Results:

Serologic data are available for 11 participants at 7/8 months. One hundred percent (11/11) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at 7/8 months for all vaccinees was 955.7 mIU/ml.

Among the participants with serology data available at 12 months, 100% (12/12) were positive for anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees was 448.7 mIU/ml.

Study 809

RESULTS (Contd): Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for at least 17 participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	17(3/18)	24(4/17)	6(1/17)
Systemic	6(1/18)	6(1/17)	12(2/17)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Tables 3.

There were no serious or alarming reactions attributable to vaccine.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0909
POPULATION : HEALTHY ADULTS
DATE : 10 MAR
LOT : 0944
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SCREENING : NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	7.1%	(1/14)	0%	(0/14)	0.4	1.9	
2 MONTHS	67%	(4/6)	33%	(2/6)	7.7	32.7	184.9
3 MONTHS	71%	(5/7)	71%	(5/7)	7.2	25.9	25.9
6 MONTHS	93%	(14/15)	80%	(12/15)	33.7	66.9	66.0
7/8 MONTHS	100%	(11/11)	100%	(11/11)	955.7	955.7	955.7
12 MONTHS	100%	(12/12)	92%	(11/12)	448.7	448.7	697.5

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	3 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (16.7%)
SORENESS	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (11.1%)
STIFFNESS/TIGHTNESS	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
SYSTEMIC	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
WHOLE BODY/GENERAL	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
FEVER (TEMP. NOT REPORTED)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
HEADACHE	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
PERSONS WITH COMPLAINTS	3 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (16.7%)
PERSONS WITH NO COMPLAINTS	15 (83.3%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)		15 (83.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (17 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	4 (23.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (23.5%)
SORENESS	4 (23.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (23.5%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.9%)	1 (5.9%)		1 (5.9%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.9%)	1 (5.9%)		1 (5.9%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.9%)		1 (5.9%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.9%)	0 (0.0%)		1 (5.9%)
PERSONS WITH COMPLAINTS	4 (23.5%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.9%)	1 (5.9%)		4 (23.5%)
PERSONS WITH NO COMPLAINTS	13 (76.5%)	17 (100.0%)	17 (100.0%)	16 (94.1%)	16 (94.1%)	16 (94.1%)		13 (76.5%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (17 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
SORENESS	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
SYSTEMIC	1 (5.9%)	1 (5.9%)	2 (11.8%)	2 (11.8%)	1 (5.9%)	0 (0.0%)		2 (11.8%)
RESPIRATORY	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	0 (0.0%)		1 (5.9%)
UPPER RESPIRATORY INFECT., NOS	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	0 (0.0%)		1 (5.9%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
NECK PAIN	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
SHOULDER PAIN	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
ARM PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
OTHER	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)		1 (5.9%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (17 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
PERSONS WITH COMPLAINTS	1 (5.9%)	1 (5.9%)	3 (17.6%)	2 (11.8%)	1 (5.9%)	0 (0.0%)		3 (17.6%)
PERSONS WITH NO COMPLAINTS	16 (94.1%)	16 (94.1%)	14 (82.4%)	15 (88.2%)	16 (94.1%)	17 (100.0%)		14 (82.4%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (18 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	2 (18.2%)	3 (21.4%)	3 (23.1%)	3 (23.1%)	3 (21.4%)	3 (21.4%)			3 (21.4%)
< 99	7 (63.6%)	10 (71.4%)	10 (76.9%)	8 (61.5%)	11 (78.6%)	9 (64.3%)			6 (42.9%)
99 - 99.9	1 (9.1%)	1 (7.1%)	0 (0.0%)	2 (15.4%)	0 (0.0%)	2 (14.3%)			4 (28.6%)
101 - 101.9	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (7.1%)
TEMPERATURE TAKEN	11 (61.1%)	14 (77.8%)	13 (72.2%)	13 (72.2%)	14 (77.8%)	14 (77.8%)			14 (77.8%)
TEMPERATURE NOT TAKEN	7 (38.9%)	4 (22.2%)	5 (27.8%)	5 (27.8%)	4 (22.2%)	4 (22.2%)			4 (22.2%)

00368

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (17 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	0 (0.0%)	1 (10.0%)	1 (10.0%)	1 (10.0%)	1 (11.1%)	2 (22.2%)			0 (0.0%)
< 99	10 (100.0%)	8 (80.0%)	7 (70.0%)	8 (80.0%)	8 (88.9%)	6 (66.7%)			6 (60.0%)
99 - 99.9	0 (0.0%)	1 (10.0%)	2 (20.0%)	1 (10.0%)	0 (0.0%)	1 (11.1%)			4 (40.0%)
TEMPERATURE TAKEN	10 (58.8%)	10 (58.8%)	10 (58.8%)	10 (58.8%)	9 (52.9%)	9 (52.9%)			10 (58.8%)
TEMPERATURE NOT TAKEN	7 (41.2%)	7 (41.2%)	7 (41.2%)	7 (41.2%)	8 (47.1%)	8 (47.1%)			7 (41.2%)

Table 3 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (17 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (12.5%)	1 (12.5%)	2 (28.6%)	1 (12.5%)	2 (25.0%)	1 (12.5%)			1 (12.5%)
< 99	6 (75.0%)	6 (75.0%)	4 (57.1%)	7 (87.5%)	5 (62.5%)	7 (87.5%)			6 (75.0%)
99 - 99.9	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)			0 (0.0%)
101 - 101.9	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (12.5%)
TEMPERATURE TAKEN	8 (47.1%)	8 (47.1%)	7 (41.2%)	8 (47.1%)	8 (47.1%)	8 (47.1%)			8 (47.1%)
TEMPERATURE NOT TAKEN	9 (52.9%)	9 (52.9%)	10 (58.8%)	9 (52.9%)	9 (52.9%)	9 (52.9%)			9 (52.9%)

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 811.
PURPOSE:	To evaluate antibody and clinical responses to several dose levels of commercial hepatitis B plasma derived vaccine (H-B-VAX) and yeast recombinant hepatitis B vaccine in the following populations who are initially seronegative for hepatitis B virus markers: 1. Predialysis Patients 2. Health Care Personnel
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot # 974/C-K446 (20 mcg HBsAg/ml) Hepatitis B Plasma Vaccine Lot # 1510J (20 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Peter J. Grob, M.D. Section of Clinical Immunology Department of Medicine University Hospital Haldeliweg 4 CH-8044 Zurich Switzerland
SECONDARY INVESTIGATORS:	U. Binswanger, M.D., Professor Department of Medicine Nephrology Section University Hospital Zurich C. Descoeudres, M.D. Hemodialysis Station Inselspital Berne A. Blumberg, M.D., Professor Nephrology Kantonspital Aarau A. Many, M.D., P.D. Hemodialysis Unit Kantonsspital Winterthur H. Iselin, M.D. Hemodialysis Unit Neumunster Spital Zurich

Study 811

SECONDARY INVESTIGATORS: (Cont.)	K. Zaruba, M.D., P.D. Hemodialysis Station City Hospital Waid Zurich W. Herwig, M.D. Hemodialysis Station Kantonsspital Chur H.-J. Gloor, M.D. Hemodialysis Station Kantonsspital Schaffhausen J. Nadig, M.D. Hemodialysis Unit Kantonsspital Winterthur H. I. Joller-Jemelka, M.D. Section of Clinical Immunology Department of Medicine University Hospital Zurich
STUDY LOCATION:	University Hospital Haldeliweg 4 CH - 8044 Zurich Switzerland
DATE INITIATED:	April 10, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	One study population consists of 59 predialysis patients who have renal disease with functional impairment or end-stage renal disease that will shortly require dialysis treatment. The other population is comprised of 11 health care personnel. Subjects in both populations must be adults of either sex (pregnant women excluded). They must be initially negative for all hepatitis B serologic markers, have a normal ALT level, and must not previously have received any hepatitis B vaccine.

Study 811

PROCEDURE:

Patients are randomly assigned to one of 5 groups. Health care personnel constitute a sixth group.

Group	Vaccine/Dose/Regimen
1	Recombinant vaccine; 0.5 ml (10 mcg) at 0, 1 and 6 months
2	Recombinant vaccine; 1.0 ml (20 mcg) at 0, 1 and 6 months
3	Recombinant vaccine; 2x1.0 ml (40 mcg) at 0, 1 and 6 months
4	H-B-VAX; 1.0 ml (20 mcg) at 0, 1 and 6 months
5	H-B-VAX; 2x1.0 ml (40 mcg) at 0, 1 and 6 months
6	Recombinant vaccine; 0.5 ml (10 mcg) at 0, 1 and 6 months

All injections will be intramuscular. Patients in Groups 3 and 5 will have the vaccine administered in divided dose (i.e., 2 injections - one injection in each of two contralateral limbs).

Vaccine recipients will be asked to record their temperature for 5 days after each injection and to note any local or systemic complaints. Study participants will be bled 1 to 10 days prior to vaccination to verify eligibility for the study.

Follow-up samples will be obtained at 1, 3, 6 and 8 months following the initial vaccine injection. Blood samples will also be obtained at 12 and 24 months from subjects who are positive for anti-HBs at 8 months. All serum samples will be assayed for anti-HBc, anti-HBs, HBsAg and ALT by the investigator, and may be assayed for yeast antibody at MSDRL. In addition, participants who show an anti-HBs titer $\geq$ 25 mIU/ml will have their serum tested to determine the proportions of anti-a and anti-d activity.

Study 811

RESULTS:

HEALTH CARE PERSONNEL

10 mcg Lot #974/C-K446 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
11	8	8

2. Serologic Results:

Serology data are available for seven participants at 7/8 months. Eighty-six percent (6/7) of the subjects seroconverted for anti-HBs (S/N ≥2.1) at that time. Eighty-three percent (5/6) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 7/8 months for all vaccinees was 275.1 mIU/ml and 1076.6 mIU/ml for responders with a titer of mIU/ml ≥10.

Among subjects with serology data available at 12 months, 83% (5/6) were positive for anti-HBs (mIU/ml ≥10). The GMT at that time was 44.1 mIU/ml for all vaccinees and 324.9 mIU/ml for responders with a titer of mIU/ml ≥10.

Refer to Table 1 for anti-HBs responses and GMTs through 12 months of follow-up.

3. Clinical Complaints:

Clinical follow-up data are available for at least six participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No.		
	1	2	3
Injection Site	0(0/7)	0(0/7)	0(0/6)
Systemic	28(2/7)	0(0/7)	17(1/6)

Study 811

RESULTS (CONT.): Listings of specific clinical complaints are not presently available. There have been no reports of serious or alarming reactions attributable to vaccine.

Table 1.

Antibody Responses Among Health Care Personnel
Following Vaccination with 10 mcg Injections of Yeast Recombinant
Hepatitis B Vaccine Lot # 974/C-K446 at 0, 1, and 6 Months
in Study B11

Time (Months)	% (Proportion) with Anti-HBs		GMT (mIU/ml)		
	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	Responders S/N ≥ 2.1	Responders mIU/ml ≥ 10
1	0 (0/9)	0 (0/9)	0.3	---	---
3	38 (3/8)	38 (3/8)	2.4	77.5	77.5
6	38 (3/8)	25 (2/8)	2.2	63.1	225.0
7/8	86 (6/7)	83 (5/6)*	275.1*	1076.6*	1076.6*
12	83 (5/6)	83 (5/16)	44.1	324.9	324.9

* Based on 6 subjects (5 responders) for whom numeric titers are available.

STUDY 813

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 813
PURPOSE:	To evaluate antibody and clinical responses to several dose levels of yeast recombinant hepatitis B vaccine among the following populations: 1. Health Care Personnel (Seronegative) 2. Preimmune Adults
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 972/C-K444 (10 mcg HBsAg/ml) Lot B19541/18071/C-L220 (10 mcg HBsAg/0.5 ml) Lot B5860/22123/C-M125 (20 mcg HBsAg/ml) Lot B5861/22124/C-M126 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Morton Davidson, M.D. New York University Medical Center University Hospital 560 First Avenue New York, NY 10016
SECONDARY INVESTIGATOR:	Saul Krugman, M.D. Professor Department of Pediatrics New York University Medical Center 550 First Avenue New York, NY 10016
STUDY LOCATION:	New York University Medical Center University Hospital 560 First Avenue New York, NY 10016
DATE INITIATED:	February 1, 1984
DATE COMPLETED:	In progress.

Study 813

STUDY POPULATIONS: Under the original protocol and subsequent addenda, the following groups of health care personnel are included in the study. Participants may be of either sex, but pregnant women are excluded. Initially seronegative subjects have not previously received any hepatitis B vaccine.

Addendum No.	Characteristics	Number	Vaccine Lot No.#	Regimen
Initial protocol	Initially seronegative	50	972/C-K444	10 mcg (1.0 ml) at 0, 1, and 6 months
Add. #1	Initially seronegative	50	972/C-K444	5 mcg (0.5 ml) at 0, 1, and 6 months
Add. #2	Initially seronegative	50	972/C-K444	2.5 mcg (0.25 ml) at 0, 1, and 6 months
Add. #3	Initially seronegative	50	819541/18071/ C-L220	10 mcg (0.5 ml) at 0, 1, and 6 months
Add. #4	Initially seronegative	50	819541/18071/ C-L220	5 mcg (0.25 ml) at 0, 1, and 6 months
Add. #5	Initially seronegative; ≥40 years of age	50	85860/22123/ C-M125	20 mcg (1.0 ml) at 0, 1, and 6 months
Add. #5	Initially seronegative; ≥40 years of age	50	85861/22124/ C-M126	10 mcg (1.0 ml) at 0, 1, and 6 months
Add. #6	Vaccinated 3-5 yrs previously with plasma derived hepatitis B vaccine (HEPTAVAX-B)	100	85861/22124/ C-M126	10 mcg (1.0 ml) at time 0
Add. #7	Vaccinated previously with three 2.5 mcg doses of recombinant vaccine under Add. #2.	50	85861/22124/ C-M126	5 mcg (0.5 ml) or 10 mcg (1.0 ml) at time 0

Study 813

PROCEDURE:

Participants receive intramuscular injections of vaccine according to the regimens outlined above under STUDY POPULATIONS. Those enrolled under addendum #5 who fail to develop antibody following 3 injections of vaccine or have only a transient response that becomes negative by 12 months after the first dose may receive a fourth injection of vaccine.

Participants will be asked to record their temperature for 5 days after each injection of vaccine and to note any local or systemic complaints. Unexpected or serious reactions are to be reported immediately to the study physician.

Blood samples will be obtained from the initially seronegative groups prior to and on the day of the first vaccination. Follow-up samples will be obtained 1, 2, 3, 6, 8, 12 and 24 months after the initial injection of vaccine (initial protocol and addenda #1-5). Follow-up samples from persons vaccinated under addendum #6 are only taken 1 month after vaccination while persons enrolled under addendum #7 have blood samples taken 2 weeks, 4 weeks, and 6 months after vaccination.

Blood samples will be assayed for HBsAg, anti-HBc, anti-HBs and ALT by Dr. Krugman's laboratory and may be assayed for yeast antibody by the Merck Sharp and Dohme Research Laboratories. Samples with an anti-HBs titer $\geq$25 mIU/ml may be tested to determine the relative proportions of anti-a and anti-d activity.

RESULTS:

HEALTH CARE PERSONNEL:

2.5 mcg lot 972/C-K444 at 0, 1, and 6 months
5.0 mcg lot 972/C-K444 at 0, 1, and 6 months
5.0 mcg lot 1807I/C-L220 at 0, 1, and 6 months
10.0 mcg lot 972/C-K444 at 0, 1, and 6 months
10.0 mcg lot 1807I/C-L220 at 0, 1, and 6 months
10.0 mcg lot 22124/C-M126 at 0, 1, and 6 months
20.0 mcg lot 22123/C-M125 at 0, 1, and 6 monts

Study B13

RESULTS:

1. Number Vaccinated:

Dose Level	Lot	Injection No. 1	2	3	
2.5 mcg	C-K444	61	61	60	(Addendum #2)
5.0 mcg	C-K444	60	59	58	(Addendum #1)
5.0 mcg	C-L220	61	61	57	(Addendum #4)
10.0 mcg	C-K444	62	59	53	(Initial Protocol)
10.0 mcg	C-L220	62	62	56	(Addendum #3)
10.0 mcg	C-M126	7	3	--	(Addendum #5)
20.0 mcg	C-M125	7	4	--	(Addendum #5)

2. Serologic Results:

Seven/eight month serologic data are available for 40, 43, and 36 participants in the 2.5 mcg, 5 mcg, and 10 mcg dose regimens, respectively. Anti-HBs responses at that time are summarized below:

Dose Level	% with Anti-HBs S/N ≥2.1	% with Anti-HBs mIU/ml ≥10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥2.1	GMT (mIU/ml) Responders mIU/ml ≥10
2.5 mcg	100 (40/40)	97 (39/40)	291.5	291.5	321.5
5 mcg	98 (42/43)	95 (41/43)	523.8	625.7	693.9
10 mcg	100 (36/36)	100 (36/36)	1509.3	1509.3	1509.3

Serologic results are not presently available for the 7 participants who have received 20 mcg injections of vaccine.

Refer to Table 1 for anti-HBs responses and GMTs, by dose regimen, through 12 months of follow-up.

Study 813

RESULTS: (Contd)

3. Clinical Complaints

Clinical follow-up data are available for at least 60, 78, 77, and 2 participants after each injection in the 2.5 mcg, 5 mcg, 10 mcg, and 20 mcg dose regimens, respectively. The overall frequencies of complaints are presented below

Type of Complaint	Dose Level	Frequency in % by Injection 1	2	3
Injection site	2.5 mcg	21 (13/61)	12 (7/61)	5 (3/60)
	5 mcg	22 (27/121)	11 (13/119)	12 (9/78)
	10 mcg	30 (38/129)	15 (18/119)	17 (13/77)
	20 mcg	0 (0/6)	0 (0/2)	
Systemic	2.5 mcg	13 (8/61)	3 (2/61)	2 (1/60)
	5 mcg	17 (20/121)	13 (15/119)	6 (5/78)
	10 mcg	16 (20/129)	11 (13/119)	5 (4/77)
	20 mcg	17 (1/6)	50 (1/2)	

Refer to Tables 2 through 5 for listings of specific clinical complaints by injection and dose regimen. Maximum temperature data are presented in Tables 6 through 9.

Reaction Possibly Related to Vaccine

A 23 year-old female developed pruritic hives on her back and legs within 24 hours of receiving the first 10 mcg injection of vaccine lot C-L220. All symptoms resolved by day 4 post vaccination. The subject received the second injection of vaccine and within 24 hours again developed hives on her back, arms and left hand. All symptoms resolved by day 4 post vaccination. She received the third injection of vaccine with no evidence of hives. The subject's medical history is significant for an allergy to contrast dye (developed hives during administration of dye for CAT scan). The development of hives post injections one and two is considered probably vaccine related.

Study 813

PUBLICATIONS:

Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985; 1:108-9.

Davidson M, Krugman S. Recombinant yeast hepatitis B vaccine: Side effects and immunogenicity compared with plasma-derived hepatitis B vaccine. Submitted for publication to Hepatitis Scientific Memoranda.

Table 1

Antibody Responses Among Initially Seronegative Health Care Personnel Following Vaccination with 10, 5, and 2.5 mcg Injections of Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months in Study 813

	10 mcg					5 mcg					2.5 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
Time Months	S/N≥2.1	mIU/ml≥10	All Vaccinees	----Responders -- S/N≥2.1	mIU/ml≥10	S/N≥2.1	mIU/ml≥10	All Vaccinees	----Responders---- S/N≥2.1	mIU/ml≥10	S/N≥2.1	mIU/ml≥10	All Vaccinees	--- Responders - S/N≥2.1	mIU/ml≥10
1	46(48/104)	24(25/104)	2.0	18.4	63.9	35(37/105)	20(21/105)	1.3	18.3	59.8	27(16/60)	15(9/60)	1.0	23.6	65.9
2	89(86/97)	72(70/97)	24.9	43.7	70.9	85(84/99)	55(54/99)	14.4	28.7	79.8	71(37/52)	44(23/52)	7.0	25.2	65.0
3	92(87/95)	86(82/95)	56.5	89.1	108.1	92(93/101)	80(81/101)	30.9	46.0	63.7	86(48/56)	63(35/56)	17.0	33.3	63.2
6	97(89/92)	93(86/92)	95.7	116.2	129.2	93(94/101)	84(85/101)	45.8	66.6	85.0	86(49/57)	70(40/57)	17.2	32.1	46.9
7/8	100(36/36)	100(36/36)	1509.3	1509.3	1509.3	98(42/43)	95(41/43)	523.8	625.7	693.9	100(40/40)	97(39/40)	291.5	291.5	321.5
12	96(43/45)	96(43/45)	313.5	433.1	433.1	98(56/57)	91(52/57)	212.5	239.0	326.7	96(45/47)	87(41/47)	98.1	127.0	172.3

2340I-7
1/13/85

00383

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (61 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	11 (18.0%)	8 (13.1%)	5 (8.2%)	2 (3.3%)	2 (3.3%)	2 (3.3%)		13 (21.3%)
SORENESS	2 (3.3%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (4.9%)
TENDERNESS	9 (14.8%)	7 (11.5%)	4 (6.6%)	2 (3.3%)	2 (3.3%)	2 (3.3%)		9 (14.8%)
ERYTHEMA (REDNESS)	2 (3.3%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)		2 (3.3%)
WARMTH	2 (3.3%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)		2 (3.3%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
SYSTEMIC	0 (0.0%)	3 (4.9%)	2 (3.3%)	3 (4.9%)	3 (4.9%)	4 (6.6%)		8 (13.1%)
WHOLE BODY/GENERAL	0 (0.0%)	2 (3.3%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.6%)		3 (4.9%)
SWEATING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)		1 (1.6%)
FATIGUE/WEAKNESS	0 (0.0%)	2 (3.3%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)		3 (4.9%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	2 (3.3%)	1 (1.6%)	1 (1.6%)	2 (3.3%)		2 (3.3%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (1.6%)		1 (1.6%)

00384

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (61 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)		1 (1.6%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	1 (1.6%)		1 (1.6%)
MUSCLE STIFFNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	1 (1.6%)		1 (1.6%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.6%)		3 (4.9%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)		1 (1.6%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (1.6%)		2 (3.3%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
DIMINISHED APPETITE	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
PERSONS WITH COMPLAINTS	11 (18.0%)	10 (16.4%)	7 (11.5%)	5 (8.2%)	5 (8.2%)	6 (9.8%)		20 (32.8%)
PERSONS WITH NO COMPLAINTS	50 (82.0%)	51 (83.6%)	54 (88.5%)	56 (91.8%)	56 (91.8%)	55 (90.2%)		41 (67.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (61 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	5 (8.2%)	3 (4.9%)	3 (4.9%)	1 (1.6%)	1 (1.6%)	0 (0.0%)		7 (11.5%)
SORENESS	2 (3.3%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.3%)
TENDERNESS	3 (4.9%)	2 (3.3%)	2 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (6.6%)
ERYTHEMA (REDNESS)	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	0 (0.0%)		1 (1.6%)
SYSTEMIC	1 (1.6%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)		2 (3.3%)
WHOLE BODY/GENERAL	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
HEADACHE	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (1.6%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
WHEEZES	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
PERSONS WITH COMPLAINTS	6 (9.8%)	3 (4.9%)	4 (6.6%)	2 (3.3%)	1 (1.6%)	0 (0.0%)		9 (14.8%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (61 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	55 (90.2%)	58 (95.1%)	57 (93.4%)	59 (96.7%)	60 (98.4%)	61 (100.0%)	52 (85.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00387

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (60 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	3 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (5.0%)
TENDERNESS	3 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (5.0%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)		1 (1.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)		1 (1.7%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	0 (0.0%)		1 (1.7%)
COUGH	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)		1 (1.7%)
PERSONS WITH COMPLAINTS	3 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)		4 (6.7%)
PERSONS WITH NO COMPLAINTS	57 (95.0%)	60 (100.0%)	60 (100.0%)	59 (98.3%)	59 (98.3%)	59 (98.3%)		56 (93.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (121 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	22 (18.2%)	12 (9.9%)	4 (3.3%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	27 (22.3%)
INFLAMMATION	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
PAIN	2 (1.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
SORENESS	14 (11.6%)	8 (6.6%)	3 (2.5%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	17 (14.0%)
TENDERNESS	6 (5.0%)	3 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (5.8%)
STIFFNESS/TIGHTNESS	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
PRURITIS (ITCHING)	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
ECCHYMOSIS	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
SYSTEMIC	14 (11.6%)	9 (7.4%)	6 (5.0%)	4 (3.3%)	4 (3.3%)	3 (2.5%)	20 (16.5%)
WHOLE BODY/GENERAL	9 (7.4%)	4 (3.3%)	4 (3.3%)	3 (2.5%)	3 (2.5%)	3 (2.5%)	13 (10.7%)
FEVER (TEMP. NOT REPORTED)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
SWEATING	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (121 PATIENTS) - DOSE 1						NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION						
	0	1	2	3	4	5	
FLUSH	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
FATIGUE/WEAKNESS	6 (5.0%)	2 (1.7%)	3 (2.5%)	2 (1.7%)	2 (1.7%)	2 (1.7%)	9 (7.4%)
MALAISE	3 (2.5%)	2 (1.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (3.3%)
HEADACHE	2 (1.7%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	4 (3.3%)
LIGHTHEADED	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
RESPIRATORY	3 (2.5%)	3 (2.5%)	1 (0.8%)	2 (1.7%)	2 (1.7%)	1 (0.8%)	5 (4.1%)
PHARYNGITIS (SORE THROAT)	1 (0.8%)	2 (1.7%)	1 (0.8%)	2 (1.7%)	1 (0.8%)	1 (0.8%)	3 (2.5%)
UPPER RESPIRATORY INFECT., NOS	2 (1.7%)	2 (1.7%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	2 (1.7%)
WHEEZES	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
MUSCULOSKELETAL	2 (1.7%)	3 (2.5%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.5%)
ARTHRITIS, MONOARTICULAR	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
ARTHRALGIA, MONOARTICULAR	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
ARTHRALGIA (OTHER)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (121 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
BACK PAIN	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
OTHER	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
DIGESTIVE SYSTEM	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
NAUSEA	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
ABDOMEN DISTENDED	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
NERVOUS SYSTEM	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
VERTIGO/DIZZINESS	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
IRRITABILITY	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
PERSONS WITH COMPLAINTS	34 (28.1%)	20 (16.5%)	9 (7.4%)	5 (4.1%)	4 (3.3%)	3 (2.5%)	41 (33.9%)
PERSONS WITH NO COMPLAINTS	87 (71.9%)	101 (83.5%)	112 (92.6%)	116 (95.9%)	117 (96.7%)	118 (97.5%)	80 (66.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (120 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	11 (9.2%)	5 (4.2%)	3 (2.5%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	13 (10.9%)
PAIN	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
SORENESS	8 (6.7%)	4 (3.4%)	3 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (6.7%)
TENDERNESS	2 (1.7%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	3 (2.5%)
WHEAL/WHEAL AND FLARE	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
SYSTEMIC	3 (2.5%)	8 (6.7%)	7 (5.9%)	4 (3.4%)	3 (2.5%)	3 (2.5%)	15 (12.6%)
WHOLE BODY/GENERAL	2 (1.7%)	3 (2.5%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	2 (1.7%)	9 (7.6%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
FLUSH	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.8%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	2 (1.7%)
FATIGUE/WEAKNESS	1 (0.8%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	4 (3.4%)
MALAISE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (120 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
HEADACHE	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.5%)
RESPIRATORY	0 (0.0%)	3 (2.5%)	4 (3.4%)	1 (0.8%)	0 (0.0%)	1 (0.8%)	5 (4.2%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	2 (1.7%)	3 (2.5%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	4 (3.4%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	2 (1.7%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
OTHER	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
HEMIC AND LYMPHATIC	1 (0.8%)	1 (0.8%)	2 (1.7%)	2 (1.7%)	2 (1.7%)	1 (0.8%)	3 (2.5%)
LYMPHADENOPATHY, GENERAL	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	1 (0.8%)	2 (1.7%)
LYMPHADENOPATHY, CERVICAL	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
DIGESTIVE SYSTEM	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
DIARRHEA	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
NAUSEA	0 (0.0%)	2 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
PERSONS WITH COMPLAINTS	13 (10.9%)	12 (10.1%)	9 (7.6%)	4 (3.4%)	3 (2.5%)	3 (2.5%)	24 (20.2%)
PERSONS WITH NO COMPLAINTS	106 (89.1%)	107 (89.9%)	110 (92.4%)	115 (96.6%)	116 (97.5%)	116 (97.5%)	95 (79.8%)

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (120 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (115 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	8 (10.3%)	3 (3.8%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	9 (11.5%)
SORENESS	2 (2.6%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.6%)
TENDERNESS	5 (6.4%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	6 (7.7%)
PRURITIS (ITCHING)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
SYSTEMIC	2 (2.6%)	3 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (6.4%)
WHOLE BODY/GENERAL	1 (1.3%)	3 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (5.1%)
FATIGUE/WEAKNESS	0 (0.0%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.6%)
MALAISE	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
HEADACHE	1 (1.3%)	2 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)
ACHINESS	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
HEMIC AND LYMPHATIC	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
LYMPHADENOPATHY, GENERAL	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (115 PATIENTS) - DOSE 3						NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION						
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	9 (11.5%)	6 (7.7%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	13 (16.7%)
PERSONS WITH NO COMPLAINTS	69 (88.5%)	72 (92.3%)	77 (98.7%)	77 (98.7%)	78 (100.0%)	78 (100.0%)	65 (83.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (132 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	27 (20.9%)	17 (13.2%)	10 (7.8%)	3 (2.3%)	2 (1.6%)	2 (1.6%)		38 (29.5%)
PAIN	2 (1.6%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (2.3%)
SORENESS	13 (10.1%)	7 (5.4%)	4 (3.1%)	2 (1.6%)	1 (0.8%)	1 (0.8%)		18 (14.0%)
TENDERNESS	11 (8.5%)	7 (5.4%)	4 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		15 (11.6%)
ERYTHEMA (REDNESS)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
ECCHYMOSIS	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
RASH, NOS	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
SYSTEMIC	10 (7.6%)	11 (8.5%)	8 (6.2%)	6 (4.7%)	3 (2.3%)	3 (2.3%)		20 (15.5%)
WHOLE BODY/GENERAL	5 (3.9%)	3 (2.3%)	2 (1.6%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		8 (6.2%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (1.6%)
FATIGUE/WEAKNESS	3 (2.3%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)		4 (3.1%)
MALAISE	1 (0.8%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (1.6%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (132 PATIENTS) - DOSE 1						NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION						
	0	1	2	3	4	5	
HEADACHE	1 (0.8%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	2 (1.6%)
INFECTIOUS SYNDROMES	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
INFLUENZA, NOS	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
INTEGUMENTARY SYSTEM	1 (0.8%)	2 (1.6%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	3 (2.3%)
URTICARIA/HIVES	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
PRURITIS/ITCHING	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
RASH, NOS	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
RESPIRATORY	1 (0.8%)	2 (1.6%)	2 (1.6%)	2 (1.6%)	2 (1.6%)	2 (1.6%)	5 (3.9%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	2 (1.6%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (0.8%)	2 (1.6%)	1 (0.8%)	2 (1.6%)	1 (0.8%)	3 (2.3%)
UPPER RESPIRATORY INFECT., NOS	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	3 (2.3%)
HEMIC AND LYMPHATIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
LYMPHADENOPATHY, CERVICAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)

Table 4 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (132 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
MUSCULOSKELETAL	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
NECK STIFFNESS	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
DIGESTIVE SYSTEM	3 (2.3%)	2 (1.6%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (3.9%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
DIARRHEA	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (1.6%)
NAUSEA	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (1.6%)
VOMITING	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
OTHER	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
UROGENITAL SYSTEM	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		2 (1.6%)
URINARY TRACT INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
DYSURIA	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
OTHER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
ORGANS OF SPECIAL SENSE	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)

Table 4 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (132 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
BLURRED VISION	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
PERSONS WITH COMPLAINTS	32 (24.8%)	26 (20.2%)	17 (13.2%)	9 (7.0%)	5 (3.9%)	5 (3.9%)	49 (38.0%)
PERSONS WITH NO COMPLAINTS	97 (75.2%)	103 (79.8%)	112 (86.8%)	120 (93.0%)	124 (96.1%)	124 (96.1%)	80 (62.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00400

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (125 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	13 (10.9%)	10 (8.4%)	7 (5.9%)	2 (1.7%)	1 (0.8%)	1 (0.8%)		18 (15.1%)
PAIN	1 (0.8%)	2 (1.7%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)		3 (2.5%)
SORENESS	5 (4.2%)	4 (3.4%)	3 (2.5%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		6 (5.0%)
TENDERNESS	7 (5.9%)	4 (3.4%)	3 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		9 (7.6%)
STIFFNESS/TIGHTNESS	2 (1.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (1.7%)
SYSTEMIC	5 (4.2%)	9 (7.6%)	7 (5.9%)	5 (4.2%)	6 (5.0%)	6 (5.0%)		13 (10.9%)
WHOLE BODY/GENERAL	3 (2.5%)	5 (4.2%)	3 (2.5%)	2 (1.7%)	2 (1.7%)	2 (1.7%)		8 (6.7%)
FATIGUE/WEAKNESS	3 (2.5%)	2 (1.7%)	1 (0.8%)	2 (1.7%)	2 (1.7%)	2 (1.7%)		5 (4.2%)
MALAISE	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		3 (2.5%)
HEADACHE	0 (0.0%)	2 (1.7%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (1.7%)
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (0.8%)	2 (1.7%)	2 (1.7%)	1 (0.8%)	1 (0.8%)		2 (1.7%)
URTICARIA/HIVES	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)		1 (0.8%)

00401

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (125 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PRURITIS/ITCHING	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
RESPIRATORY	1 (0.8%)	2 (1.7%)	1 (0.8%)	2 (1.7%)	4 (3.4%)	4 (3.4%)		5 (4.2%)
PHARYNGITIS (SORE THROAT)	1 (0.8%)	2 (1.7%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	2 (1.7%)		3 (2.5%)
LARYNGITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
BRONCHITIS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)		1 (0.8%)
COUGH	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
HEMIC AND LYMPHATIC	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
LYMPHADENOPATHY, GENERAL	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
LYMPHADENOPATHY, CERVICAL	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
MUSCULOSKELETAL	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
MYALGIA	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)
DIGESTIVE SYSTEM	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (0.8%)

00402

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (125 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
ABDOMINAL PAINS/CRAMPS	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
DIARRHEA	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
PERSONS WITH COMPLAINTS	16 (13.4%)	16 (13.4%)	14 (11.8%)	7 (5.9%)	7 (5.9%)	7 (5.9%)	27 (22.7%)
PERSONS WITH NO COMPLAINTS	103 (86.6%)	103 (86.6%)	105 (88.2%)	112 (94.1%)	112 (94.1%)	112 (94.1%)	92 (77.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (109 PATIENTS) - DOSE 3						NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION						
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	11 (14.3%)	10 (13.0%)	6 (7.8%)	6 (7.8%)	5 (6.5%)	5 (6.5%)	13 (16.9%)
PAIN	1 (1.3%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
SORENESS	8 (10.4%)	6 (7.8%)	3 (3.9%)	3 (3.9%)	2 (2.6%)	2 (2.6%)	9 (11.7%)
TENDERNESS	2 (2.6%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	3 (3.9%)
ERYTHEMA (REDNESS)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	2 (2.6%)
INDURATION	0 (0.0%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
PAPULE(S)	0 (0.0%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
STIFFNESS/TIGHTNESS	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
SYSTEMIC	1 (1.3%)	2 (2.6%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	4 (5.2%)
WHOLE BODY/GENERAL	1 (1.3%)	2 (2.6%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	4 (5.2%)
MALAISE	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
HEADACHE	0 (0.0%)	1 (1.3%)	2 (2.6%)	1 (1.3%)	1 (1.3%)	0 (0.0%)	2 (2.6%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (109 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
ACHINESS	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
PERSONS WITH COMPLAINTS	12 (15.6%)	12 (15.6%)	7 (9.1%)	6 (7.8%)	6 (7.8%)	5 (6.5%)	15 (19.5%)
PERSONS WITH NO COMPLAINTS	65 (84.4%)	65 (84.4%)	70 (90.9%)	71 (92.2%)	71 (92.2%)	72 (93.5%)	62 (80.5%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (7 PATIENTS) - DOSE 1 — DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)
WHOLE BODY/GENERAL	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)
SENSATION OF WARMTH, GENERAL	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)
PERSONS WITH COMPLAINTS	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)
PERSONS WITH NO COMPLAINTS	5 (83.3%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	5 (83.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0613
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (4 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
SYSTEMIC	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)		1 (50.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (50.0%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (50.0%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (50.0%)
RESPIRATORY	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)		1 (50.0%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)		1 (50.0%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)		1 (50.0%)
EARACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)		1 (50.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)		1 (50.0%)
PERSONS WITH NO COMPLAINTS	2 (100.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)		1 (50.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 6

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (61 PATIENTS) - DOSE 1 — DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
NORMAL	60 (98.4%)	59 (96.7%)	60 (98.4%)	60 (98.4%)	60 (98.4%)	59 (98.3%)		59 (96.7%)
< 99	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.7%)		1 (1.6%)
99 - 99.9	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
TEMPERATURE TAKEN	61 (100.0%)	61 (100.0%)	61 (100.0%)	61 (100.0%)	61 (100.0%)	60 (98.4%)		61 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)		0 (0.0%)

Table 6 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (61 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	60 (98.4%)	61 (100.0%)	60 (98.4%)	61 (100.0%)	61 (100.0%)	61 (100.0%)		59 (96.7%)
< 99	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
99 - 99.9	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.6%)
TEMPERATURE TAKEN	61 (100.0%)	61 (100.0%)	61 (100.0%)	61 (100.0%)	61 (100.0%)	61 (100.0%)		61 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 6 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (60 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	60 (100.0%)	60 (100.0%)	60 (100.0%)	60 (100.0%)	60 (100.0%)	60 (100.0%)		60 (100.0%)
TEMPERATURE TAKEN	60 (100.0%)	60 (100.0%)	60 (100.0%)	60 (100.0%)	60 (100.0%)	60 (100.0%)		60 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (121 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	114 (94.2%)	117 (96.7%)	116 (96.7%)	115 (95.8%)	117 (98.3%)	116 (95.9%)			109 (90.1%)
< 99	2 (1.7%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)			2 (1.7%)
99 - 99.9	4 (3.3%)	2 (1.7%)	2 (1.7%)	5 (4.2%)	2 (1.7%)	4 (3.3%)			8 (6.6%)
100 - 100.9	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			2 (1.7%)
TEMPERATURE TAKEN	121 (100.0%)	121 (100.0%)	120 (99.2%)	120 (99.2%)	119 (98.3%)	121 (100.0%)			121 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	0 (0.0%)			0 (0.0%)

Table 7 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (120 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	113 (95.0%)	114 (95.8%)	114 (95.8%)	116 (97.5%)	115 (96.6%)	116 (97.5%)			110 (92.4%)
< 99	4 (3.4%)	3 (2.5%)	4 (3.4%)	2 (1.7%)	2 (1.7%)	2 (1.7%)			5 (4.2%)
99 - 99.9	2 (1.7%)	2 (1.7%)	1 (0.8%)	1 (0.8%)	2 (1.7%)	1 (0.8%)			4 (3.4%)
TEMPERATURE TAKEN	119 (99.2%)	119 (99.2%)	119 (99.2%)	119 (99.2%)	119 (99.2%)	119 (99.2%)			119 (99.2%)
TEMPERATURE NOT TAKEN	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)			1 (0.8%)

00812

Table 7 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (115 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
NORMAL	78 (100.0%)	78 (100.0%)	78 (100.0%)	78 (100.0%)	78 (100.0%)	78 (100.0%)		78 (100.0%)
TEMPERATURE TAKEN	78 (67.8%)	78 (67.8%)	78 (67.8%)	78 (67.8%)	78 (67.8%)	78 (67.8%)		78 (67.8%)
TEMPERATURE NOT TAKEN	37 (32.2%)	37 (32.2%)	37 (32.2%)	37 (32.2%)	37 (32.2%)	37 (32.2%)		37 (32.2%)

Table 8

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (132 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	114 (89.1%)	118 (91.5%)	119 (93.0%)	119 (93.0%)	118 (92.2%)	118 (92.2%)			111 (86.0%)
< 99	4 (3.1%)	7 (5.4%)	5 (3.9%)	2 (1.6%)	4 (3.1%)	5 (3.9%)			4 (3.1%)
99 - 99.9	10 (7.8%)	4 (3.1%)	4 (3.1%)	6 (4.7%)	6 (4.7%)	5 (3.9%)			13 (10.1%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)			1 (0.8%)
TEMPERATURE TAKEN	128 (97.0%)	129 (97.7%)	128 (97.0%)	128 (97.0%)	128 (97.0%)	128 (97.0%)			129 (97.7%)
TEMPERATURE NOT TAKEN	4 (3.0%)	3 (2.3%)	4 (3.0%)	4 (3.0%)	4 (3.0%)	4 (3.0%)			3 (2.3%)

Table 8 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (125 PATIENTS) - DOSE 2 DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
NORMAL	109 (92.4%)	112 (94.9%)	112 (94.9%)	113 (95.8%)	114 (96.6%)	111 (94.1%)		104 (88.1%)
< 99	4 (3.4%)	3 (2.5%)	4 (3.4%)	2 (1.7%)	2 (1.7%)	1 (0.8%)		3 (2.5%)
99 - 99.9	5 (4.2%)	3 (2.5%)	2 (1.7%)	3 (2.5%)	2 (1.7%)	5 (4.2%)		10 (8.5%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)		1 (0.8%)
TEMPERATURE TAKEN	118 (94.4%)	118 (94.4%)	118 (94.4%)	118 (94.4%)	118 (94.4%)	118 (94.4%)		118 (94.4%)
TEMPERATURE NOT TAKEN	7 (5.6%)	7 (5.6%)	7 (5.6%)	7 (5.6%)	7 (5.6%)	7 (5.6%)		7 (5.6%)

Table 8 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (109 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	71 (92.2%)	71 (93.4%)	72 (93.5%)	72 (94.7%)	72 (93.5%)	72 (93.5%)			71 (92.2%)
< 99	3 (3.9%)	2 (2.6%)	3 (3.9%)	2 (2.6%)	3 (3.9%)	3 (3.9%)			1 (1.3%)
99 - 99.9	2 (2.6%)	3 (3.9%)	2 (2.6%)	2 (2.6%)	2 (2.6%)	2 (2.6%)			4 (5.2%)
100 - 100.9	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (1.3%)
TEMPERATURE TAKEN	77 (70.6%)	76 (69.7%)	77 (70.6%)	76 (69.7%)	77 (70.6%)	77 (70.6%)			77 (70.6%)
TEMPERATURE NOT TAKEN	32 (29.4%)	33 (30.3%)	32 (29.4%)	33 (30.3%)	32 (29.4%)	32 (29.4%)			32 (29.4%)

Table 9
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (7 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	3 (50.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	3 (50.0%)			3 (50.0%)
< 99	2 (33.3%)	3 (50.0%)	3 (50.0%)	3 (50.0%)	2 (33.3%)	3 (50.0%)			1 (16.7%)
99 - 99.9	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)			2 (33.3%)
TEMPERATURE TAKEN	6 (85.7%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	6 (85.7%)	6 (85.7%)			6 (85.7%)
TEMPERATURE NOT TAKEN	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)			1 (14.3%)

Table 9 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBIHANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (4 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	1 (50.0%)	2 (100.0%)	2 (100.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)			0 (0.0%)
99 - 99.9	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (50.0%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)			1 (50.0%)
TEMPERATURE TAKEN	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)			2 (50.0%)
TEMPERATURE NOT TAKEN	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)			2 (50.0%)

IMMUNOGENICITY OF RECOMBINANT YEAST HEPATITIS B VACCINE

SIR,—In Dr Jilg and colleagues' study (Nov 24, p 1174) in thirty recipients of recombinant hepatitis B vaccine "the immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels". They compared a 10 μg dose of recombinant vaccine with a 20 μg dose of plasma-derived vaccine.

As indicated in the table, our results in a similar study in one hundred and seven seronegative health professionals, 21–30 years of age, revealed essentially the same immune response in recipients of 5 μg and 10 μg doses of recombinant yeast hepatitis B vaccine when compared with a comparable group who received 20 μg dose of plasma-derived vaccine.

Valid conclusions cannot be drawn from studies in thirty or a hundred vaccinees. More extensive studies will be required to evaluate anti-HBs response and its persistence in recipients of recombinant hepatitis B vaccine. In the meantime, our initial results are encouraging.

NYU Medical Center,
New York, NY 10016, USA

MORTON DAVIDSON
SAUL KRUGMAN

SEROCONVERSION RATES AND GEOMETRIC MEAN TITERS (GMT) OF SERONEGATIVE INDIVIDUALS, ADULTS GIVEN RECOMBINANT OR PLASMA-DERIVED HEPATITIS B VACCINE

	Recombinant vaccine†						Plasma derived (20 μg)‡	
	10 μg			5 μg				
Time* (mo)	Anti-HBs response	mIU/ml (GMT)	S/N ratio (GMT)	Anti-HBs response	mIU/ml (GMT)	S/N ratio (GMT)	Anti-HBs response	S/N ratio (GMT)
0	..	..	..	..	..	..	..	..
1	22/51 (43%)	62	19	21/56 (37%)	95	25	10/47 (21%)	39
2	48/51 (94%)	88	37	51/54 (94%)	60	10	34/47 (72%)	97
3	50/51 (98%)	165	53	53/56 (95%)	120	51	43/47 (91%)	70
6	49/50 (98%)	321	83	51/56 (91%)	104	42	44/47 (94%)	94
7/8	45/45 (100%)	1011	164	49/50 (98%)	830	126	45/47 (96%)	161

*Vaccine given at 0, 1, and 6 months. Follow-up to 7 months (plasma derived) or 8 months (recombinant). †Assay in WHO-II unit. ‡Assay in IU.

Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985; 1:108-9.

RECOMBINANT YEAST HEPATITIS B VACCINE: SIDE EFFECTS AND IMMUNOGENICITY COMPARED WITH PLASMA-DERIVED HEPATITIS B VACCINE.

Morton Davidson and Saul Krugman
NYU Medical Center, New York, N.Y.

A yeast recombinant hepatitis B vaccine (Merck Lot no. 972/C-K444) was evaluated in 107 seronegative health professionals, 21-30 years of age. The clinical and antibody responses were compared with the results of a previous similar study using a plasma-derived hepatitis B vaccine (Merck Lot no. 751).

The vaccine was administered at 0, 1 and 6 months to the following three groups: 1) 51 adults who received a 10 mcg dose of recombinant vaccine; 2) 56 adults who received a 5 mcg dose of recombinant vaccine, and 3) 47 adults who received a 20 mcg dose of plasma-derived vaccine. The three groups included medical students, house staff, and nurses who were of comparable age and sex.

Results

Side effects were negligible in all three groups. They consisted of transient, local soreness at the site of the inoculation in about 25% of the vaccinees in each group. No systemic reactions were observed.

The seroconversion rates and geometric mean titers are summarized in the Table. The results are essentially the same for all three groups. Under the conditions of this study the 5 mcg and 10 mcg doses of recombinant hepatitis B vaccine were just as immunogenic as a 20 mcg dose of plasma-derived hepatitis B vaccine.

Comment

A recent report by Jilg et al (Lancet 1984; 2:1174-75) described a similar study in 30 seronegative medical students and laboratory workers whose age and sex were comparable to those in our groups. They stated that "the immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels." Our results in 107 similar recipients of the recombinant hepatitis B vaccine do not support this conclusion.

It is obvious that valid conclusions cannot be drawn from studies involving either 30 or 100 vaccinees. More extensive studies will be required to determine anti-HBs response and its persistence in recipients of recombinant hepatitis B vaccines.

Davidson M, Krugman S. Recombinant yeast hepatitis B vaccine: Side effects and immunogenicity compared with plasma-derived hepatitis B vaccine. Submitted for publication to Hepatitis Scientific Memoranda.

TABLE

Seroconversion Rates and Geometric Mean Titers of Seronegative Adults Who Received Recombinant Yeast Hepatitis B Vaccine (Merck Lot No. 972/C-K444) or Plasma-Derived Hepatitis B Vaccine (Merck Lot No. 751).

Time Interval (Months)	Recombinant Hepatitis B Vaccine					
	10 mcg dose			5 mcg dose		
	anti-HBs response	mIU/ml GMT	S/N Ratio GMT	anti-HBs response	mIU/ml GMT	S/N Ratio GMT
0	-	-	-	-	-	-
1	22/51 (43%)	42	19	21/56 (37%)	55	25
2	48/51 (94%)	88	37	51/56 (91%)	69	38
3	50/51 (98%)	145	52	52/56 (93%)	128	51
6	49/50 (98%)	321	63	53/56 (95%)	184	42
8	45/46 (98%)	1911	164	49/50 (98%)	839	124

Vaccine given at 0, 1 and 6 months.
Age Range: 21 - 30 years

Time Interval (Months)	Plasma-Derived Hepatitis B Vaccine 20 mcg dose	
	anti-HBs response	S/N Ratio GMT
0	-	-
1	18/47 (38%)	20
2	34/47 (79%)	37
3	45/47 (96%)	79
6	44/47 (94%)	94
7	46/47 (98%)	141

Vaccine given at 0, 1 and 6 months.
Age range: 21 - 30 years

L

Janurary 1986

REPORT NO. 3
in Support for a License Application for

RECOMBIVAX
(Yeast Recombinant Hepatitis B Vaccine, MSD)
CLINICAL DATA*
VOLUME 2 OF 3

Merck Sharp & Dohme Research Laboratories

STUDY 815

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 815
PURPOSE:	To compare antibody and clinical responses to yeast recombinant and plasma-derived hepatitis B vaccine among: 1 Mentally retarded individuals who are negative for hepatitis B virus serologic markers. 2. Health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	1. Yeast Recombinant Hepatitis B Vaccine Lot 993/C-K937 (20 mcg/HBsAg/ml) 2. Plasma-Derived Hepatitis B Vaccine Lot 2277K (20 mcg HBsAg/ml
PRIMARY INVESTIGATOR:	Solko W. Schalm, M.D. Department of Internal Medicine and Gastroenterology University Hospital Dijkzigt Rotterdam, The Netherlands
SECONDARY INVESTIGATORS:	Dr. Rudolf A. Heijtink Department of Virology Erasmus University Rotterdam, The Netherlands Dr. Maria Alida van de Velde Dr. Mr. Willem van den Bergh - Stichting Noordwijk, The Netherlands
STUDY LOCATION:	Dr. Mr. Willem van den Bergh-Stichting Noordwijk, The Netherlands University Hospital Dijkzigt Rotterdam, The Netherlands
DATE STUDY INITIATED:	December, 1985
DATE STUDY COMPLETED:	In progress

Study 815

STUDY POPULATION: The study population consists of approximately 90 mentally retarded individuals. and 90 health care personnel, who are negative for HBsAg, anti-HBc, anti-HBs, have a normal ALT and have not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Mentally retarded individuals and health care personnel are randomly assigned to receive either yeast recombinant or plasma-derived hepatitis B vaccine, stratified by sex and age.

Mentally retarded individuals and health care personnel receive a 0.5 ml (10 mcg HBsAg) or a 1.0 ml (20 mcg HBsAg) intramuscular injection of yeast recombinant vaccine or a 1.0 ml (20 mcg HBsAg) intramuscular injection of plasma-derived vaccine at 0, 1, and 6 months.

The temperature of each vaccine recipient and any local or systemic complaints are recorded for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately three weeks before the first injection of vaccine. Post-vaccination blood samples are obtained from mentally retarded individuals at 3, 7, and 12 months and from health care personnel at 1, 2, 3, 6, 7, 9 and 12 months. Blood samples are obtained at 24 months from those participants who have seroconverted.

All serum samples are assayed for HBsAg, anti-HBc, anti-HBs and ALT. Samples may be assayed for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested for anti-a and anti-d subtype specificity.

RESULTS: Clinical follow-up data and serologic results are not yet available. The study continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 816
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among: 1. adult dialysis patients negative for hepatitis B serologic markers. 2. health care personnel negative for hepatitis B serologic markers. 3. adult dialysis patients negative for hepatitis B serologic markers, who previously received plasma-derived hepatitis B vaccine and were nonresponders (anti-HBs negative).
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 974/C-K446 (20 mcg HBsAg/ml) Lot 986/C-K733 (20 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Stanley Plotkin, M.D./Stuart Starr, M.D. Division of Preventive Medicine Joseph Stokes, Jr. Research Institute Children's Hospital of Philadelphia 34 Street and Civic Center Boulevard Philadelphia, Pennsylvania 19104
STUDY LOCATION:	Biomedical Applications of Lehigh Valley 2015 Hamilton Avenue Allentown, Pennsylvania 18104 Dialysis, Inc. 1230 Burmont Road Drexel Hill, Pennsylvania The Kidney Center of Delaware Count 15th Street and Upland Avenue Chester, Pennsylvania 19013 The Kidney Center of Chester County 960 East Lincoln Highway Downington, Pennsylvania 19335

Study 816

DATE STUDY INITIATED: May 14, 1984

DATE STUDY COMPLETED: In progress

STUDY POPULATION: The study population consists of 40-50 adult dialysis patients (including previous nonresponders to plasma-derived vaccine), and 20-25 health care personnel, of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, and have a normal ALT level. Dialysis patients (excluding nonresponders to plasma-derived vaccine) and health care personnel have not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Dialysis patients are assigned to one of two groups, stratified by sex and age, to assure that patients in the two groups are similar. Health care personnel constitute a third group.

Dialysis patients receive 1.0 ml (20 mcg HBsAg) or 2 x 1.0 ml (40 mcg HBsAg) intramuscular injections of vaccine at 0, 1, and 6 months. Health care personnel receive 0.5 ml (10 mcg HBsAg) intramuscular injections of vaccine according to the same regimen. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 3, 6, 8, 12 and 24 months.

All serum samples are assayed for HBsAg, anti-HBs, anti-HBc, and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested to determine anti-a and anti-d subtype specificity.

RESULTS: <u>HEALTH CARE PERSONNEL</u>

10 mcg Lot 974/C-K446 at 0, 1, and 6 months

Study 816

RESULTS: (Contd)

1. Number Vaccinated:

Injection No.		
1	2	3
8	8	6

2. Serologic Results:

Serologic data at 7/8 months are available for 5 health care personnel. At 7/8 months, 80% (4/5) of health care personnel seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees was 37.9 mIU/ml at that time. Among responders with a titer of S/N ≥2.1 and mIU/ml ≥10 the GMT was 127.2 mIU/ml.

By 12 months, 60% (3/5) of health care personnel retained an anti-HBs titer of mIU/ml ≥10. The GMT for all vaccinees was 16.4 mIU/ml at that time.

Anti-HBs responses at 1 through 12 months are included in Table 1.

3. Clinical Results:

Clinical follow-up data are available for 8 health care personnel following the first two injections and for 6 health care personnel following the third injection of vaccine. Clinical complaints and maximum temperatures reported following each injection are provided in Tables 2 and 3. In summary:

Clinical Complaint	% Frequency by Injection No.		
	1	2	3
Injection Site	25 (2/8)	25 (2/8)	17 (1/6)
Systemic	38 (3/8)	25 (2/8)	17 (1/6)

Study 816

RESULTS: (Contd) No serious or alarming adverse reactions attributable to vaccination have been reported.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK446
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	25%	(2/8)	13%	(1/8)	1.2	13.2	86.5
3 MONTHS	40%	(2/5)	40%	(2/5)	7.1	355.5	355.5
6 MONTHS	75%	(3/4)	50%	(2/4)	6.6	18.4	30.6
7/8 MONTHS	80%	(4/5)	80%	(4/5)	37.9	127.2	127.2
12 MONTHS	80%	(4/5)	60%	(3/5)	16.4	44.7	88.9

00428

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (8 PATIENTS) - DOSE 1						NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION						
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
PAIN	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
SORENESS	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
SYSTEMIC	1 (12.5%)	1 (12.5%)	1 (12.5%)	3 (37.5%)	2 (25.0%)	2 (25.0%)	3 (37.5%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	1 (12.5%)	1 (12.5%)	2 (25.0%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	1 (12.5%)	1 (12.5%)	2 (25.0%)
RESPIRATORY	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
UPPER RESPIRATORY INFECT., NOS	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)
WRIST PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)
HIP PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	1 (12.5%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (8 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						
CLINICAL COMPLAINTS	0	1	2	3	4	5	NUMBER WITH COMPLAINTS
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
PERSONS WITH COMPLAINTS	3 (37.5%)	1 (12.5%)	1 (12.5%)	3 (37.5%)	2 (25.0%)	2 (25.0%)	4 (50.0%)
PERSONS WITH NO COMPLAINTS	5 (62.5%)	7 (87.5%)	7 (87.5%)	5 (62.5%)	6 (75.0%)	6 (75.0%)	4 (50.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (8 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	2 (25.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (25.0%)
SORENESS	2 (25.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (25.0%)
SYSTEMIC	1 (12.5%)	0 (0.0%)	2 (25.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)		2 (25.0%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (25.0%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (12.5%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (12.5%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (12.5%)
NECK PAIN	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (12.5%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)		1 (12.5%)
NAUSEA	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)		1 (12.5%)
NERVOUS SYSTEM	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (12.5%)
VERTIGO/DIZZINESS	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (12.5%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (8 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	2 (25.0%)	1 (12.5%)	2 (25.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)		2 (25.0%)
PERSONS WITH NO COMPLAINTS	6 (75.0%)	7 (87.5%)	6 (75.0%)	7 (87.5%)	8 (100.0%)	8 (100.0%)		6 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (6 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
SORENESS	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
SYSTEMIC	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)		1 (16.7%)
DIGESTIVE SYSTEM	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)		1 (16.7%)
NAUSEA	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)		1 (16.7%)
PERSONS WITH COMPLAINTS	2 (33.3%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)		2 (33.3%)
PERSONS WITH NO COMPLAINTS	4 (66.7%)	5 (83.3%)	5 (83.3%)	5 (83.3%)	5 (83.3%)	5 (83.3%)		4 (66.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (8 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	7 (87.5%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	7 (87.5%)	8 (100.0%)		7 (87.5%)
99 - 99.9	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)		1 (12.5%)
TEMPERATURE TAKEN	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)		8 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (8 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	3 (37.5%)	3 (37.5%)	3 (37.5%)	3 (37.5%)	3 (37.5%)	3 (37.5%)			3 (37.5%)
< 99	5 (62.5%)	5 (62.5%)	5 (62.5%)	5 (62.5%)	5 (62.5%)	5 (62.5%)			5 (62.5%)
TEMPERATURE TAKEN	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)			8 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (6 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	2 (33.3%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	2 (33.3%)			2 (33.3%)
< 99	4 (66.7%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	4 (66.7%)			4 (66.7%)
TEMPERATURE TAKEN	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)			6 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 834
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 979/C-K564 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Mario Rizzetto, M.D. Division of Gastroenterology Molinette Hospital Turin, ITALY
SECONDARY INVESTIGATORS:	Caterina Canavese, M.D. Piero Stratta, M.D. Ferruccio Bonino, M.D. Molinette Hospital Turin, ITALY
STUDY LOCATION:	Molinette Hospital Turin, ITALY
DATE STUDY INITIATED:	August, 1985
DATE STUDY COMPLETED:	In progress.
STUDY POPULATION:	The study population consists of 25-30 health care personnel of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.
STUDY PROCEDURE:	Eligible study participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine at 0, 1, and 6 months. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

STUDY PROCEDURE: (Cont.)

A blood sample is obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12 and 24 months.

All serum samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer ≥25 mIU/ml may be tested to determine anti-a and anti-d subtype specificity.

RESULTS:

HEALTH CARE PERSONNEL

10 mcg Lot 979/C-K564 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
25	0	0

2. Serologic Results:

Serologic data are not presently available.

3. Clinical Results:

Clinical follow-up data are not yet available. No serious or alarming adverse experiences attributable to vaccine have been reported.

REACTION POSSIBLY RELATED TO VACCINE

A 40 year-old female developed a "few ecchymotic flat lesions on the lateral aspect of her breasts, bilaterally" four days after the first injection of vaccine. Over the following two days, the lesions increased, the next day vomiting occurred. All symptoms disappeared over the next 36 hours and the subject has remained well. There was no fever. WBC, hemoglobin, platelets, and coagulation profile were normal. The patient has no history of allergies to exogenous substances. No further vaccine was administered to this patient.

STUDY 835

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 835
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 979/C-K564
PRIMARY INVESTIGATOR:	Stanley M. Lemon, M.D. Division of Infectious Disease Department of Medicine 547 Burnett-Womack Clinical Sciences Bldg. 229H University of North Carolina School of Medicine Chapel Hill, North Carolina 27514
SECONDARY INVESTIGATOR:	Jack T. Stapleton, M.D. Division of Infectious Diseases Department of Medicine 547 Burnett-Womack Clinical Sciences Bldg. 229H University of North Carolina School of Medicine Chapel Hill, North Carolina 27514
STUDY LOCATION:	The University of North Carolina School of Medicine North Carolina Memorial Hospital Chapel Hill, North Carolina 27514
DATE STUDY INITIATED:	October 26, 1984
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 25-30 health care personnel of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 835

STUDY PROCEDURE:

Eligible study participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine at 0, 1 and 6 months. Vaccine recipients record their temperatures and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two weeks before and on the day of the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12 and 24 months.

All serum samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested to determine anti-a and anti-d type specificity.

RESULTS:

HEALTH CARE PERSONNEL

10 mcg Lot 979/C-K564 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
29	29	23

Two persons initially anti-HBs positive received vaccine. One subject displayed a marked boost in titer after one injection of vaccine. The other subject developed a protective level of antibody ($\geq$10 mIU/ml) by 10 months post-vaccination.

2. Serologic Results:

Serologic data at 7-9 months are available for 19 study participants. At 7-9 months, 100% (19/19) of vaccine recipients seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees and responders (S/N $\geq$2.1 and $\geq$10 mIU/ml) was 560.9 mIU/ml at that time. Anti-HBs responses at 1 through 7-9 months are included in Table 1.

Study 835

RESULTS: (Cont.)

3. Clinical Results:

Clinical follow-up data are available for 26 study participants following the first injection, 25 participants following the second, and for 23 participants following the third injection of vaccine. Clinical complaints and maximum temperatures are provided in Tables 2 and 3. In summary:

Clinical Complaint	% Frequency by Injection No.		
	1	2	3
Injection Site	27(7/26)	28(7/25)	30(7/23)
Systemic	23(6/26)	16(4/25)	13(3/23)

No serious or alarming adverse reactions attributable to vaccination have been reported.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK564
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	30%	(8/27)	15%	(4/27)	0.9	13.9	77.2
2 MONTHS	73%	(19/26)	42%	(11/26)	7.2	23.2	89.1
3 MONTHS	83%	(5/6)	67%	(4/6)	25.3	61.5	103.6
6 MONTHS	95%	(18/19)	89%	(17/19)	38.4	50.2	57.1
7/9 MONTHS	100%	(19/19)	100%	(19/19)	560.9	560.9	560.9

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (29 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	6 (23.1%)	3 (11.5%)	3 (11.5%)	1 (3.8%)	0 (0.0%)	0 (0.0%)		7 (26.9%)
SORENESS	5 (19.2%)	3 (11.5%)	3 (11.5%)	1 (3.8%)	0 (0.0%)	0 (0.0%)		7 (26.9%)
NUMBNESS	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
SYSTEMIC	3 (11.5%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	2 (7.7%)	2 (7.7%)		6 (23.1%)
WHOLE BODY/GENERAL	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)		4 (15.4%)
CHILLS	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
HEADACHE	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)		3 (11.5%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)		1 (3.8%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)		1 (3.8%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)		1 (3.8%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)		1 (3.8%)
MUSCULOSKELETAL	2 (7.7%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)		2 (7.7%)

00442

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (29 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
ARTHRALGIA, MONOARTICULAR	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
MYALGIA	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
NECK PAIN	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
EARACHE	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
IRRITABILITY	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.8%)
PERSONS WITH COMPLAINTS	8 (30.8%)	4 (15.4%)	4 (15.4%)	2 (7.7%)	2 (7.7%)	2 (7.7%)		12 (46.2%)
PERSONS WITH NO COMPLAINTS	18 (69.2%)	22 (84.6%)	22 (84.6%)	24 (92.3%)	24 (92.3%)	24 (92.3%)		14 (53.8%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (29 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	4 (16.0%)	4 (16.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		7 (28.0%)
PAIN	2 (8.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (12.0%)
SORENESS	2 (8.0%)	4 (16.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (20.0%)
TENDERNESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
ERYTHEMA (REDNESS)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
PRURITIS (ITCHING)	0 (0.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (8.0%)
SYSTEMIC	0 (0.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	2 (8.0%)		4 (16.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)		2 (8.0%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
MALAISE	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)		2 (8.0%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)		1 (4.0%)
VIRAL INFECTION, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)		1 (4.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (29 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
RASH, NOS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)		1 (4.0%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)		1 (4.0%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)		1 (4.0%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)		1 (4.0%)
MYALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)		1 (4.0%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
DIARRHEA	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
NAUSEA	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
PERSONS WITH COMPLAINTS	4 (16.0%)	6 (24.0%)	2 (8.0%)	0 (0.0%)	1 (4.0%)	2 (8.0%)		9 (36.0%)
PERSONS WITH NO COMPLAINTS	21 (84.0%)	19 (76.0%)	23 (92.0%)	25 (100.0%)	24 (96.0%)	23 (92.0%)		16 (64.0%)

00445

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (29 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH NO DATA	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)		1 (3.8%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (23 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	6 (26.1%)	4 (17.4%)	2 (8.7%)	1 (4.3%)	1 (4.3%)	0 (0.0%)	7 (30.4%)
PAIN ON INJECTION	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
SORENESS	6 (26.1%)	3 (13.0%)	2 (8.7%)	1 (4.3%)	1 (4.3%)	0 (0.0%)	6 (26.1%)
ERYTHEMA (REDNESS)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
SWELLING	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
PRURITIS (ITCHING)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
SYSTEMIC	0 (0.0%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	3 (13.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
CHILLS	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
FLUSH	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (4.3%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (4.3%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (23 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	1 (4.3%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
DIARRHEA	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
EYES, BURNING	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
PERSONS WITH COMPLAINTS	6 (26.1%)	5 (21.7%)	2 (8.7%)	1 (4.3%)	1 (4.3%)	1 (4.3%)	7 (30.4%)
PERSONS WITH NO COMPLAINTS	17 (73.9%)	18 (78.3%)	21 (91.3%)	22 (95.7%)	22 (95.7%)	22 (95.7%)	16 (69.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (29 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	2 (6.0%)	2 (6.0%)	2 (6.0%)	2 (6.0%)	2 (8.3%)	2 (8.7%)			2 (8.0%)
< 99	19 (76.0%)	21 (84.0%)	20 (80.0%)	20 (80.0%)	19 (79.2%)	19 (82.6%)			15 (60.0%)
99 - 99.9	4 (16.0%)	2 (8.0%)	3 (12.0%)	1 (4.0%)	1 (4.2%)	2 (8.7%)			5 (20.0%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)	2 (8.3%)	0 (0.0%)			3 (12.0%)
TEMPERATURE TAKEN	25 (86.2%)	25 (86.2%)	25 (86.2%)	25 (86.2%)	24 (82.8%)	23 (79.3%)			25 (86.2%)
TEMPERATURE NOT TAKEN	4 (13.8%)	4 (13.8%)	4 (13.8%)	4 (13.8%)	5 (17.2%)	6 (20.7%)			4 (13.8%)

00449

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (29 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (4.0%)	1 (4.0%)	1 (4.3%)	1 (4.2%)	1 (4.2%)	1 (4.3%)			1 (4.0%)
< 99	20 (80.0%)	19 (76.0%)	18 (78.3%)	20 (83.3%)	21 (87.5%)	19 (82.6%)			15 (60.0%)
99 - 99.9	4 (16.0%)	4 (16.0%)	4 (17.4%)	3 (12.5%)	2 (8.3%)	3 (13.0%)			8 (32.0%)
103 - 103.9	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (4.0%)
TEMPERATURE TAKEN	25 (86.2%)	25 (86.2%)	23 (79.3%)	24 (82.8%)	24 (82.8%)	23 (79.3%)			25 (86.2%)
TEMPERATURE NOT TAKEN	4 (13.8%)	4 (13.8%)	6 (20.7%)	5 (17.2%)	5 (17.2%)	6 (20.7%)			4 (13.8%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0835
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (23 PATIENTS) - DOSE 3								
	DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
NORMAL	1 (5.0%)	1 (5.0%)	1 (4.8%)	1 (5.3%)	1 (5.3%)	1 (5.3%)			1 (4.8%)
< 99	17 (85.0%)	16 (80.0%)	17 (81.0%)	17 (89.5%)	16 (84.2%)	16 (84.2%)			16 (76.2%)
99 - 99.9	2 (10.0%)	3 (15.0%)	3 (14.3%)	1 (5.3%)	2 (10.5%)	2 (10.5%)			4 (19.0%)
TEMPERATURE TAKEN	20 (87.0%)	20 (87.0%)	21 (91.3%)	19 (82.6%)	19 (82.6%)	19 (82.6%)			21 (91.3%)
TEMPERATURE NOT TAKEN	3 (13.0%)	3 (13.0%)	2 (8.7%)	4 (17.4%)	4 (17.4%)	4 (17.4%)			2 (8.7%)

00451

STUDY 838

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study B38.
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine in the following, initially seronegative, adult populations: 1. Dialysis Patients 2. Predialysis Patients 3. Health Care Personnel
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #986/C-K733 (20 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Professor Dr. Friedrich Deinhardt Director Max v. Pettenkofer Institute Pettenkoferstr. 9a 8000 Muenchen 2 West Germany
SECONDARY INVESTIGATORS:	Dr. Wolfgang Jilg Max v. Pettenkofer Institute Pettenkoferstr. 9a 8000 Muenchen 2 West Germany Professor Dr. Juergen Bommer Medizinische Universitatsklinik Bergheimer Str. 56 6900 Heidelberg 1 West Germany Professor Dr. R. Mueller Medizinische Hochschule Hannover Abt. f. Innere Medizin Karl-Wiechert-Allee 9 D-3000 Hannover-Kleefeld West Germany Professor Dr. Horst Braas Staedtische Krankenanstalten Medizinische Klinik II Bremserstr. 79 D-6700 Ludwigshafen West Germany

Study 838

SECONDARY INVESTIGATORS: (Cont.)

Dr. Bernhard Weinel
Staedtische Krankenanstalten
Medizinische Klinik II
Bremserstr. 79
D-6700 Ludwigshafen
West Germany

STUDY LOCATIONS: Munich, Heidelberg, Hannover, and Ludwigshafen, West Germany

DATE INITIATED: June 7, 1984

DATE COMPLETED: In progress

STUDY POPULATIONS: Under the original protocol and subsequent addenda, the following groups are enrolled in the study. Participants may be of either sex, but pregnant women are excluded. Prospective vaccine recipients must be negative for hepatitis B serologic markers, have a normal ALT level and may not have received any hepatitis B vaccine (except as noted under addendum #2).

Protocol/ Addendum #	Population	Approx. Number	Regimen
Initial protocol	Health Care Personnel	25	10 mcg (0.5 ml) at 0, 1, and 6 months
Initial protocol	Dialysis Patients	50	40 mcg (2 x 1.0 ml) at 0, 1 and 6 months
Add. #1	Dialysis Patients	20	20 mcg (1.0 ml) at 0, 1, 2, 3, 4, and 6 months
Add. #1	Dialysis Patients	20	40 mcg (2 x 1.0 ml) at 0, 1, 2, 3, 4, and 6 months

Study 838

STUDY POPULATIONS: (Cont.)

Protocol/ Addendum #	Population	Approx. Number	Regimen
Add. #2	Initial protocol subjects who do not form anti-HBs after 3 doses of vaccine		10 mcg (0.5 ml) for health care personnel; 40 mcg (2 x 1.0 ml) for dialysis patients
Add. #3	Predialysis patients	10	40 mcg (2 x 1.0 ml) at 0, 1, and 6 months

PROCEDURE:

Participants receive intramuscular injections of vaccine according to the regimens outlined above under STUDY POPULATIONS.

Study participants will be asked to record their temperature for five days after each injection and to note any local or systemic complaints.

Serum samples will be obtained prior to and on the day of vaccination. Follow-up blood specimens will be obtained 1, 2, 3, 6, 8, 12 and 24 months post the initial injection of vaccine. Nonresponders who receive a fourth injection of vaccine under addendum #2 will have a blood sample taken one month after this injection. Serum samples will be assayed for HBsAg, anti-HBs, anti-HBc and ALT by Dr. Deinhardt's laboratory. Samples may also be assayed at MSDRL for yeast antibody. Those that are positive for anti-HBs with a titer of $\geq$25 mIU/ml may be assayed for anti-a and anti-d subtype specificity.

Study 838

RESULTS:

HEALTH CARE PERSONNEL:

10 mcg Lot #986/C-K733 at 0, 1, and 6 months.

1. Number Vaccinated:

Injection No.		
1	2	3
22	19	17

2. Serologic Results:

Serologic data are available for 17 participants at 7/8 months of follow-up. Ninety-four percent (16/17) of the subjects seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months for all vaccinees was 284.8 mIU/ml and 437.1 for responders (mIU/ml ≥10).

Refer to Table 1 for anti-HBs responses and GMTs through 10 months of follow-up.

3. Clinical Complaints:

Clinical follow-up data are available for 22 and 13 participants after injections 1 and 2, respectively. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No.		
	1	2	3
Injection Site	18(4/22)	8(1/13)	---
Systemic	27(6/22)	8(1/13)	---

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming adverse experiences attributable to vaccine.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK733
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% [illegible] ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	19%	(4/21)	9.5%	(2/21)	0.6	13.6	43.0
2 MONTHS	58%	(11/19)	47%	(9/19)	4.1	27.0	39.2
3 MONTHS	82%	(14/17)	71%	(12/17)	15.7	36.5	46.9
6 MONTHS	83%	(10/12)	83%	(10/12)	26.9	66.2	66.2
7/8 MONTHS	94%	(16/17)	94%	(16/17)	284.8	437.1	437.1
10 MONTHS	100%	(9/9)	100%	(9/9)	509.4	509.4	509.4

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (22 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	4 (18.2%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (18.2%)
PAIN	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.5%)
SORENESS	3 (13.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (13.6%)
SWELLING	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.5%)
SYSTEMIC	2 (9.1%)	4 (18.2%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		6 (27.3%)
WHOLE BODY/GENERAL	2 (9.1%)	4 (18.2%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		6 (27.3%)
FATIGUE/WEAKNESS	2 (9.1%)	3 (13.6%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (22.7%)
HEADACHE	0 (0.0%)	1 (4.5%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (9.1%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		1 (4.5%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		1 (4.5%)
PERSONS WITH COMPLAINTS	6 (27.3%)	4 (18.2%)	3 (13.6%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		9 (40.9%)
PERSONS WITH NO COMPLAINTS	16 (72.7%)	18 (81.8%)	19 (86.4%)	22 (100.0%)	22 (100.0%)	21 (95.5%)		13 (59.1%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (22 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (13 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (7.7%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.7%)
PAIN	1 (7.7%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.7%)
SYSTEMIC	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.7%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.7%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.7%)
PERSONS WITH COMPLAINTS	1 (7.7%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (15.4%)
PERSONS WITH NO COMPLAINTS	12 (92.3%)	11 (84.6%)	13 (100.0%)	13 (100.0%)	13 (100.0%)	13 (100.0%)		11 (84.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00459

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (22 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	10 (90.9%)	11 (91.7%)	10 (90.9%)	11 (100.0%)	9 (90.0%)	8 (88.9%)		9 (75.0%)
99 - 99.9	1 (9.1%)	1 (8.3%)	1 (9.1%)	0 (0.0%)	1 (10.0%)	1 (11.1%)		3 (25.0%)
TEMPERATURE TAKEN	11 (50.0%)	12 (54.5%)	11 (50.0%)	11 (50.0%)	10 (45.5%)	9 (40.9%)		12 (54.5%)
TEMPERATURE NOT TAKEN	11 (50.0%)	10 (45.5%)	11 (50.0%)	11 (50.0%)	12 (54.5%)	13 (59.1%)		10 (45.5%)

00460

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (13 PATIENTS) - DOSE 2 — DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
< 99	7 (100.0%)	7 (100.0%)	7 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)			7 (100.0%)
TEMPERATURE TAKEN	7 (53.8%)	7 (53.8%)	7 (53.8%)	6 (46.2%)	6 (46.2%)	6 (46.2%)			7 (53.8%)
TEMPERATURE NOT TAKEN	6 (46.2%)	6 (46.2%)	6 (46.2%)	7 (53.8%)	7 (53.8%)	7 (53.8%)			6 (46.2%)

00461

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 841.
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #978/C-K 563 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATORS:	Arie J. Zuckerman, M.D. Professor of Microbiology Director, Department of Medical Microbiology London School of Hygiene and Tropical Medicine Keppel Street London WC1E 7HT United Kingdom Iain Murray-Lyon, M.D. Consultant Physician Charing Cross Hospital London W.6. United Kingdom
SECONDARY INVESTIGATORS:	Dr. John Coleman Charing Cross Hospital London W.6. United Kingdom Dr. Michael Anderson Charing Cross Hospital London W.6. United Kingdom
STUDY LOCATION:	Charing Cross Hospital London W.6. United Kingdom
DATE INITIATED:	May 1985.
DATE COMPLETED:	In progress.
STUDY POPULATION:	The study population will consist of 80-100 health care personnel of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, and have not previously received any hepatitis B vaccine.

Study 841

PROCEDURE:

Eligible participants will receive a 1.0 ml injection of vaccine in the deltoid muscle at 0, 1, and 6 months. Study participants will be asked to take and record their temperatures for five days after each injection of vaccine and to record any local or systemic complaints that they may have. They will be asked to notify the study physician immediately if any unexpected or serious reaction occurs.

Blood specimens will be obtained prior to and 1, 2, 3, 6, 8, 12, and 24 months following the first injection. All samples will be assayed in Dr. Zuckerman's laboratory for HBsAg, anti-HBc and anti-HBs. Samples may also be assayed for yeast antibody and subtype specificity.

RESULTS:

Serologic and clinical follow-up data are not presently available. No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 859
PURPOSE:	This study is designed to evaluate antibody and clinical responses to hepatitis B yeast recombinant vaccine among health care personnel who are negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #978/C-K563 (10 mcg HBsAg)
PRINCIPAL INVESTIGATOR:	Nathan Clumeck, M.D. Assistant Department Head Section of Infectious Diseases Hospital of St. Pierre Rue Haute, 322 Brussels, BELGIUM
SECONDARY INVESTIGATOR:	Pierre Reding, M.D. Gastroenterology Service Hospital St. Pierre Rue Haute, 322 Brussels, BELGIUM
STUDY LOCATION:	Hospital of St. Pierre Section of Infectious Disease Department of Internal Medicine Rue Haute, 322 Brussels, BELGIUM
DATE INITIATED:	March 12, 1985
DATE COMPLETED:	In progress.
STUDY POPULATION:	The study population will consist of 30 to 50 health care personnel of either sex (excluding pregnant women), who are negative for anti-HBc, anti-HBs, HBsAg, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 859

STUDY PROCEDURE:

Participants receive a 1.0 ml intramuscular injection of vaccine on Day 0, 1, and 6 months. Prior to receipt of the vaccine, a serum sample is obtained from participants to screen for HBsAg, anti-HBc, yeast antibody and ALT levels. The vaccinees are asked to record their temperature for five days after each injection and note any local or systemic complaints. If any unexpected or serious reaction occurs, they are asked to notify the study physician immediately.

Follow-up blood samples will be obtained 1, 2, 3, 6, 8, 12, and 24 months after the first injection of vaccine. The samples will be assayed for HBsAg, anti-HBc, anti-HBs, ALT and yeast antibody. Samples with an anti-HBs titer $\geq$25 mIU/ml will be assayed for anti-a and anti-d sub-type specificity. Assays for ALT will be done by Dr. Clumeck in Belgium. All other assays on post-vaccination sera will be performed at MSDRL in West Point.

RESULTS:

HEALTH CARE PERSONNEL

10 mcg lot #978/C-K563 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
31	31	0

2. Serologic Results:

Serologic data are available for 30 participants. At three months, 80% (24/30) of the vaccinees seroconverted for anti-HBs (S/N $\geq$2.1). Fifty-three percent (16/30) of the subjects developed protective levels of anti-HBs (mIU/ml $\geq$10).

The GMT at three months for all vaccinees was 11.8 mIU/ml while it was 60.0 mIU/ml for responders with a titer of mIU/ml $\geq$10.

Refer to Table 1 for anti-HBs responses and GMTs through three months of follow-up.

Study 859

RESULTS (CONT.):

One subject (case (b) (6) was found to be anti-HBs positive on the day of the first injection. There was no rise in antibody level after the first injection and a >4-fold rise in anti-HBs after the second injection.

3. Clinical Complaints:

A summary of frequencies of clinical complaints are not yet available. However, no serious or alarming events attributable to vaccine have been reported. Vaccination and follow-up continues in progress.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0859
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK563
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	RESPONDERS	
						S/N >= 2.1	MIU/ML >= 10
1 MONTH	33%	(10/30)	10%	(3/30)	1.1	9.2	31.4
2 MONTHS	63%	(19/30)	53%	(16/30)	8.2	38.3	58.1
3 MONTHS	80%	(24/30)	53%	(16/30)	11.8	27.5	60.0

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 860.
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #978/C-K563 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Professor Dr. R. Laufs Director, Institute for Medical Microbiology and Immunology at the University of Hamburg Martinistrasse 52 2000 Hamburg 20 WEST GERMANY
SECONDARY INVESTIGATORS:	K. Katzner, M.D. S. Gaterman, M.D. Institute for Medical Microbiology and Immunology at the University of Hamburg Martinistrasse 52 2000 Hamburg 20 WEST GERMANY
STUDY LOCATION:	Institute for Medical Microbiology and Immunology at the University of Hamburg Martinistrasse 52 2000 Hamburg 20 WEST GERMANY
DATE INITIATED:	December 28, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 60 health care personnel of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 860

PROCEDURE:

Participants receive a 1.0 ml intramuscular injection of vaccine on Day 0, 1, and 6 months. Prior to receipt of the vaccine, a serum sample is obtained from participants to screen for HBsAg, anti-HBc, and anti-HBc, yeast antibody and ALT levels. The vaccine recipients are asked to record their temperature for 5 days after each injection and note any local or systemic complaints. If any unexpected or serious reaction occurs, they are asked to notify the study physician immediately.

Follow-up blood samples will be obtained 1, 2, 3, 6, 8, 12, and 24 hours post the first injection of vaccine. The samples will be assayed for HBsAg, anti-HBc, anti-HBs, and ALT in Dr. Laufs' laboratory and may be assayed for yeast antibody at MSDRL. In addition, an aliquot of serum from participants with an anti-HBs titer ≥25 mIU/ml will be sent to MSDRL to be assayed for anti-a and anti-d sub-type specificity of anti-HBs antibody.

RESULTS:

HEALTH CARE PERSONNEL:

10 mcg of Lot #978/C-K563 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
60	59	59

2. Serologic Results:

Serologic data are available for 56 participants at 7/8 months. One hundred percent (56/56) of the subjects seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 7/8 months was 2421.1 mIU/ml (all vaccinees and responders by either cutoff).

Refer to Table 1 for GMTs and anti-HBs responses for other time intervals.

Study 860

RESULTS (CONT.):

One subject was found to be seropositive for anti-HBs on the day of her first injection. At one month post the first injection of vaccine, she had a >4-fold boost in anti-HBs titer.

3. Clinical Complaints:

Clinical follow-up data are available for at least 47 participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	20(11/55)	28(15/54)	28(13/47)
Systemic	20(11/55)	11(6/54)	11(5/47)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming reactions attributable to vaccine.

ALT Elevations

Four subjects had ALT elevations 1.5 to 3.5 times the upper limit of normal day 0 through 5 months, 3 months after the second injection, one month after the second injection, and four months after the second injection, respectively. In all cases, the elevated ALT level(s) have returned to normal. None of the subjects was positive for HBsAg or anti-HBc.

One subject (case (b)(6)) who had an elevated ALT level 1.5 times the upper limit of normal prior to the first injection of vaccine, continued to have ALT elevations at each subsequent bleed (1, 2, 3, 5 and 7 months post the first injection). The ALT elevations range from 2.0 to 3.5 times the upper limit of normal. The subject is HBsAg and anti-HBc negative. Further serum samples and laboratory evaluation are pending.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK563
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS		GMT (MIU/ML)		
				RESPONDERS	
	S/N >= 2.1	MIU/ML >= 10	ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	43% (25/58)	21% (12/58)	1.3	8.6	19.4
2 MONTHS	90% (52/58)	83% (48/58)	60.7	60.7	74.8
3 MONTHS	96% (54/56)	95% (53/56)	127.1	127.1	135.0
6 MONTHS	100% (58/58)	98% (57/58)	217.0	217.0	229.7
7/8 MONTHS	100% (56/56)	100% (56/56)	2421.1	2421.1	2421.1

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (60 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	10 (16.2%)	3 (5.5%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		11 (20.0%)
PAIN	9 (16.4%)	3 (5.5%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		10 (18.2%)
TENDERNESS	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
SWELLING	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
SYSTEMIC	3 (5.5%)	4 (7.3%)	5 (9.1%)	4 (7.3%)	3 (5.5%)	0 (0.0%)		11 (20.0%)
WHOLE BODY/GENERAL	3 (5.5%)	2 (3.6%)	4 (7.3%)	2 (3.6%)	2 (3.6%)	0 (0.0%)		8 (14.5%)
FLUSH	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
FATIGUE/WEAKNESS	1 (1.8%)	0 (0.0%)	2 (3.6%)	1 (1.8%)	1 (1.8%)	0 (0.0%)		4 (7.3%)
HEADACHE	1 (1.8%)	2 (3.6%)	2 (3.6%)	2 (3.6%)	2 (3.6%)	0 (0.0%)		5 (9.1%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
MUSCULOSKELETAL	0 (0.0%)	2 (3.6%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.6%)

00472

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (60 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
ARTHRALGIA (OTHER)	0 (0.0%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
SHOULDER PAIN	0 (0.0%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
DIGESTIVE SYSTEM	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	0 (0.0%)		2 (3.6%)
NAUSEA	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
GASTROENTERITIS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	0 (0.0%)		1 (1.8%)
UROGENITAL SYSTEM	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
OTHER	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
PERSONS WITH COMPLAINTS	12 (21.8%)	7 (12.7%)	8 (14.5%)	4 (7.3%)	3 (5.5%)	0 (0.0%)		17 (30.9%)
PERSONS WITH NO COMPLAINTS	43 (78.2%)	48 (87.3%)	47 (85.5%)	51 (92.7%)	52 (94.5%)	55 (100.0%)		38 (69.1%)
PERSONS WITH NO DATA	5 (8.3%)	5 (8.3%)	5 (8.3%)	5 (8.3%)	5 (8.3%)	5 (8.3%)		5 (8.3%)

00473

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (59 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	13 (24.1%)	6 (11.1%)	4 (7.4%)	2 (3.7%)	1 (1.9%)	1 (1.9%)	15 (27.8%)
PAIN	10 (18.5%)	4 (7.4%)	2 (3.7%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	12 (22.2%)
TENDERNESS	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)
SWELLING	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)
PRURITIS (ITCHING)	1 (1.9%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)
ECCHYMOSIS	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)
SYSTEMIC	3 (5.6%)	3 (5.6%)	3 (5.6%)	5 (9.3%)	3 (5.6%)	3 (5.6%)	6 (11.1%)
WHOLE BODY/GENERAL	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	2 (3.7%)
HEADACHE	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	2 (3.7%)
INFECTIOUS SYNDROMES	1 (1.9%)	1 (1.9%)	1 (1.9%)	2 (3.7%)	1 (1.9%)	1 (1.9%)	2 (3.7%)
INFLUENZA, NOS	1 (1.9%)	1 (1.9%)	1 (1.9%)	2 (3.7%)	1 (1.9%)	1 (1.9%)	2 (3.7%)
RESPIRATORY	1 (1.9%)	1 (1.9%)	1 (1.9%)	2 (3.7%)	2 (3.7%)	2 (3.7%)	2 (3.7%)

00174

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (59 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER
CLINICAL COMPLAINTS	0	1	2	3	4	5	WITH COMPLAINTS
RHINITIS	1 (1.9%)	1 (1.9%)	1 (1.9%)	2 (3.7%)	2 (3.7%)	2 (3.7%)	2 (3.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)
PERSONS WITH COMPLAINTS	16 (29.6%)	9 (16.7%)	7 (13.0%)	7 (13.0%)	4 (7.4%)	4 (7.4%)	20 (37.0%)
PERSONS WITH NO COMPLAINTS	38 (70.4%)	45 (83.3%)	47 (87.0%)	47 (87.0%)	50 (92.6%)	50 (92.6%)	34 (63.0%)
PERSONS WITH NO DATA	5 (8.5%)	5 (8.5%)	5 (8.5%)	5 (8.5%)	5 (8.5%)	5 (8.5%)	5 (8.5%)

00475

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (59 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	9 (19.6%)	8 (17.0%)	3 (6.4%)	2 (4.3%)	1 (2.1%)	0 (0.0%)		13 (27.7%)
PAIN	8 (17.4%)	4 (8.5%)	2 (4.3%)	1 (2.1%)	0 (0.0%)	0 (0.0%)		9 (19.1%)
SORENESS	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
PRURITIS (ITCHING)	1 (2.2%)	2 (4.3%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	0 (0.0%)		4 (8.5%)
HEMATOMA	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
SYSTEMIC	2 (4.3%)	1 (2.1%)	2 (4.3%)	2 (4.3%)	3 (6.4%)	1 (2.1%)		5 (10.6%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)		1 (2.1%)
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	0 (0.0%)		1 (2.1%)
RESPIRATORY	1 (2.2%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)		1 (2.1%)
RHINITIS	1 (2.2%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)		1 (2.1%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (59 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)	0 (0.0%)	2 (4.3%)
DIARRHEA	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
NAUSEA	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
GASTROENTERITIS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)	0 (0.0%)	1 (2.1%)
ORGANS OF SPECIAL SENSE	1 (2.2%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)
CONJUNCTIVITIS	1 (2.2%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)
PERSONS WITH COMPLAINTS	11 (23.9%)	9 (19.1%)	5 (10.6%)	4 (8.5%)	4 (8.5%)	1 (2.1%)	17 (36.2%)
PERSONS WITH NO COMPLAINTS	35 (76.1%)	38 (80.9%)	42 (89.4%)	43 (91.5%)	43 (91.5%)	46 (97.9%)	30 (63.8%)
PERSONS WITH NO DATA	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	1 (2.1%)

Table 3
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (60 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	15 (37.5%)	30 (54.5%)	29 (52.7%)	25 (46.3%)	26 (47.3%)	24 (45.3%)		12 (21.8%)
99 - 99.9	23 (57.5%)	22 (40.0%)	25 (45.5%)	27 (50.0%)	27 (49.1%)	27 (50.9%)		35 (63.6%)
100 - 100.9	1 (2.5%)	2 (3.6%)	1 (1.8%)	2 (3.7%)	2 (3.6%)	2 (3.8%)		6 (10.9%)
101 - 101.9	1 (2.5%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.6%)
TEMPERATURE TAKEN	40 (66.7%)	55 (91.7%)	55 (91.7%)	54 (90.0%)	55 (91.7%)	53 (88.3%)		55 (91.7%)
TEMPERATURE NOT TAKEN	20 (33.3%)	5 (8.3%)	5 (8.3%)	6 (10.0%)	5 (8.3%)	7 (11.7%)		5 (8.3%)

Table 3 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (59 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	17 (39.5%)	26 (48.1%)	29 (53.7%)	25 (47.2%)	27 (50.0%)	27 (55.1%)			15 (27.8%)
99 - 99.9	25 (58.1%)	24 (44.4%)	22 (40.7%)	27 (50.9%)	26 (48.1%)	21 (42.9%)			33 (61.1%)
100 - 100.9	1 (2.3%)	4 (7.4%)	3 (5.6%)	1 (1.9%)	1 (1.9%)	1 (2.0%)			6 (11.1%)
TEMPERATURE TAKEN	43 (72.9%)	54 (91.5%)	54 (91.5%)	53 (89.8%)	54 (91.5%)	49 (83.1%)			54 (91.5%)
TEMPERATURE NOT TAKEN	16 (27.1%)	5 (8.5%)	5 (8.5%)	6 (10.2%)	5 (8.5%)	10 (16.9%)			5 (8.5%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (59 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	15 (37.5%)	14 (31.1%)	19 (43.2%)	22 (47.8%)	23 (51.1%)	24 (54.5%)		11 (23.9%)
99 - 99.9	22 (55.0%)	28 (62.2%)	23 (52.3%)	21 (45.7%)	18 (40.0%)	18 (40.9%)		27 (58.7%)
100 - 100.9	3 (7.5%)	2 (4.4%)	2 (4.5%)	3 (6.5%)	3 (6.7%)	2 (4.5%)		6 (13.0%)
102 - 102.9	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)		2 (4.3%)
TEMPERATURE TAKEN	40 (67.8%)	45 (76.3%)	44 (74.6%)	46 (78.0%)	45 (76.3%)	44 (74.6%)		46 (78.0%)
TEMPERATURE NOT TAKEN	19 (32.2%)	14 (23.7%)	15 (25.4%)	13 (22.0%)	14 (23.7%)	15 (25.4%)		13 (22.0%)

PROGRAM: Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 869

PURPOSE: To evaluate immunological and clinical responses to yeast recombinant hepatitis B vaccine in health care personnel who are negative for hepatitis B virus serologic markers.

VACCINE: Yeast Recombinant Hepatitis B Vaccine
Lot #81991D/18068/C-L217

PRIMARY INVESTIGATORS:

James G. Rankin, MB, BS, FRACP, FRCP(C)
Director, Canadian Liver Foundation
Epidemiology Unit and Professor
Faculty of Medicine
University of Toronto
12 Queen's Park Crescent West
Toronto, Ontario M5S 1A8, Canada

Randall A. Coates, MD, MHSc
Assistant Professor
Canadian Liver Foundation
Epidemiology Unit
University of Toronto
12 Queen's Park Crescent West
Toronto, Ontario M5S 1A8, Canada

SECONDARY INVESTIGATORS:

David Stewart, MD, DECH, CCFP
Medical Director, Department of
Occupational Health and Safety
2075 Bayview Avenue
Sunnybrook Medical Centre
Toronto, Ontario M4N 3M5, Canada

Mabel L. Halliday, MD, DPH, MSc
Assistant Professor
Canadian Liver Foundation
Epidemiology Unit
12 Queen's Park Crescent West
University of Toronto
Toronto, Ontario M5S 1A8, Canada

STUDY LOCATION: Sunnybrook Medical Centre
2075 Bayview Avenue
Toronto, Ontario M4N 3M5, Canada

Study 869

DATE INITIATED: May 1985

DATE COMPLETED: In progress.

STUDY POPULATION: The study population will consist of health care personnel of either sex (excluding pregnant women) who are negative for hepatitis B virus serologic markers, have a normal ALT level and have not previously received any hepatitis B vaccine.

PROCEDURE: The study will be conducted in two stages. Stage I will include 30 participants and Stage II 120 participants. Participants will receive a 0.5 ml (10µg HBsAg) intramuscular injection of vaccine at 0, 1 and 6 months. Study subjects will be asked to record their temperatures and any local or systemic complaints for five days after each injection.

Blood samples will be obtained prior to vaccination, on Day 0, and at 1, 2, 3, 6, 8, 12 and 24 months post the initial injection. The pre and two-month sample will be tested for ALT. All samples will be assayed for HBsAg, anti-HBs and anti-HBc. Pre-vaccination tests will be performed in Toronto and post vaccination tests will be completed by MSDRL. Assays may also be done for yeast antibodies and anti-HBs subtype specificity.

RESULTS: HEALTH CARE PERSONNEL:

10 mcg lot #81991D/18068/C-L217 at 0, 1, and 6 months

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
10 mcg	71	71	0

Study 869

RESULTS: (Cont.)

2. Serologic Response:

Serologic data are available for 68 participants who received two injections of vaccine. At one month, 32% (22/68) of the participants seroconverted for anti-HBs S/N $\geq$ 2.1. Twelve percent (8/68) developed protective levels of anti-HBs (mIU/ml $\geq$ 10).

The GMT at one month for all vaccinees was 1.2 mIU/ml and 44.8 mIU/ml for responders with a titer of mIU/ml $\geq$10.

Serologic follow-up continues in progress.

3. Clinical Complaints:

Clinical follow-up data are available for 71 participants after injections one and two. The overall frequencies of complaints are presented below:

Type of Complaint	Frequency in % by Injection No. 1	2
Injection site	24 (17/71)	10 (7/71)
Systemic	30 (21/71)	17 (12/71)

Refer to Table 1 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 2.

There were no serious or alarming reactions attributable to vaccine.

Study 869

Reactions Reported to the OoBRR

One subject, a 46 year-old female health care worker, reported the onset of generalized pruritis 9 hours after administration of vaccine. Pruritis continued during the following 24 hours accompanied by irritability, nausea and parasthesias under the left breast. These symptoms resolved on the second and third days post vaccination. However, the participant reported that her extremities felt stiff and heavy. Her past medical history is significant for parasthesias which occurred 1 year prior to vaccination when a mass was surgically removed from her left breast. The investigator felt the subjects reaction had an emotional component and was probably not related to administration of vaccine.

Table 1

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (71 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	14 (19.7%)	7 (9.9%)	3 (4.2%)	1 (1.4%)	1 (1.4%)	1 (1.4%)		17 (23.9%)
INFLAMMATION	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
PAIN	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.8%)
SORENESS	9 (12.7%)	3 (4.2%)	2 (2.8%)	1 (1.4%)	1 (1.4%)	1 (1.4%)		10 (14.1%)
TENDERNESS	2 (2.8%)	2 (2.8%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (5.6%)
PRURITIS (ITCHING)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.8%)
SYSTEMIC	12 (16.9%)	6 (8.5%)	7 (9.9%)	6 (8.5%)	7 (9.9%)	2 (2.8%)		21 (29.6%)
WHOLE BODY/GENERAL	7 (9.9%)	0 (0.0%)	2 (2.8%)	1 (1.4%)	1 (1.4%)	0 (0.0%)		10 (14.1%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
CHILLS	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
SWEATING	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.8%)
SENSATION OF WARMTH, GENERAL	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)

Table 1 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (71 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
MALAISE	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
HEADACHE	2 (2.8%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	5 (7.0%)
LIGHTHEADED	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)
ACHINESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
HOT AND COLD FLASHES	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
RESPIRATORY	2 (2.8%)	2 (2.8%)	2 (2.8%)	3 (4.2%)	4 (5.6%)	1 (1.4%)	5 (7.0%)
RHINITIS	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	2 (2.8%)
PHARYNGITIS (SORE THROAT)	2 (2.8%)	1 (1.4%)	2 (2.8%)	3 (4.2%)	4 (5.6%)	1 (1.4%)	5 (7.0%)
MUSCULOSKELETAL	2 (2.8%)	2 (2.8%)	2 (2.8%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	5 (7.0%)
ARTHRALGIA (OTHER)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
SHOULDER PAIN	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	2 (2.8%)
NECK STIFFNESS	0 (0.0%)	2 (2.8%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	2 (2.8%)

Table 1 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (71 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
ARM PAIN	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)
OTHER	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
DIGESTIVE SYSTEM	3 (4.2%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	5 (7.0%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
NAUSEA	3 (4.2%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (5.6%)
VOMITING	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	2 (2.8%)
NERVOUS SYSTEM	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	3 (4.2%)
PARESTHESIAS	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
TWITCH/LOCAL SPASMS	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)
PERSONS WITH COMPLAINTS	23 (32.4%)	12 (16.9%)	9 (12.7%)	7 (9.9%)	8 (11.3%)	3 (4.2%)	32 (45.1%)
PERSONS WITH NO COMPLAINTS	48 (67.6%)	59 (83.1%)	62 (87.3%)	64 (90.1%)	63 (88.7%)	68 (95.8%)	39 (54.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 1 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (71 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	7 (9.9%)	3 (4.2%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (9.9%)
SORENESS	3 (4.2%)	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.2%)
TENDERNESS	2 (2.8%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)
STIFFNESS/TIGHTNESS	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
PRURITIS (ITCHING)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
SYSTEMIC	7 (9.9%)	6 (8.5%)	5 (7.0%)	3 (4.2%)	4 (5.6%)	3 (4.2%)	12 (16.9%)
WHOLE BODY/GENERAL	5 (7.0%)	3 (4.2%)	3 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (12.7%)
FATIGUE/WEAKNESS	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)
MALAISE	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.8%)
HEADACHE	3 (4.2%)	2 (2.8%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (7.0%)
LIGHTHEADED	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
HOT FLASHES	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)

Table 1 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (71 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RESPIRATORY	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	2 (2.8%)
RHINITIS	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
COUGH	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
HEMIC AND LYMPHATIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
LYMPHADENOPATHY, CERVICAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
DIGESTIVE SYSTEM	2 (2.8%)	3 (4.2%)	2 (2.8%)	2 (2.8%)	2 (2.8%)	1 (1.4%)	4 (5.6%)
DIARRHEA	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
NAUSEA	2 (2.8%)	2 (2.8%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	3 (4.2%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)
DIMINISHED APPETITE	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
OTHER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)
NERVOUS SYSTEM	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)

Table 1 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (71 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PARESTHESIAS	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
PERSONS WITH COMPLAINTS	13 (18.3%)	9 (12.7%)	6 (8.5%)	3 (4.2%)	4 (5.6%)	3 (4.2%)	18 (25.4%)
PERSONS WITH NO COMPLAINTS	58 (81.7%)	62 (87.3%)	65 (91.5%)	68 (95.8%)	67 (94.4%)	68 (95.8%)	53 (74.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00490

Table 2

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (71 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (1.4%)	1 (1.4%)	1 (1.5%)	1 (1.4%)	1 (1.4%)	1 (1.4%)		1 (1.4%)
< 99	66 (94.3%)	66 (94.3%)	63 (92.6%)	62 (89.9%)	64 (92.8%)	68 (95.8%)		54 (76.1%)
99 - 99.9	2 (2.9%)	3 (4.3%)	4 (5.9%)	5 (7.2%)	3 (4.3%)	2 (2.8%)		13 (18.3%)
100 - 100.9	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)		3 (4.2%)
TEMPERATURE TAKEN	70 (98.6%)	70 (98.6%)	68 (95.8%)	69 (97.2%)	69 (97.2%)	71 (100.0%)		71 (100.0%)
TEMPERATURE NOT TAKEN	1 (1.4%)	1 (1.4%)	3 (4.2%)	2 (2.8%)	2 (2.8%)	0 (0.0%)		0 (0.0%)

Table 2 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (71 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (1.4%)	1 (1.4%)	1 (1.5%)	1 (1.5%)	1 (1.4%)	1 (1.5%)		1 (1.4%)
< 99	63 (90.0%)	64 (92.8%)	58 (86.6%)	63 (92.6%)	65 (92.9%)	59 (89.4%)		57 (80.3%)
99 - 99.9	5 (7.1%)	3 (4.3%)	7 (10.4%)	3 (4.4%)	3 (4.3%)	5 (7.6%)		11 (15.5%)
100 - 100.9	1 (1.4%)	1 (1.4%)	1 (1.5%)	1 (1.5%)	1 (1.4%)	1 (1.5%)		2 (2.8%)
TEMPERATURE TAKEN	70 (98.6%)	69 (97.2%)	67 (94.4%)	68 (95.8%)	70 (98.6%)	66 (93.0%)		71 (100.0%)
TEMPERATURE NOT TAKEN	1 (1.4%)	2 (2.8%)	4 (5.6%)	3 (4.2%)	1 (1.4%)	5 (7.0%)		0 (0.0%)

STUDY 877

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 877
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among healthy adults who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 979/C-K564 (10 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Professor Oon Chong Jin University Department of Medicine I Singapore General Hospital Singapore 0316 Republic of Singapore
SECONDARY INVESTIGATOR:	Dr. Richard Guan University Department of Medicine I Singapore General Hospital Singapore 0316 Republic of Singapore
STUDY LOCATION:	Singapore General Hospital Singapore 0316 Republic of Singapore
DATE STUDY INITIATED:	January 26, 1985
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 25-30 healthy adults of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 877

STUDY PROCEDURE:

Eligible study participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine at 0, 1, and 6 months. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12 and 24 months.

All serum samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples may be assayed for yeast antibody. In addition, samples with an anti-HBs titer ≥25 mIU/ml may be tested to determine anti-a and anti-d subtype specificity.

RESULTS:

HEALTHY ADULTS

10 mcg Lot 979/C-K564 at 0, 1, and 6 months.

1. Number Vaccinated:

Injection No.		
1	2	3
31	31	31

2. Serologic Results:

Serologic data at 7-8 months are available for 29 study participants. Immune responses to vaccine were measured using an enzyme-linked immunosorbent assay (ELISA) to detect anti-HBs antibody. At 7-8 months 97% (28/29) of vaccine recipients seroconverted (mIU/ml ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees was 508.9 mIU/ml. Among responders with a titer of mIU/ml ≥10 the GMT was 663.7 mIU/ml. Anti-HBs responses at 1 through 7-8 months are included in Table 1.

Study 877

RESULTS: (Contd)

3. Clinical Complaints:

No serious or alarming adverse reactions attributable to vaccination have been reported.

Study 877

Table 1

Antibody Responses* Among Initially Seronegative Healthy Adults
Following Vaccination with 10 mcg Doses of
Yeast Recombinant Hepatitis B Vaccine
Lot 979/C-K564 at 0, 1, and 6 Months in Study 877

Time (Months)	% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders	
	mIU/ml ≥2.1	mIU/ml ≥10		mIU/ml ≥2.1	mIU/ml ≥10
1	0 (0/31)	0 (0/31)	0.3	--	--
2	48 (15/31)	32 (10/31)	2.1	16.4	26.9
3	71 (22/31)	55 (17/31)	6.1	21.0	28.7
6	77 (24/31)	65 (20/31)	12.1	35.5	49.4
7-8	97 (28/29)	97 (28/29)	508.9	663.7	663.7

* ELISA

2393I/85I/4
1/3/86

STUDY 880

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 880
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 81990D/18066/C-L215 (10 mcg HBsAg/.5 ml) Lot 81766B/18067/C-L216 (10 mcg HBsAg/.5 ml) Lot 81991D/18068/C-L217 (10 mcg HBsAg/.5 ml) Lot 81992A/18070/C-L219 (10 mcg HBsAg/.5 ml) Lot 81954I/18071/C-L220 (10 mcg HBsAg/.5 ml)
PRIMARY INVESTIGATOR:	Gary P. Wormser, M.D. Department of Infectious Diseases West Chester County Medical Center Macy Pavilion 208 S.E. Valhalla, New York 10595
SECONDARY INVESTIGATOR:	Katherine Small, M.D. Robert L. Yarrish, M.D. West Chester County Medical Center Macy Pavilion 208 S.E. Valhalla, New York 10595
STUDY LOCATION:	West Chester County Medical Center Macy Pavilion 207 S.E. Valhalla, New York 10595
DATE STUDY INITIATED:	April 1, 1985
DATE STUDY COMPLETED:	In progress

Study 880

STUDY POPULATION: The study population consists of approximately 250 health care personnel of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Health care personnel are assigned to one of the five lots of vaccine, stratified by sex and age, to assure that recipients of each lot are similar. Approximately fifty persons are assigned to each lot of vaccine.

Eligible study participants receive a 0.5 ml (10 mcg HBsAg) intramuscular injection of one of the five lots of vaccine at 0, 1 and 6 months. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

Blood samples are obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 7/8, 12 and 24 months.

All serum samples are assayed for HBsAg, anti-HBc, and anti-HBs. ALT testing is performed on all pre-vaccination and 2 month post-vaccination samples. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested for anti-a and anti-d subtype specificity.

RESULTS: HEALTH CARE PERSONNEL

10 mcg Lot 81990D/18066/C-L215 at 0, 1, and 6 months
10 mcg Lot 81766B/18067/C-L216 at 0, 1, and 6 months
10 mcg Lot 81991D/18068/C-L217 at 0, 1, and 6 months
10 mcg Lot 81992A/18070/C-L219 at 0, 1, and 6 months
10 mcg Lot 81954I/18071/C-L220 at 0, 1, and 6 months

Study 880

RESULTS: (Cont.)

1. Number Vaccinated:

Lot	Injection No. 1	2	3
C-L215	48	48	40
C-L216	43	43	24
C-L217	53	53	26
C-L219	46	46	25
C-L220	43	43	38

2. Serologic Results:

Serologic data at 7/8 months are available for 33 (lot C-L215), 24 (lot C-L216), 23(lot C-L217), 25 (lot C-L219) and 34 (lot C-L220) study participants. At 7/8 months anti-HBs responses are as follows:

Lot	% Anti-HBs Positive S/N ≥2.1	mIU/ml ≥10	GMT (mIU/ml) All Vaccinees	Responders S/N ≥2.1	mIU/ml ≥10
C-L215	100(33/33)	94(31/33)	591.2	591.2	799.3
C-L216	100(24/24)	100(24/24)	1187.6	1187.6	1187.6
C-L217	96(22/23)	91(21/23)	345.8	476.4	593.6
C-L219	92(23/25)	92(23/25)	332.6	612.0	612.0
C-L220	100(34/34)	100(34/34)	1012.0	1012.0	1012.0

Anti-HBs responses at 1 through 7/8 months are included in Tables 1-5.

Study 880

RESULTS: (Cont.) 3. Clinical Results:

Clinical follow-up data are available for 233, 221, and 99 study participants following the first, second and third injections of vaccine, respectively. Clinical complaints and maximum temperatures reported following each injection are provided in Tables 6-15.

Clinical Complaint	Lot	% Frequency By Injection No. 1	2	3
Injection Site	C-L215	8(4/48)	13(6/46)	4(1/24)
	C-L216	9(4/43)	5(2/43)	9(1/11)
	C-L217	11(6/53)	4(2/53)	0(0/17)
	C-L219	17(8/46)	9(4/46)	6(1/17)
	C-L220	0(0/43)	9(4/43)	7(2/30)
Systemic	C-L215	2(1/48)	2(1/46)	4(1/24)
	C-L216	17(8/43)	2(1/43)	0(0/11)
	C-L217	13(7/53)	4(2/53)	0(0/17)
	C-L219	9(4/46)	0(0/46)	6(1/17)
	C-L220	7(3/43)	5(2/43)	3(1/30)

No serious or alarming adverse reactions attributable to vaccination have been reported.

ALT Elevations

One subject whose pre-vaccination ALT level was normal had a transient elevated level of this enzyme at 2 months post-vaccination. A follow-up serum sample obtained 1 week later showed a decreasing ALT. A reason for the ALT elevation was not ascertained. The subject has not developed anti-HBs after two injections of vaccine and has not been reported to show any clinical or serologic signs (HBsAg or anti-HBc) of hepatitis B through 6 months of follow-up.

Study 880

RESULTS: (Cont.)

HBV Markers (Anti-HBc)

In two subjects, the 6 (C-L219) and 8 (C-L220) month post-vaccination serum samples, respectively, were borderline positive for anti-HBc. All previous serum samples were negative for anti-HBc. The two subjects developed anti-HBs at 1 and 2 months, respectively. Both subjects have remained HBsAg negative and there has been no report of clinical illness.

Events Reported to OoBRR

A 25 year-old female subject recorded a temperature of 100.1°F several days after administration of a second injection of vaccine (lot C-L215). A CBC completed at that time revealed a normal WBC with a normal differential but a platelet count greater than 1 x $10^6/mm^3$ was noted. Bone marrow examination revealed numerous megakaryocytes. A pre-existing myeloproliferative disorder is considered the most likely diagnosis.

Table 1

Antibody Responses Among Initially Seronegative Health Care Personnel Following Vaccination with 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot 81990D/18066/C-L215 at 0, 1, and 6 Months in Study 880

Time (Months)	% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1 Month	24 (11/46)	13 (6/46)	0.9	12.5	33.0
2 Months	76 (32/42)	50 (21/42)	11.1	30.0	77.5
3 Months	86 (32/37)	73 (27/37)	31.9	58.7	95.4
6 Months	86 (31/36)	64 (23/36)	23.0	36.8	71.8
7/8 Months	100 (33/33)	94 (31/33)	591.2	591.2	799.3

Table 2

Antibody Responses Among Initially Seronegative Health Care Personnel Following Vaccination with 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot 81766B/18067/C-L216 at 0, 1, and 6 Months in Study 880

Time (Months)	% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1 Month	20 (8/41)	7 (3/41)	0.7	9.3	39.6
2 Months	86 (32/37)	65 (24/37)	14.4	25.2	45.4
3 Months	86 (25/29)	76 (22/29)	18.7	34.2	45.7
6 Months	100 (22/22)	100 (22/22)	51.5	51.5	51.5
7/8 Months	100 (24/24)	100 (24/24)	1187.6	1187.6	1187.6

2398I/9
1/28/86

00503

Table 3

Antibody Responses Among Initially Seronegative Health Care Personnel Following Vaccination with 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot 819910/18068/C-L217 at 0, 1, and 6 Months in Study 880

Time (Months)	% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1 Month	19 (10/52)	8 (4/52)	0.8	14.5	91.2
2 Months	75 (36/48)	58 (28/48)	12.1	33.6	58.8
3 Months	84 (32/38)	68 (26/38)	23.6	48.7	77.4
6 Months	87 (26/30)	77 (23/30)	27.5	53.5	69.7
7/8 Months	96 (22/23)	91 (21/23)	345.8	476.4	593.6

2398I/10
1/28/86

00504

Table 4

Antibody Responses Among Initially Seronegative Health Care Personnel Following Vaccination with 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot B1992A/18070/C-L219 at 0, 1, and 6 Months in Study 880

Time (Months)	% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1 Month	22 (10/45)	9 (4/45)	0.7	10.7	36.7
2 Months	64 (27/42)	40 (17/42)	6.3	27.2	69.1
3 Months	66 (21/32)	59 (19/32)	9.5	51.7	63.9
6 Months	90 (27/30)	73 (22/30)	29.7	48.0	77.2
7/8 Months	92 (23/25)	92 (23/25)	332.6	612.0	612.0

23981/11
1/28/86

00505

Table 5

Antibody Responses Among Initially Seronegative Health Care Personnel Following Vaccination with 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot 81954I/18071/C-L220 at 0, 1, and 6 Months in Study 880

Time (Months)	% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1 Month	40 (17/43)	21 (9/43)	1.7	14.6	63.8
2 Months	84 (36/43)	60 (26/43)	16.6	30.6	60.8
3 Months	97 (34/35)	83 (29/36)	50.5	55.6	84.8
6 Months	97 (37/38)	89 (34/38)	39.5	43.2	53.1
7/8 Months	100 (34/34)	100 (34/34)	1012.0	1012.0	1012.0

Table 6

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (48 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
[illegible]ON, LOCAL (INJECT. SITE)	1 (2.1%)	3 (6.3%)	1 (2.1%)	1 (2.1%)	0 (0.0%)	0 (0.0%)		4 (8.3%)
[illegible]RENESS	1 (2.1%)	2 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (6.3%)
[illegible]ENDERNESS	0 (0.0%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
[illegible]MIC	0 (0.0%)	1 (2.1%)	1 (2.1%)	1 (2.1%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
[illegible] BODY/GENERAL	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
ILLNESS, NOS	0 (0.0%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (2.1%)	1 (2.1%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
PERSONS WITH COMPLAINTS	1 (2.1%)	4 (8.3%)	2 (4.2%)	2 (4.2%)	0 (0.0%)	0 (0.0%)		5 (10.4%)
PERSONS WITH NO COMPLAINTS	47 (97.9%)	44 (91.7%)	46 (95.8%)	46 (95.8%)	48 (100.0%)	48 (100.0%)		43 (89.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00507

Table 6 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (48 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
...ON, LOCAL (INJECT. SITE)	4 (8.7%)	3 (6.5%)	2 (4.3%)	1 (2.2%)	1 (2.2%)	0 (0.0%)		6 (13.0%)
...HENESS	4 (8.7%)	3 (6.5%)	2 (4.3%)	1 (2.2%)	1 (2.2%)	0 (0.0%)		6 (13.0%)
...C	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
...TORY	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
...PPER RESPIRATORY INFECT., NOS	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
PERSONS WITH COMPLAINTS	5 (10.9%)	3 (6.5%)	2 (4.3%)	1 (2.2%)	1 (2.2%)	0 (0.0%)		6 (13.0%)
PERSONS WITH NO COMPLAINTS	41 (89.1%)	43 (93.5%)	44 (95.7%)	45 (97.8%)	45 (97.8%)	46 (100.0%)		40 (87.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 6 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
...ON, LOCAL (INJECT. SITE)	0 (0.0%)	1 (4.2%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.2%)
...ENESS	0 (0.0%)	1 (4.2%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.2%)
...	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.2%)
...ODY/GENERAL	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.2%)
...ALAISE	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.2%)
PERSONS WITH COMPLAINTS	1 (4.2%)	1 (4.2%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.2%)
PERSONS WITH NO COMPLAINTS	23 (95.8%)	23 (95.8%)	23 (95.8%)	24 (100.0%)	24 (100.0%)	24 (100.0%)		23 (95.8%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (48 PATIENTS) - DOSE 1 — DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
< 99	36 (80.0%)	38 (84.4%)	35 (79.5%)	36 (81.8%)	37 (88.1%)	37 (92.5%)		25 (55.6%)
99 - 99.9	8 (17.8%)	7 (15.6%)	9 (20.5%)	8 (18.2%)	5 (11.9%)	3 (7.5%)		19 (42.2%)
100 - 100.9	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
TEMPERATURE TAKEN	45 (93.8%)	45 (93.8%)	44 (91.7%)	44 (91.7%)	42 (87.5%)	40 (83.3%)		45 (93.8%)
TEMPERATURE NOT TAKEN	3 (6.3%)	3 (6.3%)	4 (8.3%)	4 (8.3%)	6 (12.5%)	8 (16.7%)		3 (6.3%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (48 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	34 (89.5%)	35 (94.6%)	33 (86.8%)	35 (94.6%)	36 (97.3%)	32 (91.4%)			28 (73.7%)
99 - 99.9	4 (10.5%)	2 (5.4%)	5 (13.2%)	2 (5.4%)	1 (2.7%)	3 (8.6%)			10 (26.3%)
TEMPERATURE TAKEN	38 (79.2%)	37 (77.1%)	38 (79.2%)	37 (77.1%)	37 (77.1%)	35 (72.9%)			38 (79.2%)
TEMPERATURE NOT TAKEN	10 (20.8%)	11 (22.9%)	10 (20.8%)	11 (22.9%)	11 (22.9%)	13 (27.1%)			10 (20.8%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (40 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	11 (78.6%)	13 (92.9%)	13 (92.9%)	10 (76.9%)	13 (92.9%)	11 (91.7%)		8 (57.1%)
99 - 99.9	3 (21.4%)	1 (7.1%)	1 (7.1%)	3 (23.1%)	1 (7.1%)	1 (8.3%)		6 (42.9%)
TEMPERATURE TAKEN	14 (35.0%)	14 (35.0%)	14 (35.0%)	13 (32.5%)	14 (35.0%)	12 (30.0%)		14 (35.0%)
TEMPERATURE NOT TAKEN	26 (65.0%)	26 (65.0%)	26 (65.0%)	27 (67.5%)	26 (65.0%)	28 (70.0%)		26 (65.0%)

Table 8

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL216
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (43 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
...TION, LOCAL (INJECT. SITE)	2 (4.7%)	1 (2.3%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		4 (9.3%)
...NESS	2 (4.7%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		3 (7.0%)
...ERNESS	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
...STHEMA (REDNESS)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
...WELLING	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
SYSTEMIC	2 (4.7%)	3 (7.0%)	2 (4.7%)	3 (7.0%)	1 (2.3%)	0 (0.0%)		8 (18.6%)
WHOLE BODY/GENERAL	1 (2.3%)	2 (4.7%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		3 (7.0%)
SWEATING	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
...ATIGUE/WEAKNESS	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
HEADACHE	0 (0.0%)	1 (2.3%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		2 (4.7%)
RESPIRATORY	0 (0.0%)	1 (2.3%)	1 (2.3%)	3 (7.0%)	0 (0.0%)	0 (0.0%)		3 (7.0%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.7%)	0 (0.0%)	0 (0.0%)		2 (4.7%)

Table 8 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL216
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (43 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
MUSCULOSKELETAL	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
ARTHRALGIA (OTHER)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
DIGESTIVE SYSTEM	0 (0.0%)	2 (4.7%)	2 (4.7%)	1 (2.3%)	1 (2.3%)	0 (0.0%)		4 (9.3%)
DIARRHEA	0 (0.0%)	2 (4.7%)	2 (4.7%)	1 (2.3%)	1 (2.3%)	0 (0.0%)		4 (9.3%)
NAUSEA	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
NERVOUS SYSTEM	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
VERTIGO/DIZZINESS	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
PERSONS WITH COMPLAINTS	4 (9.3%)	4 (9.3%)	2 (4.7%)	3 (7.0%)	1 (2.3%)	0 (0.0%)		9 (20.9%)
PERSONS WITH NO COMPLAINTS	39 (90.7%)	39 (90.7%)	41 (95.3%)	40 (93.0%)	42 (97.7%)	43 (100.0%)		34 (79.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 8 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL218
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (43 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)		2 (4.7%)
INFLAMMATION	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
SORENESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)		1 (2.3%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (2.3%)		1 (2.3%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)		1 (2.3%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)		1 (2.3%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)		1 (2.3%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)		1 (2.3%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)		1 (2.3%)
PERSONS WITH COMPLAINTS	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (2.3%)		2 (4.7%)
PERSONS WITH NO COMPLAINTS	42 (97.7%)	43 (100.0%)	43 (100.0%)	43 (100.0%)	42 (97.7%)	42 (97.7%)		41 (95.3%)
... WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 8 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL216
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REALTION, LOCAL (INJECT. SITE)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (9.1%)
SORENESS	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (9.1%)
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (9.1%)
PERSONS WITH NO COMPLAINTS	11 (100.0%)	11 (100.0%)	10 (90.9%)	11 (100.0%)	11 (100.0%)	11 (100.0%)		10 (90.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 9

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CL216
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (43 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	33 (94.3%)	33 (94.3%)	33 (97.1%)	30 (93.8%)	33 (100.0%)	30 (100.0%)			29 (82.9%)
99 - 99.9	2 (5.7%)	2 (5.7%)	1 (2.9%)	2 (6.3%)	0 (0.0%)	0 (0.0%)			6 (17.1%)
TEMPERATURE TAKEN	35 (81.4%)	35 (81.4%)	34 (79.1%)	32 (74.4%)	33 (76.7%)	30 (69.8%)			35 (81.4%)
TEMPERATURE NOT TAKEN	8 (18.6%)	8 (18.6%)	9 (20.9%)	11 (25.6%)	10 (23.3%)	13 (30.2%)			8 (18.6%)

00517

Table 9 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL216
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (43 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	23 (92.0%)	22 (100.0%)	22 (91.7%)	21 (95.5%)	21 (95.5%)	19 (90.5%)		20 (80.0%)
99 - 99.9	2 (8.0%)	0 (0.0%)	2 (8.3%)	1 (4.5%)	1 (4.5%)	2 (9.5%)		5 (20.0%)
TEMPERATURE TAKEN	25 (58.1%)	22 (51.2%)	24 (55.8%)	22 (51.2%)	22 (51.2%)	21 (48.8%)		25 (58.1%)
TEMPERATURE NOT TAKEN	18 (41.9%)	21 (48.8%)	19 (44.2%)	21 (48.8%)	21 (48.8%)	22 (51.2%)		18 (41.9%)

Table 9 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL216
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (18 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	5 (83.3%)	5 (83.3%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	5 (100.0%)			5 (83.3%)
99 - 99.9	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (16.7%)
TEMPERATURE TAKEN	6 (33.3%)	6 (33.3%)	6 (33.3%)	6 (33.3%)	6 (33.3%)	5 (27.8%)			6 (33.3%)
TEMPERATURE NOT TAKEN	12 (66.7%)	12 (66.7%)	12 (66.7%)	12 (66.7%)	12 (66.7%)	13 (72.2%)			12 (66.7%)

Table 10

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (53 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	4 (7.5%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)		6 (11.3%)
PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)		1 (1.9%)
SORENESS	4 (7.5%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (9.4%)
SYSTEMIC	3 (5.7%)	3 (5.7%)	1 (1.9%)	1 (1.9%)	2 (3.8%)	0 (0.0%)		7 (13.2%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	0 (0.0%)		3 (5.7%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)		2 (3.8%)
HEADACHE	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)		2 (3.8%)
INFECTIOUS SYNDROMES	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
HERPES LABIALIS, RECURRENT	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
RESPIRATORY	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
PHARYNGITIS (SORE THROAT)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
MUSCULOSKELETAL	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.8%)

00520

Table 10 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : D880
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (53 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
NECK PAIN	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
ARM PAIN	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)		2 (3.8%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)		1 (1.9%)
PERSONS WITH COMPLAINTS	6 (11.3%)	4 (7.5%)	1 (1.9%)	1 (1.9%)	3 (5.7%)	0 (0.0%)		12 (22.6%)
PERSONS WITH NO COMPLAINTS	47 (88.7%)	49 (92.5%)	52 (98.1%)	52 (98.1%)	50 (94.3%)	53 (100.0%)		41 (77.4%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 10 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

: 0880
:
: CL217
: 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (53 PATIENTS) - DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)		2 (3.8%)
PAIN ON INJECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)		1 (1.9%)
SORENESS	2 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.8%)
SYSTEMIC	1 (1.9%)	1 (1.9%)	1 (1.9%)	2 (3.8%)	0 (0.0%)	0 (0.0%)		2 (3.8%)
WHOLE BODY/GENERAL	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
FATIGUE/WEAKNESS	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
MALAISE	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
HEADACHE	0 (0.0%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)		1 (1.9%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)		2 (3.8%)
NECK STIFFNESS	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)		2 (3.8%)
PERSONS WITH COMPLAINTS	2 (3.8%)	1 (1.9%)	1 (1.9%)	2 (3.8%)	0 (0.0%)	1 (1.9%)		2 (3.8%)
PERSONS WITH NO COMPLAINTS	51 (96.2%)	52 (98.1%)	52 (98.1%)	51 (96.2%)	53 (100.0%)	52 (98.1%)		51 (96.2%)

Table 10 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

: 0880
:
NUMBER : CL217
: 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (53 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 10 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

: 0880
:
NUMBER : CL217
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)		17 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 11

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (53 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
< 99	34 (89.5%)	38 (100.0%)	33 (86.8%)	35 (92.1%)	35 (94.6%)	33 (94.3%)		29 (76.3%)
99 - 99.9	4 (10.5%)	0 (0.0%)	4 (10.5%)	3 (7.9%)	2 (5.4%)	2 (5.7%)		8 (21.1%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.6%)
TEMPERATURE TAKEN	38 (71.7%)	38 (71.7%)	38 (71.7%)	38 (71.7%)	37 (69.8%)	35 (66.0%)		38 (71.7%)
TEMPERATURE NOT TAKEN	15 (28.3%)	15 (28.3%)	15 (28.3%)	15 (28.3%)	16 (30.2%)	18 (34.0%)		15 (28.3%)

00525

Table 11 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (53 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	28 (87.5%)	27 (87.1%)	28 (96.6%)	27 (96.4%)	25 (89.3%)	23 (88.5%)			23 (71.9%)
99 - 99.9	4 (12.5%)	4 (12.9%)	1 (3.4%)	1 (3.6%)	3 (10.7%)	2 (7.7%)			8 (25.0%)
102 - 102.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)			1 (3.1%)
TEMPERATURE TAKEN	32 (60.4%)	31 (58.5%)	29 (54.7%)	28 (52.8%)	28 (52.8%)	26 (49.1%)			32 (60.4%)
TEMPERATURE NOT TAKEN	21 (39.6%)	22 (41.5%)	24 (45.3%)	25 (47.2%)	25 (47.2%)	27 (50.9%)			21 (39.6%)

00526

Table 11 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL217
DOSE : 10 MCG

	TOTAL VACCINEES (26 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER
MAX TEMPERATURE (DEG F, ORAL)	0	1	2	3	4	5		WITH MAX TEMP
< 99	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)		5 (100.0%)
TEMPERATURE TAKEN	5 (19.2%)	5 (19.2%)	5 (19.2%)	5 (19.2%)	5 (19.2%)	5 (19.2%)		5 (19.2%)
TEMPERATURE NOT TAKEN	21 (80.8%)	21 (80.8%)	21 (80.8%)	21 (80.8%)	21 (80.8%)	21 (80.8%)		21 (80.8%)

Table 12

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL219
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (46 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	8 (17.4%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		8 (17.4%)
PAIN	2 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (4.3%)
SORENESS	5 (10.9%)	2 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (10.9%)
RASH, NOS	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
SYSTEMIC	1 (2.2%)	1 (2.2%)	2 (4.3%)	2 (4.3%)	1 (2.2%)	0 (0.0%)		4 (8.7%)
WHOLE BODY/GENERAL	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
SWEATING	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	2 (4.3%)	2 (4.3%)	1 (2.2%)	0 (0.0%)		2 (4.3%)
SINUSITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	2 (4.3%)	1 (2.2%)	1 (2.2%)	0 (0.0%)		2 (4.3%)
DIGESTIVE SYSTEM	1 (2.2%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (4.3%)

Table 12 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL219
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (46 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
DIARRHEA	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
NAUSEA	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
VOMITING	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
[illegible]INS WITH COMPLAINTS	8 (17.4%)	3 (6.5%)	2 (4.3%)	2 (4.3%)	1 (2.2%)	0 (0.0%)		10 (21.7%)
[illegible]INS WITH NO COMPLAINTS	38 (82.6%)	43 (93.5%)	44 (95.7%)	44 (95.7%)	45 (97.8%)	46 (100.0%)		36 (78.3%)
[illegible]INS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00529

Table 12 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL219
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (46 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	3 (6.5%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (8.7%)
INFLAMMATION	3 (6.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (6.5%)
TENDERNESS	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.2%)
SUBJECTS WITH COMPLAINTS	3 (6.5%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (8.7%)
SUBJECTS WITH NO COMPLAINTS	43 (93.5%)	45 (97.8%)	46 (100.0%)	46 (100.0%)	46 (100.0%)	46 (100.0%)		42 (91.3%)
SUBJECTS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 12 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL219
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 3 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
PAIN	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
ITCH	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)		1 (5.9%)
WHOLE BODY/GENERAL	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)		1 (5.9%)
HEADACHE	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)		1 (5.9%)
PERSONS WITH COMPLAINTS	1 (5.9%)	2 (11.8%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)		2 (11.8%)
PERSONS WITH NO COMPLAINTS	16 (94.1%)	15 (88.2%)	16 (94.1%)	16 (94.1%)	16 (94.1%)	16 (94.1%)		15 (88.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00531

Table 13

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL219
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (46 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	33 (86.8%)	35 (94.6%)	34 (91.9%)	31 (86.1%)	34 (91.9%)	33 (97.1%)		26 (68.4%)
99 - 99.9	5 (13.2%)	2 (5.4%)	3 (8.1%)	5 (13.9%)	3 (8.1%)	1 (2.9%)		12 (31.6%)
TEMPERATURE TAKEN	38 (82.6%)	37 (80.4%)	37 (80.4%)	36 (78.3%)	37 (80.4%)	34 (73.9%)		38 (82.6%)
TEMPERATURE NOT TAKEN	8 (17.4%)	9 (19.6%)	9 (19.6%)	10 (21.7%)	9 (19.6%)	12 (26.1%)		8 (17.4%)

Table 13 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0860
TREATMENT :
LOT NUMBER : CL219
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (46 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	23 (88.5%)	24 (92.3%)	21 (80.8%)	25 (96.2%)	19 (73.1%)	20 (87.0%)		17 (65.4%)
99 - 99.9	3 (11.5%)	2 (7.7%)	5 (19.2%)	1 (3.8%)	7 (26.9%)	3 (13.0%)		9 (34.6%)
TEMPERATURE TAKEN	26 (56.5%)	26 (56.5%)	26 (56.5%)	26 (56.5%)	26 (56.5%)	23 (50.0%)		26 (56.5%)
TEMPERATURE NOT TAKEN	20 (43.5%)	20 (43.5%)	20 (43.5%)	20 (43.5%)	20 (43.5%)	23 (50.0%)		20 (43.5%)

Table 13 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL219
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (21 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	10 (83.3%)	8 (72.7%)	9 (81.8%)	10 (90.9%)	9 (81.8%)	9 (81.8%)		7 (58.3%)
99 - 99.9	2 (16.7%)	3 (27.3%)	2 (18.2%)	1 (9.1%)	2 (18.2%)	2 (18.2%)		5 (41.7%)
TEMPERATURE TAKEN	12 (57.1%)	11 (52.4%)	11 (52.4%)	11 (52.4%)	11 (52.4%)	11 (52.4%)		12 (57.1%)
TEMPERATURE NOT TAKEN	9 (42.9%)	10 (47.6%)	10 (47.6%)	10 (47.6%)	10 (47.6%)	10 (47.6%)		9 (42.9%)

Table 14

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (43 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
[illegible]TIC	0 (0.0%)	3 (7.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (7.0%)
[illegible] BODY/GENERAL	0 (0.0%)	3 (7.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (7.0%)
[illegible]TIGUE/WEAKNESS	0 (0.0%)	2 (4.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (4.7%)
HEADACHE	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
[illegible]NS WITH COMPLAINTS	0 (0.0%)	3 (7.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (7.0%)
[illegible]NS WITH NO COMPLAINTS	43 (100.0%)	40 (93.0%)	43 (100.0%)	43 (100.0%)	43 (100.0%)	43 (100.0%)		40 (93.0%)
[illegible]NS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 14 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

: 0880
:
: CL220
: 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (43 PATIENTS) - DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
[illegible], LOCAL (INJECT. SITE)	4 (9.3%)	3 (7.0%)	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		4 (9.3%)
PAIN	1 (2.3%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
SORENESS	2 (4.7%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (4.7%)
INDURATION	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
HEMATOMA	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
SYSTEMIC	0 (0.0%)	2 (4.7%)	2 (4.7%)	2 (4.7%)	0 (0.0%)	0 (0.0%)		2 (4.7%)
[illegible] BODY/GENERAL	0 (0.0%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
HEADACHE	0 (0.0%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
[illegible]PIRATORY	0 (0.0%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)		1 (2.3%)
PERSONS WITH COMPLAINTS	4 (9.3%)	5 (11.6%)	3 (7.0%)	3 (7.0%)	0 (0.0%)	0 (0.0%)		6 (14.0%)
PERSONS WITH NO COMPLAINTS	39 (90.7%)	38 (88.4%)	40 (93.0%)	40 (93.0%)	43 (100.0%)	43 (100.0%)		37 (86.0%)

00536

Table 14 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

: 0880
:
: CL220
: 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (43 PATIENTS) - DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 14 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.7%)
SORENESS	0 (0.0%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.7%)
SYSTEMIC	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
WHOLE BODY/GENERAL	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
MALAISE	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
N, WITH COMPLAINTS	1 (3.3%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (10.0%)
N, WITH NO COMPLAINTS	29 (96.7%)	28 (93.3%)	28 (93.3%)	30 (100.0%)	30 (100.0%)	30 (100.0%)		27 (90.0%)
N, WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 15

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0680
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (43 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	36 (85.7%)	40 (95.2%)	38 (95.0%)	38 (95.0%)	36 (94.7%)	32 (100.0%)			31 (73.8%)
99 - 99.9	6 (14.3%)	2 (4.8%)	2 (5.0%)	2 (5.0%)	2 (5.3%)	0 (0.0%)			11 (26.2%)
TEMPERATURE TAKEN	42 (97.7%)	42 (97.7%)	40 (93.0%)	40 (93.0%)	38 (88.4%)	32 (74.4%)			42 (97.7%)
TEMPERATURE NOT TAKEN	1 (2.3%)	1 (2.3%)	3 (7.0%)	3 (7.0%)	5 (11.6%)	11 (25.6%)			1 (2.3%)

Table 15 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0880
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (43 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	37 (92.5%)	36 (90.0%)	37 (94.9%)	38 (97.4%)	37 (94.9%)	33 (94.3%)			31 (77.5%)
99 - 99.9	3 (7.5%)	4 (10.0%)	2 (5.1%)	1 (2.6%)	2 (5.1%)	2 (5.7%)			9 (22.5%)
TEMPERATURE TAKEN	40 (93.0%)	40 (93.0%)	39 (90.7%)	39 (90.7%)	39 (90.7%)	35 (81.4%)			40 (93.0%)
TEMPERATURE NOT TAKEN	3 (7.0%)	3 (7.0%)	4 (9.3%)	4 (9.3%)	4 (9.3%)	8 (18.6%)			3 (7.0%)

Table 15 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0080
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (38 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	17 (85.0%)	19 (95.0%)	18 (90.0%)	19 (95.0%)	18 (94.7%)	16 (94.1%)		16 (80.0%)
99 - 99.9	3 (15.0%)	1 (5.0%)	2 (10.0%)	1 (5.0%)	1 (5.3%)	1 (5.9%)		4 (20.0%)
TEMPERATURE TAKEN	20 (52.6%)	20 (52.6%)	20 (52.6%)	20 (52.6%)	19 (50.0%)	17 (44.7%)		20 (52.6%)
TEMPERATURE NOT TAKEN	18 (47.4%)	18 (47.4%)	18 (47.4%)	18 (47.4%)	19 (50.0%)	21 (55.3%)		18 (47.4%)

PROGRAM:	Alum-Adsorbed Recombinant Hepatitis B Vaccine, Study 882
PURPOSE:	To evaluate antibody and clinical responses to 10 mcg doses of recombinant hepatitis B vaccine in healthy adult male volunteers.
VACCINE:	Recombinant Hepatitis B Vaccine - Alum Adsorbed: Lot #819900/18066/C-L215
PRIMARY INVESTIGATOR:	Shiro Iino, M.D. First Department of Internal Medicine Faculty of Medicine University of Tokyo Hongo, Bunkyo-ku, Tokyo Tokyo, Japan
STUDY LOCATION:	Tokyo and Osaka, Japan
DATE INITIATED:	February 26, 1985
DATE COMPLETED:	In progress
STUDY POPULATION:	The population consists of 40 healthy adults (20 to 59 years of age) who are negative for hepatitis B virus serologic markers, have normal liver function tests and have not previously received any hepatitis B vaccine.
STUDY PROCEDURE:	Each participant receives a 10 mcg intramuscular injection of vaccine on day 0, 1 and 6 months. Study subjects are asked to record their temperatures and any local or systemic complaints for five days after each injection. Serum samples are obtained prior to vaccination, and at 1, 2, 3, 4, 5, 6, 7, 9 and 12 months post initial injection. All specimens are assayed for HBsAg, anti-HBs, anti-HBc and several other laboratory examinations by the (b) (4) Samples may also be assayed at (b) (4) for yeast antibody.

Study 882

RESULTS:

INITIALLY SERONEGATIVE HEALTHY ADULTS

10 mcg lot #819900/18066/C-L215 at 0, 1, and 6 months

1. Number Vaccinated:

Dose Level	Injection Number		
	1	2	3
10 mcg	40	40	40

2. Serologic Results:

When the cutoff was S/N $\geq$2.1, the anti-HBs seroconversion rate was 33% (13/40) one month after the first injection, and 100% (40/40) at 7 months. Table 1 lists antibody responses for up to nine months of follow-up.

3. Clinical Complaints:

Clinical follow-up data are available for 40 participants following each injection.

Type of Complaint	Dose Level	Frequency in % by Injection No.		
		1	2	3
Injection Site	10 mcg	10 (4/40)	13 (5/40)	10 (4/40)
Systemic	10 mcg	8 (3/40)	3 (1/40)	5 (2/40)

There have been serious or alarming adverse reactions attributable to vaccine reported.

Study 882

Table 1

Antibody Responses Among Healthy Male Adults Following Vaccination with 10 mcg Doses of Recombinant Vaccine Lot C-L215 at 0, 1, and 6 Months

RIA Cut-Off Index	Anti-HBs Response								
	Before	1 Mo.	2 Mos.	3 Mos.	4 Mos.	5 Mos.	6 Mos.	7 Mos.	9 Mos.
<2.1	40	27	12	8	4	4	4		
2.1-21		12	23	24	24	18	20	5	5
21-103		1	5	8	9	13	13	3	3
105-208					3	4	3	24	19
210-						1		8	12
Seroconversion %		32.5	70.0	80.0	90.0	90.0	90.0	100	100

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 883
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 81954I/18071/C-L220 (10 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Stanley Plotkin, M.D./Stuart Starr, M.D. Division of Preventive Medicine Joseph Stokes, Jr. Research Institute Children's Hospital of Philadelphia Philadelphia, Pennsylvania 19104
SECONDARY INVESTIGATOR:	Vernon Brightman, DMD, DDS Univ. of Pennsylvania School of Dental Medicine Philadelphia, Pennsylvania 19104
STUDY LOCATION:	University of Pennsylvania School of Dental Medicine 4001 Spruce Street Philadelphia, Pennsylvania 19104
DATE STUDY INITIATED:	November 13, 1984
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of approximately 50 healthy dental students of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 883

STUDY PROCEDURE:

Eligible study participants receive a 0.25 ml (5 mcg HBsAg) or 0.5 ml (10 mcg HBsAg) intramuscular injection of vaccine at 0, 1, and 6 months. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 2 weeks, 1, 2, 3, 6, 8, 12 and 24 months.

All serum samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested for anti-a and anti-d subtype specificity.

RESULTS:

HEALTH CARE PERSONNEL

5 mcg Lot 81954I/18071/C-L220 at 0, 1, and 6 months
10 mcg Lot 81954I/18071/C-L220 at 0, 1, and 6 months

1. Number Vaccinated:

Dose (mcg)	Injection No. 1	2	3
5	25	25	24
10	28	28	27

2. Serologic Results:

Serologic data at 7-8 months are available for 20 study participants who received a 5 mcg dose and 24 participants who received a 10 mcg dose of vaccine.

Study 883

RESULTS: (Cont.)

At 7-8 months, anti-HBs responses are as follows:

Dose (mcg)	% Anti-HBs Positive S/N ≥2.1	% Anti-HBs Positive mIU/ml ≥10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥2.1	GMT (mIU/ml) Responders mIU/ml ≥10
5	100(20/20)	95(19/20)	215.3	215.3	259.0
10	100(24/24)	96(23/24)	863.2	863.2	1084.9

3. Clinical Results:

Clinical follow-up data are available for 25 (5 mcg dose) and 28 (10 mcg dose) study participants following the first two injections and for 23 (5 mcg dose) and 27 (10 mcg dose) participants following the third injection of vaccine. Clinical complaints and maximum temperatures reported following each injection are provided in Tables 2-5. In summary:

Clinical Complaint	Dose (mcg)	% Frequency by Injection No. 1	2	3
Injection Site	5	4(1/25)	0(0/25)	4(1/23)
	10	7(2/28)	4(1/28)	4(1/27)
Systemic	5	28(7/25)	4(1/25)	13(3/23)
	10	29(8/28)	18(5/28)	15(4/27)

No serious or alarming adverse reactions attributable to vaccination have been reported.

ALT Elevations

Alanine aminotransferase levels were normal in all vaccine recipients except for elevations at 8 months in two participants. Case Nos. (b) (6) had ALT levels of 116 and 122, respectively, at 8 months. However, the serum sample obtained from Case No. (b) (6) was hemolyzed. Subsequent serum samples have not been obtained from this individual.

Study 883

ALT Elevations (Contd)

Case No. (b) (6) had a normal ALT level at 12 months. Neither individual has shown any clinical or serologic signs (HBsAg or anti-HBc) of hepatitis B.

HBV Markers (HBsAg)

One initially seronegative vaccine recipient (5 mcg dose) had a 6-month post-vaccination serum sample marginally positive for HBsAg (S/N = 2.4). The same serum sample was reported negative on retest (S/N $\leq$2.1). All other post-vaccination samples, including the sample obtained at 8 months, were negative for HBsAg. All serum samples were negative for anti-HBc. Alanine aminotransferase levels were normal. The subject developed anti-HBs at 3 months.

Events Reported to OoBRR

A (b) (6) developed persistent cough and tiredness. He was seen by a physician approximately 4 months after his second injection (10 mcg dose) of vaccine and was tentatively diagnosed as having chronic lymphatic leukemia. The illness is felt not to be related to the vaccine.

Table 1

Antibody Responses Among Initially Seronegative Health Care Personnel Following Vaccination with 5 or 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot 819541/18071/C-L220 at 0, 1, and 6 Months in Study 883

Time (Months)	5 mcg					10 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders				All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
2 weeks	13 (3/24)	4 (1/24)	0.5	5.4	10.4	4 (1/28)	4(1/28)	0.4	22.2	22.2
1	12 (3/25)	8 (2/25)	0.6	12.4	16.7	14 (4/28)	7 (2/28)	0.6	15.5	50.9
2	59 (13/22)	41 (9/22)	5.3	23.5	40.2	65 (17/26)	31 (8/26)	4.3	12.2	31.8
3	79 (19/24)	54 (13/24)	10.1	21.1	40.3	86 (24/28)	64 (18/28)	11.9	21.9	34.3
6	81 (17/21)	57 (12/21)	10.8	20.4	36.0	85 (22/26)	85 (22/26)	30.3	46.7	54.4
7/8	100 (20/20)	95 (19/20)	215.3	215.3	259.0	100 (24/24)	96 (23/24)	863.2	863.2	1084.9

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
SORENESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
SYSTEMIC	6 (24.0%)	4 (16.0%)	3 (12.0%)	3 (12.0%)	3 (12.0%)	2 (8.0%)	7 (28.0%)
WHOLE BODY/GENERAL	3 (12.0%)	2 (8.0%)	1 (4.0%)	2 (8.0%)	2 (8.0%)	1 (4.0%)	3 (12.0%)
CHILLS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
SWEATING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
FATIGUE/WEAKNESS	3 (12.0%)	2 (8.0%)	1 (4.0%)	2 (8.0%)	2 (8.0%)	1 (4.0%)	3 (12.0%)
LIGHTHEADED	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
ACHINESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
INTEGUMENTARY SYSTEM	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
PRURITIS/ITCHING	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
PIMPLE	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RESPIRATORY	2 (8.0%)	2 (8.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	3 (12.0%)
RHINITIS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
UPPER RESPIRATORY INFECT., NOS	2 (8.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	2 (8.0%)
COUGH	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
DIGESTIVE SYSTEM	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	2 (8.0%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)
NAUSEA	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
DIMINISHED APPETITE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
NERVOUS SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)
VERTIGO/DIZZINESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)
PERSONS WITH COMPLAINTS	7 (28.0%)	4 (16.0%)	3 (12.0%)	3 (12.0%)	3 (12.0%)	2 (8.0%)	8 (32.0%)
PERSONS WITH NO COMPLAINTS	18 (72.0%)	21 (84.0%)	22 (88.0%)	22 (88.0%)	22 (88.0%)	23 (92.0%)	17 (68.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
WHOLE BODY/GENERAL	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
HEADACHE	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
PERSONS WITH COMPLAINTS	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
PERSONS WITH NO COMPLAINTS	23 (95.8%)	24 (100.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	24 (96.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (24 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
SORENESS	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
SYSTEMIC	3 (13.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)		3 (13.0%)
WHOLE BODY/GENERAL	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
HEADACHE	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
RESPIRATORY	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
UPPER RESPIRATORY INFECT., NOS	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
DIGESTIVE SYSTEM	1 (4.3%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
NAUSEA	1 (4.3%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
PERSONS WITH COMPLAINTS	4 (17.4%)	0 (0.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)		4 (17.4%)
PERSONS WITH NO COMPLAINTS	19 (82.6%)	23 (100.0%)	23 (100.0%)	22 (95.7%)	23 (100.0%)	23 (100.0%)		19 (82.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (25 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	22 (88.0%)	20 (80.0%)	22 (88.0%)	22 (88.0%)	24 (96.0%)	24 (96.0%)		17 (68.0%)
99 - 99.9	3 (12.0%)	4 (16.0%)	3 (12.0%)	3 (12.0%)	1 (4.0%)	1 (4.0%)		7 (28.0%)
100 - 100.9	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
TEMPERATURE TAKEN	25 (100.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)		25 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (25 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	19 (82.6%)	22 (95.7%)	23 (95.8%)	24 (100.0%)	23 (95.8%)	23 (100.0%)		18 (75.0%)
99 - 99.9	4 (17.4%)	1 (4.3%)	1 (4.2%)	0 (0.0%)	1 (4.2%)	0 (0.0%)		6 (25.0%)
TEMPERATURE TAKEN	23 (92.0%)	23 (92.0%)	24 (96.0%)	24 (96.0%)	24 (96.0%)	23 (92.0%)		24 (96.0%)
TEMPERATURE NOT TAKEN	2 (8.0%)	2 (8.0%)	1 (4.0%)	1 (4.0%)	1 (4.0%)	2 (8.0%)		1 (4.0%)

00555

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0863
TREATMENT :
LOT NUMBER : CL220
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (24 PATIENTS) - DOSE 3 — DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
NORMAL	2 (8.7%)	2 (8.7%)	2 (8.7%)	2 (8.7%)	2 (8.7%)	2 (8.7%)			2 (8.7%)
< 99	19 (82.6%)	20 (87.0%)	21 (91.3%)	21 (91.3%)	19 (82.6%)	21 (91.3%)			18 (78.3%)
99 - 99.9	1 (4.3%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	2 (8.7%)	0 (0.0%)			2 (8.7%)
101 - 101.9	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (4.3%)
TEMPERATURE TAKEN	23 (95.8%)	23 (95.8%)	23 (95.8%)	23 (95.8%)	23 (95.8%)	23 (95.8%)			23 (95.8%)
TEMPERATURE NOT TAKEN	1 (4.2%)	1 (4.2%)	1 (4.2%)	1 (4.2%)	1 (4.2%)	1 (4.2%)			1 (4.2%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	2 (7.1%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (7.1%)
SORENESS	2 (7.1%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (7.1%)
SYSTEMIC	7 (25.0%)	2 (7.1%)	3 (10.7%)	0 (0.0%)	1 (3.6%)	0 (0.0%)		8 (28.6%)
WHOLE BODY/GENERAL	7 (25.0%)	1 (3.6%)	2 (7.1%)	0 (0.0%)	1 (3.6%)	0 (0.0%)		7 (25.0%)
FEVER (TEMP. NOT REPORTED)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.6%)
SWEATING	1 (3.6%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.6%)
SENSATION OF WARMTH, GENERAL	2 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (7.1%)
FATIGUE/WEAKNESS	3 (10.7%)	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (10.7%)
MALAISE	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.6%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)		1 (3.6%)
RESPIRATORY	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.6%)
UPPER RESPIRATORY INFECT., NOS	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.6%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0881
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
CARDIOVASCULAR	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
HYPOTENSION	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
NAUSEA	0 (0.0%)	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
DIMINISHED APPETITE	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
NERVOUS SYSTEM	3 (10.7%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (10.7%)
VERTIGO/DIZZINESS	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
THOUGHT IMPAIRMENT	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
TREMOR	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
CONJUNCTIVITIS	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
PERSONS WITH COMPLAINTS	7 (25.0%)	2 (7.1%)	3 (10.7%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	8 (28.6%)
PERSONS WITH NO COMPLAINTS	21 (75.0%)	26 (92.9%)	25 (89.3%)	28 (100.0%)	27 (96.4%)	28 (100.0%)	20 (71.4%)

00558

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
SORENESS	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
SYSTEMIC	2 (7.1%)	2 (7.1%)	1 (3.6%)	2 (7.1%)	1 (3.7%)	1 (3.7%)	5 (17.9%)
WHOLE BODY/GENERAL	2 (7.1%)	1 (3.6%)	1 (3.6%)	2 (7.1%)	1 (3.7%)	1 (3.7%)	4 (14.3%)
SWEATING	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
FATIGUE/WEAKNESS	1 (3.6%)	0 (0.0%)	0 (0.0%)	2 (7.1%)	1 (3.7%)	1 (3.7%)	4 (14.3%)
MALAISE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	1 (3.7%)	0 (0.0%)	1 (3.6%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
HOT AND COLD FLASHES	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
HOT FLASHES	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
RESPIRATORY	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	2 (7.1%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.6%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.6%)
CARDIOVASCULAR	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.6%)
PALLOR	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.6%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.6%)	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)		2 (7.1%)
NAUSEA	0 (0.0%)	1 (3.6%)	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)		2 (7.1%)
PERSONS WITH COMPLAINTS	3 (10.7%)	2 (7.1%)	1 (3.6%)	2 (7.1%)	1 (3.7%)	1 (3.7%)		5 (17.9%)
PERSONS WITH NO COMPLAINTS	25 (89.3%)	26 (92.9%)	27 (96.4%)	26 (92.9%)	26 (96.3%)	26 (96.3%)		23 (82.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (27 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
SORENESS	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
SYSTEMIC	4 (14.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	4 (14.8%)
WHOLE BODY/GENERAL	4 (14.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (14.8%)
FEVER (TEMP. NOT REPORTED)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
FATIGUE/WEAKNESS	3 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (11.1%)
ACHINESS	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
CARDIOVASCULAR	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
PALLOR	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)
PERSONS WITH COMPLAINTS	4 (14.8%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	4 (14.8%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (27 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH NO COMPLAINTS	23 (85.2%)	26 (96.3%)	27 (100.0%)	26 (96.3%)	27 (100.0%)	26 (96.3%)		23 (85.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00563

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0683
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (28 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	17 (60.7%)	27 (96.4%)	24 (85.7%)	26 (96.3%)	24 (88.9%)	22 (81.5%)			15 (53.6%)
99 - 99.9	11 (39.3%)	1 (3.6%)	4 (14.3%)	1 (3.7%)	3 (11.1%)	5 (18.5%)			13 (46.4%)
TEMPERATURE TAKEN	28 (100.0%)	28 (100.0%)	28 (100.0%)	27 (96.4%)	27 (96.4%)	27 (96.4%)			28 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	1 (3.6%)	1 (3.6%)			0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (28 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	24 (85.7%)	27 (96.4%)	27 (96.4%)	26 (92.9%)	26 (96.3%)	25 (92.6%)			21 (75.0%)
99 - 99.9	4 (14.3%)	1 (3.6%)	1 (3.6%)	2 (7.1%)	1 (3.7%)	2 (7.4%)			7 (25.0%)
TEMPERATURE TAKEN	28 (100.0%)	28 (100.0%)	28 (100.0%)	28 (100.0%)	27 (96.4%)	27 (96.4%)			28 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	1 (3.6%)			0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0883
TREATMENT :
LOT NUMBER : CL220
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (27 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
< 99	19 (76.0%)	23 (85.2%)	25 (92.6%)	26 (96.3%)	25 (92.6%)	24 (88.9%)		18 (66.7%)
99 - 99.9	6 (24.0%)	4 (14.8%)	2 (7.4%)	1 (3.7%)	2 (7.4%)	3 (11.1%)		9 (33.3%)
TEMPERATURE TAKEN	25 (92.6%)	27 (100.0%)	27 (100.0%)	27 (100.0%)	27 (100.0%)	27 (100.0%)		27 (100.0%)
TEMPERATURE NOT TAKEN	2 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

STUDY 885

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 885
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among healthy adults who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 81990D/18066/C-L215 81766B/18067/C-L216 81991D/18068/C-L217 81992A/18070/C-L219 81954I/18071/C-L220
PRIMARY INVESTIGATOR:	Alan I. Leibowitz, M.D. Associate Professor of Medicine University of South Florida School of Medicine Tampa, Florida 33612
SECONDARY INVESTIGATOR:	John T. Sinnott, M.D. Ben G. Yango, M.D. University of South Florida School of Medicine Tampa, Florida, 33612
STUDY LOCATION:	University of South Florida Medical Center Tampa, Florida 33612 Affiliated hospitals and other area health facilities.
DATE INITIATED:	July, 1985
DATE COMPLETED:	In progress.
STUDY POPULATION:	The study population will consist of approximately 250 healthy adults of either sex (excluding pregnant women), who are negative for hepatitis B virus serologic markers, have normal liver function tests and have not prebiously received any hepatitis B vaccine.

Study 885

PROCEDURE:

Participants are assigned to one of five lots of vaccine, stratified by sex and age (50 persons per lot). All study subjects receive a 10 mcg dose intramuscular injection of vaccine at 0, 1 and 6 months. Participants are asked to record their temperatures and any local or systemic complaints for five days after each injection.

Blood samples are obtained prior to vaccination and at 1, 2, 3, 6, 8, 12 and 24 months post initial injection. All specimens are assayed for HBsAg, anti-HBs, and anti-HBc by MSDRL. ALT levels will be tested pre-vaccination and at two and eight months post initial injection at the University of South Florida. Samples with an anti-HBs titer ≥25 mIU/ml may be tested for anti-a and anti-d activity. Samples may also be assayed for yeast antibody at MSDRL.

RESULTS:

HEALTHY ADULTS

10 mcg Lot 81990D/18066/C-L215 at 0, 1, and 6 months
10 mcg Lot 81766B/18067/C-L216 at 0, 1, and 6 months
10 mcg Lot 81991D/18068/C-L217 at 0, 1, and 6 months
10 mcg Lot 81992A/18070/C-L219 at 0, 1, and 6 months
10 mcg Lot 81954I/18071/C-L220 at 0, 1, and 6 months

1. Number Vaccinated:

Lot	Injection No. 1	2	3
81990D/18066/C-L215	0	0	0
81766B/18067/C-L216	0	0	0
81991D/18068/C-L217	50	0	0
81992A/18070/C-L219	50	50	0
81954I/18071/C-L220	50	50	0

2. Serologic Results:

No serologic results are currently available.

3. Clinical Complaints:

There have been no serious or alarming adverse reactions attributable to vaccine.

STUDY 889

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 889
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among: 1. Mentally retarded individuals who are negative for hepatitis B virus serologic markers. 2. Health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 993/C-K937 (20 mcg/HBsAg/ml)
PRIMARY INVESTIGATOR:	Robert P. Perrillo, M.D. Director, Gastroenterology Veterans Administration Medical Center St. Louis, Missouri 63125
SECONDARY INVESTIGATOR:	Oliver H. Lowry, M.D. Department of Pharmacology Washington Univ. School of Medicine St. Louis, Missouri 63110
STUDY LOCATION:	Beverly Farms Foundation Godfrey, Illinois 62035 Veterans Administration Medical Center St. Louis, Missouri 63125
DATE STUDY INITIATED:	June 19, 1985
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of approximately 250 mentally retarded individuals, above 5 years of age, and 50 health care personnel, who are negative for HBsAg, anti-HBc, anti-HBs, have a normal ALT and have not previously received any hepatitis B vaccine.

Study 889

STUDY PROCEDURE:

Mentally retarded individuals are randomly assigned to one of two groups, stratified by sex and age. Health care personnel constitute a third group.

Mentally retarded individuals receive a 0.5 ml (10 mcg HBsAg) or a 1.0 ml (20 mcg HBsAg) intramuscular injection of vaccine at 0, 1, and 6 months. Health care personnel receive a 0.5 ml (10 mcg HBsAg) intramuscular injection of vaccine according to the same regimen.

The temperature of each vaccine recipient and any local or systemic complaints are recorded for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 3, 6, 10 and 24 months.

All serum samples are assayed for HBsAg, anti-HBc and anti-HBs. The pre-vaccination and 3 month post-vaccination samples are also tested for ALT. Samples may be assayed for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested for anti-a and anti-d subtype specificity.

RESULTS:

HEALTH CARE PERSONNEL

10 mcg Lot 993/C-K937 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
88	82	74

One person with an initial ALT level approximately 1.5 times normal (69) received vaccine. A post-vaccination ALT level is not yet available. Three month post-vaccination samples will be tested for ALT.

Study 889

RESULTS: (Contd)

2. Serologic Results:

Serologic data at 1 month are available for 82 health care personnel.

At 1 month 17% (14/82) of vaccine recipients seroconverted (S/N ≥2.1) and 6% (5/82) developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees was 0.5 mIU/ml at that time. Among responders with a titer of S/N ≥2.1, the GMT at 1 month was 6.3 mIU/ml, while for responders with a titer of mIU/ml ≥10 the GMT was 25 mIU/ml.

3. Clinical Results:

Clinical follow-up data are available for 82 health care personnel following two injections of vaccine. Clinical complaints and maximum temperatures reported following each injection are provided in Tables 1 and 2. In summary:

Clinical Complaint	% Frequency by Injection No. 1	2	3
Injection Site	1 (1/82)	0 (0/82)	NA
Systemic	5 (4/82)	6 (5/82)	NA

No serious or alarming adverse reactions attributable to vaccination have been reported.

Events Reported to OoBRR

A 37 year-old female noted facial warmth and flushing 14 hours after receiving the first injection of vaccine. Within the next 3 hours she developed facial urticaria. She was treated with cold packs. All symptoms subsided within 12 hours. The subject was treated with Benadryl prior to the second and third injections, and had no post-vaccination reactions.

Table 1

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (82 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
SORENESS	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
SYSTEMIC	1 (1.2%)	2 (2.4%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (4.9%)
WHOLE BODY/GENERAL	0 (0.0%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
FLUSH	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
HEADACHE	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
ITCHING, FACIAL	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
URTICARIA, FACIAL	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
DIGESTIVE SYSTEM	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
NAUSEA	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
VOMITING	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
NERVOUS SYSTEM	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (82 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PARESTHESIAS	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
PERSONS WITH COMPLAINTS	1 (1.2%)	3 (3.7%)	2 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (6.1%)
PERSONS WITH NO COMPLAINTS	81 (98.8%)	79 (96.3%)	80 (97.6%)	82 (100.0%)	82 (100.0%)	82 (100.0%)		77 (93.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00573

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0689
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (82 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	2 (2.4%)	2 (2.4%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	5 (6.1%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	2 (2.4%)
HEADACHE	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	2 (2.4%)
INTEGUMENTARY SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
PRURITIS/ITCHING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
TONSILLITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
NAUSEA	0 (0.0%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
VOMITING	0 (0.0%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
PERSONS WITH COMPLAINTS	0 (0.0%)	2 (2.4%)	2 (2.4%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	5 (6.1%)
PERSONS WITH NO COMPLAINTS	82 (100.0%)	80 (97.6%)	80 (97.6%)	81 (98.8%)	80 (97.6%)	81 (98.8%)	77 (93.9%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (82 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER
CLINICAL COMPLAINTS	0	1	2	3	4	5	WITH COMPLAINTS
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (82 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	70 (87.5%)	67 (84.8%)	60 (80.0%)	68 (88.3%)	68 (89.5%)	69 (89.6%)			50 (61.7%)
99 - 99.9	7 (8.7%)	11 (13.9%)	12 (16.0%)	9 (11.7%)	7 (9.2%)	8 (10.4%)			25 (30.9%)
100 - 100.9	2 (2.5%)	1 (1.3%)	3 (4.0%)	0 (0.0%)	1 (1.3%)	0 (0.0%)			5 (6.2%)
101 - 101.9	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (1.2%)
TEMPERATURE TAKEN	80 (97.6%)	79 (96.3%)	75 (91.5%)	77 (93.9%)	76 (92.7%)	77 (93.9%)			81 (98.8%)
TEMPERATURE NOT TAKEN	2 (2.4%)	3 (3.7%)	7 (8.5%)	5 (6.1%)	6 (7.3%)	5 (6.1%)			1 (1.2%)

Table 2 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0689
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (82 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	69 (84.1%)	70 (85.4%)	76 (92.7%)	76 (92.7%)	73 (90.1%)	76 (92.7%)			61 (74.4%)
99 - 99.9	12 (14.6%)	9 (11.0%)	4 (4.9%)	4 (4.9%)	8 (9.9%)	6 (7.3%)			17 (20.7%)
100 - 100.9	1 (1.2%)	3 (3.7%)	2 (2.4%)	2 (2.4%)	0 (0.0%)	0 (0.0%)			4 (4.9%)
TEMPERATURE TAKEN	82 (100.0%)	82 (100.0%)	82 (100.0%)	82 (100.0%)	81 (98.8%)	82 (100.0%)			82 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)			0 (0.0%)

00577

STUDY 891

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 891
PURPOSE:	To compare the antibody and clinical responses to recombinant hepatitis B vaccine and plasma-derived hepatitis B vaccine among healthy adults and children who are negative for hepatitis B virus serologic markers.
VACCINES:	1. Yeast Recombinant Hepatitis B Vaccine Lot 979/C-K564 (10 mcg HBsAg/ml) 2. Plasma-Derived Hepatitis B Vaccine Lot 0027L (20 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Dr. Hu Zong-Han Department of Biological Products Inspection Bureau of Pharmaceutical and Biological Inspection Ministry of Health Temple of Heaven, West Gate Beijing, People's Republic of China
SECONDARY INVESTIGATOR:	Dr. Shi Guiyong Director of Epidemic Department Chinese Medical University Shen Yang, People's Republic of China
STUDY LOCATION:	Shen Yang Municipal Anti-Epidemic Station Shen Yang, People's Republic of China
DATE STUDY INITIATED:	December, 1985
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 200 healthy adults and 200 healthy children of either sex (exluding pregnant women), who are negative for HBsAg, anti-HBc and HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 891

STUDY PROCEDURE: Participants are grouped by age and randomly assigned to receive the yeast recombinant or plasma-derived hepatitis B vaccine as follows:

Group	Population	Vaccine	Dose	Number	Regimen
1	Adults (≥30 years)	Recombinant	10 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
2	Adults (18-29 years)		10 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
3	Children (5-10 years)		5 mcg	100	0.5 ml intramuscular injection of vaccine at 0, 1, and 6 months
4	Adults (≥30 years)	Plasma	20 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
5	Adults (18-29 years)		20 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
6	Children (5-10 years)		10 mcg	100	0.5 ml intramuscular injection of vaccine at 0, 1, and 6 months

Study participants or the participant's parent or guardian record their temperature or that of their child, and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two to three weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 3, 6, 7, 8, 9, 12, and 24 months. All serum samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT.

Study 891

RESULTS: (Contd) To date 100 adults and children have received one injection of yeast recombinant or plasma-derived hepatitis B vaccine. No serious or alarming reactions attributable to vaccination have been reported. Clinical follow-up data and serologic results are not yet available. The study continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 894
PURPOSE:	To compare immunologic responses to yeast recombinant versus plasma hepatitis B vaccine in homosexual males and to compare differences, if any, in adverse reactions to the two vaccines.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 978/C-K563 Plasma-Derived Hepatitis B Vaccine (HEPTAVAX) Lot 1014/C-M252
PRIMARY INVESTIGATOR:	B. Frank Polk, M.D. Director, Infectious Disease Epidemiology Program Johns Hopkins Univ. School of Hygiene & Public Health Baltimore, MD
SECONDARY INVESTIGATORS:	Lois Eldred, P.A. Robin Fox, M.S. Edward Fuchs, P.A. Richard Kaslow, M.D. Nancy Odaka, M.H.S. Rachel Solomon, M.H.S.
STUDY LOCATION:	The Johns Hopkins Hospital Baltimore, MD
DATE INITIATED:	April, 1985
DATE COMPLETED:	In progress.
STUDY POPULATION:	The study population consists of 300-350 homosexual males who are negative for all hepatitis B markers and have not received any hepatitis B vaccine. The men are concurrently enrolled in a study to help the AIDS research effort (SHARE) at the Johns Hopkins University Hospital.

Study 894

PROCEDURE:

Eligible participants are randomized to receive an injection of either 20 mcg plasma or 10 mcg recombinant vaccine at 0, 1 and 6 months. Participants are asked to record their temperatures for 5 days after each injection and to note any local or systemic complaints.

Bloof specimens are obtained prior to vaccination and at 1, 6, 9 and 12 months post initial injection. After the first year of follow-up, serum samples are collected every 6 months for another two years. Baseline serum samples are assayed for HBsAg, anti-HBs and ALT. Follow-up serum samples are tested for development of anti-HBs antibodies.

RESULTS:

HOMOSEXUAL MALES:

10 mcg Lot 978/C-K563 yeast recombinant at 0, 1 and 6 months
20 mcg Lot 1014/C-M252 plasma at 0, 1 and 6 months

1. Number Vaccinated:

Vaccine	Injection No. 1	2	3
Yeast Recombinant	87	63	1
Plasma	88	70	0

2. Serologic Results:

No serological results are presently available.

Study 894

RESULTS: (Contd)

3. Clinical Complaints:

Clinical follow-up data are available for 83, 60, and 1 participants following injections one, two, and three of yeast recombinant vaccine, and for 88 and 67 participants following injections one and two of plasma vaccine. Specific complaints and maximum temperatures reported during the 5 days following each injection are provided in Tables 1 through 4.

There have been no serious or alarming adverse reactions attributable to either vaccine to date.

Type	Vaccine	Frequency in % by Injection No. 1	2	3
Injection Site	Recombinant	30(25/83)	35(21/60)	0(0/1)
	Plasma	42(37/88)	36(24/67)	
Systemic	Recombinant	29(24/83)	18(11/60)	0(0/1)
	Plasma	35(31/88)	25(17/67)	

Table 1

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (87 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	15 (16.5%)	14 (16.9%)	8 (9.6%)	4 (4.9%)	2 (2.5%)	0 (0.0%)	25 (30.1%)
SORENESS	14 (17.3%)	14 (16.9%)	8 (9.6%)	4 (4.9%)	1 (1.2%)	0 (0.0%)	23 (27.7%)
STIFFNESS/TIGHTNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
HEMATOMA	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
SYSTEMIC	9 (11.1%)	11 (13.3%)	13 (15.7%)	11 (13.4%)	3 (3.7%)	4 (4.9%)	24 (28.9%)
WHOLE BODY/GENERAL	2 (2.5%)	5 (6.0%)	4 (4.8%)	2 (2.4%)	1 (1.2%)	2 (2.5%)	10 (12.0%)
CHILLS	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
FATIGUE/WEAKNESS	0 (0.0%)	5 (6.0%)	2 (2.4%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	6 (7.2%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	1 (1.2%)	2 (2.4%)
CHEST PAIN	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
LIGHTHEADED	2 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
INTEGUMENTARY SYSTEM	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	2 (2.4%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (87 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
RASH, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
OTHER	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
RESPIRATORY	1 (1.2%)	1 (1.2%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	1 (1.2%)		2 (2.4%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
UPPER RESPIRATORY INFECT., NOS	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)		1 (1.2%)
HEMIC AND LYMPHATIC	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)		1 (1.2%)
LYMPHADENOPATHY, GENERAL	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)		1 (1.2%)
MUSCULOSKELETAL	4 (4.9%)	3 (3.6%)	6 (7.2%)	4 (4.9%)	1 (1.2%)	0 (0.0%)		8 (9.6%)
ARTHRALGIA, MONOARTICULAR	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
ARTHRALGIA (OTHER)	2 (2.5%)	2 (2.4%)	4 (4.8%)	1 (1.2%)	1 (1.2%)	0 (0.0%)		5 (6.0%)
MYOSITIS	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
MYALGIA	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
MUSCLE STIFFNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (87 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
SORE CHEST	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
DIGESTIVE SYSTEM	1 (1.2%)	2 (2.4%)	2 (2.4%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		6 (7.2%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
NAUSEA	1 (1.2%)	2 (2.4%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		4 (4.8%)
VOMITING	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
OTHER	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
UROGENITAL SYSTEM	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
KIDNEY PAIN	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
PERSONS WITH COMPLAINTS	21 (25.9%)	23 (27.7%)	19 (22.9%)	13 (15.9%)	5 (6.2%)	4 (4.9%)		42 (50.6%)
PERSONS WITH NO COMPLAINTS	60 (74.1%)	60 (72.3%)	64 (77.1%)	69 (84.1%)	76 (93.8%)	77 (95.1%)		41 (49.4%)
PERSONS WITH NO DATA	5 (5.8%)	4 (4.6%)	4 (4.6%)	5 (5.7%)	5 (5.8%)	5 (5.8%)		4 (4.6%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (63 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	16 (26.7%)	11 (18.3%)	5 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (35.0%)
SORENESS	16 (26.7%)	11 (18.3%)	5 (8.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (35.0%)
SYSTEMIC	5 (8.3%)	4 (6.7%)	6 (10.2%)	6 (10.2%)	5 (8.3%)	3 (5.1%)	11 (18.3%)
WHOLE BODY/GENERAL	2 (3.3%)	3 (5.0%)	3 (5.1%)	4 (6.8%)	2 (3.3%)	1 (1.7%)	5 (8.3%)
FATIGUE/WEAKNESS	1 (1.7%)	2 (3.3%)	2 (3.4%)	3 (5.1%)	2 (3.3%)	1 (1.7%)	3 (5.0%)
CHEST PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
LIGHTHEADED	1 (1.7%)	1 (1.7%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (1.7%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
OTHER	0 (0.0%)	1 (1.7%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	1 (1.7%)
MUSCULOSKELETAL	1 (1.7%)	1 (1.7%)	1 (1.7%)	1 (1.7%)	2 (3.3%)	1 (1.7%)	3 (5.0%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (63 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
ARTHRALGIA, MONOARTICULAR	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.7%)
ARTHRALGIA (OTHER)	0 (0.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)	2 (3.3%)	1 (1.7%)		2 (3.3%)
DIGESTIVE SYSTEM	2 (3.3%)	0 (0.0%)	1 (1.7%)	2 (3.4%)	2 (3.3%)	1 (1.7%)		4 (6.7%)
DIARRHEA	2 (3.3%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)		3 (5.0%)
NAUSEA	1 (1.7%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)	1 (1.7%)		2 (3.3%)
VOMITING	1 (1.7%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	1 (1.7%)	1 (1.7%)		2 (3.3%)
ABDOMEN DISTENDED	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	0 (0.0%)		1 (1.7%)
UROGENITAL SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	0 (0.0%)		1 (1.7%)
KIDNEY PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	0 (0.0%)		1 (1.7%)
PSYCHIATRIC/BEHAVIORAL	1 (1.7%)	1 (1.7%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.7%)
DREAMS, BIZARRE, UNUSUAL	1 (1.7%)	1 (1.7%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.7%)
PERSONS WITH COMPLAINTS	20 (33.3%)	15 (25.0%)	11 (18.6%)	6 (10.2%)	5 (8.3%)	3 (5.1%)		28 (46.7%)
PERSONS WITH NO COMPLAINTS	40 (66.7%)	45 (75.0%)	48 (81.4%)	53 (89.8%)	55 (91.7%)	56 (94.9%)		32 (53.3%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CY563
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (63 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH NO DATA	2 (3.2%)	2 (3.2%)	2 (3.3%)	2 (3.3%)	2 (3.2%)	2 (3.3%)		2 (3.2%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (1 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)		1 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2

PATIENT COUNT MAXIMUM TEMPERATURES

STUDY : 0894
TREATMENT :
LOT NUMBER : CK563
DOSE :
10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (87 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	2 (2.6%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.3%)			2 (2.4%)
< 99	64 (83.1%)	73 (91.2%)	76 (92.7%)	75 (93.8%)	74 (92.5%)	70 (90.9%)			61 (73.5%)
99 - 99.9	11 (14.3%)	4 (5.0%)	4 (4.9%)	4 (5.0%)	4 (5.0%)	5 (6.5%)			16 (19.3%)
100 - 100.9	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	1 (1.2%)	1 (1.3%)			3 (3.6%)
101 - 101.9	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (1.2%)
TEMPERATURE TAKEN	77 (88.5%)	80 (92.0%)	82 (94.3%)	80 (92.0%)	80 (92.0%)	77 (88.5%)			83 (95.4%)
TEMPERATURE NOT TAKEN	10 (11.5%)	7 (8.0%)	5 (5.7%)	7 (8.0%)	7 (8.0%)	10 (11.5%)			4 (4.6%)

Table 2 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES

STUDY : 0894
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (63 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	3 (5.3%)	3 (5.3%)	3 (5.4%)	3 (5.4%)	3 (5.4%)	3 (5.5%)			3 (5.3%)
< 99	44 (77.2%)	49 (86.0%)	49 (87.5%)	44 (78.6%)	45 (80.4%)	46 (83.6%)			35 (61.4%)
99 - 99.9	9 (15.8%)	4 (7.0%)	2 (3.6%)	6 (10.7%)	8 (14.3%)	5 (9.1%)			15 (26.3%)
100 - 100.9	1 (1.8%)	1 (1.8%)	2 (3.6%)	3 (5.4%)	0 (0.0%)	1 (1.8%)			4 (7.0%)
TEMPERATURE TAKEN	57 (90.5%)	57 (90.5%)	56 (88.9%)	56 (88.9%)	56 (88.9%)	55 (87.3%)			57 (90.5%)
TEMPERATURE NOT TAKEN	6 (9.5%)	6 (9.5%)	7 (11.1%)	7 (11.1%)	7 (11.1%)	8 (12.7%)			6 (9.5%)

Table 2 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES

STUDY : 0694
TREATMENT :
LOT NUMBER : CK563
DOSE : 10 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (1 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)			0 (0.0%)
< 99	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (100.0%)
TEMPERATURE TAKEN	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)			1 (100.0%)
TEMPERATURE NOT TAKEN	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 3

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CH252
DOSE : 20 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (88 PATIENTS) - DOSE 1 DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	23 (27.4%)	17 (19.3%)	9 (10.3%)	4 (4.7%)	1 (1.1%)	1 (1.2%)	37 (42.0%)
SORENESS	23 (27.4%)	17 (19.3%)	9 (10.3%)	4 (4.7%)	1 (1.1%)	1 (1.2%)	37 (42.0%)
SYSTEMIC	12 (14.3%)	22 (25.0%)	15 (17.2%)	9 (10.5%)	7 (8.0%)	7 (8.1%)	31 (35.2%)
WHOLE BODY/GENERAL	9 (10.7%)	15 (17.0%)	7 (8.0%)	7 (8.1%)	6 (6.9%)	4 (4.7%)	24 (27.3%)
CHILLS	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	2 (2.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
FATIGUE/WEAKNESS	7 (8.3%)	10 (11.4%)	5 (5.7%)	5 (5.8%)	4 (4.6%)	3 (3.5%)	16 (18.2%)
HEADACHE	3 (3.6%)	4 (4.5%)	2 (2.3%)	2 (2.3%)	2 (2.3%)	1 (1.2%)	9 (10.2%)
LIGHTHEADED	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
PAIN	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
HERPES LABIALIS, RECURRENT	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CM252
DOSE : 20 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (88 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
INTEGUMENTARY SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.1%)
RASH, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.1%)
MUSCULOSKELETAL	2 (2.4%)	6 (6.8%)	4 (4.6%)	4 (4.7%)	2 (2.3%)	3 (3.5%)	9 (10.2%)
ARTHRALGIA (OTHER)	1 (1.2%)	5 (5.7%)	3 (3.4%)	3 (3.5%)	1 (1.1%)	2 (2.3%)	8 (9.1%)
MYOSITIS	1 (1.2%)	1 (1.1%)	1 (1.1%)	1 (1.2%)	1 (1.1%)	1 (1.2%)	1 (1.1%)
DIGESTIVE SYSTEM	1 (1.2%)	5 (5.7%)	6 (6.9%)	2 (2.3%)	0 (0.0%)	1 (1.2%)	10 (11.4%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
DIARRHEA	0 (0.0%)	3 (3.4%)	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.4%)
NAUSEA	1 (1.2%)	2 (2.3%)	3 (3.4%)	2 (2.3%)	0 (0.0%)	1 (1.2%)	6 (6.8%)
VOMITING	0 (0.0%)	1 (1.1%)	2 (2.3%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
OTHER	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
PSYCHIATRIC/BEHAVIORAL	2 (2.4%)	1 (1.1%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	2 (2.3%)
EMOTIONAL LABILITY	1 (1.2%)	1 (1.1%)	1 (1.1%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.1%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CM252
DOSE : 20 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (88 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
IRRITABILITY	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
PERSONS WITH COMPLAINTS	31 (36.9%)	33 (37.5%)	21 (24.1%)	12 (14.0%)	8 (9.2%)	8 (9.3%)		54 (61.4%)
PERSONS WITH NO COMPLAINTS	53 (63.1%)	55 (62.5%)	66 (75.9%)	74 (86.0%)	79 (90.8%)	78 (90.7%)		34 (38.6%)
PERSONS WITH NO DATA	1 (1.2%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	1 (1.1%)	2 (2.3%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 8894
TREATMENT :
LOT NUMBER : CM252
DOSE : 20 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (70 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	20 (30.3%)	13 (19.4%)	3 (4.5%)	2 (3.0%)	1 (1.5%)	0 (0.0%)	24 (35.8%)
SORENESS	20 (30.3%)	13 (19.4%)	3 (4.5%)	2 (3.0%)	0 (0.0%)	0 (0.0%)	23 (34.3%)
HEMATOMA	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	2 (3.0%)
SYSTEMIC	7 (10.6%)	10 (14.9%)	6 (9.1%)	7 (10.4%)	6 (9.1%)	6 (9.1%)	17 (25.4%)
WHOLE BODY/GENERAL	3 (4.5%)	5 (7.5%)	5 (7.6%)	5 (7.5%)	4 (6.1%)	4 (6.1%)	10 (14.9%)
FATIGUE/WEAKNESS	2 (3.0%)	5 (7.5%)	5 (7.6%)	5 (7.5%)	4 (6.1%)	4 (6.1%)	9 (13.4%)
HEADACHE	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
INFECTIOUS SYNDROMES	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
HERPES GENITALIS, RECURRENT	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)
INTEGUMENTARY SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.5%)	1 (1.5%)
RASH, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.5%)	1 (1.5%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (1.5%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS

STUDY : 0894
TREATMENT :
LOT NUMBER : CM252
DOSE : 20 MCG

CLINICAL COMPLAINTS	TOTAL VACCINEES (70 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (1.5%)	0 (0.0%)	0 (0.0%)		1 (1.5%)
MUSCULOSKELETAL	2 (3.0%)	2 (3.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)		4 (6.0%)
ARTHRALGIA, MONOARTICULAR	1 (1.5%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.5%)
ARTHRALGIA (OTHER)	1 (1.5%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.0%)
MYALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)		1 (1.5%)
DIGESTIVE SYSTEM	2 (3.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (4.5%)
NAUSEA	2 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.0%)
LOOSE STOOL	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.5%)
PSYCHIATRIC/BEHAVIORAL	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)		1 (1.5%)
INSOMNIA/DISTURBED SLEEP	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)		1 (1.5%)
PERSONS WITH COMPLAINTS	23 (34.8%)	21 (31.3%)	9 (13.6%)	9 (13.4%)	7 (10.6%)	6 (9.1%)		34 (50.7%)
PERSONS WITH NO COMPLAINTS	43 (65.2%)	46 (68.7%)	57 (86.4%)	58 (86.6%)	59 (89.4%)	60 (90.9%)		33 (49.3%)
PERSONS WITH NO DATA	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)	1 (1.5%)		1 (1.5%)

Table 4

PATIENT COUNT MAXIMUM TEMPERATURES

STUDY : 0896
TREATMENT :
LOT NUMBER : CM252
DOSE : 20 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (80 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (1.3%)	3 (3.6%)	3 (3.7%)	4 (5.0%)	4 (4.9%)	4 (5.0%)			2 (2.4%)
< 99	62 (80.5%)	70 (84.3%)	67 (81.7%)	66 (82.5%)	70 (86.4%)	70 (87.5%)			56 (66.7%)
99 - 99.9	14 (18.2%)	10 (12.0%)	11 (13.4%)	9 (11.2%)	6 (7.4%)	4 (5.0%)			24 (28.6%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	2 (2.5%)			2 (2.4%)
TEMPERATURE TAKEN	77 (87.5%)	83 (94.3%)	82 (93.2%)	80 (90.9%)	81 (92.0%)	80 (90.9%)			84 (95.5%)
TEMPERATURE NOT TAKEN	11 (12.5%)	5 (5.7%)	6 (6.8%)	8 (9.1%)	7 (8.0%)	8 (9.1%)			4 (4.5%)

Table 4 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES

STUDY : 0894
TREATMENT :
LOT NUMBER : CH252
DOSE :
20 MCG

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (70 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	3 (4.8%)	4 (6.2%)	3 (4.6%)	4 (6.3%)	4 (6.3%)	4 (6.3%)			2 (3.0%)
< 99	54 (87.1%)	57 (87.7%)	57 (87.7%)	56 (87.5%)	56 (87.5%)	55 (85.9%)			52 (77.6%)
99 - 99.9	5 (8.1%)	4 (6.2%)	5 (7.7%)	4 (6.3%)	4 (6.3%)	5 (7.8%)			13 (19.4%)
TEMPERATURE TAKEN	62 (88.6%)	65 (92.9%)	65 (92.9%)	64 (91.4%)	64 (91.4%)	64 (91.4%)			67 (95.7%)
TEMPERATURE NOT TAKEN	8 (11.4%)	5 (7.1%)	5 (7.1%)	6 (8.6%)	6 (8.6%)	6 (8.6%)			3 (4.3%)

00600

PROTOCOL:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 898.
PURPOSE:	To evaluate antibody and clinical responses of initially seronegative healthy adults to 10 and 20 mcg injections of yeast recombinant hepatitis B vaccine.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #85860/22123/C-M125 (20 mcg HBsAg/ml) Lot #85861/22124/C-M126 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Robert Bishop, M.D. Health Services WP38-4 Merck Sharp and Dohme West Point, PA 19486
SECONDARY INVESTIGATOR:	E. P. Avencena, M.D. Health Services WP38-4 Merck Sharp and Dohme West Point, PA 19486
STUDY LOCATION:	Merck Sharp and Dohme West Point, PA 19486
DATE INITIATED:	November 18, 1985
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population will consist of approximately 40 employees of Merck & Co., Inc. of either sex (excluding pregnant women) who are 40 years of age or older, are negative for HBsAg, anti-HBc, and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

STUDY PROCEDURE

Eligible participants receive a 1.0 ml (10 mcg or 20 mcg HBsAg) intramuscular injection of vaccine in the deltoid muscle on day 0, and at 1 and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of the vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) is obtained from each participant 1-2 weeks before the first injection of vaccine is given. Post-vaccination blood samples are taken at 1, 2, 3, 6, and 8 months following the first injection from all vaccine recipients and at 12 and 24 months from those who develop antibody by 8 months. All samples will be tested for HBsAg, anti-HBc, and anti-HBs. The prevaccination sample and the two month post-vaccination sample will also be tested for ALT.

Subjects who fail to develop antibody following three injections of vaccine and those who have a transient antibody response that becomes negative by 12 months after the first injection may receive a fourth injection of vaccine. An additional blood sample will be taken one month after the fourth injection of vaccine.

RESULTS:

One person has received a single 10 mcg injection of vaccine, while two persons have received single 20 mcg injections of vaccine. None had any complaints. Post-vaccination serologic results are not yet available.

STUDY 900

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 900.
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among healthy male homosexuals who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #85861/22124/CM126 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATORS:	Arie J. Zuckerman, M.D. Professor of Microbiology Director, Department of Medical Microbiology London School of Hygiene and Tropical Medicine Keppel Street London WC1E 7HT United Kingdom Iain Murray-Lyon, M.D. Consultant Physician Charing Cross Hospital London W.6. United Kingdom
SECONDARY INVESTIGATORS:	Dr. John Coleman Charing Cross Hospital London W.6. United Kingdom Dr. Michael Anderson Charing Cross Hospital London W.6. United Kingdom
STUDY LOCATION:	Charing Cross Hospital London W.6. United Kingdom
DATE INITIATED:	August 1985.
DATE COMPLETED:	In progress.
STUDY POPULATION:	The study population will consist of approximately 200 healthy male homosexuals who are negative for HBsAg, anti-HBc and anti-HBs, and have not previously received any hepatitis B vaccine.

Study 900

PROCEDURE:

Prior to enrollment in the study, all prospective participants will receive a full medical examination. Any evidence of possible immune deficiency will eliminate a candidate from receiving vaccine. A blood sample will also be obtained prior to vaccination and assayed for hepatitis B serologic markers and for antibodies to HTLV III.

Eligible participants will receive a 1.0 ml injection of vaccine in the deltoid muscle at 0, 1, and 6 months. Study participants will be asked to take and record their temperatures for five days after each injection of vaccine and to record any local or systemic complaints that they may have. They will be asked to notify the study physician immediately if any unexpected or serious reaction occurs.

Follow-up blood samples will be obtained at 1, 2, 3, 6, 8, 12, and 24 months following the first injection of vaccine. All samples will be assayed for HBsAg, anti-HBc and anti-HBs. The 12 and 24 month samples will also be tested for antibodies to HTLV III. Assays will be performed in Dr. Zuckerman's laboratory. In addition, samples may be assayed for yeast antibodies and anti-HBs subtype specificity by MSDRL.

Subjects who fail to develop anti-HBs following three doses of vaccine (nonresponders) and those who have a transient antibody response (transient responders) that becomes negative by 12 months after the first dose, may receive a fourth injection of vaccine. An additional blood sample will be taken one month after the fourth dose.

A complete physical examination will be repeated at 6, 12, and 24 months.

RESULTS:

Serologic and clinical follow-up data are not currently available. No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 904
PURPOSE:	To evaluate clinical and antibody responses among initially seronegative healthy adults 20 years of age or older to 10 mcg doses of yeast recombinant hepatitis B vaccine
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #89426/22930/C-M178 (10 mcg HBsAg/0.5 ml) Lot #819910/18068/C-L217 (10 mcg HBsAg/0.5 ml)
PRIMARY INVESTIGATOR:	Harold A. Kessler, M.D. Assistant Professor of Medicine and Immunology/Microbiology Section of Infectious Diseases Department of Medicine Rush-Presbyterian-St. Luke's Medical Center 1753 West Congress Parkway Chicago, IL 60612
SECONDARY INVESTIGATORS:	Constance Ann Benson, M.D. Rush-Presbyterian-St. Luke's Medical Center Section of Infectious Diseases 1753 West Congress Parkway Chicago, IL 60612 Alan A. Harris, M.D. Rush-Presbyterian-St. Luke's Medical Center Section of Infectious Diseases 1753 West Congress Parkway Chicago, IL 60612
STUDY LOCATION:	Rush-Presbyterian-St. Luke's Medical Center 1753 West Congress Parkway Chicago, IL 60612
DATE INITIATED:	October, 1985
DATE COMPLETED:	In progress.

Study 904

STUDY POPULATION:

The study population will consist of approximately 100 healthy adults of either sex (excluding pregnant women) who are 20 years of age or older, are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level, and have not previously received any hepatitis B vaccine.

PROCEDURE:

Participants will be assigned to one of two groups as defined below:

Group	Number of Participants	Vaccine Lot	Dose Volume (HBsAg)
1	50	89426/22930/C-M718	0.5 ml (10 mcg)
2	50	81991D/18068/C-L217	0.5 ml (10 mcg)

Participation in either group 1 or 2 will be determined by a randomization schedule provided by Merck Sharp & Dohme.

Eligible participants receive a 0.5 ml injection of vaccine in the deltoid muscle at 0, 1, and 6 months. Study subjects are asked to take and record their temperatures for five days after each injection of vaccine and to record any local or systemic complaints.

A blood sample will be obtained at 1-2 weeks prior to the first injection of vaccine. Post-vaccination blood samples (10-15 ml) will be obtained at 1, 2, 3, 6, and 8 months following the first dose of vaccine from all vaccinees and at 12 and 24 months from those who have developed antibody by 8 months. All samples will be tested for HBsAg, anti-HBc, and anti-HBs. The sample taken 2 months after the first dose of vaccine will also be tested for ALT.

Subjects who fail to develop antibody following three doses of vaccine (nonresponders) and those who have a transient antibody response (transient responders) that becomes negative by 12 months after the first dose, may receive a fourth dose of vaccine. An additional blood sample will be taken one month after the fourth dose.

Sera may also be assayed for yeast antibodies and anti-HBs subtype specificity.

All assays will be done at Rush-Presbyterian-St. Luke's Medical Center.

Study 904

RESULTS:

HEALTHY ADULTS:

10 mcg Lot #89426/22930/C-M178 at 0, 1, and 6 months
10 mcg Lot 81991D/18068/C-L217 at 0, 1, and 6 months

1. Number Vaccinated:

	Injection No.		
	1	2	3
Lot C-M178	50	50	0
Lot C-L217	50	50	0

2. Serologic Results:

Serologic data are not yet available.

3. Clinical Complaints:

Clinical follow-up data are not yet available. No serious or alarming advierse experiences have been reported.

The study continues in progress.

PROGRAM: Yeast Recombinant Hepatitis B Vaccine, Study 907

PURPOSE: To evaluate antibody and clinical responses to 10 mcg doses of yeast recombinant hepatitis B vaccine following intramuscular or subcutaneous administration.

VACCINE: Yeast Recombinant Hepatitis B Vaccine Lot C-L215 (10 mcg HBsAg/0.5 ml)

PRIMARY INVESTIGATOR:
Shiro Iino, M.D.
First Department of Internal Medicine
Faculty of Medicine, University of Tokyo
Hongo, Bunkyo-ku, Tokyo
Japan

Tetsuo Kuroki, M.D.
Third Department of Internal Medicine
Medical School, Osaka City University
Asahi-cho, Abeno-ku, Osaka
Japan

SECONDARY INVESTIGATORS:
Takeyuki Monna, M.D.
Professor
Department of Public Health
Medical School, Osaka City University

Hiroko Oka, M.D.
Third Department of Internal Medicine
Medical School, Osaka City University
Japan

STUDY LOCATION: Tokyo and Osaka
Japan

DATE INITIATED: May 7, 1985

DATE COMPLETED: In progress.

STUDY POPULATION:

Population	Number of Subjects	Regimen
Healthy adults	124	10 mcg (0.5 ml) at 0, 1, and 6 months I.M. or S.C.

Study 907

PROCEDURE:

Participants received intramuscular or subcutaneous injections of vaccine according to the regimen outlined above under STUDY POPULATION. Participants were asked to record their temperature daily for three days after each injection and to note any local or systemic complaints.

Serum samples were obtained before vaccination. Follow- up blood specimens have been or will be obtained 1, 2, 4, 6, 7, 9 and 12 months after the initial dose of vaccine. Serum samples have been or will be assayed for HBsAg, anti-HBs, anti-HBc and several other laboratory exami- nations by the (b) (4) Samples may also be assayed at the (b) (4) for yeast antibody.

RESULTS:

1. Number Vaccinated:

Injection No.		
1	2	3
124	124	121

2. Serologic Results:

The anti-HBs seroconversion proportions were 28% (16/57) and 28% (17/61) at one month after the first dose, 93% (52/56) and 87% (53/61) at 6 months and 98% (54/55) and 97% (56/58) at 7 months with intramuscular and subcutaneous injections, respectively.

3. Clinical Complaints:

Route of Injection	Type of Complaints	Frequency in % by Injection No. 1	2	3
I.M.	Injection Site	19.4% (12/62)	11.3% (7/62)	*
	Systemic	9.7% (6/62)	14.5% (9/62)	*
S.C.	Injection Site	16.1% (10/62)	11.3% (7/62)	*
	Systemic	16.1% (10/62)	8.1% (5/62)	*

There were no serious or alarming reactions attributed to vaccination.

* not yet analyzed

Study 907

RESULTS: (Contd) TABLE 1

Antibody Responses Among Healthy Adults
Following Vaccination with 10 mcg Doses of
Recombinant Vaccine Lot C-L215 at 0, 1, and 6 Months

RIA Cut-Off Index	Anti-HBs Response (S/N)											
	Before		1 mo.		2 mos.		4 mos.		6 mos.		7 mos.	
	I.M.	S.C.	I.M.	S.C.	I.M.	S.C.	I.M.	S.C.	I.M.	S.C.	I.M.	S.C.
<2.1	57	61	41	44	13	18	6	10	4	8	1	2
2.1- 21			14	16	31	38	24	30	25	36	0	7
21-103			2	1	12	5	26	20	25	16	6	12
105-208					1		1	1	2	1	31	32
100-											17	5
Seroconversion %			28.1	27.9	77.2	70.1	89.5	83.6	92.9	86.9	98.2	96.6

PROGRAM: Yeast Recombinant Hepatitis B Vaccine, Study 912

PURPOSE: To evaluate antibody and clinical responses to 10 mcg doses of yeast recombinant hepatitis B vaccine following intramuscular or subcutaneous administration.

VACCINE: Yeast Recombinant Hepatitis B Vaccine Lot C-L220 (10 mcg HBsAg/0.5 ml)

PRIMARY INVESTIGATORS:

Tatsuo Shimizu, M.D.
Director
Division of Internal Medicine
Osaka Red Cross Hospital
Fudegasaki-machi, Tennoji-ku, Osaka
Japan

Masahiro Nakao, M.D.
Director
Division of Internal Medicine
Shirokita Municipal Hospital
Takadono, Asahi-ku, Osaka
Japan

Toshiaki Marumo, M.D.
Director
Division of Internal Medicine
Sumiyoshi Municipal Hospital
Higashi-Kagaya, Suminoe-ku, Osaka
Japan

Yuriko Tsubakio, M.D.
Division of Pediatrics
Osaka Municipal Mothers' and Children's Hospital
Umeminami, Nishinari-ku, Osaka
Japan

Yuichi Kobayashi, M.D.
Director
Division of Internal Medicine
Domyoji Municipal Hospital
Domyoji, Fujiidera
Japan

Tomohiro Kurahori, M.D.
Director
Ashiya Municipal Hospital
Asahigaoka-machi, Ashiya
Japan

Study 912

PRIMARY INVESTIGATORS: (Contd)	Akio Todo, M.D. Director Division of Internal Medicine Kobe Central Municipal Hospital Minatojima-machi, Chuo-ku, Kobe Japan
SECONDARY INVESTIGATORS:	Seigo Takamatsu, M.D. Division of Internal Medicine Osaka Red Cross Hospital Masayoshi Fujisawa, M.D. Division of Internal Medicine Sumiyoshi Municipal Hospital Fumiaki Ohnishi, M.D. Division of Internal Medicine Domyoji Municipal Hospital Dr. Tetsuzo Koda, M.D. Division of Internal Medicine Ashiya Municipal Hospital Dr. Eiji Komori, M.D. Division of Internal Medicine Kobe Central Municipal Hospital
STUDY LOCATION:	Osaka, Domyoji, Ashiya and Kobe Japan
DATE INITIATED:	September 2, 1985
DATE COMPLETED:	In progress.

STUDY POPULATION:

Population	Number of Subjects	Regimen
Healthy health care personnel	175	10 mcg (0.5 ml) at 0, 1, and 6 months I.M. or S.C.

Study 912

PROCEDURE:

Participants received intramuscular or subcutaneous injections of vaccine according to the regimen outlined above under STUDY POPULATION. Participants were asked to record their temperature daily for three days after each injection and to note any local or systemic complaints.

Serum samples were obtained before vaccination. Follow-up blood specimens have been or will be obtained 1, 2, 4, 6, 7, 9 and 12 months after the initial dose of vaccine. Serum samples have been or will be assayed for HBsAg, anti-HBs, anti-HBc and several other laboratory examinations by the (b) (4). Samples may also be assayed at the for yeast antibody.

RESULTS:

1. Number Vaccinated:

Injection Number		
1	2	3
124	124	*

* not yet vaccinated

2. Serologic Results:

The anti-HBs seroconversion proportions were 45% (38/84) and 22% (19/85) at one month after the first dose and 75% (56/75) and 59% (43/83) at one month after the second dose with intramuscular and subcutaneous injections, respectively.

3. Clinical Complaints:

Route of Injection	Type of Complaints	Frequency in % by Injection No. 1	2	3
I.M.	Injection Site	3.4% (3/87)	0 % (0/85)	
	Systemic	23.0% (20/87)	10.6% (9/85)	
S.C.	Injection Site	6.8% (6/88)	9.1% (9/88)	
	Systemic	27.3% (24/88)	12.5% (11/88)	

There were no serious or alarming reactions attributed to vaccination.

Study 912

RESULTS: (Contd)

TABLE 1

Antibody Responses Among Healthy Adults Following Vaccination with 10 mcg Doses of Recombinant Vaccine Lot C-L220 at 0 and 1 Month

RIA Cut-Off Index	Anti-HBs Response (S/N)					
	Before		1 mo.		2 mos.	
	I.M.	S.C.	I.M.	S.C.	I.M.	S.C.
<2.1	84	85	46	66	19	30
2.1- 21			39	18	36	32
21-103			9	1	19	11
105-208					1	
100-						
Seroconversion %			45.2	22.4	74.7	58.9

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 914
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #85861/22124/C-M126 (10 mcg HBsAg/ml)
PRIMARY INVESTIGATORS:	Alain Burette, M.D. venue 1' Echevinage 19-1180 Bruxelles Belgiu, Michel Deltenre, M.D. rue des Hippocampes 20-1080 Bruxelles Belgium
STUDY LOCATION:	Hospital Brugman Bruxelles Belgium
DATE INITIATED:	November 21, 1985
DATE COMPLETED:	In progress.
STUDY POPULATION:	The study population will consist of approximately 20 health care personnel of either sex (excluding pregnant women) who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.
PROCEDURE:	Eligible participants receive a 1.0 ml (10 mcg HBsAg) injection of vaccine into the deltoid muscle at 0, 1, and 6 months. Study participants are asked to take and record their temperatures for five days after each injection of vaccine and to record any local or systemic complaints. They are also asked to notify the study physician immediately if any unexpected or serious reaction occurs.

Study 914

PROCEDURE: (Contd)

A blood sample (10-15 ml) will be obtained from each participant approximately 2 weeks prior to the first injection of vaccine. Follow-up blood samples will be obtained at 1, 2, 3, 6, and 8 months following the first injection of vaccine from all vaccinees and at 12 and 24 months from those who have developed antibody by 8 months. All serum samples will be tested for HBsAg, Anti-HBc and anti-HBs. The 2 month post-vaccination sample will also be tested for ALT. If any subject experiences clinical symptoms compatible with hepatitis, blood samples drawn at that time will also be tested for ALT.

Subjects who fail to develop antibody following three doses of vaccine and those who have only a transient antibody response that becomes negative by 12 months after the first dose may receive a fourth dose of vaccine. An additional blood sample will be taken one month after the fourth dose.

Assays for HBsAg, anti-HBs and anti-HBc on the pre-vaccination serum samples and all ALT assays will be performed in Belgium. The Merck Sharp & Dohme Research Laboratories in West Point, Pennsylvania will perform post-vaccination assays for HBsAg, anti-HBc, and anti-HBs. Assays also may be done for yeast antibodies and anti-HBs subtype specificity.

RESULTS:

HEALTH CARE PERSONNEL:

10 mcg Lot #85861/22124/C-M126 at 0, 1, and 6 months

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
10 mcg	20	20	0

2. Serologic Results:

Serologic data are not yet available.

3. Clinical Complaints:

Clinical follow-up data are not yet available. However, the study investigator states that no local or general sign of intolerance has been observed. The study continues in progress.

HEALTHY TEENAGERS

SUMMARY - HEALTHY TEENAGERS

To date, 165 healthy male teenagers, 15-20 years old, have been immunized with yeast recombinant hepatitis B vaccine. Antibody and clinical responses to 10, 5 and 2.5 mcg doses of the vaccine administered at 0, 1 and 6 months in the deltoid muscle were evaluated in armed forces recruits who were negative for hepatitis B markers. Fifty-five recruits received each dose level. The vaccine was highly immunogenic and well tolerated in this population. Clinical complaints were mild and transient. Protective levels of antibody (mIU/ml $\geq$10) were induced in greater than 94% of vaccine recipients after 3 injections regardless of dose level administered. Ninety-eight to 100% of vaccine recipients developed protective levels of antibody after 2 injections of either 5 or 10 mcg doses of vaccine.

Immunogenicity

Antibody to hepatitis B surface antigen was measured at 1, 3, 6, 7 and 12 months postvaccination. At 7 months serologic data were available for 52, 54 and 53 vaccinees who received 10, 5 and 2.5 mcg doses, respectively.The seroconversion rate at 7 months was 100% for all dose levels when the cutoff was S/N $\geq$2.1. When the cutoff was mIU/ml $\geq$10, the seroconversion rates were 100% for 5 and 10 mcg and 94% for 2.5 mcg. At 12 months, 100% of those who received 5 or 10 mcg doses of vaccine continue to have protective levels of antibody, while 91% (48/53) of those who received 2.5 mcg doses continue to have protective levels of anti-BHs. Table 1 shows seroconversion rates for up to 12 months of follow-up. A significant effect of log dose level on seroconversion rates was seen at 3 months ($p = 0.006$) and 6 months ($p = 0.030$) when the cutoff was S/N $\geq$2.1, although the minimum seroconversion rates at these times were 91% and 94%, respectively (see Appendix 1 for methods used in statistical analysis). When the cutoff was mIU/ml $\geq$10 a significant effect was seen at 3 ($p < 0.001$), 6 ($p < 0.001$) and 7 months ($p = 0.033$). Seroconversion rates increased with log dose level.

Statistical analysis showed that log titers increased significantly with dose level at all time points ($p < 0.01$). Figure 1 illustrates this dose-response relationship at 7 months. Geometric mean titers for all vaccinees at 7 months were 3056.9 mIU/ml, 2553.4 mIU/ml and 846.3 mIU/ml for 10, 5 and 2.5 mcg doses, respectively (Table 1). Figure 1 gives confidence intervals on the predicted GMT at 7 months by dose in healthy teenagers. At 12 months geometric mean titers for all vaccinees were 583.1 mIU/ml, 498.1 mIU/ml and 324.7 mIU/ml for 10, 5 and 2.5 mcg doses respectively.

Safety

Clinical data following the first two injections of vaccine in 165 vaccinees were available for statistical analysis. Clinical data following the third injection in 164 vaccinees was summarized but not analyzed (Table 2). The incidences of local (injection site) complaints, of systemic complaints, of either local or systemic complaints, and of fever (oral temperature of 100°F or more) were analyzed. The incidence following the first, second, or third injection respectively, was defined as the number of subjects with the complaint

at any time during the 5 day period following vaccination divided by the number reporting while the total incidence was the sum of complaints over the three injections divided by the number with follow-up. In general, the vaccine was well tolerated in this population. Clinical complaints were mild and transient. The incidences of local complaints, of systemic complaints, of either injection site or systemic complaint, and of fever were evaluated as a function of log dose level. No significant trend was found after the first or second injection. Almost no fever was reported after either injection or at any dose level. The only local complaint reported was soreness (13%) and the only systemic complaints were malaise (6%) and headache (2%). The incidence of each complaint tended to be lower after the second injection. Clinical complaints following the third injection were minimal. The only complaint reported was injection site soreness (2-6%).

Study #819

Table 1

Antibody Responses Among Initially Seronegative Healthy Teenagers Following Vaccination with 10, 5, or 2.5 mcg Doses of Yeast Recombinant Hepatitis Vaccine B Lot 979/C-K564 or Lot 985/C-K732 at 0, 1 and 6 Months in Study 819

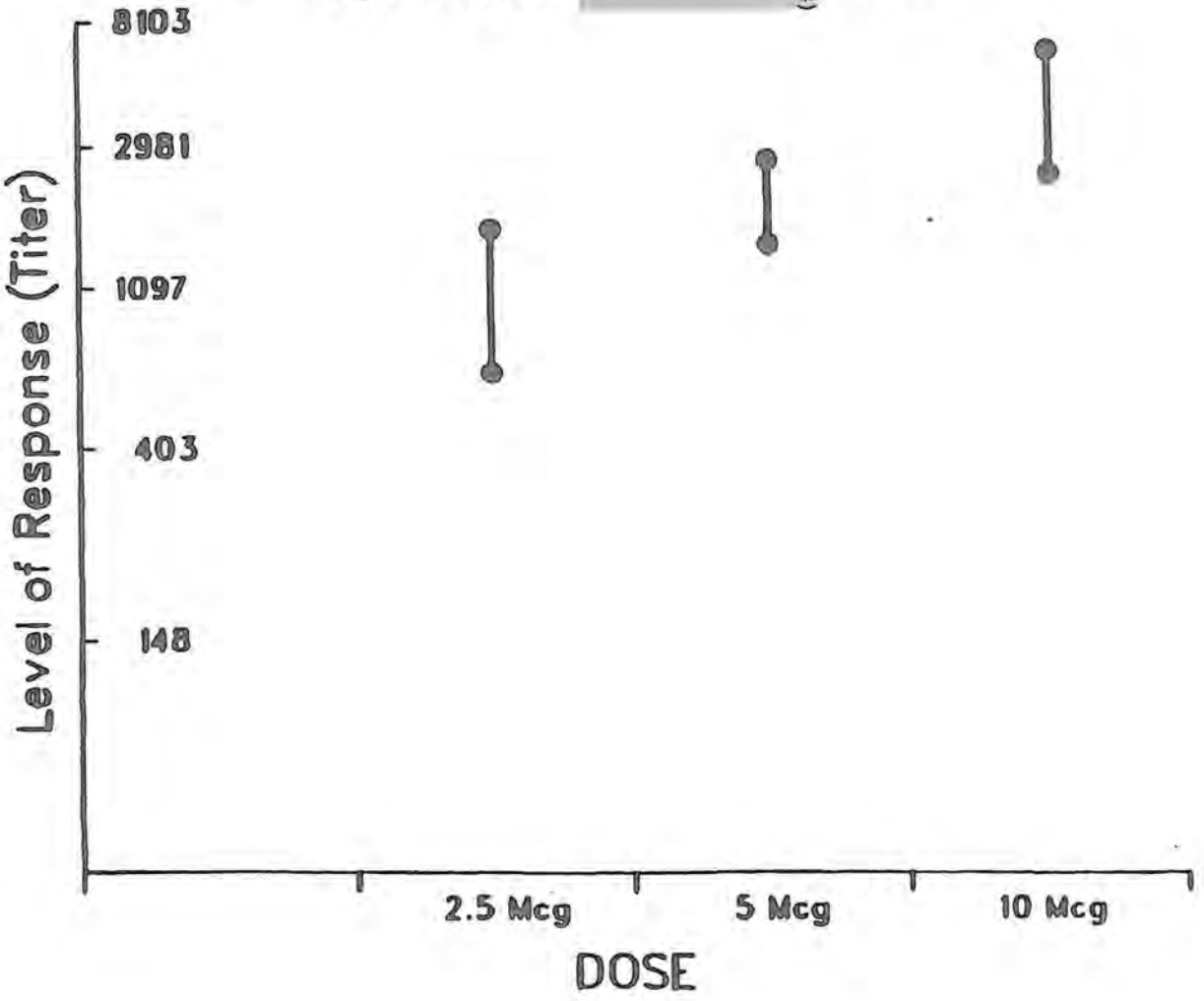
	10 mcg (Lot C-K564)					5 mcg (Lot C-K732)					2.5 mcg (Lot C-K732)				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time Mos.	S/N ≥ 2.1	mIU/ml ≥10	All Vaccinees	S/N ≥ 2.1	mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥10	All Vaccinees	S/N ≥ 2.1	mIU/ml 10	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	S/N ≥ 2.1	mIU/ml ≥ 10
1	67(36/54)	39(21/54)	10.7	32.8	116.6	59(32/54)	19(10/54)	4.0	10.5	58.5	59(32/54)	26(14/54)	4.3	9.90	24.5
3	100(53/53)	95(51/53)	213.3	213.3	245.8	100(54/54)	94(51/54)	107.9	107.9	127.4	91(49/54)	67(36/54)	23.7	31.8	63.3
6	100(53/53)	98(52/53)	199.0	199.0	211.0	100(54/54)	100(54/54)	107.5	107.5	107.5	94(48/51)	71(36/51)	24.7	31.3	59.4
7	100(52/52)	100(52/52)	3056.9	3056.9	3056.9	100(54/54)	100(54/54)	2553.3	2553.3	2553.3	100(53/53)	94(50/53)	846.3	846.3	1131.8
12	100(54/54)	100(54/54)	583.1	583.1	583.1	100(54/54)	100(54/54)	498.1	498.1	498.1	92(49/53)	91(48/53)	324.7	498.8	547.1

2477I/5
12/31/85

00619

FIGURE 1

Confidence Intervals on the Predicted Mean at 7 Months
By Dose in Healthy Teenagers
Who Received Yeast Recombinant Hepatitis B Vaccine
Prepared by the [redacted] (b) (4) Method



02900

Table 2

Percent (Proportion) of Healthy Teenagers (Ages 15-20) with Clinical Complaints During a 5-Day Period Following Vaccination With Yeast Recombinant Hepatitis B Vaccine

Study 819

Type of Complaint	First Injection	Second Injection	Third Injection	Total
	2.5 mcg of Vaccine			
Local (Injection Site)	12.7 (7/55)	1.8 (1/55)	1.9 (1/54)	4.8 (8/164)
Systemic	5.5 (3/55)	0 (0/55)	0 (0/54)	1.8 (3/164)
Any Local or Systemic	12.7 (7/55)	1.8 (1/55)	1.9 (1/54)	4.8 (8/164)
Fever ≥100° F (Oral)	0 (0/55)	0 (0/55)	0 (0/54)	(0) (0/164)
	5 mcg of Vaccine			
Local (Injection Site)	5.5 (3/55)	9.1 (5/55)	5.5 (3/55)	4.8 (8/165)
Systemic	3.6 (2/55)	3.6 (2/55)	0 (0/55)	2.4 (4/165)
Any Local or Systemic	9.1 (5/55)	9.1 (5/55)	5.5 (3/55)	6.1 (10/165)
Fever ≥100° F (Oral)	1.8 (1/55)	0 (0/55)	0 (0/55)	0.6 (1/165)
	10 mcg of Vaccine			
Local (Injection Site)	9.1 (5/55)	5.5 (3/55)	0 (0/55)	4.8 (8/165)
Systemic	5.5 (3/55)	0 (0/55)	0 (0/55)	1.8 (3/165)
Any Local or Systemic	12.7 (7/55)	5.5 (3/55)	0 (0/55)	6.1 (10/165)
Fever ≥ 100°F (Oral)	0 (0/55)	0 (0/55)	0 (0/55)	0 (0/165)

APPENDIX 1

STATISTICAL METHODS

All tests of significance were two-sided at 0.05 significance level.

A. Clinical Complaints

1. The incidence of the various clinical complaints in dialysis patients on the three dose regimen, healthy teenagers and healthy children were evaluated as a function of log dose level using the Mantel-Haenszel Test[1] for trend.

2. All other differences in the incidences of the various clinical complaints in dialysis patients due to dose level or regimen and in health care personnel receiving vaccine from consistency lots were assessed by the Likelihood Ratio Chi-Square.

B. Seroconversion Rates

1. The effect of dose level on seroconversion rates in healthy adults, healthy teenagers and healthy children was analyzed over studies using the Mantel Haenszel Test[1] for trend.

2. Differences in seroconversion rates in healthy adults due to age or sex were evaluated over studies using the Mantel Haenszel Test[1] for heterogeneity.

3. Differences in seroconversion rates due to age in healthy children, dose level in dialysis patients, and vaccine lot in health care personnel were assessed by the Likelihood Ratio Chi-Square.

C. Level of Response (Titers)

The effect of age, sex, lot (consistency lots only in Study 880), or dose level (all other studies) in health care personnel and other healthy adults, of dose level in healthy teenagers, of dose level and age in healthy children, and of dose level and regimen in dialysis patients were analyzed by fitting these variables to a regression model. Subjects who were negative for antibody to hepatitis B surface antigen were assigned a titer of 0.3 mIU/ml in the analysis.

REFERENCE

1. Tarone RE, Ware J: On Distribution-Free Tests for Equality of Survival Distributions. Biometrika 64: 156-160, 1977.

STUDY 819

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 819
PURPOSE:	To compare antibody and clinical responses to 5 and 10 mcg doses of the vaccine among teenagers who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #979/C-K564 - 10 mcg HBsAg/ml Lot #985/C-K732 - 5 mcg HBsAg/ml
PRIMARY INVESTIGATOR:	George Papaevangelou, M.D. Professor of Epidemiology & Medical Statistics National Center for Viral Hepatitis Athens School of Hygiene P. O. Box 14085 Athens 11522, Greece
SECONDARY INVESTIGATOR:	Charalambos Vissoulis, M.D. Associate Professor of Medicine University of Athens Medical School 47 Skoufa Street Athens 10672, Greece
STUDY LOCATION:	Greek Naval Base Poros, Greece
DATE INITIATED:	May 12, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 165 teenagers (15 - 20 years of age) who are armed forces recruits, who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 819

PROCEDURE:

Eligible participants are allocated by means of a prearranged balanced randomization list with code numbers to receive a 1.0 ml (10 mcg or 5 mcg) intramuscular injection of vaccine at 0, 1 and 6 months. Fifty-five receive 10 mcg doses and 55 receive 5 mcg doses.

As per an addendum to this study, 55 recruits receive a 0.5 ml (2.5 mcg) injection of vaccine at 0, 1 and 6 months.

Vaccinees are asked to record their temperature daily for 5 days after each injection and also to record any local or systemic complaints they may have during this period.

A blood specimen (10 - 15 ml) is obtained from each participant approximately two weeks before the first vaccination. Post-vaccination blood samples are obtained at 1, 3, 6, 7, 12 and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs and ALT. These assays are completed by Dr. Papaevangelou.

RESULTS:

HEALTHY TEENAGERS:

10 mcg Lot 979/C-K564 at 0, 1 and 6 months
5 mcg Lot 985/C-K732 at 0, 1 and 6 months
2.5 mcg Lot 985/C-K732 at 0, 1 and 6 months

1. Number Vaccinated:

Dose Level	Injection Number 1	2	3
10 mcg	55	55	55
5 mcg	55	55	55
2.5 mcg	55	55	54

Three individuals, one from each group, were seropositive at the time of immunization and are excluded from the serologic analysis.

Study 819

RESULTS: (CONT'D) 2. Serologic Results:

At 7 months serologic data are available for 52, 54, and 53 study participants who received 10, 5, and 2.5 mcg doses, respectively. The seroconversion rates at 7 months were 100% for all dose levels when the cutoff was S/N ≥2.1. When the cutoff was mIU/ml ≥10. The rates were 100% for 5 and 10 mcg and 94% for 2.5 mcg. At 7 and 12 months the following anti-HBs responses were noted. Table 1 shows seroconversion rates and GMT's through 12 months of follow-up.

Time (Months)	Dose Level	% with Anti-HBs S/N ≥ 2.1	% with Anti-HBs mIU/ml ≥ 10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥ 2.1	GMT (mIU/ml) Responders mIU/ml ≥ 10
7	10 mcg	100(52/52)	100(52/52)	3056.9	3056.9	3056.9
12	10 mcg	100(54/54)	100(54/54)	583.1	583.1	583.1
7	5 mcg	100(54/54)	100(54/54)	2553.3	2553.3	2553.3
12	5 mcg	100(54/54)	100(54/54)	498.1	498.1	498.1
7	2.5 mcg	100(53/53)	94(50/53)	846.3	846.3	1131.8
12	2.5 mcg	92(49/53)	91(48/53)	324.7	498.8	547.1

3. Clinical Complaints

Clinical follow-up data are available for 55, 55, and 54 participants following each injection of 10, 5 and 2.5 mcg doses, respectively. Data following the third injection has not yet been entered into the data base. Specific complaints and maximum temperatures reported during the five days following the first two injections are provided in Tables 2 through 7.

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	10 mcg	9(5/55)	6(3/55)	0(0/55)
	5 mcg	6(3/55)	9(5/55)	6(3/55)
	2.5 mcg	13(7/55)	2(1/55)	2(1/54)
Systemic	10 mcg	6(3/55)	0(0/55)	0(0/55)
	5 mcg	4(2/55)	4(2/55)	0(0/55)
	2.5 mcg	6(3/55)	0(0/55)	0(0/54)

Study 819

RESULTS (CONT'D):

The vaccine was well tolerated. All complaints were mild and transient. There were no serious or alarming adverse reactions attributable to vaccine.

HBsAg

One recipient (Case (b) (6) of 5 mcg doses became borderline positive for HBsAg at 3 months (S/N=2.11). His ALT level at this time was within normal limits and he was negative for anti-HBc. His pre-bleed and 1, 6 and 7 and 12 month bleedings were negative for HBsAg and anti-HBc. There is no evidence to suggest that this individual has become infected. It appears likely that the low positive test for HBsAg was spurious.

PUBLICATIONS:

Dandolos E, Roumeliotou-Karayannis A, Richardson SC, Papaevaneglou G. Safety and immunogenicity of a recombinant hepatitis B vaccine. Accepted for publication in J Med Virology 1985.

Papaevangelou G, Dandolos E, Roumeliotou-Karayannis A, Richardson SC. Immunogenicity of recombinant hepatitis B vaccine. Lancet 1985; 1:455-6.

Study #819

Table 1

Antibody Responses Among Initially Seronegative Healthy Teenagers Following Vaccination with 10, 5, or 2.5 mcg Doses of Yeast Recombinant Hepatitis Vaccine B Lot 979/C-K564 or Lot 985/C-K732 at 0, 1 and 6 Months in Study 819

	10 mcg (Lot C-K564)					5 mcg (Lot C-K732)					2.5 mcg (Lot C-K732)				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time Mos.	S/N ≥ 2.1	mIU/ml ≥10	All Vaccinees	S/N ≥ 2.1	mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥10	All Vaccinees	S/N ≥ 2.1	mIU/ml 10	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	S/N ≥ 2.1	mIU/ml ≥ 10
1	67(36/54)	39(21/54)	10.7	32.8	116.6	59(32/54)	19(10/54)	4.0	10.5	58.5	59(32/54)	26(14/54)	4.3	9.90	24.5
3	100(53/53)	95(51/53)	213.3	213.3	245.8	100(54/54)	94(51/54)	107.9	107.9	127.4	91(49/54)	67(36/54)	23.7	31.8	63.3
6	100(53/53)	98(52/53)	199.0	199.0	211.0	100(54/54)	100(54/54)	107.5	107.5	107.5	94(48/51)	71(36/51)	24.7	31.3	59.4
7	100(52/52)	100(52/52)	3056.9	3056.9	3056.9	100(54/54)	100(54/54)	2553.3	2553.3	2553.3	100(53/53)	94(50/53)	846.3	846.3	1131.8
12	100(54/54)	100(54/54)	583.1	583.1	583.1	100(54/54)	100(54/54)	498.1	498.1	498.1	92(49/53)	91(48/53)	324.7	498.8	547.1

24771/5
12/31/85

02900

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTHY TEENAGERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (55 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	0 (0.0%)	5 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (9.1%)
SORENESS	0 (0.0%)	0 (0.0%)	5 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		5 (9.1%)
SYSTEMIC	0 (0.0%)	1 (1.8%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (5.5%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (1.8%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (5.5%)
MALAISE	0 (0.0%)	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.6%)
HEADACHE	0 (0.0%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.6%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (1.8%)	6 (10.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		7 (12.7%)
PERSONS WITH NO COMPLAINTS	0 (0.0%)	54 (98.2%)	49 (89.1%)	55 (100.0%)	0 (0.0%)	0 (0.0%)		48 (87.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTHY TEENAGERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (55 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	2 (3.6%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (5.5%)
SORENESS	2 (3.6%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (5.5%)
PERSONS WITH COMPLAINTS	2 (3.6%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (5.5%)
PERSONS WITH NO COMPLAINTS	53 (96.4%)	52 (94.5%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		52 (94.5%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00630

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTHY TEENAGERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (55 PATIENTS) - DOSE 1								DAYS POST VACCINATION	NUMBER WITH MAX TEMP
	0	1	2	3	4	5				
< 99	0 (0.0%)	54 (98.2%)	50 (90.9%)	55 (100.0%)	0 (0.0%)	0 (0.0%)				49 (89.1%)
99 - 99.9	0 (0.0%)	1 (1.8%)	5 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)				6 (10.9%)
TEMPERATURE TAKEN	0 (0.0%)	55 (100.0%)	55 (100.0%)	55 (100.0%)	0 (0.0%)	0 (0.0%)				55 (100.0%)
TEMPERATURE NOT TAKEN	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (100.0%)	55 (100.0%)				0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0619
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTHY TEENAGERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (55 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	55 (100.0%)	53 (96.4%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		53 (96.4%)
99 - 99.9	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.6%)
TEMPERATURE TAKEN	55 (100.0%)	55 (100.0%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		55 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (100.0%)	55 (100.0%)	55 (100.0%)		0 (0.0%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK732
DOSE : 5 MCG
PATIENT CLASS: HEALTHY TEENAGERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (55 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	0 (0.0%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.5%)
SORENESS	0 (0.0%)	0 (0.0%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.5%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
MALAISE	0 (0.0%)	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	5 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (9.1%)
PERSONS WITH NO COMPLAINTS	0 (0.0%)	55 (100.0%)	50 (90.9%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	50 (90.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK732
DOSE : 5 MCG
PATIENT CLASS: HEALTHY TEENAGERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (55 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	5 (9.1%)	5 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (9.1%)
SORENESS	5 (9.1%)	5 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (9.1%)
SYSTEMIC	2 (3.6%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
WHOLE BODY/GENERAL	2 (3.6%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
MALAISE	2 (3.6%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.6%)
HEADACHE	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
PERSONS WITH COMPLAINTS	5 (9.1%)	5 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (9.1%)
PERSONS WITH NO COMPLAINTS	50 (90.9%)	50 (90.9%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	50 (90.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK732
DOSE : 5 MCG
PATIENT CLASS: HEALTHY TEENAGERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (55 PATIENTS) - DOSE 1 — DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
< 99	0 (0.0%)	54 (98.2%)	51 (92.7%)	55 (100.0%)	0 (0.0%)	0 (0.0%)		50 (90.9%)
99 - 99.9	0 (0.0%)	1 (1.8%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (7.3%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
TEMPERATURE TAKEN	0 (0.0%)	55 (100.0%)	55 (100.0%)	55 (100.0%)	0 (0.0%)	0 (0.0%)		55 (100.0%)
TEMPERATURE NOT TAKEN	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (100.0%)	55 (100.0%)		0 (0.0%)

006355

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK732
DOSE : 5 MCG
PATIENT CLASS: HEALTHY TEENAGERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (55 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	53 (96.4%)	53 (96.4%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		53 (96.4%)
99 - 99.9	2 (3.6%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.6%)
TEMPERATURE TAKEN	55 (100.0%)	55 (100.0%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		55 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (100.0%)	55 (100.0%)	55 (100.0%)		0 (0.0%)

Table 6

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK732
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY TEENAGERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (55 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	7 (12.7%)	7 (12.7%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (12.7%)
SORENESS	7 (12.7%)	7 (12.7%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (12.7%)
SYSTEMIC	3 (5.5%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.5%)
WHOLE BODY/GENERAL	3 (5.5%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.5%)
MALAISE	3 (5.5%)	3 (5.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.5%)
PERSONS WITH COMPLAINTS	7 (12.7%)	7 (12.7%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (12.7%)
PERSONS WITH NO COMPLAINTS	48 (87.3%)	48 (87.3%)	53 (96.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	48 (87.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 6 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK732
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY TEENAGERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (55 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
SORENESS	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
PERSONS WITH COMPLAINTS	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
PERSONS WITH NO COMPLAINTS	54 (98.2%)	55 (100.0%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	54 (98.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK732
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY TEENAGERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (55 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	55 (100.0%)	53 (96.4%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			53 (96.4%)
99 - 99.9	0 (0.0%)	2 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			2 (3.6%)
TEMPERATURE TAKEN	55 (100.0%)	55 (100.0%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			55 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (100.0%)	55 (100.0%)	55 (100.0%)			0 (0.0%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0819
TREATMENT :
LOT NUMBER : CK732
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY TEENAGERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (55 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
< 99	55 (100.0%)	55 (100.0%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		55 (100.0%)
TEMPERATURE TAKEN	55 (100.0%)	55 (100.0%)	55 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		55 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	55 (100.0%)	55 (100.0%)	55 (100.0%)		0 (0.0%)

Journal of Medical Virology 17:57–62 (1985)

Safety and Immunogenicity of a Recombinant Hepatitis B Vaccine

E. Dandolos, A. Roumeliotou-Karayannis, S.C. Richardson, and G. Papaevangelou

National Centre for Viral Hepatitis, Athens School of Hygiene, Athens, Greece

A hepatitis B vaccine produced in yeast by recombinant DNA technology was evaluated using 5-μg and 10-μg doses in a randomized trial lasting 7 months in 110 male armed forces recruits aged 17–19 years. Results were compared to those of an identical trial of a plasma-derived vaccine. No allergic reactions were observed, and the rate of mild side effects was similar to the plasma-derived vaccine. Seroconversion rates in the first month were 60% (33/55) and 67% (37/55) with the 5-μg and 10-μg doses of the recombinant vaccine, respectively. All participants seroconverted by 3 months, and none lost antibody. These results are very similar to those for plasma-derived vaccine. Comparison of titres of antibody to hepatitis B surface antigen (anti-HBs) showed a slightly higher level with the 10-μg than with the 5-μg dose of the recombinant vaccine. Geometric mean titres of anti-HBs after the booster dose were similar in the 5-μg and 10-μg dose recombinant vaccine groups (2,620 and 2,748 IU/l, respectively) and in the 5-μg plasma-derived vaccine group (3,591 IU/l) but significantly higher (9,227 IU/l) with the 10-μg dose of the plasma-derived vaccine. These results confirm the safety and immunogenicity of the recombinant vaccine, although further study is needed on the duration of immunity.

Key words: active immunoprophylaxis, hepatitis B, plasma-derived hepatitis B vaccine, recombinant hepatitis B vaccine

INTRODUCTION

The safety and immunogenicity of plasma-derived hepatitis B vaccines have been amply demonstrated by clinical trials in various high-risk groups in different parts of the world [Szmuness et al, 1980; Maupas et al, 1981; Beasley et al, 1983]. However, the high cost and limited availability have prevented widespread use of these vaccines, especially in the less developed areas where they are needed most. Vaccination programmes are at present generally limited to groups at high risk of infection, such as hospital personnel. Within these programmes, acceptance may have been affected by unfounded loss of confidence in the safety of the vaccine, following

Accepted for publication April 1, 1985.

Address reprint requests to Prof. G. Papaevangelou, National Centre for Viral Hepatitis, Athens School of Hygiene, P.O. Box 14085, Athens 115 21, Greece.

isons at each time point. All analyses were carried out after logarithmic transformation of anti-HBs titres.

RESULTS

The trial was completed in all but two recruits, both the losses being from the group receiving the 10-μg dose. One was lost from the study after receiving the second dose and the other after the booster dose. No participant developed either clinical or asymptomatic viral hepatitis, and neither anaphylactoid nor other allergic reactions were observed. Mild side effects were reported, but no case of fever above 37.5°C was noted, and no local discomfort or pain lasting for more than 1 day. The overall frequency of side effects was very similar to that reported for the plasma-derived vaccine in the earlier study (Table I).

The two groups receiving recombinant vaccine showed a similar and rapid immune response (Table II). Both of the recruits who did not complete follow-up had already seroconverted in the first month. All participants had seroconverted by 3 months, and none lost antibody. These rates are very similar to those recorded in the trial of the plasma-derived vaccine. Differences in seroconversion rates at 1 month between the four groups in Table II are not significant ($\chi^2_3 = 5.26$; $P = 0.15$).

Geometric mean titres (GMT) of anti-HBs are shown in Table III. Multivariate comparison between the two recombinant vaccine groups shows that they do not differ in rates of increase of anti-HBs ($F_{3,104} = 1.99$; $P > 0.1$). The 10-μg group had significantly higher GMT of antibody overall than the 5-μg group ($t_{105} = 2.08$; $P < 0.05$), although the difference appears to be small after the booster dose.

Multivariate comparisons of the anti-HBs profiles in the 5-μg and 10-μg recombinant vaccine groups against the corresponding plasma-derived vaccine groups show

TABLE I. Frequency of Side Effects by Type of Vaccine (Summed Over Administrations of Vaccine)

Side effect	Recombinant vaccine (%)	Plasma-derived vaccine (%)
Local pain	6.0	9.0
Fever <37.5°C	16.3	11.1
Other	2.3	2.3
Total	24.6	22.4

TABLE II. Number (%) of Seroconverted (anti-HBs > 2.1 IU/l) by Month and Type of Vaccine

	Recombinant vaccine		Plasma-derived vaccine	
Month	5 μg (N = 55)	10 μg (N = 55)	5 μg (N = 50)	10 μg (N = 50)
1	33 (60)	37 (67)	40 (80)	32 (64)
3	55 (100)	54 (100)[a]	49 (98)	49 (98)
6	55 (100)	54 (100)[a]	49 (98)	49 (98)
7	55 (100)	53 (100)[b]	49 (98)	50 (100)

[a]One person lost to follow-up.
[b]Two persons lost.

population, with all participants in both the trials of recombinant and plasma-derived vaccines being males of similar age living under exactly similar conditions.

Comparison of the 5-μg and 10-μg doses of recombinant vaccine shows a small advantage to the 10-μg dose overall in terms of GMT anti-HBs, although any final difference is slight. Davidson and Krugman [1985], with older vaccinees of both sexes, reported a final (8 months) GMT anti-HBs in the 10-μg group more than double that in the 5-μg group, although the statistical significance is not stated. Irrespective of dose, all participants in our trial reached the 10 IU/l generally regarded as protective. Only five (4.6%; two from the 5-μg group and three from the 10-μg group) had titres lower than 100 IU/l.

Our results confirm reports of the safety and immunogenicity of the Merck Sharp and Dohme recombinant yeast hepatitis B vaccine [Jilg et al, 1984b; Davidson and Krugman, 1985]. The minor differences observed in the immune response stress the need for more extensive studies in various population groups under consideration for vaccination, before the appropriate dose and vaccination scheme are decided. Similarly, further follow-up is required to establish the duration of protective levels of antibody [Jilg et al, 1984a; Davidson and Krugman, 1985]. Finally, in assessing the efficacy of the vaccine, information concerning the quality of the anti-HBs induced should complement the data on the anti-HBs levels achieved [Brown et al, 1984].

ACKNOWLEDGMENTS

This study was supported by a grant from the Ministry of Health and Welfare of Greece.

REFERENCES

Beasley RP, Lee GC, Roan C, Hwang L, Lan C, Huang F, Chen C (1983): Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet ii:1099–1102.

Brown SE, Zuckerman AJ, Howard CR, Steward MW (1984): Affinity of antibody responses in man to hepatitis B vaccine determined with synthetic peptides. Lancet ii:184–187.

Davidson M, Krugman S (1985): Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet i:108–109.

Hollinger FB, Adam E, Heiberg D, Melnick JL (1982): Response to hepatitis B vaccine in a young adult population. In Szmuness W, Alter HJ, Maynard JE (eds): "Viral Hepatitis. 1981 International Symposium." Philadelphia: Franklin Institute Press, pp 451–466.

Jilg W, Schmidt M, Deinhardt F, Zachoval R (1984a): Hepatitis B vaccination: How long does protection last? Lancet ii:458.

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F (1984b): Clinical evaluation of a recombinant hepatitis B vaccine. Lancet ii:1174–1175.

Maupas P, Chiron JP, Barin F, Courageot P, Goudeau A, Perrin J, Denis F, Diop Mar I (1981): Efficacy of hepatitis B vaccine in prevention of early HBsAg carrier state in children. Controlled trial in an endemic area (Senegal). Lancet i:289–292.

McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR (1984): Human hepatitis B vaccine from recombinant yeast. Nature 307:178–180.

Morrison DF (1976): "Multivariate Statistical Methods," (2nd ed). New York: McGraw-Hill.

Papaevangelou G, Roumeliotou-Karayannis A, Vissoulis C, Richardson SC, Krugman S (1985): Immunogenicity of a 5 μg dose hepatitis B vaccine. Journal of Medical Virology. 15:65–69.

Papaevangelou G, Roumeliotou-Karayannis A, Vissoulis C, Stathopoulou P, Kolaitis N, Krugman S (1983): Safety and immunogenicity of a further reduced dose (10 mcg) of the hepatitis B vaccine.

IMMUNOGENICITY OF RECOMBINANT HEPATITIS B VACCINE

SIR,—Jilg et al[1] have compared the immunogenicity of recombinant[2] and plasma derived hepatitis B vaccines. We report for comparison the results of a similar trial of the recombinant vaccine in a younger age group. 55 male armed forces recruits, aged 17–19, all of whom were susceptible to hepatitis B virus were given

IMMUNE RESPONSES AFTER RECOMBINANT (n = 55) OR PLASMA (n = 50) HEPATITIS B VACCINATION

Month	Seroconversion		GMT anti-HBs (IU/l)	
	Recombinant	Plasma	Recombinant	Plasma
1	37 (67%)	32 (64%)	11	4
3	54 (100%)*	49 (98%)	106	238
6	54 (100%)*	49 (98%)	189	492
7	53 (100%)†	50 (100%)	2749	[illegible]

*1 lost to follow-up. †2 lost.

10 µg of recombinant vaccine (lot 979/C-K 564, Merck Sharp and Dohme) intramuscularly at 0, 1, and 6 months. The results can be compared with those in another group of recruits of the same age who had been given 10 µg of the same manufacturer's plasma-derived vaccine at 0, 1, and 6 months in an earlier study.[3]

Seroconversion rates and geometric mean antibody titres (GMT) of anti-HBs (see table) were substantially higher than those reported by Jilg et al.[1] The final GMT was 2749 IU/l (95% confidence interval: 1676–4506) compared with 911 IU/l for 12 males reported by Jilg et al.[1] After the booster dose, all vaccinees had an anti-HBs titre above the protection level of 10 IU/l; 43 (81%) had titres above 1000 IU/l. The stronger immune response in our study than in Jilg's may be explained by the fact that our vaccinees were younger (17–19 vs 21–34). We observed only minor side-effects in 20% of participants; this is as reported by Jilg et al.[1]

The seroconversion rates were the same as those obtained in our earlier trial of a 10 µg dose of the plasma-derived vaccine.[3] In contrast to Jilg et al[1] GMT antibody levels in our recombinant group in the first 3 months were similar ($p>0 \cdot 05$) to those induced by the plasma-derived vaccine, although levels after the booster dose were significantly lower ($p<0 \cdot 001$) in the recombinant group (Mann-Whitney tests, separately at each time).

Our results accord with those of Jilg et al in confirming the safety and immunogenicity of the Merck Sharp and Dohme recombinant vaccine. The minor differences in immune responses show the need for further trials in population groups under consideration for vaccination, before a dose and vaccination scheme are decided on. In assessing the efficacy of this vaccine, information on the quality of the anti-HBs induced should complement the anti-HBs levels achieved.[4]

National Centre for Viral Hepatitis,
Athens School of Hygiene,
Athens 11521, Greece

G. PAPAEVANGELOU
E. DANDOLOS
A. ROUMELIOTOU-KARAYANNIS
S. C. RICHARDSON

1. Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. *Lancet* 1984; ii: 1174–75.
2. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984; 307: 178–80.
3. Papaevangelou G, Roumeliotou A, Vissoulis C, [illegible], [illegible]. Safety and immunogenicity of a further reduced dose (10 µg) of the hepatitis B vaccine. *Develop Biol Standard* 1983; 54: 399–[illegible].
4. Brown SE, Zuckerman AJ, Howard CR, Steward MW. Affinity of antibody responses in man to hepatitis B vaccine determined with synthetic peptides. *Lancet* 1984; ii: 184–87.

Papaevangelou G, Dandolos E, Roumeliatou-Karayannis A, Richardson SC. Immunogenicity of recombinant hepatitis B vaccine. Lancet 1985; 1:455-6.

STUDY 891

SUMMARY - HEALTHY CHILDREN

To date, a total of 258 healthy infants and children, 3 months to 11 years of age who were negative for hepatitis B markers, have been vaccinated with hepatitis B recombinant vaccine. Clinical data for all 3 injections are available on 100 infants and children. Seven to 8 month serology data are available on 97 infants and children. Antibody and clinical responses to 5, 2.5 and 1.25 mcg doses of the vaccine administered at 0, 1 and 6 months were evaluated. The vaccine was very immunogenic and well tolerated in this population. Clinical complaints were minimal and transient. In general, children 3 months to 11 years show an earlier response and develop higher titers of antibody than do adults. Seroconversion (S/N $\geq$2.1) exceeded 94% after 2 doses regardless of dose level. Protective levels of antibody (mIU/ml $\geq$10) were induced in 100% of vaccine recipients, one month after the third injection, regardless of dose level administered. At 12 months, all children surveyed still had titers of mIU/ml $\geq$10.

Immunogenicity

Antibody to hepatitis B surface antigen was measured at 1, 2, 3, 6, 7/8 and 12 months post vaccination. Data from study 809 involving 80 children who received either 5, 2.5 or 1.25 mcg doses were statistically analyzed. No significant effect of log dose level on seroconversion rates was found using either a cutoff of S/N $\geq$2.1 or mIU/ml $\geq$10 (see Appendix I for statistical methods used). Seroconversion for all three dose levels and either cutoff was greater than 82% at 3 months, 91% at 6 months and 100% at 7/8 months (Table 1).

When each dose level was analyzed for the effect of age on seroconversion rates, younger children (under 4 years vs 5-12 years) who received the 2.5 mcg dose showed a significantly higher rate at 1 month for a cutoff of S/N $>$2.1 ($p = 0.028$) and at 3 months when the cutoff was mIU/ml $\geq$10 ($p = 0.022$) (Table 2). However, seroconversion was excellent for both age groups by 6 months.

Log titers increased significantly with log dose level at 6 ($p = 0.03$) and 7/8 months ($p < 0.01$) (Table 3). Geometric mean titers for all vaccinees at 7 months were 15965.5 mIU/ml, 6230.2 mIU/ml and 2181.1 mIU/ml for 5, 2.5 and 1.25 mcg doses, respectively. Geometric mean titers at 12 months were 3481.6 mIU/ml, 3051.5 mIU/ml and 819.2 mIU/ml for 5, 2.5 and 1.25 mcg doses, respectively. Figure 1 presents confidence limits on the mean predicted titer at each dose level for a one year old and a 9 year old.

Serologic data from children vaccinated with 5 mcg doses in study 865 were summarized but not included in the statistical analysis. Twenty-one of these children received three injections at 0 and 1 and 6 months, while ninety-six received two injections given at 0 and 1 month. Table 1 illustrates that seroconversion rates at 6 months were 98% and 85% for a cutoff of S/N $\geq$2.1 and mIU/ml $\geq$10, respectively. For those children who received a third injection at 6 months, seroconversion rates increased to 100% regardless of cutoff. A large boost in titer was seen among those children who received the third injection

(Table 3). Geometric mean titers at 8 months were 1894.81 mIU/ml and 84.50 mIU/ml for those in the three and two immunization groups, respectively.

Safety

Clinical complaints among children following 231 injections given in study 809 were available for analysis (Tables 4-6). The incidence of local (injection site) complaints, of systemic complaints, of either local or systemic complaints and of fever (oral temperature of 100°F or more) were analyzed. The incidence at each dose was defined as the number of subjects with the complaint at any time during the 5 day period following vaccination divided by the number reporting; while the total was the sum over the three injections divided by the number of injections with follow-up (Table 4). The frequency of systemic complaints is shown in Tables 5 and 6. All complaints were minimal and transient. The statistical methods used in this analysis are shown in Appendix 1.

None of the incidences of complaints were found to be a function of log dose level. Children who received 2.5 mcg of vaccine tended to report fewer complaints with each dose level. However, the incidences of local and systemic complaints were highest after the second injection in children who received 5 mcg of vaccine. Over all doses and dose levels, fever (oral temperature of 100°F or greater) occurred after 12.7% (24/189) of injections with follow-up. Injection site complaints (15/229, 2.2%) reported were soreness, tenderness, or ecchymosis, while systemic complaints most often were respiratory (18/229 injections, 3.5%) or fatigue (7/229 injections, 3.1%).

Clinical data from children following 282 injections of 5 mcg doses in study 865 were summarized but not included in the statistical analysis (Tables 4 and 7). Fever was reported after 10.3% (29/282) of injections with follow-up. The only injection site complaint was soreness (1.8%), while systemic complaints were mainly digestive (2.5%) or respiratory (1.4%).

The vaccine has been well tolerated in this population. No serious reactions have been reported.

In summary, the vaccine has been well tolerated by infants and children. Although seroconversion rates were excellent with all dosages of vaccine utilized, the highest antibody titers were obtained with the 5 mcg dose of vaccine.

FIGURE 1

Confidence Intervals on the Predicted Mean at 7/8 Months
By Age and Dose in Healthy Children
Who Received Yeast Recombinant Hepatitis B Vaccine
Prepared by the (b) (4) Method

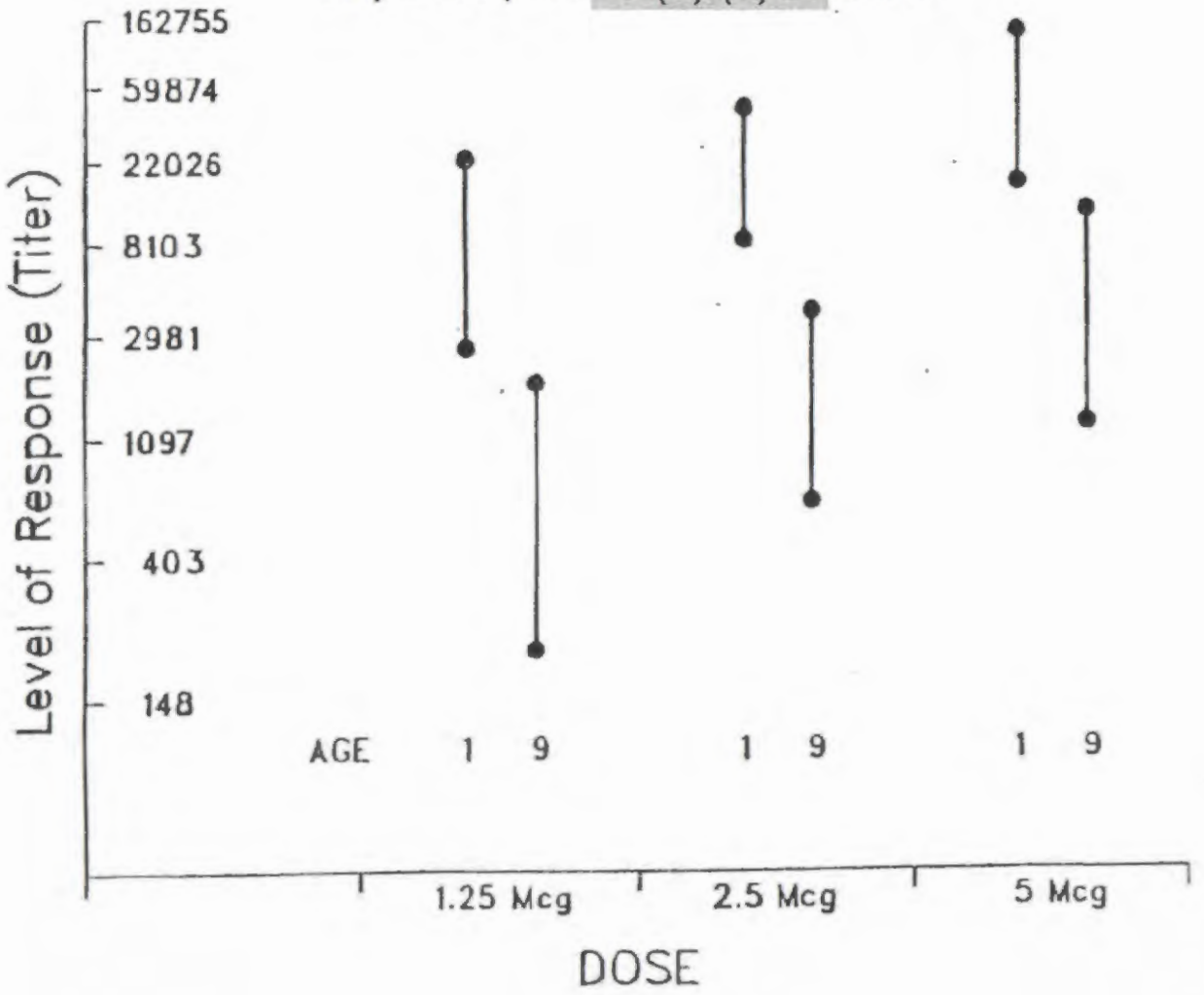


Table 1

Percent Seroconversion (Proportion) by Dose in Healthy Children Who Received Yeast Recombinant Hepatitis B Vaccine

Study No.	Dose	Month 1		Month 3		Month 6		Month 7/8		Month 12	
		S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml≥10	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10
809	1.25	40.0 (10/25)	8.0 (2/25)	100.0 (7/7)	85.7 (6/7)	100.0 (21/21)	90.5 (19/21)	100.0 (17/17)	100.0 (17/17)	100.0 (9/9)	100.0 (9/9)
809	2.50	44.4 (12/27)	22.2 (6/27)	100.0 (17/17)	82.4 (14/17)	96.4 (27/28)	92.9 (26/28)	100.0 (21/21)	100.0 (21/21)	100.0 (19/19)	100.0 (19/19)
809	5.0	47.0 (9/19)	16.0 (3/19)	100.0 (10/10)	100.0 (10/10)	100.0 (19/19)	100.0 (26/28)	100.0 (14/14)	100.0 (14/14)	100.0 (13/13)	100.0 (13/13)
865	5.0	36.6 (52/142)	13.4 (19/142)	94.0 (110/117)	81.2 (95/117)	97.9 (94/96)	85.4 (82/96)	100.0 (21/21)* 95.8 (23/24)**	100.0 (21/21)* 87.5 (21/24)**	-	-

* Received a 3rd injection at 6 months.

** Did not receive a third injection at 6 months.

Table 2

Percent Seroconversion (Proportion) By Dose and Age Group in Healthy Children
Who Received Yeast Recombinant Hepatitis B Vaccine (Study 809)

Dose (MCG)	Age Group (Years)	Month 1		Month 3		Month 6		Month 7/8*	
		S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10
1.25	<=4	41.7 (5/12)	8.3 (1/12)	100.0 (3/3)	100.0 (3/3)	100.0 (8/8)	100.0 (8/8)	100.0 (7/7)	100.0 (7/7)
1.25	5 - 12	38.5 (5/13)	7.7 (1/13)	100.0 (4/4)	75.0 (3/4)	100.0 (13/13)	84.6 (11/13)	100.0 (10/10)	100.0 (10/10)
2.50	<=4	64.3 (9/14)	35.7 (5/14)	100.0 (9/9)	100.0 (9/9)	100.0 (15/15)	93.3 (14/15)	100.0 (12/12)	100.0 (12/12)
2.50	5 - 12	23.1 (3/13)	7.7 (1/13)	100.0 (8/8)	62.5 (5/8)	92.3 (12/13)	92.3 (12/13)	100.0 (9/9)	100.0 (9/9)
5.0	<=4	54.5 (6/11)	18.2 (2/11)	100.0 (6/6)	100.0 (6/6)	100.0 (11/11)	100.0 (11/11)	100.0 (8/8)	100.0 (8/8)
5.00	5 - 12	37.5 (3/8)	12.5 (1/8)	100.0 (4/4)	100.0 (4/4)	100.0 (8/8)	100.0 (8/8)	100.0 (6/6)	100.0 (6/6)

* Month 7/8 included 9 month data when 7 or 8 month was not available.

Table 3

Geometric Mean Titers by Dose in Healthy Children Who
Received Yeast Recombinant Hepatitis B Vaccine

Study #	Dose	Month 1				Month 3				Month 6				Month 7/8				Month 12			
		GMT (mIU/ml)				GMT (mIU/ml)				GMT (mIU/ml)				GMT (mIU/ml)				GMT (mIU/ml)			
				Responders				Responders				Responders				Responders				Responders	
		N	All Vacc.	S/N ≥2.1	mIU/ml ≥10	N	All Vacc.	S/N ≥2.1	mIU/ml ≥10	N	All Vacc.	S/N ≥2.1	mIU/ml ≥10	N	All Vacc.	S/N ≥2.1	mIU/ml ≥10	N	All Vacc.	S/N ≥2.1	mIU/ml ≥10
809	1.25	25	1.2	7.4	69.7	7	52.7	52.7	77.5	21	75.9	75.9	100.7	14	2181.1	2181.1	2181.1	9	819.2	819.2	819.2
809	2.50	27	1.9	11.4	28.9	17	86.9	86.9	144.7	28	125.2	156.5	175.7	21	6230.2	6230.2	6230.2	19	3051.5	3051.5	3051.5
809	5.0	19	2.0	11.7	63.9	10	189.3	189.3	189.3	19	308.4	308.4	308.4	14	15965.5	15965.5	15965.5	13	3481.6	3481.6	3481.6
865	5.0	142	0.9	8.8	26.1	117	44.7	63.5	81.2	96	59.4	74.7	98.6	21 24	1894.8* 84.5**	1894.8* 107.9**	1894.8* 144.9**				

* Received a third injection at 6 months.

** Did not receive a third injection at 6 months.

Table 4

Percent (Proportion) of Healthy Children (Ages 1-12) with Clinical Complaints During a 5-Day Period Following Vaccination With Yeast Recombinant Hepatitis B Vaccine

Study 809

Type of Complaint	First Injection	Second Injection	Third Injection	All Injections
	1.25 mcg of Vaccine			
Local (Injection Site)	0 (0/26)	0 (0/26)	4.0 (1/25)	1.3 (1/77)
Systemic	19.2 (5/26)	11.5 (3/26)	12.0 (3/25)	14.3 (11/77)
Any Local or Systemic	19.2 (5/26)	11.5 (3/26)	16.0 (4/25)	15.6 (12/77)
Fever ≥100° F (Oral)	20.0 (4/20)	11.1 (2/18)	7.1 (1/14)	13.5 (7/52)
	2.5 mcg of Vaccine			
Local (Injection Site)	6.3 (2/32)	3.2 (1/31)	0 (0/30)	3.2 (3/93)
Systemic	18.8 (6/32)	12.6 (4/31)	6.7 (2/30)	12.9 (12/93)
Any Local or Systemic	21.9 (7/32)	16.1 (5/31)	6.7 (2/30)	15.1 (14/93)
Fever ≥100° F (Oral)	13.3 (4/30)	11.5 (3/26)	11.5 (3/26)	12.2 (10/82)
	5 mcg of Vaccine			
Local (Injection Site)	0 (0/21)	5.6 (1/18)	0 (0/20)	1.7 (1/59)
Systemic	14.3 (3/21)	22.2 (4/18)	5.0 (1/20)	13.6 (8/59)
Any Local or Systemic	14.3 (3/21)	27.8 (5/18)	5.0 (1/20)	15.3 (9/59)
Fever ≥ 100°F (Oral)	19.1 (4/21)	6.3 (1/16)	11.1 (2/18)	12.7 (7/55)

Study 865

Type of Complaint	First Injection	Second Injection	Third Injection	All Injections
	5 mcg of Vaccine			
Local (Injection Site)	2.1 (3/141)	1.7 (2/116)	0 (0/25)	1.8 (5/282)
Systemic	5.7 (8/141)	4.3 (5/116)	4.0 (1/25)	5.0 (14/282)
Any Local or Systemic	7.8 (11/141)	6.0 (7/116)	4.0 (1/25)	6.7 (19/282)
Fever ≥ 100°F (Oral)	9.9 (14/141)	12.1 (14/116)	4.0 (1/25)	10.3 (29/282)

Table 5

Frequency of Systemic Complaints by Body System Occurring Within 5 Days Among Healthy Children Following 231 Injections of Yeast Recombinant Hepatitis B Vaccine

Study: 809
Number of Vaccine Recipients: 80

Body System/Complaint	Frequency as % (Number)
Whole Body/General	5 (12)
Fatigue/Weakness	3 (7)
Headache	0.8 (2)
Sweating	0.4 (1)
Bruise from venipuncture	0.4 (1)
Illness, NOS	0.4 (1)
Digestive	4 (10)
Diarrhea	2 (5)
Vomiting	1.3 (3)
Diminished Appetite	0.4 (1)
Loose Stool	0.4 (1)
Nausea	0.4 (1)
Teething	0.4 (1)
Respiratory	4 (9)
Upper Respiratory Infection, NOS	2.6 (6)
Pharyngitis	0.8 (2)
Rhinitis	0.8 (2)
Cough	0.4 (1)
Croup	0.4 (1)
Psychiatric/Behavioral	2 (5)
Irritability	1.7 (4)
Insomnia/Disturbed Sleep	0.4 (1)
Infectious Syndromes	2 (4)
Viral Infection	1.7 (4)
Integumentary	1 (3)
Papular rash	0.8 (2)
Rash, NOS	0.4 (1)
Urticaria/Hives	0.4 (1)
Organs of Special Sense	0.4 (1)
Otitis Media	0.4 (1)

Table 6

Percentage (Number) of Healthy Children with Specific Systemic Complaints During a 5 Day Period Following 231 Injections of Yeast Recombinant Hepatitis B Vaccine

Study: 809
Number of Vaccine Recipients: 80

Complaint Frequency 1 - 3%	
Fatigue/Weakness	3 (7)
Upper Respiratory Infection NOS	2.6 (6)
Diarrhea	2 (5)
Vomiting	1.3 (3)
Irritability	1.7 (4)
Viral Infection	1.7 (4)
Complaint Frequency 0.5 - 0.97%	
Headache	0.8 (2)
Pharyngitis	0.8 (2)
Rhinitis	0.8 (2)
Papular Rash	0.8 (2)
Complaint Frequency 0.1 - 0.49%	
Sweating	0.4 (1)
Bruise from venipuncture	0.4 (1)
Illness, NOS	0.4 (1)
Diminished Appetite	0.4 (1)
Loose Stool	0.4 (1)
Nausea	0.4 (1)
Teething	0.4 (1)
Cough	0.4 (1)
Croup	0.4 (1)
Insomnia/Disturbed Sleep	0.4 (1)
Rash, NOS	0.4 (1)
Urticaria/Hives	0.4 (1)
Otitis Media	0.4 (1)

Table 7

Frequency of Systemic Complaints by Body System Occurring Within 5 Days Among Healthy Children Following 282 Injections of Recombinant Hepatitis B Vaccine

Study: 865
Number of Vaccine Recipients: 141

Body System	# Complaints	Frequency as %
Digestive	7	2.5
Respiratory	4	1.4
Whole Body	3	1.1

APPENDIX 1

STATISTICAL METHODS

All tests of significance were two-sided at 0.05 significance level.

A. Clinical Complaints

1. The incidence of the various clinical complaints in dialysis patients on the three dose regimen, healthy teenagers and healthy children were evaluated as a function of log dose level using the Mantel-Haenszel Test[1] for trend.

2. All other differences in the incidences of the various clinical complaints in dialysis patients due to dose level or regimen and in health care personnel receiving vaccine from consistency lots were assessed by the Likelihood Ratio Chi-Square.

B. Seroconversion Rates

1. The effect of dose level on seroconversion rates in healthy adults, healthy teenagers and healthy children was analyzed over studies using the Mantel Haenszel Test[1] for trend.

2. Differences in seroconversion rates in healthy adults due to age or sex were evaluated over studies using the Mantel Haenszel Test[1] for heterogeneity.

3. Differences in seroconversion rates due to age in healthy children, dose level in dialysis patients, and vaccine lot in health care personnel were assessed by the Likelihood Ratio Chi-Square.

C. Level of Response (Titers)

The effect of age, sex, lot (consistency lots only in Study 880), or dose level (all other studies) in health care personnel and other healthy adults, of dose level in healthy teenagers, of dose level and age in healthy children, and of dose level and regimen in dialysis patients were analyzed by fitting these variables to a regression model. Subjects who were negative for antibody to hepatitis B surface antigen were assigned a titer of 0.3 mIU/ml in the analysis.

REFERENCE

1. Tarone RE, Ware J: On Distribution-Free Tests for Equality of Survival Distributions. Biometrika 64: 156-160, 1977.

HEALTHY CHILDREN

Study 809 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

Healthy adults and children (1-11 years of age), who are seronegative for hepatitis B virus markers, are enrolled in Study 809. Healthy children receive either 1.25 mcg or 2.5 mcg injections of vaccine lot C-K723 or 2.5 mcg or 5 mcg injections of lot C-K444. All injections are administered at 0, 1, and 6 months.

Twenty-six children have received two 1.25 mcg injections of vaccine and 25 of these have received the third injection. At 7/8 months, 100% (14/14) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees was 2181.1 mIU/ml.

Thirty-two children have received two 2.5 mcg injections of vaccine and 30 of these have received the third injection. At 7/8 months, 100% (21/21) of the vaccinees seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees was 6230.2 mIU/ml.

In the 5 mcg dose regimen, 22 children have received two injections of vaccine and 21 of these have received the third injection. At 7/8 months, 100% (14/14) of the children seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees was 15965.5 mIU/ml.

Anti-HBs titers were higher in the children who received 5 mcg injections than in the children who received 1.25 mcg or 2.5 mcg injections of vaccine.

No serious or alarming adverse experiences related to vaccine have been reported. The study continues in progress.

Study 865 - Hone Kong - Dr. E. K. Yeoh

Healthy infants and children, ages 3 months through 11 years, who are negative for hepatitis B serologic markers are enrolled in Study 865. The children are assigned to receive 5 mcg injections of vaccine lot C-K732 at 0 and 1 months or at 0, 1, and 6 months.

Ninety children, in the two injection regimen, have received one 5 mcg injection of vaccine and 70 of these have received the second injection. At 6 months, 98% (49/50) of the children seroconverted (S/N $\geq$2.1) for anti-HBs and 94% (47/50) developed protective levels of antibody (mIU/ml $\geq$10). The GMT for all vaccinees at that time was 81.6 mIU/ml and 102.5 for responders (mIU/ml $\geq$10). At 8 months, 87.5% (21/24) of the vaccinees were positive for anti-HBs (mIU/ml $\geq$10) with a GMT of 145.0 mIU/ml.

Eighty-eight children, in the three injection regimen, have received the first 5 mcg injection of vaccine. Seventy-two and 46 subjects have been administered the second and third injections, respectively. At 8 months, 100%

Study 865 - Hong Kong - Dr. E. K. Yeoh (Cont.)

(21/21) seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees as 1894.8 mIU/ml.

No serious or alarming adverse reactions attributable to vaccine have been reported. Vaccination and follow-up continue in progress.

Study 891 - China - Dr. Z. H. Hu

The study population consists of healthy adults and healthy children who are negative for hepatitis B serologic markers. Healthy adults receive either 10 mcg injections of yeast recombinant vaccine or 20 mcg injections of plasma-derived vaccine. Healthy children received either 5 mcg injections of yeast recombinant vaccine or 10 mcg injections of plasma-derived vaccine. All injections are administered at 0, 1, and 6 months. Yeast recombinant vaccine lot C-K564 and plasma-derived vaccine lot 0027L are being utilized.

Twenty-five children have received the first injection of yeast recombinant vaccine and 25 have received the first injection of plasma-derived vaccine. None have received second or third injections of vaccine. Serology data are not presently available. No serious or alarming adverse events attributable to vaccine have been reported. Vaccination and follow-up continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 809
PURPOSE:	To evaluate antibody and clinical responses to various doses of vaccine in the following initially seronegative populations: 1. Healthy Children (1-11 years of age) 2. Healthy Adults
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot # 972/C-K444 (10 mcg HBsAg/ml) 985/C-K732 (5 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Drs. Stanley Plotkin and Stuart Starr Division of Preventive Medicine Joseph Stokes, Jr. Research Institute Children's Hospital of Philadelphia 34th Street and Civic Center Blvd. Philadelphia, PA 19104
STUDY LOCATIONS:	The Pediatric Medical Associates 420 Township Line Road Havertown, PA 19083 George A. Starkweather, M.D. 1001 Pennsylvania Avenue Havertown, PA 19083
DATE INITIATED:	February 2, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of healthy children (ages 1-11 years) and healthy adults who are negative for HBsAg, anti-HBc, and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 809

PROCEDURE:

Children in the study receive a 0.5 ml (5 mcg HBsAg) or a 0.25 ml (2.5 mcg HBsAg) intramuscular injection of lot # 972/C-K444 vaccine at 0, 1 and 6 months or a 0.5 ml (2.5 mcg HBsAg) or 0.25 ml (1.25 mcg HBsAg) injection of lot # 985/C-K732 vaccine according to the same time schedule. Adults receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of lot # 972/C-K444 vaccine at 0, 1 and 6 months. Vaccine recipients (or the parent or guardian in the case of a minor) are asked to record their temperature daily for five days after each injection of vaccine and to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) is obtained from each prospective vaccine recipient one to two weeks before the first vaccination. Post-vaccination bleedings are obtained at 1, 3, 7 and 12 months from some of the children and at 2, 6, 8 and 12 months from others. Post-vaccination bleedings are obtained from adult vaccine recipients at 1, 2, 3, 6, 8, 12 and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples may also be tested for yeast antibody and those with an anti-HBs titer $\geq$ 25 mIU/ml may be tested for the proportions of anti-a and anti-d activity.

RESULTS:

HEALTHY CHILDREN:

1.25 mcg Lot # 985/C-K732 at 0, 1, and 6 months
2.5 mcg Lot # 985/C-K732 at 0, 1, and 6 months
2.5 mcg Lot # 972/C-K444 at 0, 1, and 6 months
5 mcg Lot # 972/C-K444 at 0, 1, and 6 months

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
1.25 mcg	26	26	25
2.5 mcg	32	32	30
5 mcg	22	22	21

Study 809

RESULTS: (Cont.)

2. Serologic Results:

Serologic data are available for 14, 22, and 14 participants at 7/8 months, who received 1.25 mcg, 2.5 mcg and 5 mcg injections of vaccine, respectively. One hundred percent of the subjects (all dose levels) seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at that time. Anti-HBs responses and GMTs for 7/8 month data are summarized in the following table.

Dose Level	% with Anti-HBs S/N ≥ 2.1	% with Anti-HBs mIU/ml ≥ 10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥ 2.1	GMT (mIU/ml) Responders mIU/ml ≥ 10
1.25 mcg	100(14/14)	100 (14/14)	2181.1	2181.1	2181.1
2.5 mcg	100(21/21)	100 (21/21)	6230.2	6230.2	6230.2
5 mcg	100(14/14)	100 (14/14)	15965.5	15965.5	15965.5

Among participants with serology data at 12 months, 100% (9/9), 95% (18/19) and 100% (13/13) were positive for anti-HBs (mIU/ml ≥10) from dose level 1.25 mcg, 2.5 mcg and 5.0 mcg, respectively. The GMTs for all vaccinees from these dose levels were 819.2, 3051.5, and 3481.6 mIU/ml, respectively.

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for at least 25, 30, and 18 participants, after each injection, in the 1.25 mcg, 2.5 mcg, and 5 mcg dose level, respectively. The overall frequencies of complaints follow.

Study 809

RESULTS (CONT.):

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	1.25 mcg	0(0/26)	0(0/26)	4(1/25)
	2.5 mcg	6(2/32)	3(1/31)	0(0/30)
	5.0 mcg	0(0/21)	6(1/18)	0(0/20)
Systemic	1.25 mcg	19(5/26)	12(3/26)	12(3/25)
	2.5 mcg	19(6/32)	13(4/31)	7(2/30)
	5.0 mcg	14(3/21)	22(4/18)	5(1/20)

Refer to Tables 2 through 4 for listings of specific complaints by injection number and dose level. Maximum temperature data are provided in Tables 5 through 7.

There have been no serious or alarming reactions attributable to vaccine.

Table 1

Antibody Responses Among Healthy Children Following Vaccination with
1.25, 2.5, or 5 mcg Injections of Yeast Recombinant Hepatitis B Vaccine
Lot # 972/C-K444 and 985/C-K732 at 0, 1, and 6 Months

	1.25 mcg					2.5 mcg					5 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Mos.)	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	40 (10/25)	8 (2/25)	1.2	7.4	69.7	44 (12/27)	22 (6/27)	1.9	11.4	28.9	47 (9/19)	16 (3/19)	2.0	11.7	63.9
2	92 (11/12)	58 (7/12)	26.2	36.0	129.2	88 (7/8)	63 (5/8)	37.8	75.5	236.4	100 (6/6)	67 (4/6)	23.7	23.7	43.5
3	100 (7/7)	86 (6/7)	52.7	52.7	77.5	100 (11/11)	82 (14/11)	86.9	86.9	144.7	100 (10/10)	100 (10/10)	189.3	189.3	189.3
6	100 (21/21)	90 (19/21)	75.9	75.9	100.7	96 (27/28)	93 (26/28)	125.2	156.5	175.7	100 (19/19)	100 (19/19)	308.4	308.4	308.4
7/8	100 (14/14)	100 (14/14)	2181.1	2181.1	2181.1	100 (21/21)	100 (21/21)	6230.2	6230.2	6230.2	100 (14/14)	100 (14/14)	15965.5	15965.5	15965.5
12	100 (9/9)	100 (9/9)	819.2	819.2	819.2	100 (19/19)	95 (18/19)	3051.5	3051.5	4205.1	100 (13/13)	100 (13/13)	3481.6	3481.6	3481.6

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK732
DOSE : 1.25 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	1 (3.8%)	2 (7.7%)	1 (3.8%)	3 (11.5%)	3 (11.5%)	2 (7.7%)	5 (19.2%)
WHOLE BODY/GENERAL	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
FATIGUE/WEAKNESS	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
VIRAL INFECTION, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
INTEGUMENTARY STSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
PAPULAR RASH	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
RESPIRATORT	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
COUGH	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
DIARRHEA	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0609
TREATMENT :
LOT NUMBER : CK732
DOSE : 1.25 MCG
PATIENT CLASS: HEALTHY CHILDREN

	TOTAL VACCINEES (26 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						
CLINICAL COMPLAINTS	0	1	2	3	4	5	NUMBER WITH COMPLAINTS
DIMINISHED APPETITE	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
OTITIS MEDIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	2 (7.7%)
IRRITABILITY	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
INSOMNIA/DISTURBED SLEEP	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
PERSONS WITH COMPLAINTS	1 (3.8%)	2 (7.7%)	1 (3.8%)	3 (11.5%)	3 (11.5%)	2 (7.7%)	5 (19.2%)
PERSONS WITH NO COMPLAINTS	25 (96.2%)	24 (92.3%)	25 (96.2%)	23 (88.5%)	23 (88.5%)	24 (92.3%)	21 (80.8%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK732
DOSE : 1.25 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	2 (7.7%)	2 (7.7%)	2 (7.7%)	1 (3.8%)	2 (7.7%)	2 (7.7%)	3 (11.5%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
SWEATING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
RESPIRATORY	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
PHARYNGITIS (SORE THROAT)	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)
DIGESTIVE SYSTEM	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)
DIARRHEA	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)
PSYCHIATRIC/BEHAVIORAL	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
IRRITABILITY	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK732
DOSE : 1.25 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	2 (7.7%)	2 (7.7%)	2 (7.7%)	1 (3.8%)	2 (7.7%)	2 (7.7%)	3 (11.5%)
PERSONS WITH NO COMPLAINTS	24 (92.3%)	24 (92.3%)	24 (92.3%)	25 (96.2%)	24 (92.3%)	24 (92.3%)	23 (88.5%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK732
DOSE : 1.25 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (25 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
SORENESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (4.0%)	2 (8.0%)	3 (12.0%)	0 (0.0%)		3 (12.0%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)		2 (8.0%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
ILLNESS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)		1 (4.0%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)	2 (8.0%)	0 (0.0%)		2 (8.0%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)		1 (4.0%)
LOOSE STOOL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.0%)	0 (0.0%)		1 (4.0%)
PERSONS WITH COMPLAINTS	1 (4.0%)	0 (0.0%)	1 (4.0%)	2 (8.0%)	3 (12.0%)	0 (0.0%)		4 (16.0%)
PERSONS WITH NO COMPLAINTS	24 (96.0%)	25 (100.0%)	24 (96.0%)	23 (92.0%)	22 (88.0%)	25 (100.0%)		21 (84.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	2 (6.3%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.3%)
SORENESS	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
TENDERNESS	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
SYSTEMIC	1 (3.1%)	2 (6.3%)	1 (3.1%)	0 (0.0%)	2 (6.3%)	3 (9.4%)		6 (18.8%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)		1 (3.1%)
HEADACHE	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)		1 (3.1%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	2 (6.3%)	1 (3.1%)		3 (9.4%)
VIRAL INFECTION, NOS	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	2 (6.3%)	1 (3.1%)		3 (9.4%)
RESPIRATORY	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)		2 (6.3%)
UPPER RESPIRATORY INFECT., NOS	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
CROUP	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)		1 (3.1%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NAUSEA	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
PERSONS WITH COMPLAINTS	3 (9.4%)	3 (9.4%)	1 (3.1%)	0 (0.0%)	2 (6.3%)	3 (9.4%)		7 (21.9%)
PERSONS WITH NO COMPLAINTS	29 (90.6%)	29 (90.6%)	31 (96.9%)	32 (100.0%)	30 (93.8%)	29 (90.6%)		25 (78.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.2%)
SORENESS	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.2%)
SYSTEMIC	1 (3.2%)	2 (6.5%)	1 (3.2%)	0 (0.0%)	1 (3.2%)	0 (0.0%)		4 (12.9%)
WHOLE BODY/GENERAL	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.2%)
FATIGUE/WEAKNESS	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.2%)
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.2%)
URTICARIA/HIVES	0 (0.0%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.2%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)		1 (3.2%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)		1 (3.2%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.5%)
DIARRHEA	0 (0.0%)	1 (3.2%)	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.5%)
PERSONS WITH COMPLAINTS	2 (6.5%)	3 (9.7%)	1 (3.2%)	0 (0.0%)	1 (3.2%)	0 (0.0%)		5 (16.1%)

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH NO COMPLAINTS	29 (90.5%)	28 (90.3%)	30 (96.8%)	31 (100.0%)	30 (96.8%)	31 (100.0%)		26 (83.9%)
PERSONS WITH NO DATA	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)		1 (3.1%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
SYSTEMIC	1 (3.3%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		2 (6.7%)
WHOLE BODY/GENERAL	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
HEADACHE	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
RESPIRATORY	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
UPPER RESPIRATORY INFECT., NOS	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
VOMITING	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
PERSONS WITH COMPLAINTS	1 (3.3%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)		2 (6.7%)
PERSONS WITH NO COMPLAINTS	29 (96.7%)	30 (100.0%)	29 (96.7%)	29 (96.7%)	30 (100.0%)	30 (100.0%)		28 (93.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (22 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	1 (4.8%)	1 (4.8%)	2 (9.5%)	3 (14.3%)	3 (14.3%)	0 (0.0%)	3 (14.3%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.5%)	2 (9.5%)	0 (0.0%)	2 (9.5%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	1 (4.8%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	1 (4.8%)
INTEGUMENTART SYSTEM	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	1 (4.8%)
PAPULAR RASH	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	1 (4.8%)
RASH, NOS	1 (4.8%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (4.8%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	1 (4.8%)
PERSONS WITH COMPLAINTS	1 (4.8%)	1 (4.8%)	2 (9.5%)	3 (14.3%)	3 (14.3%)	0 (0.0%)	3 (14.3%)
PERSONS WITH NO COMPLAINTS	20 (95.2%)	20 (95.2%)	19 (90.5%)	18 (85.7%)	18 (85.7%)	21 (100.0%)	18 (85.7%)
PERSONS WITH NO DATA	1 (4.5%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	1 (4.5%)

Table 4 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (22 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
ECCHYMOSIS	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
SYSTEMIC	2 (11.1%)	2 (11.1%)	1 (5.6%)	2 (11.1%)	0 (0.0%)	1 (5.6%)	4 (22.2%)
WHOLE BODY/GENERAL	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	3 (16.7%)
FATIGUE/WEAKNESS	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	2 (11.1%)
BRUISE FROM VENIPUNCTURE	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (5.6%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
TEETHING	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)

Table 4 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (22 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PSYCHIATRIC/BEHAVIORAL	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (11.1%)
IRRITABILITY	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (11.1%)
PERSONS WITH COMPLAINTS	2 (11.1%)	3 (16.7%)	1 (5.6%)	2 (11.1%)	0 (0.0%)	1 (5.6%)		5 (27.8%)
PERSONS WITH NO COMPLAINTS	16 (88.9%)	15 (83.3%)	17 (94.4%)	16 (88.9%)	18 (100.0%)	17 (94.4%)		13 (72.2%)
PERSONS WITH NO DATA	4 (18.2%)	4 (18.2%)	4 (18.2%)	4 (18.2%)	4 (18.2%)	4 (18.2%)		4 (18.2%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTHY CHILDREN

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
SYSTEMIC	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)		1 (5.0%)
RESPIRATORY	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)		1 (5.0%)
UPPER RESPIRATORY INFECT., NOS	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)		1 (5.0%)
PERSONS WITH COMPLAINTS	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)		1 (5.0%)
PERSONS WITH NO COMPLAINTS	19 (95.0%)	19 (95.0%)	19 (95.0%)	19 (95.0%)	19 (95.0%)	19 (95.0%)		19 (95.0%)
PERSONS WITH NO DATA	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)		1 (4.8%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES

RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK732
DOSE : 1.25 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (26 PATIENTS) - DOSE 1 DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
NORMAL	1 (5.3%)	1 (5.3%)	2 (10.0%)	2 (10.0%)	2 (10.0%)	2 (10.0%)		1 (5.0%)
< 99	10 (52.6%)	13 (68.4%)	13 (65.0%)	12 (60.0%)	14 (70.0%)	13 (65.0%)		8 (40.0%)
99 - 99.9	6 (31.6%)	4 (21.1%)	3 (15.0%)	5 (25.0%)	4 (20.0%)	4 (20.0%)		7 (35.0%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)		1 (5.0%)
101 - 101.9	2 (10.5%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
102 - 102.9	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
103 - 103.9	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
TEMPERATURE TAKEN	19 (73.1%)	19 (73.1%)	20 (76.9%)	20 (76.9%)	20 (76.9%)	20 (76.9%)		20 (76.9%)
TEMPERATURE NOT TAKEN	7 (26.9%)	7 (26.9%)	6 (23.1%)	6 (23.1%)	6 (23.1%)	6 (23.1%)		6 (23.1%)

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK732
DOSE : 1.25 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (26 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (5.6%)	1 (5.6%)	1 (5.9%)	1 (5.6%)	1 (5.9%)	1 (6.3%)			1 (5.6%)
< 99	9 (50.0%)	10 (55.6%)	9 (52.9%)	7 (38.9%)	9 (52.9%)	9 (56.3%)			6 (33.3%)
99 - 99.9	8 (44.4%)	7 (38.9%)	6 (35.3%)	9 (50.0%)	6 (35.3%)	6 (37.5%)			9 (50.0%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (5.9%)	0 (0.0%)			1 (5.6%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)			1 (5.6%)
TEMPERATURE TAKEN	18 (69.2%)	18 (69.2%)	17 (65.4%)	18 (69.2%)	17 (65.4%)	16 (61.5%)			18 (69.2%)
TEMPERATURE NOT TAKEN	8 (30.8%)	8 (30.8%)	9 (34.6%)	8 (30.8%)	9 (34.6%)	10 (38.5%)			8 (30.8%)

Table 5 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK732
DOSE : 1.25 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (25 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)
< 99	10 (71.4%)	10 (71.4%)	8 (57.1%)	9 (64.3%)	10 (71.4%)	11 (78.6%)			6 (42.9%)
99 - 99.9	4 (28.6%)	4 (28.6%)	4 (28.6%)	5 (35.7%)	4 (28.6%)	3 (21.4%)			7 (50.0%)
102 - 102.9	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (7.1%)
TEMPERATURE TAKEN	14 (56.0%)	14 (56.0%)	14 (56.0%)	14 (56.0%)	14 (56.0%)	14 (56.0%)			14 (56.0%)
TEMPERATURE NOT TAKEN	11 (44.0%)	11 (44.0%)	11 (44.0%)	11 (44.0%)	11 (44.0%)	11 (44.0%)			11 (44.0%)

Table 6

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (32 PATIENTS) - DOSE 1								
	DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
NORMAL	3 (10.0%)	3 (10.3%)	3 (10.0%)	3 (10.0%)	3 (10.3%)	3 (10.0%)			3 (10.0%)
< 99	14 (46.7%)	20 (69.0%)	16 (53.3%)	20 (66.7%)	17 (58.6%)	18 (60.0%)			10 (33.3%)
99 - 99.9	11 (36.7%)	5 (17.2%)	8 (26.7%)	5 (16.7%)	7 (24.1%)	7 (23.3%)			13 (43.3%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (3.3%)	2 (6.7%)	1 (3.4%)	2 (6.7%)			1 (3.3%)
101 - 101.9	2 (6.7%)	1 (3.4%)	2 (6.7%)	0 (0.0%)	1 (3.4%)	0 (0.0%)			3 (10.0%)
TEMPERATURE TAKEN	30 (93.8%)	29 (90.6%)	30 (93.8%)	30 (93.8%)	29 (90.6%)	30 (93.8%)			30 (93.8%)
TEMPERATURE NOT TAKEN	2 (6.3%)	3 (9.4%)	2 (6.3%)	2 (6.3%)	3 (9.4%)	2 (6.3%)			2 (6.3%)

Table 6 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (32 PATIENTS) - DOSE 2								
	DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
NORMAL	5 (20.0%)	5 (20.8%)	5 (20.8%)	5 (20.0%)	5 (20.8%)	5 (20.8%)			5 (19.2%)
< 99	10 (40.0%)	10 (41.7%)	13 (54.2%)	14 (56.0%)	14 (58.3%)	13 (54.2%)			8 (30.8%)
99 - 99.9	7 (28.0%)	8 (33.3%)	6 (25.0%)	6 (24.0%)	4 (16.7%)	5 (20.8%)			10 (38.5%)
100 - 100.9	3 (12.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (4.2%)			3 (11.5%)
TEMPERATURE TAKEN	25 (78.1%)	24 (75.0%)	24 (75.0%)	25 (78.1%)	24 (75.0%)	24 (75.0%)			26 (81.3%)
TEMPERATURE NOT TAKEN	7 (21.9%)	8 (25.0%)	8 (25.0%)	7 (21.9%)	8 (25.0%)	8 (25.0%)			6 (18.8%)

Table 6 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
DOSE : 2.5 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	5 (19.2%)	5 (19.2%)	6 (23.1%)	5 (19.2%)	5 (19.2%)	5 (19.2%)			5 (19.2%)
< 99	9 (34.6%)	14 (53.8%)	13 (50.0%)	13 (50.0%)	16 (61.5%)	16 (61.5%)			4 (15.4%)
99 - 99.9	11 (42.3%)	7 (26.9%)	6 (23.1%)	7 (26.9%)	4 (15.4%)	5 (19.2%)			14 (53.8%)
100 - 100.9	1 (3.8%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)			3 (11.5%)
TEMPERATURE TAKEN	26 (86.7%)	26 (86.7%)	26 (86.7%)	26 (86.7%)	26 (86.7%)	26 (86.7%)			26 (86.7%)
TEMPERATURE NOT TAKEN	4 (13.3%)	4 (13.3%)	4 (13.3%)	4 (13.3%)	4 (13.3%)	4 (13.3%)			4 (13.3%)

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (22 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (4.8%)	1 (5.0%)	1 (4.8%)	1 (5.0%)	1 (5.0%)	1 (5.0%)			1 (4.8%)
< 99	9 (42.9%)	11 (55.0%)	11 (52.4%)	11 (55.0%)	12 (60.0%)	10 (50.0%)			5 (23.8%)
99 - 99.9	8 (38.1%)	7 (35.0%)	7 (33.3%)	8 (40.0%)	6 (30.0%)	8 (40.0%)			11 (52.4%)
100 - 100.9	3 (14.3%)	1 (5.0%)	2 (9.5%)	0 (0.0%)	1 (5.0%)	1 (5.0%)			4 (19.0%)
TEMPERATURE TAKEN	21 (95.5%)	20 (90.9%)	21 (95.5%)	20 (90.9%)	20 (90.9%)	20 (90.9%)			21 (95.5%)
TEMPERATURE NOT TAKEN	1 (4.5%)	2 (9.1%)	1 (4.5%)	2 (9.1%)	2 (9.1%)	2 (9.1%)			1 (4.5%)

Table 7 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (22 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	3 (18.8%)	3 (18.8%)	3 (20.0%)	3 (18.8%)	3 (18.8%)	3 (21.4%)			3 (18.8%)
< 99	7 (43.8%)	8 (50.0%)	8 (53.3%)	9 (56.3%)	9 (56.3%)	8 (57.1%)			5 (31.3%)
99 - 99.9	5 (31.3%)	4 (25.0%)	3 (20.0%)	3 (18.8%)	3 (18.8%)	3 (21.4%)			7 (43.8%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.3%)	1 (6.3%)	0 (0.0%)			0 (0.0%)
101 - 101.9	1 (6.3%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (6.3%)
TEMPERATURE TAKEN	16 (72.7%)	16 (72.7%)	15 (68.2%)	16 (72.7%)	16 (72.7%)	14 (63.6%)			16 (72.7%)
TEMPERATURE NOT TAKEN	6 (27.3%)	6 (27.3%)	7 (31.8%)	6 (27.3%)	6 (27.3%)	8 (36.4%)			6 (27.3%)

Table 7 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES

RECOMBINANT HEPATITIS B VACCINE

STUDY : 0809
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTHY CHILDREN

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (21 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	4 (22.2%)	4 (22.2%)	4 (22.2%)	4 (22.2%)	4 (22.2%)	4 (22.2%)			4 (22.2%)
< 99	4 (22.2%)	9 (50.0%)	11 (61.1%)	10 (55.6%)	11 (61.1%)	11 (61.1%)			2 (11.1%)
99 - 99.9	8 (44.4%)	4 (22.2%)	3 (16.7%)	4 (22.2%)	3 (16.7%)	3 (16.7%)			10 (55.6%)
100 - 100.9	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (5.6%)
101 - 101.9	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (5.6%)
TEMPERATURE TAKEN	18 (85.7%)	18 (85.7%)	18 (85.7%)	18 (85.7%)	18 (85.7%)	18 (85.7%)			18 (85.7%)
TEMPERATURE NOT TAKEN	3 (14.3%)	3 (14.3%)	3 (14.3%)	3 (14.3%)	3 (14.3%)	3 (14.3%)			3 (14.3%)

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 865
PURPOSE:	To evaluate antibody and clinical responses to two or three 5 mcg doses of vaccine among healthy infants and children, ages 3 months through 11 years, who are seronegative for hepatitis B markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot # 985/C-K732 (5 mcg/ml)
PRIMARY INVESTIGATOR:	Prof. E. K. Yeoh, M.D. Consultant Physician Medical A Unit Queen Elizabeth Hospital Wylie Road Kowloon, Hong Kong
SECONDARY INVESTIGATOR:	W. K. Chang, M.P., B.S., F.R.C. Path. Consultant Microbiologist Queen Mary Hospital Pokfulam Road Hong Kong Ching Lung Lai, M.B., M.R.C.P., F.R.C.P. Consultant Physician Queen Mary Hospital Pokfulam Road Hong Kong
STUDY LOCATION:	Queen Elizabeth Hospital Wylie Road Kowloon, Hong Kong Queen Mary Hospital Pokfulam Road Hong Kong
DATE INITIATED:	2/1/85
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population will consist of 100-200 infants and children, ages 3 months through 11 years, who are negative for hepatitis B serologic markers and have not previously received any hepatitis B vaccine.

Study 865

PROCEDURE:

Participants are randomly assigned to one of 2 groups with 50-100 children or infants in each group. Group one receives intramuscular injections of vaccine at 0 and 1 month (5 mcg doses). Participants in group 2 receive their injections at 0, 1 and 6 months. The parent or guardian is asked to record the child's temperature for 5 days after each injection and note any local or systemic complaints.

Blood samples are obtained prior to vaccination and at 1, 3, 6, 8, 12 and 24 months post initial injection. All samples are assayed for HBsAg, anti-HBs, anti-HBc and ALT by Dr. Yeoh. Some samples may be tested for yeast antibody at MSDRL. Samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested to determine anti-a and anti-d activity.

RESULTS:

HEALTHY INFANTS AND CHILDREN:

5 mcg Lot #985/C-K732 at 0 and 1 month
5 mcg Lot #985/C-K732 at 0, 1, and 6 months

1. Number Vaccinated:

Group #	Dose Level	Injection No. 1	2	3
1	5 mcg	90	70	-
2	5 mcg	88	72	46

2. Serologic Results:

Serologic data at 6 months are available for 24 participants in the two injection regimen. At that time 98% (49/50) of the children seroconverted (S/N $\geq$2.1) for anti-HBs and 94% (47/50) developed protective levels of antibody (mIU/ml $\geq$10). Among the 21 participants for whom 8 month serologic data are available in the three injection regimen, 100% (21/21) seroconverted and developed protective levels of antibody (mIU/ml $\geq$10).

A large boost in titer was seen among those children who received the third injection. Geometric mean titers at 8 months were 1894.8

Study 865

RESULTS (CONT.)

mIU/ml and 84.50 mIU/ml for those in the three and two injection groups, respectively. Table 1 lists seroconversion rates and GMTs for one to three months of follow-up.

3. Clinical Complaints:

Clinical follow-up data are available for 142, 117 and 25 participants following injections one, two and three, respectively.

Type of Complaint	Frequency in % by Injection		
Injection Site	2 (3/141)	2 (2/116)	0 (0/25)
Systemic	6 (8/141)	4 (5/116)	4 (1/25)

There have been no serious or alarming adverse experiences attributable to the vaccine.

Table 1

Antibody Responses Among Healthy Children and Infants Following Vaccination with
5 mcg Injections of Yeast Recombinant Hepatitis B Vaccine
Lot #985/C-K732 at 0, 1, and 6 Months or 0 and 1 Month in Study 865

	Group 1 0 and 1 Month					Group 2 0, 1 and 6 Months				
Time (Months)	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	S/N ≥ 2.1	mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	S/N ≥ 2.1	mIU/ml ≥ 10
1	33(23/70)	11(8/70)	0.8	8.6	21.9	40(29/72)	15(11/72)	1.1	9.1	29.7
3	97(57/59)	83(49/59)	52.9	63.5	93.7	91(53/58)	79(46/58)	37.7	63.4	88.6
6	98(49/50)	94(47/50	81.6	91.5	102.5	98(45/46)	76(35/46)	42.1	58.9	93.7
8	96(23/24)	88(21/24)	84.5	107.9	144.9	100(21/21)	100(21/21)	1894.8	1894.8	1894.8

23921/3
1/18/86

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 891
PURPOSE:	To compare the antibody and clinical responses to recombinant hepatitis B vaccine and plasma-derived hepatitis B vaccine among healthy adults and children who are negative for hepatitis B virus serologic markers.
VACCINES:	1. Yeast Recombinant Hepatitis B Vaccine Lot 979/C-K564 (10 mcg HBsAg/ml) 2. Plasma-Derived Hepatitis B Vaccine Lot 0027L (20 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Dr. Hu Zong-Han Department of Biological Products Inspection Bureau of Pharmaceutical and Biological Inspection Ministry of Health Temple of Heaven, West Gate Beijing, People's Republic of China
SECONDARY INVESTIGATOR:	Dr. Shi Guiyong Director of Epidemic Department Chinese Medical University Shen Yang, People's Republic of China
STUDY LOCATION:	Shen Yang Municipal Anti-Epidemic Station Shen Yang, People's Republic of China
DATE STUDY INITIATED:	December, 1985
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 200 healthy adults and 200 healthy children of either sex (exluding pregnant women), who are negative for HBsAg, anti-HBc and HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Study 891

STUDY PROCEDURE: Participants are grouped by age and randomly assigned to receive the yeast recombinant or plasma-derived hepatitis B vaccine as follows:

Group	Population	Vaccine	Dose	Number	Regimen
1	Adults (≥30 years)	Recombinant	10 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
2	Adults (18–29 years)		10 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
3	Children (5–10 years)		5 mcg	100	0.5 ml intramuscular injection of vaccine at 0, 1, and 6 months
4	Adults (≥30 years)	Plasma	20 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
5	Adults (18–29 years)		20 mcg	50	1.0 ml intramuscular injection of vaccine at 0, 1, and 6 months
6	Children (5–10 years)		10 mcg	100	0.5 ml intramuscular injection of vaccine at 0, 1, and 6 months

Study participants or the participant's parent or guardian record their temperature or that of their child, and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two to three weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 3, 6, 7, 8, 9, 12, and 24 months. All serum samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT.

Study 891

RESULTS: (Contd) To date 100 adults and children have received one injection of yeast recombinant or plasma-derived hepatitis B vaccine. No serious or alarming reactions attributable to vaccination have been reported. Clinical follow-up data and serologic results are not yet available. The study continues in progress.

DIALYSIS/PRE-DIALYSIS

SUMMARY - DIALYSIS AND PREDIALYSIS PATIENTS

To date, 288 patients with chronic renal insufficiency, including 210 patients who are receiving dialysis treatments (dialysis patients) and 78 patients who are not yet receiving such treatments (predialysis patients), have received one or more injections of the yeast recombinant vaccine.

Predialysis patients receive an injection of the yeast recombinant hepatitis B vaccine (10, 20, or 40 mcg dose) at 0, 1, and 6 months. Dialysis patients receive an injection of the vaccine (20, 40, or 100 mcg dose) either at 0, 1, and 6 months or according to a more intensified regimen (20 or 40 mcg dose) at 0, 1, 2, 3, 4 and 5 months. In four of the studies, patients received the vaccine as an intramuscular injection in the deltoid. However, in one study (Study 838), vaccine was administered in the buttock.

Post-vaccination clinical data are available on 135 dialysis and 49 predialysis patients following the third injection of vaccine, and for 33 dialysis patients following a sixth injection. Serologic data following the last injection of vaccine are available for 50 predialysis patients and 84 dialysis patients who received three injections of vaccine and 32 dialysis patients on the six injection regimen.

IMMUNOGENICITY

Predialysis Patients

Deltoid Injection: At 7-8 months 15% (10 mcg dose), 68% (20 mcg dose) and 67% (40 mcg dose) of predialysis patients who received three injections of vaccine in the deltoid had an anti-HBs titer of S/N $\geq$2.1. Protective levels of antibody (S/N or mIU/ml $\geq$10) were induced in 15% (10 mcg dose), 58% (20 mcg dose), and 61% (40 mcg dose) of vaccine recipients. Among patients with a minimum titer of S/N $\geq$2.1, and for whom titers are currently available in units of mIU/ml, the geometric mean titers were 67.7 mIU/ml (10 mcg dose), 213.7 mIU/ml (20 mcg dose), and 120.9 mIU/ml (40 mcg dose) at this time. For responders with titers of at least 10 mIU/ml, the geometric mean titers were 67.7 mIU/ml (10 mcg dose), 120.9 mIU/ml (20 mg dose) and 186.4 mIU/ml (40 mcg dose). By 12 months titers had declined with 0% (10 mcg dose), 50% (20 mcg dose), and 40% (40 mcg dose) still retaining titers of S/N or mIU/ml $\geq$10 (Table 1).

Buttock Injection: One month after the first injection of vaccine, 13% of predialysis patients receiving a 10 mcg dose in the buttock have detectable antibody (S/N $\geq$2.1) with a geometric mean titer among responders of 4.6 mIU/ml. None had achieved a titer of mIU/ml $\geq$10 (Table 1).

Dialysis Patients

Deltoid Injection: At 7/8 months, among dialysis patients who had completed the standard three injection regimen in the deltoid, 59% (20 mcg dose) and 94%

(40 mcg dose) had an anti-HBs titer of S/N ≥2.1, while 48% (20 mcg dose) and 88% (40 mcg dose) achieved protective levels of antibody (mIU/ml ≥10). The geometric mean titers at 7-8 months for patients with anti-HBs ≥2.1 S/N was 69.1 mIU/ml (20 mcg dose) and 331.8 mIU/ml (40 mcg dose), while for responders with a titer of mIU/ml ≥10 the GMTs were 118.6 mIU/ml (20 mcg dose) and 445.5 mIU/ml (40 mcg dose) (Table 2). Forty mcg doses of vaccine produced significantly higher seroconversion rates (S/N ≥2.1 and mIU/ml ≥10) and levels of response (GMT of all vaccinees) at 3, 6, and 7-8 months (See Appendix 1 for statistical methods). By 12 months antibody levels had declined with 41% (20 mcg dose) and 71% (40 mcg dose) still retaining titers of mIU/ml ≥10. Geometric mean titers of responders with protective levels of antibody decreased to 79.9 mIU/ml (20 mcg dose) and 165.6 mIU/ml (40 mcg dose).

At 3 months (2 months after the second injection) 68% of dialysis patients receiving 100 mcg doses of vaccine in the deltoid seroconverted (S/N ≥2.1), with 25% developing protective levels of antibody (mIU/ml ≥10). The GMT of responders with antibody levels of S/N ≥2.1 was 8.4 mIU/ml at this time, while among responders with titers of mIU/ml ≥10 the GMT was 33.3 mIU/ml (Table 2). This study is still in progress and serologic results are not yet available after the third dose of vaccine.

Buttock Injection: At 7-8 months 64% of dialysis patients who received 40 mcg doses of vaccine in the buttock at 0, 1, and 6 months had an anti-HBs titer of S/N ≥2.1, while 58% achieved a protective titer of mIU/ml ≥10. By 10 months, 65% still retained titers of S/N ≥2.1, although the proportion with titers of mIU/ml ≥10 had declined slightly to 54%. At 7/8 months the geometric mean titers of responders with titers of S/N ≥2.1 was 90.2 mIU/ml, while responders with titers of mIU/ml ≥10 had a GMT of 115.5 mIU/ml. The GMT of responders with protective levels of antibody remained fairly constant through 10 months (Table 3).

Among dialysis patients administered vaccine in the buttock at 0, 1, 2, 3, 4, and 5 months, 56% (20 mcg dose) and 69% (40 mcg dose) seroconverted (S/N ≥2.1) at 6 months, with 44% (20 mcg dose) and 69% (40 mcg dose) achieving a protective titer of mIU/ml ≥10 (Table 3). There were no significant differences found in these seroconversion rates by dose level at either cutoff. At 10 months, 50% (20 mcg dose) and 67% (40 mcg dose) retained an anti-HBs titer of S/N ≥2.1, while 44% (20 mcg dose) and 50% still retained titers of mIU/ml ≥10. Responders with S/N ≥2.1 had a geometric mean titer of 87.3 mIU/ml (20 mcg dose) and 189.8 mIU/ml (40 mcg dose) at 6 months. Responders with mIU/ml ≥10 had GMTs of 190 mIU/ml for both the 20 and 40 mcg doses at this time. Through six months, levels of response (all vaccinees) were not shown to increase significantly with log dose level. By 10 months the geometric mean titers among patients with protective levels of antibody declined to 55 mIU/ml (20 mcg) and 27.7 mIU/ml (40 mcg).

When seroconversion rates and titers among dialysis patients who received three 40 mcg doses of vaccine in the buttock are compared to those who received six 40 mcg doses of vaccine in the buttock, the two regimens were not shown to be significantly different one month after the last injection of vaccine. (The statistical analysis included two subjects with 9 month data instead of 7/8 month data in addition to those subjects summarized above at 7/8 months).

SAFETY

The vaccine has been very well tolerated in predialysis and dialysis patients. No serious reactions attributable to vaccination have been reported. Most importantly none has occurred to date among individuals who have received at least two 100 mcg doses or as many as six 40 mcg doses of vaccine.

Predialysis Patients

Among predialysis patients, mild transient injection site reactions and systemic complaints were reported following injection of vaccine at frequencies of 6% and 8%, respectively (Table 4). The frequency of complaints after the first injection was higher than after the second or third injections. The most frequent injection site reaction was soreness (6%) (Table 7). The most frequent specific systemic complaints were nausea (3%), symptoms of upper respiratory infection (2%), chills (1%), and headache (1%) (Table 8). A temperature $\geq$100°F oral was reported following 8% of all injections (Table 4).

Dialysis Patients

The incidences of local (injection site) complaints, of systemic complaints, of either local or systemic complaints, and of fever (oral temperature of 100°F or more) were analyzed statistically to evaluate the safety of the vaccine in dialysis patients (See Appendix 1 for statistical methods). The incidence at each injection was defined as the number of subjects with the complaint at any time during the five-day period following vaccination divided by the number reporting, while the total was the sum of complaints following the three or six injections divided by the number of injections with follow-up.

Mild transient injection site reactions and systemic complaints were reported in dialysis patients following injection of vaccine at frequencies of 3% and 7%, respectively (Tables 5, 6).

Among those dialysis patients who received three injections of 20, 40, or 100 mcg administered in the deltoid or the buttock (Studies 816, 825, 838), local complaints increased significantly with log dose level at the second injection while systemic complaints decreased with dose level at the first injection. The most frequent injection site reaction was soreness (3%) (Tables 9, 11), and the most common systemic complaint was fatigue (2%) (Tables 10, 11). A temperature of $\geq$100°F (oral) was reported following 4% of all injections (Table 5). The rate of complaints appeared to be highest after the first injection and lowest after the second injection.

Among dialysis patients who received six injections of 20 or 40 mcg of vaccine administered in the buttock, complaints were not shown to be a function of log dose level . Very few complaints were reported at either dose level. No trend was found in incidence of complaints over the six injections for either dose level. A single individual reported an injection site reaction (pruritis) (Table 12), while systemic complaints occurring at

frequencies ≥1% included fatigue/weakness (5%), nausea (2%), headache (1%) and arthralgia (1%) (Table 13). A temperature of ≥100°F (oral) was reported following 4% of all injections (Table 8).

The three and six injection regimens in dialysis patients who received 20 or 40 mcg doses of vaccine in the deltoid or buttock were compared at each of the first three injections to determine if monthly injections caused greater or fewer complaints than those spaced further apart. The only significant difference found was in the incidence of systemic complaints after the second injection in dialysis patients who received 40 mcg doses of vaccine. Ten percent (2/20) of dialysis patients on the six injection regimen had a systemic complaint versus 0% (0/83) on the three injection regimen.

Although significant differences in complaint frequencies were found over dose levels, they were not of clinical consequence. The incidence of any clinical complaint was low.

SUMMARY

Predialysis and dialysis patients did not respond to the vaccine as well as healthy adults. The response rate and level of anti-HBs attained after three injections of vaccine does increase with dose level, and it would appear that responses are better if vaccine is administered in the deltoid rather than the buttock. Preliminary data suggest that 100 mcg doses of vaccine may induce antibody earlier than lower doses. Patients vaccinated under an intensified six injection regimen did not respond better than those receiving three injections of vaccine.

Table 1

Antibody Responses Among Initially Seronegative Predialysis Patients who Received Yeast Recombinant Hepatitis B Vaccine (Three Injection Regimen)

Studies: 789, 811

	DELTOID INJECTION															BUTTOCK INJECTION				
	3 x 10 mcg					3 x 20 mcg					3 x 40 mcg					3 x 10 mcg				
	% Seroconversion		GMT (mIU/ml)			% Seroconversion		GMT (mIU/ml) **			% Seroconversion		GMT (mIU/ml) **			% Seroconversion		GMT (mIU/ml)		
				Responders			S/N or		Responders			S/N or		Responders					Responders	
Time (Mos.)	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10 *	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10 *	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	0 (0/14)	0 (0/14)	0.3	---	---	0 (0/28)	0 (0/28)	0.3 (14)	—	--	4 (1/28)	0 (0/28)	0.3 (13)	--	--	13 (1/8)	0 (0/8)	0.7	4.6	---
3	0 (0/14)	0 (0/14)	0.3	---	---	22 (6/27)	7 (2/27)	0.5 (14)	90.0	90.0	23 (6/26)	12 (3/26)	0.3 (12)	--	—					
6	0 (0/13)	0 (0/13)	0.3	—		38 (8/21)	29 (6/21)	1.0 (14)	23.6	23.6	42 (8/19)	26 (5/19)	1.7 (12)	19.4	19.4					
7/8	15 (2/13)	15 (2/13)	0.7	67.7	67.7	68 (13/19)	58 (11/19)	13.8 (12)	213.7	213.7	67 (12/18)	61 (11/18)	23.6 (11)	120.9	186.4					
12	8 (1/12)	0 (0/12)	0.4	6.0	---	71 (10/14)	50 (7/14)	8.5 (10)	78.5	78.5	40 (4/10)	40 (4/10)	3.3 (10)	117.3	117.3					

* Serologic results obtained in Study 789 reported in S/N only.
** GMTs summarized obtained in Study 811 only. (N)

31251/1
1/22/86

Table 2

Antibody Responses Among Initially Seronegative Dialysis Patients
Who Received Yeast Recombinant Hepatitis B Vaccine In the Deltoid (Three Injection Regimen)

Studies: 816, 825

Time (Mos.)	3 x 20 mcg					3 x 40 mcg					3 x 100 mcg				
	% Seroconversion		GMT (mIU/ml)			% Seroconversion		GMT (mIU/ml)			% Seroconversion		GMT (S/N)		
				Responders					Responders					Responders	
	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	8 (2/26)	4 (1/26)	0.4	5.4	18.5	15 (4/26)	8 (2/26)	0.6	8.1	17.9	13 (5/38)	0 (0/38)	1.3	3.0	---
3	21 (5/24)	4 (1/24)	0.6	6.5	76.1	52 (13/25)	28 (7/25)	2.3	15.0	32.9	68 (19/28)	25 (7/28)	4.4	8.4	33.3
6	33 (8/24)	13 (3/24)	1.0	6.4	21.7	81 (13/16)	63 (10/16)	10.8	21.5	35.2					
7/8	59 (17/29)	48 (14/29)	7.8	69.1	118.6	94 (16/17)	88 (15/17)	219.7	331.8	445.5					
12	52 (15/29)	41 (12/29)	5.1	49.2	79.9	81 (17/21)	71 (15/21)	41.6	107.9	165.6					

Table 3

Antibody Responses Among Initially Seronegative Dialysis Patients Who Received Yeast Recombinant Hepatitis B Vaccine In The Buttock

Study 838

Time (Mos.)	3 x 40 mcg					6 x 40 mcg					6 x 20 mcg				
	% Seroconversion		GMT (mIU/ml)**			% Seroconversion		GMT (mIU/ml)**			% Seroconversion		GMT (mIU/ml)**		
				Responders					Responders					Responders	
	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	0 (0/48)	0 (0/48)	0.3	---	---	0 (0/20)	0 (0/20)	0.3	---	---	0 (0/20)	0 (0/20)	0.3	---	---
3	35 (16/46)	22 (10/46)	1.3	16.5	31.0	35 (7/20)	20 (4/20)	1.2	17.4	33.5	32 (6/19)	26 (5/19)	1.2	23.6	31.4
6	34 (12/35)	29 (10/35)	1.4	26.1	33.8	69 (11/16)	69 (11/16)	32.2	189.8	189.8	56 (9/16)	44 (7/16)	9.7	87.3	190.0
7/8	64 (23/36)	58 (21/36)	12.3	90.2	115.5										
10	65 (24/37)	54 (20/37)	12.8	73.8	117.6	67 (10/15)	60 (9/15)	6.7	24.5	27.7	50 (9/18)	44 (8/18)	4.7	45.0	55.0

31251/3
1/5/86

00700

Table 4

Percent of Predialysis Patients With Clinical Complaints*
During a Five-Day Period Following Vaccination With
Yeast Recombinant Hepatitis B Vaccine (Three Injection Regimen)

Studies: 789, 811

10 mcg Dose - Deltoid Injection

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Injection Site	0 (0/14)	0 (0/14)	0 (0/12)	0 (0/40)
Systemic	0 (0/14)	0 (0/14)	8 (1/12)	3 (1/40)
Any Local or Systemic Complaint	0 (0/14)	0 (0/14)	8 (1/12)	3 (1/40)
Temperature ≥100°F Oral	7 (0/14)	0 (0/13)	0 (0/11)	3 (1/38)

20 mcg Dose - Deltoid Injection

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Injection Site	18 (5/28)	11 (3/28)	5 (1/20)	12 (9/76)
Systemic	18 (5/28)	14 (4/28)	10 (2/20)	15 (11/76)
Any Local or Systemic Complaint	29 (8/28)	21 (6/28)	15 (3/20)	22 (17/76)
Temperature ≥100°F Oral	7 (2/27)	12 (3/26)	10 (2/20)	10 (7/73)

40 mcg Dose - Deltoid Injection

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Injection Site	7 (2/27)	4 (1/26)	0 (0/17)	4 (3/70)
Systemic	4 (1/27)	8 (2/26)	6 (1/17)	6 (4/70)
Any Local or Systemic Complaint	11 (3/27)	8 (2/26)	6 (1/17)	9 (6/70)
Temperature ≥100°F Oral	7 (2/27)	8 (2/26)	18 (3/17)	10 (7/70)

40 mcg Dose - Buttock Injection

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Injection Site	0 (0/8)	Data	Data	0 (0/8)
Systemic	0 (0/8)	not	not	0 (0/8)
Any Local or Systemic Complaint	0 (0/8)	available	available	0 (0/8)
Temperature ≥100°F Oral	0 (0/8)			0 (0/8)

*A complaint is recorded here if it occurred during any fraction of the five-day period following vaccination.

31091/2
1/10/86

Table 5

Percent of Dialysis Patients with Clinical Complaints*
During a Five-Day Period Following Vaccination With
Yeast Recombinant Hepatitis B Vaccine In The Deltoid
(Three Injection Regimen)

Studies: 816, 825

20 mcg Dose

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Injection Site	8 (3/38)	0 (0/34)	0 (0/33)	3 (3/105)
Systemic	24 (9/38)	3 (1/34)	12 (4/33)	13 (14/105)
Any Local or Systemic Complaint	29 (11/38)	3 (1/34)	12 (4/33)	15 (16/105)
Temperature ≥100°F Oral	5 (2/37)	0 (0/34)	9 (3/32)	5 (5/103)

40 mcg Dose

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Injection Site	11 (4/36)	3 (1/34)	0 (0/24)	5 (5/94)
Systemic	22 (8/36)	0 (0/34)	8 (2/24)	11 (10/94)
Any Local or Systemic Complaint	25 (9/36)	3 (1/34)	8 (2/24)	13 (12/94)
Temperature ≥100°F Oral	11 (4/36)	3 (1/33)	0 (0/24)	5 (5/94)

100 mcg Dose

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Injection Site	9 (4/44)	8 (3/39)	Data	8 (7/83)
Systemic	7 (3/44)	0 (0/39)	Not	4 (3/83)
Any Local or Systemic Complaint	16 (7/44)	8 (3/39)	Available	12 (10/83)
Temperature ≥100°F Oral	7 (3/43)	3 (1/39)		5 (4/82)

* A complaint is recorded here if it occurred during any fraction of the five-day period following vaccination.

Table 6

Percent of Dialysis Patients with Clinical Complaints*
During a Five-Day Period Following Vaccination
with Yeast Recombinant Hepatitis B Vaccine In The Buttock

Study 838

3 x 40 mcg Dose

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Injection Site	0 (0/51)	0 (0/49)	0 (0/38)	0 (0/138)
Systemic	8 (4/51)	0 (0/49)	3 (1/38)	4 (5/138)
Any Local or Systemic Complaint	8 (4/51)	0 (0/49)	3 (1/38)	4 (5/138)
Temperature ≥100°F Oral	4 (2/51)	0 (0/48)	3 (1/38)	2 (3/137)

6 x 40 mcg Dose

Type of Complaint	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	ALL
Injection Site	0 (0/20)	0 (0/20)	0 (0/20)	0 (0/19)	0 (0/19)	0 (0/16)	0 (0/114)
Systemic	15 (3/20)	10 (2/20)	15 (3/20)	16 (3/19)	0 (0/19)	0 (0/16)	10 (11/114)
Any Local or Systemic Complaint	15 (3/20)	10 (2/20)	15 (3/20)	16 (3/19)	0 (0/19)	0 (0/16)	10 (11/114)
Temperature ≥ 100°F Oral**	10 (2/20)	5 (1/19)	5 (1/19)	0 (0/18)	6 (1/18)	7 (1/15)	6 (6/109)

6 x 20 Mcg Dose

Type of Complaint	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	ALL
Injection Site	0 (0/20)	0 (0/20)	5 (1/20)	0 (0/20)	0 (0/20)	0 (0/17)	0.9 (1/117)
Systemic	5 (1/20)	10 (2/20)	5 (1/20)	5 (1/20)	0 (0/20)	0 (0/17)	4 (5/117)
Any Local or Systemic Complaint	5 (1/20)	10 (2/20)	10 (2/20)	5 (1/20)	0 (0/20)	0 (0/17)	5 (6/117)
Temperature ≥100°F Oral	6 (1/18)	0 (0/19)	0 (0/20)	5 (1/20)	0 (0/20)	0 (0/16)	2 (2/113)

*A complaint is recorded here if it occurred during any fraction of the five-day period following vaccination.
**Fever was reported in one vaccine recipient (temperature not recorded)

00705

31111/1
1/8/86

Table 7

Frequency of Local and Systemic Complaints
Among Predialysis Patients During a
Five-Day Period Following 186 Deltoid Injections of
Yeast Recombinant Hepatitis B Vaccine
(Three Injection Regimen)

Studies: 789, 811

Number of Vaccine Recipients: 69

Body System/ Complaint	% Frequency (Number)
Local/Injection Site	6 (11)
Soreness	6 (11)
Stiffness/Tightness	2 (3)
Ecchymosis	0.5 (1)
Pain	0.5 (1)
Swelling	0.5 (1)
Whole Body/General	3 (5)
Chills	1 (2)
Headache	1 (2)
Fatigue/Weakness	0.5 (1)
Sensation of Warmth General	0.5 (1)
Illness, Nos	0.5 (1)
Digestive	3 (5)
Nausea	3 (5)
Vomiting	0.5 (1)
Abdominal Tenderness	0.5 (1)
Respiratory	2 (4)
Upper Respiratory Infection, Nos.	2 (3)
Pharyngitis	0.5 (1)
Musculoskeletal	1 (2)
Arthralgia, Other	0.5 (1)
Shoulder Pain	0.5 (1)
Knee Pain	0.5 (1)
Psychiatric/Behavioral	1 (2)
Depression	1 (2)
Nervous System	0.5 (1)
Somnolence	0.5 (1)

wva/3151I/9
1/9/86

Table 8

Percent (Number) of Predialysis Patients With
Specific Systemic Complaints During a Five-Day Period Following
186 Deltoid Injections of Yeast Recombinant Hepatitis B Vaccine
(Three Injection Regimen)

Studies: 789, 811

Number of Vaccine Recipients: 69

Complaint Frequency 1-3%		
Nausea	3	(5)
Upper Respiratory Infection, Nos	2	(3)
Chills	1	(2)
Depression	1	(2)
Headache	1	(2)

Complaint Frequency <1%		
Abdominal Tenderness	0.5	(1)
Illness, Nos	0.5	(1)
Knee Pain	0.5	(1)
Pharyngitis (Sore Throat)	0.5	(1)
Shoulder Pain	0.5	(1)
Somnolence	0.5	(1)
Fatigue/Weakness	0.5	(1)
Arthralgia	0.5	(1)
Sensation of Warmth, General	0.5	(1)
Vomiting	0.5	(1)

Table 9

Frequency of Local and Systemic Complaints
Among Dialysis Patients During a Five-Day Period Following
341 Injections (Deltoid or Buttock) of Yeast Recombinant Hepatitis B Vaccine
(Three Injection Regimen)

Studies: 816, 838

Number of Vaccine Recipients: 127

Body System/ Complaint	% Frequency (Number)
Local/Injection Site	3 (10)
Soreness	2 (7)
Ecchymosis	0.5 (2)
Pain	0.5 (2)
Stiffness/Tightness	0.5 (2)
Whole Body/General	5 (17)
Fatigue/Weakness	2 (6)
Headache	1 (5)
Chills	1 (4)
Sensation of warmth, General	0.5 (2)
Lightheaded	0.5 (2)
Illness, Nos	0.2 (1)
Malaise	0.2 (1)
Digestive	1 (5)
Nausea	0.8 (3)
Vomiting	0.5 (2)
Increased Appetite	0.2 (1)
Diarrhea	0.2 (1)
Respiratory	0.8 (3)
Pharyngitis	0.2 (1)
Upper Respiratory Infection, Nos	0.2 (1)
Bronchitis, Nos	0.2 (1)
Musculoskeletal	1 (4)
Arthralgia, Other	0.2 (1)
Arthralgia, Mono-articular	0.2 (1)
Arthritis	0.2 (1)
Arm Pain	0.2 (1)
Hand Cramps	0.2 (1)
Muscle Cramps	0.2 (1)
Nervous System	0.8 (3)
Dizziness	0.5 (2)
Tremor	0.2 (1)
Infections Syndromes	0.2 (1)
Influenza, Nos	0.2 (1)
Psychiatric/Behavioral	0.2 (1)
Insomnia/Disturbed	0.2 (1)
Cardiovascular	0.5 (2)
Hypertension	0.2 (1)
Other	0.2 (1)

31511/7
1/21/86

Table 10

Percent (Number) of Dialysis Patients With
Specific Systemic Complaints During a Five-Day Period Following
341 Injections (Deltoid or Buttock) of Yeast Recombinant Hepatitis B Vaccine
(Three Injection Regimen)

Studies: 816, 838

Number of Vaccine Recipients: 127

Complaint Frequency 1-2%		
Fatigue/Weakness	2	(6)
Headache	1	(5)
Chills	1	(4)

Complaint Frequency <1% (Number)	
Nausea	0.8 (3)
Lightheaded	0.5 (2)
Sensation of Warmth, General	0.5 (2)
Dizziness	0.5 (2)
Vomiting	0.5 (2)
Appetite Increased	0.2 (1)
Arm Pain	0.2 (1)
Arthralgia, Other	0.2 (1)
Arthralgia, Monoarticular	0.2 (1)
Arthritis, Other	0.2 (1)
Bronchitis	0.2 (1)
Diarrhea	0.2 (1)
Hand Cramps	0.2 (1)
Hypertension	0.2 (1)
Illness, Nos	0.2 (1)
Influenza, Nos	0.2 (1)
Insomnia/Disturbed Sleep	0.2 (1)
Malaise	0.2 (1)
Muscle Cramps	0.2 (1)
Pharyngitis (Sore Throat)	0.2 (1)
Tremor	0.2 (1)
Upper Respiratory Infection, Nos	0.2 (1)
Other	0.2 (1)

Table 11

Frequency of Local and Systemic Complaints
Among Dialysis Patients During a Five-Day Period
Following 83 Deltoid Injections of Yeast Recombinant Hepatitis B Vaccine
Containing 100 mcg HBsAg (Three Injection Regimen)

Study 825

Number of Vaccine Recipients: 44

Body System/Complaint	% Frequency (Number)
Local/Injection Site	8 (7)
Soreness	7 (6)
Erythema	1 (1)
Inflammation	1 (1)
Pruritis	1 (1)
Stiffness/Tightness	1 (2)
Whole Body/General	2 (2)
Fatigue/Weakness	1 (1)
Other	1 (1)
Respiratory	1 (1)
Pharyngitis	1 (1)
Cough	1 (1)
Musculoskeletal	1 (1)
Arthralgia, Other	1 (1)

Table 12

Frequency of Local and Systemic Complaints Among Dialysis Patients During a Five-Day Period Following 231 Buttock Injections of Yeast Recombinant Hepatitis B Vaccine (Six Injection Regimen)

Study 838

Number of Vaccine Recipients: 40

Body System/ Complaint	% Frequency (Number)
Local/Injection Site	0.4 (1)
Pruritis	0.4 (1)
Whole Body/General	6 (15)
Fatigue/Weakness	5 (11)
Headache	1 (3)
Illness, Nos	0.4 (1)
Lightheaded	0.4 (1)
Chills	0.4 (1)
Digestive	3 (8)
Nausea	2 (4)
Diarrhea	0.8 (2)
Abdominal Pains/ Cramps	0.4 (1)
Diminished Appetite	0.4 (1)
Respiratory	0.4 (1)
Cough	0.4 (1)
Musculoskeletal	1 (3)
Arthralgia, Other	1 (3)
Psychiatric/Behavioral	0.4 (1)
Depression	0.4 (1)
Cardiovascular	0.8 (2)
Hypotension	0.4 (1)
Other	0.4 (1)

3162I
1/10/86

APPENDIX 1

STATISTICAL METHODS

All tests of significance were two-sided at 0.05 significance level.

A. Clinical Complaints

1. The incidence of the various clinical complaints in dialysis patients on the three dose regimen, healthy teenagers and healthy children were evaluated as a function of log dose level using the Mantel-Haenszel Test[1] for trend.

2. All other differences in the incidences of the various clinical complaints in dialysis patients due to dose level or regimen and in health care personnel receiving vaccine from consistency lots were assessed by the Likelihood Ratio Chi-Square.

B. Seroconversion Rates

1. The effect of dose level on seroconversion rates in healthy adults, healthy teenagers and healthy children was analyzed over studies using the Mantel Haenszel Test[1] for trend.

2. Differences in seroconversion rates in healthy adults due to age or sex were evaluated over studies using the Mantel Haenszel Test[1] for heterogeneity.

3. Differences in seroconversion rates due to age in healthy children, dose level in dialysis patients, and vaccine lot in health care personnel were assessed by the Likelihood Ratio Chi-Square.

C. Level of Response (Titers)

The effect of age, sex, lot (consistency lots only in Study 880), or dose level (all other studies) in health care personnel and other healthy adults, of dose level in healthy teenagers, of dose level and age in healthy children, and of dose level and regimen in dialysis patients were analyzed by fitting these variables to a regression model. Subjects who were negative for antibody to hepatitis B surface antigen were assigned a titer of 0.3 mIU/ml in the analysis.

REFERENCE

1. Tarone RE, Ware J: On Distribution-Free Tests for Equality of Survival Distributions. Biometrika 64: 156-160, 1977.

Dialysis and Predialysis Patients

Study 789 - Durham, NC - Dr. G. Hamilton

The study population consists of adults with chronic renal insufficiency (pre-dialysis) who are negative for hepatitis B serologic markers. Participants receive either 20 mcg or 40 mcg injections of yeast recombinant vaccine lot C-K446 or 40 mcg injections of plasma-derived vaccine lot 2449H or 1885K. All injections are administered at 0, 1, and 6 months.

Fifteen participants have received two 40 mcg injections of yeast recombinant vaccine and seven of these have received the third injection. At 7/8 months, 71% (5/7) of these vaccinees seroconverted for anti-HBs (S/N $\geq$2.1). Fifty-seven percent (4/7) developed protective levels of anti-HBs (S/N $\geq$10). The GMT for all vaccinees at that time was 12.7 S/N and 60.2 for responders (S/N $\geq$10).

Fourteen subjects have received two 20 mcg injections of yeast recombinant vaccine and seven of these have received the third injection. Eighty-six percent of the vaccinees seroconverted for anti-HBs (S/N $\geq$2.1) at 7/8 months. Fifty-seven percent (4/7) developed protective levels of anti-HBs (S/N $\geq$10). The GMT for all vaccinees at that time was 25.3 S/N and 130.0 for responders (S/N $\geq$10).

Sixteen predialysis patients have received two 40 mcg injections of plasma derived vaccine. Six of these have been administered the third injection. At 7/8 months, 67% (4/6) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (S/N $\geq$10). The GMT for all vaccinees at that time was 27.7 S/N and 168.6 for responders (S/N $\geq$10).

No serious or alarming adverse experiences attributable to either vaccine have been reported. The study continues in progress.

Study 811 - Switzerland - Dr. P. Grob

Predialysis patients and health care personnel are enrolled in Study 811. Predialysis patients are assigned to one of five groups and receive yeast recombinant vaccine lot C-K446 or plasma-derived vaccine (Heptavax) lot 1510J. Group 1, 2, and 3 participants receive 10 mcg, 20 mcg, and 40 mcg injections of yeast recombinant vaccine, respectively. Group 4 and 5 participants receive 20 mcg and 40 mcg injections of plasma-derived vaccine, respectively. The vaccine is administered at 0, 1, and 6 months for all groups.

Fourteen predialysis patients (group 1) have received two 10 mcg injections of yeast recombinant vaccine and 13 of these have received the third injection. At 7/8 months, 15% (2/13) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for all

Study 811 - Switzerland - Dr. P. Grob (Cont.)

vaccinees was 7.0 mIU/ml and 67.7 for responders (mIU/ml ≥10). No patient tested, seroconverted before 7/8 months.

Fourteen predialysis patients (group 2) have received two 20 mcg injections of yeast recombinant vaccine and 13 of these have received the third injection. At 7/8 months, 58% (7/12) of the subjects seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees was 13.8 mIU/ml and 213.7 for all responders (mIU/ml ≥10).

In group 3, thirteen predialysis patients have received two 40 mcg injections of yeast recombinant vaccine. Twelve of these have been administered the third injection. Sixty-four percent (7/11) seroconverted (S/N ≥2.1) for anti-HBs at 7/8 months. Fifty-four percent (6/11) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 13.6 mIU/ml and 186.4 for responders (mIU/ml ≥10).

Eleven predialysis patients (group 4) have received two 20 mcg injections of plasma-derived vaccine and 10 of these have received the third injection. At 7/8 months, 25% (2/8) of the subjects seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees was 1.3 mIU/ml and 101.2 for responders (mIU/ml ≥10).

In group 5, 11 predialysis patients received two 40 mcg injections of plasma-derived vaccine and 10 of these have received the third injection. Fifty percent (4/8) of the patients seroconverted for anti-HBs (S/N ≥2.1) at 7/8 months. Thirty-eight percent (3/8) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at 7/8 months was 8.7 mIU/ml and 791.5 for responders (mIU/ml ≥10).

There have been no serious or alarming reactions attributable to vaccine. The study continues in progress. Refer to the summary on health care personnel/healthy adults for data regarding other subjects vaccinated in this study.

Study 816 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

The study population consists of health care personnel and adult hemodialysis patients (including hemodialysis patients who were previous non-responders to plasma-derived vaccine). Health care personnel received 10 mcg injections of yeast recombinant vaccine lot C-K446. Dialaysis patients received either 20 mcg injections (group 1) or 40 mcg injections (group 2) of yeast recombinant vaccine lot C-K446. All vaccine is administered at 0, 1, and 6 months.

Thirty-nine hemodialysis patients (group 1) have received one 20 mcg injection of vaccine. Thirty-four of these have received the second injection and 32 the third injection. At 7/8 months, 57% (16/28) of the patients seroconverted

Study 816 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr (Cont.)

for anti-HBs (S/N ≥2.1). Forty-six percent (13/28) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at 7/8 months was 7.5 mIU/ml and 132.4 for responders (mIU/ml ≥10).

In group 2, 36 dialysis patients have received one 40 mcg injection of vaccine and 34 of these have received the second injection. The third injection has been administered to 24 patients. Eighty percent (16/20) of these patients seroconverted for anti-HBs (S/N ≥2.1) at 7/8 months. Seventy-five percent (15/20) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees was 81.8 mIU/ml and 418.4 for responders (mIU/ml ≥10).

No serious or alarming reactions attributable to vaccine have been reported. The study continues in progress. Refer to the summary on health care personnel/healthy adults for data regarding other subject vaccinated in this study.

Study 825 - Bethesda, MD - Dr. H. Alter

The study population consists of adult hemodialysis patients who are negative for hepatitis B serologic markers. Dialysis patients who were nonresponders to previously administered plasma-derived vaccine may also be included in the study population. Participants receive a 100 mcg injection of vaccine lot C-L915 at 0, 1, and 6 months.

Forty-four hemodialysis patients have received one 100 mcg injection of vaccine and forty-one of these have received the second injection. No subject has yet received the third injection of vaccine. Serology data are available through 3 months of follow-up. Sixty-eight percent (19/28) of the patients seroconverted for anti-HBs (S/N ≥2.1) at 3 months. Twenty-five percent (7/28) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at 3 months was 4.4 S/N and 33.3 for responders (S/N ≥10).

No serious or alarming reactions attributable to vaccine have been reported. The study continues in progress.

Study 838 - West Germany - Dr. F. Deinhardt

The population of STudy 838 consists of adult hemodialysis patients, predialysis patients and health care personnel. Yeast recombinant hepatitis B vaccine lot C-K733 is being utilized. Dialysis patients may receive 40 mcg injections at 0, 1, and 6 months, or 20 or 40 mcg injections of vaccine at 0, 1, 2, 3, 4, and 6 months. Predialysis patients receive either 10 mcg or 40 mcg injections of vaccine at 0, 1, and 6 months. All injections were administered in the buttock.

Fifty-one dialysis patients have been enrolled in the three 40 mcg injection regimen. All 51 patients have received two 40 mcg injections and 48 of these have received the third injection. At 7/8 months, 64% (23/36) of the patients seroconverted for anti-HBs (S/N ≥2.1). Fifty-eight percent (21/36) developed

Study 838 - West Germany - Dr. F. Deinhardt (Cont.)

protective levels of anti-HBs (mIU/ml ≥10). The GMT at that time for all vaccinees was 12.3 mIU/ml and 115.5 for responders (mIU/ml ≥10).

Twenty dialysis patients have been enrolled in the six 40 mcg injection regimen. All 20 subjects have received the first three injections and 19 of these have received the fourth and fifth injections. Seventeen patients have been administered all six 40 mcg injections of vaccine. At 10 months. 67% (10/15) of the patients seroconverted for anti-HBs (S/N ≥2.1). Sixty percent (9/15) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 10 months for all vaccinees was 6.7 mIU/ml and 27.7 for responders (mIU/ml ≥10).

Twenty dialysis patients in the six 20 mcg injection regimen have all received five injections of vaccine. Seventeen of these have received the sixth injection. Fifty percent (9/18) of the patients seroconverted for anti-HBs (S/N ≥2.1) at 10 months. Forty-four percent (8/18) developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT for all vaccinees was 4.7 mIU/ml and 55.0 for responders (mIU/ml ≥10).

Eight predialysis patients have been enrolled in the three 40 mcg injection regimen. All eight patients have received the first two injections of vaccine. None has yet received the third injection. Serology data are available through one month of follow-up. Thirteen percent (1/8) of the subjects seroconverted for anti-HBs (S/N ≥2.1). The GMT for all vaccinees was 0.7 mIU/ml and 4.6 mIU/ml for responders (S/N ≥2.1). None of the participants developed protective levels of anti-HBs (mIU/ml ≥10) at one month.

No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress. Refer to the summary of health care personnel/healthy adults for data regarding other subject vaccinated in this study.

STUDY 789

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 789
PURPOSE:	To compare antibody and clinical responses to plasma and yeast recombinant vaccines at 2 dose levels among uremic patients not yet undergoing dialysis who are negative for HBV markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #974/C-K446 (20 mcg HBsAg/ml) HEPTAVAX Plasma-Derived Hepatitis B Vaccine Lot 2449H (20 mcg HBsAg/ml) Lot 1885K (20 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	John Hamilton, M.D. VA Medical Center Durham, NC 27705
SECONDARY INVESTIGATOR:	Joan Drucker, M.D. Division of Infectious Diseases Duke University Medical Center Durham, NC 27710 Robert Gutman, M.D. Division of Nephrology Duke University Medical Center Durham, NC 27710
STUDY LOCATION:	Duke University Medical Center Durham, NC 27710 Veteran's Administration Medical Center 508 Fulton Street Durham, NC 27705
DATE INITIATED:	May 23, 1984
DATE COMPLETED:	In progress.
STUDY PROCEDURE:	The study population consists of 45 adults of either sex, aged 16-60 years, who have chronic renal insufficiency not severe enough to require dialysis (creatinine levels of 2.0 mgm/dl or greater), who are negative for HBsAg, anti-HBc and anti-HBs, and have a normal ALT level.

Study 789

STUDY PROCEDURE (CONT.):

To assure that patients in the treatment groups are similar, assignment to vaccine and dosage is stratified by sex, age and creatinine level. Participants are randomly assigned to one of the following groups.

Group	Vaccine	Number	Dose	Regimen
1	Lot 974	14	20 mcg	1 - 1.0 ml intramuscular injection on day 0, 1 mo. and 6 mos.
2	Lot 974	15	40 mcg	2 - 1.0 ml intramuscular injections on day 0, 1 mo. and 6 mos.
3	HEPTAVAX Lot 2449H or Lot 1885K	16	40 mcg	2 - 1.0 ml intramuscular injections on day 0, 1 mo. and 6 mos.

Vaccinees are asked to record their temperature daily for 5 days after each injection and also to record any local or systemic complaints they may have during this period.

A blood specimen (10-15 ml) is obtained from each participant approximately 2 weeks before the first vaccination. Post-vaccination blood samples are obtained at 1, 3, 6, 7, 9 and 12 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, ALT, and creatinine. Samples with anti-HBs titers $\geq$25 mIU/ml may be tested for the proportions of anti-a and anti-d activity. Samples may be tested for yeast antibody at MSDRL.

RESULTS:

Pre-Dialysis Patients:

20 mcg Lot #974/C-K446 at 0, 1, and 6 months
40 mcg Lot #974/C-K446 at 0, 1, and 6 months
40 mcg HEPTAVAX Lot #2449H at 0, 1, and 6 months
40 mcg HEPTAVAX Lot #1885K at 0, 1, and 6 months

Study 789

RESULTS (CONT.): 1. Number Vaccinated:

Dose Level	---Injection Number--- 1	2	3
40 mcg Recombinant	15	15	7
20 mcg Recombinant	14	14	7
40 mcg Plasma	16	16	6

2. Serologic Results:

Serologic data at 7/8 months are available for 7, 7, and 6 recipients of 40 mcg recombinant, 20 mcg recombinant, and 40 mcg doses of plasma-derived vaccine, respectively. The following anti-HBs responses were observed at that time. Table 1 shows seroconversion rates and GMTs for up to one year of follow-up.

Dose Level	% with Anti-HBs S/N ≥2.1	S/N ≥10	GMT (S/N) Vaccinees	S/N ≥2.1	S/N ≥10
40 mcg Recombinant	71 (5/7)	57 (4/7)	12.7	35.4	60.2
20 mcg Recombinant	86 (6/7)	57 (4/7)	25.3	43.4	130.0
40 mcg Plasma	67 (4/6)	67 (4/6)	27.7	168.6	168.6

3. Clinical Complaints

Clinical follow-up data are available for 15, 15, and 7 participants following the first, second, and third injections of 40 mcg recombinant vaccine; 14, 14, and 7 participants who received 20 mcg recombinant vaccine; and for 16, 16, and 6 who received 40 mcg of plasma vaccine.

Study 789

RESULTS (CONT.): Clinical complaints and maximum temperatures reported following each injection are provided in Tables 2-7.

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	40 mcg Recombinant	13 (2/15)	7 (1/15)	0 (0/7)
	20 mcg Recombinant	36 (5/14)	14 (2/14)	14 (1/7)
	40 mcg Plasma	6 (1/16)	6 (1/16)	17 (1/6)
Systemic	40 mcg Recombinant	7 (1/15)	13 (2/15)	14 (1/7)
	20 mcg Recombinant	29 (4/14)	29 (4/14)	29 (2/7)
	40 mcg Plasma	6 (1/16)	13 (2/16)	17 (1/6)

ALT Elevations

Vaccine recipients included one person in the 20 mcg recombinant group who had a pre-vaccination ALT level 2-3 times the upper limit of normal. His ALT level remained elevated through 9 months of follow-up but had dropped to normal at his one year bleeding. He remained negative for HBsAg and has shown no signs of infection. There was also one person in the 40 mcg plasma group and one in the 40 mcg recombinant group with normal pre-vaccination ALT levels who had transient elevated ALT levels approximately 1.5 - 2 times the upper limit of normal 2 months after the first dose of vaccine. All subsequent ALTs were normal. These subjects have not shown any clinical or serologic signs (HBsAg or anti-HBc) of hepatitis B.

Adverse Reactions Reported to OoBRR

Case (b)(6) a 30-year old male, died on (b)(6) from hemorrhage of esophageal varices and subsequent complications. He had received two 40 mcg immunizations of plasma-derived vaccine Lot 2449H, on (b)(6) and on (b)(6) The patient had a history of polycystic kidney and liver disease, as well as previous episodes of variceal bleeding. The death is not believed to be vaccine related.

Case (b)(6) a 58-year old male, had a history of hypertension and chronic renal failure (predialysis).

Table 1

Antibody Responses Among Pre-Dialysis Patients Following Vaccination with 40 or 20 mcg Doses of Recombinant Hepatitis B Vaccine Lot 0974/C-K446 or 40 mcg Doses of Plasma Vaccine Lot 2449H or Lot 1885K at 0, 1, and 6 Months in Study 789

	40 mcg Recombinant					20 mcg Recombinant					40 mcg Plasma				
	% with Anti-HBs		GMT (S/N)			% with Anti-HBs		GMT (S/N)			% with Anti-HBs		GMT (S/N)		
				Responders					Responders					Responders	
Time (Mos.)	S/N≥2.1	S/N ≥ 10	All Vaccinees	S/N≥2.1	S/N ≥ 10	S/N≥2.1	S/N ≥ 10	All Vaccinees	S/N≥2.1	S/N ≥ 10	S/N≥2.1	S/N ≥ 10	All Vaccinees	S/N≥2.1	S/N ≥ 10
1	7 (1/15)	0 (0/15)	1.0	5.7	—	0 (0/14)	0 (0/14)	0.8	—	—	13 (2/16)	0 (0/16)	1.1	4.1	—
3	43 (6/14)	21 (3/14)	3.4	12.4	29.3	38 (5/13)	8 (1/13)	2.3	7.8	26.7	67 (10/15)	40 (6/15)	5.9	14.1	30.2
6	43 (3/7)	0 (0/7)	1.7	4.1	—	57 (4/7)	29 (2/7)	3.0	7.4	21.4	60 (3/5)	60 (3/5)	6.9	37.8	37.8
7	71 (5/7)	57 (4/7)	12.7	35.4	60.2	86 (6/7)	57 (4/7)	25.3	43.3	130.0	67 (4/6)	67 (4/6)	27.7	168.6	168.6
9	100 (1/1)	100 (1/1)	12.6	12.6	12.6	100 (3/3)	33 (1/3)	14.9	14.9	141.2	100 (2/2)	100 (2/2)	73.8	73.8	73.8
12						100 (4/4)	25 (1/4)	6.0	6.0	33.3					

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (14 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	5 (35.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (35.7%)
SORENESS	5 (35.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (35.7%)
SWELLING	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
STIFFNESS/TIGHTNESS	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
SYSTEMIC	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	2 (14.3%)	1 (7.1%)	4 (28.6%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (7.1%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (7.1%)
MUSCULOSKELETAL	1 (7.1%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	2 (14.3%)
ARTHRALGIA (OTHER)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
SHOULDER PAIN	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
KNEE PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)
NERVOUS SYSTEM	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT 0CK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (14 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
SOMNOLENCE	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.1%)
PERSONS WITH COMPLAINTS	6 (42.9%)	2 (14.3%)	1 (7.1%)	1 (7.1%)	2 (14.3%)	1 (7.1%)		7 (50.0%)
PERSONS WITH NO COMPLAINTS	8 (57.1%)	12 (85.7%)	13 (92.9%)	13 (92.9%)	12 (85.7%)	13 (92.9%)		7 (50.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00722

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (14 PATIENTS) - DOSE 2						NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION						
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
SORENESS	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
STIFFNESS/TIGHTNESS	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
SYSTEMIC	1 (7.1%)	2 (14.3%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	4 (28.6%)
WHOLE BODY/GENERAL	1 (7.1%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	3 (21.4%)
CHILLS	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)
ILLNESS, NOS	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
RESPIRATORY	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
PERSONS WITH COMPLAINTS	3 (21.4%)	2 (14.3%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	5 (35.7%)

00723

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (14 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	11 (78.6%)	12 (85.7%)	13 (92.9%)	13 (92.9%)	13 (92.9%)	13 (92.9%)	9 (64.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00724

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT BCK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (7 PATIENTS) - DOSE 3 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	1 (14.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (14.3%)
SORENESS	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (14.3%)
STIFFNESS/TIGHTNESS	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (14.3%)
ECCHYMOSIS	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (14.3%)
SYSTEMIC	2 (28.6%)	1 (14.3%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	1 (14.3%)		2 (28.6%)
WHOLE BODY/GENERAL	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)		1 (14.3%)
CHILLS	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)		1 (14.3%)
DIGESTIVE SYSTEM	1 (14.3%)	1 (14.3%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	1 (14.3%)		2 (28.6%)
NAUSEA	1 (14.3%)	1 (14.3%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	1 (14.3%)		2 (28.6%)
VOMITING	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)		1 (14.3%)
PERSONS WITH COMPLAINTS	3 (42.9%)	2 (28.6%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	1 (14.3%)		3 (42.9%)
PERSONS WITH NO COMPLAINTS	4 (57.1%)	5 (71.4%)	6 (85.7%)	5 (71.4%)	5 (71.4%)	6 (85.7%)		4 (57.1%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (7 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00726

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE
LOT 8CK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (14 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	2 (14.3%)	2 (14.3%)	2 (14.3%)	2 (14.3%)	2 (14.3%)	2 (14.3%)		2 (14.3%)
< 99	9 (64.3%)	10 (71.4%)	11 (78.6%)	10 (71.4%)	9 (64.3%)	11 (78.6%)		6 (42.9%)
99 - 99.9	2 (14.3%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	3 (21.4%)	1 (7.1%)		4 (28.6%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)		1 (7.1%)
102 - 102.9	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.1%)
TEMPERATURE TAKEN	14 (100.0%)	14 (100.0%)	14 (100.0%)	14 (100.0%)	14 (100.0%)	14 (100.0%)		14 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00727

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (14 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (7.7%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)			1 (7.1%)
< 99	11 (84.6%)	9 (64.3%)	9 (64.3%)	11 (78.6%)	12 (85.7%)	12 (85.7%)			6 (42.9%)
99 - 99.9	0 (0.0%)	2 (14.3%)	3 (21.4%)	1 (7.1%)	1 (7.1%)	0 (0.0%)			4 (28.6%)
100 - 100.9	0 (0.0%)	2 (14.3%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)			1 (7.1%)
102 - 102.9	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)			2 (14.3%)
TEMPERATURE TAKEN	13 (92.9%)	14 (100.0%)	14 (100.0%)	14 (100.0%)	14 (100.0%)	14 (100.0%)			14 (100.0%)
TEMPERATURE NOT TAKEN	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

00728

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 20 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (7 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (14.3%)	2 (28.6%)	2 (28.6%)	2 (28.6%)	2 (28.6%)	2 (28.6%)		1 (14.3%)
< 99	3 (42.9%)	4 (57.1%)	4 (57.1%)	3 (42.9%)	2 (28.6%)	4 (57.1%)		2 (28.6%)
99 - 99.9	3 (42.9%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	1 (14.3%)		2 (28.6%)
100 - 100.9	0 (0.0%)	1 (14.3%)	1 (14.3%)	0 (0.0%)	1 (14.3%)	0 (0.0%)		0 (0.0%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)		1 (14.3%)
104 - 104.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)		1 (14.3%)
TEMPERATURE TAKEN	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)		7 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT BCK446

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
SORENESS	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
SYSTEMIC	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
NAUSEA	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
DEPRESSION	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
PERSONS WITH COMPLAINTS	0 (0.0%)	3 (20.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		3 (20.0%)
PERSONS WITH NO COMPLAINTS	15 (100.0%)	12 (80.0%)	14 (93.3%)	14 (93.3%)	15 (100.0%)	15 (100.0%)		12 (80.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00730

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
SORENESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
SYSTEMIC	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	2 (13.3%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
DEPRESSION	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
PERSONS WITH COMPLAINTS	1 (6.7%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	2 (13.3%)
PERSONS WITH NO COMPLAINTS	14 (93.3%)	14 (93.3%)	14 (93.3%)	15 (100.0%)	15 (100.0%)	14 (93.3%)	13 (86.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00731

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (7 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
ABDOMINAL TENDERNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)
PERSONS WITH NO COMPLAINTS	6 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	6 (85.7%)	6 (85.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00732

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBIRANT HEPATITIS B VACCINE
LOT BCK446

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (7.1%)	1 (7.1%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (7.1%)			1 (6.7%)
< 99	10 (71.4%)	11 (78.6%)	12 (80.0%)	12 (80.0%)	12 (80.0%)	11 (78.6%)			8 (53.3%)
99 - 99.9	2 (14.3%)	1 (7.1%)	0 (0.0%)	2 (13.3%)	2 (13.3%)	1 (7.1%)			4 (26.7%)
101 - 101.9	1 (7.1%)	1 (7.1%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	1 (7.1%)			2 (13.3%)
TEMPERATURE TAKEN	14 (93.3%)	14 (93.3%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	14 (93.3%)			15 (100.0%)
TEMPERATURE NOT TAKEN	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)			0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE
LOT 8CK446

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (7.1%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)			1 (6.7%)
< 99	10 (71.4%)	11 (73.3%)	10 (66.7%)	13 (86.7%)	14 (93.3%)	14 (93.3%)			8 (53.3%)
99 - 99.9	3 (21.4%)	2 (13.3%)	2 (13.3%)	1 (6.7%)	0 (0.0%)	0 (0.0%)			4 (26.7%)
100 - 100.9	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (6.7%)
101 - 101.9	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (6.7%)
TEMPERATURE TAKEN	14 (93.3%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)			15 (100.0%)
TEMPERATURE NOT TAKEN	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE
LOT #CK446

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (7 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (16.7%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)			1 (14.3%)
< 99	3 (50.0%)	5 (71.4%)	5 (71.4%)	6 (85.7%)	4 (57.1%)	4 (57.1%)			2 (28.6%)
99 - 99.9	2 (33.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)			1 (14.3%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)			1 (14.3%)
101 - 101.9	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (14.3%)			2 (28.6%)
TEMPERATURE TAKEN	6 (85.7%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)	7 (100.0%)			7 (100.0%)
TEMPERATURE NOT TAKEN	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

00735

Table 6

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE
LOT #2449H

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (16 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
SORENESS	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
SYSTEMIC	1 (6.3%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
WHOLE BODY/GENERAL	1 (6.3%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
SENSATION OF WARMTH, GENERAL	1 (6.3%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
PERSONS WITH COMPLAINTS	2 (12.5%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (12.5%)
PERSONS WITH NO COMPLAINTS	14 (87.5%)	15 (93.8%)	16 (100.0%)	16 (100.0%)	16 (100.0%)	16 (100.0%)		14 (87.5%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00736

Table 6 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE
LOT #2449H

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (16 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
PAIN	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
SYSTEMIC	0 (0.0%)	1 (6.3%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)		2 (12.5%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
ARTHRALGIA (OTHER)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)		1 (6.3%)
PERSONS WITH COMPLAINTS	1 (6.3%)	1 (6.3%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)		2 (12.5%)
PERSONS WITH NO COMPLAINTS	15 (93.8%)	15 (93.8%)	16 (100.0%)	15 (93.8%)	16 (100.0%)	16 (100.0%)		14 (87.5%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 6 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE
LOT #2449H

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (6 PATIENTS) - DOSE 3 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
SORENESS	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
SYSTEMIC	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
DIGESTIVE SYSTEM	1 (16.7%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
NAUSEA	1 (16.7%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
VOMITING	0 (0.0%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
LOOSE STOOL	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
PERSONS WITH COMPLAINTS	2 (33.3%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)		2 (33.3%)
PERSONS WITH NO COMPLAINTS	4 (66.7%)	5 (83.3%)	5 (83.3%)	5 (83.3%)	6 (100.0%)	6 (100.0%)		4 (66.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
PLASMA-DERIVED HEPATITIS B VACCINE
LOT #2449H

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (16 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)		1 (6.7%)
< 99	12 (80.0%)	12 (80.0%)	13 (86.7%)	11 (73.3%)	11 (73.3%)	12 (80.0%)		10 (66.7%)
99 - 99.9	1 (6.7%)	2 (13.3%)	1 (6.7%)	3 (20.0%)	3 (20.0%)	2 (13.3%)		3 (20.0%)
104 - 104.9	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
TEMPERATURE TAKEN	15 (93.8%)	15 (93.8%)	15 (93.8%)	15 (93.8%)	15 (93.8%)	15 (93.8%)		15 (93.8%)
TEMPERATURE NOT TAKEN	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)		1 (6.3%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
PLASMA-DERIVED HEPATITIS B VACCINE
LOT #2449H

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (16 PATIENTS) - DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
NORMAL	2 (13.3%)	2 (13.3%)	2 (13.3%)	2 (13.3%)	2 (13.3%)	2 (13.3%)			2 (12.5%)
< 99	11 (73.3%)	12 (80.0%)	13 (86.7%)	13 (86.7%)	12 (80.0%)	12 (80.0%)			11 (68.8%)
99 - 99.9	2 (13.3%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)			3 (18.8%)
TEMPERATURE TAKEN	15 (93.8%)	15 (93.8%)	15 (93.8%)	15 (93.8%)	15 (93.8%)	15 (93.8%)			16 (100.0%)
TEMPERATURE NOT TAKEN	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)			0 (0.0%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
PLASMA-DERIVED HEPATITIS B VACCINE
LOT #2449H

STUDY : 0789
TREATMENT :
DOSE : 40 MCG
PATIENT CLASS: PRE-DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (6 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)		1 (16.7%)
< 99	4 (66.7%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	5 (83.3%)	5 (83.3%)		4 (66.7%)
99 - 99.9	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
100 - 100.9	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
102 - 102.9	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (16.7%)
TEMPERATURE TAKEN	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)	6 (100.0%)		6 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

STUDY 811

PROGRAM: Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 811.

PURPOSE: To evaluate antibody and clinical responses to several dose levels of commercial hepatitis B plasma derived vaccine (H-B-VAX) and yeast recombinant hepatitis B vaccine in the following populations who are initially seronegative for hepatitis B virus markers:

1. Predialysis Patients
2. Health Care Personnel

VACCINE: Yeast Recombinant Hepatitis B Vaccine
Lot # 974/C-K446 (20 mcg HBsAg/ml)

Hepatitis B Plasma Vaccine
Lot # 1510J (20 mcg HBsAg/ml)

PRINCIPAL INVESTIGATOR:
Peter J. Grob, M.D.
Section of Clinical Immunology
Department of Medicine
University Hospital
Haldeliweg 4
CH-8044 Zurich
Switzerland

SECONDARY INVESTIGATORS:
U. Binswanger, M.D., Professor
Department of Medicine
Nephrology Section
University Hospital
Zurich

C. Descoeudres, M.D.
Hemodialysis Station
Inselspital
Berne

A. Blumberg, M.D., Professor
Nephrology
Kantonspital
Aarau

A. Hany, M.D., P.D.
Hemodialysis Unit
Kantonsspital
Winterthur

Study 811

SECONDARY INVESTIGATORS: (Cont.)	H. Iselin, M.D. Hemodialysis Unit Neumunster Spital Zurich
	K. Zaruba, M.D., P.D. Hemodialysis Station City Hospital Waid Zurich
	W. Herwig, M.D. Hemodialysis Station Kantonsspital Chur
	H.-J. Gloor, M.D. Hemodialysis Station Kantonsspital Schaffhausen
	J. Nadig, M.D. Hemodialysis Unit Kantonsspital Winterthur
	H. I. Joller-Jemelka, M.D. Section of Clinical Immunology Department of Medicine University Hospital Zurich
STUDY LOCATION:	University Hospital Haldeliweg 4 CH - 8044 Zurich Switzerland
DATE INITIATED:	April 10, 1984
DATE COMPLETED:	In progress

Study B11

STUDY POPULATION: One study population consists of 59 predialysis patients who have renal disease with functional impairment or end-stage renal disease that will shortly require dialysis treatment. The other population is comprised of 11 health care personnel. Subjects in both populations must be adults of either sex (pregnant women excluded). They must be initially negative for all hepatitis B serologic markers, have a normal ALT level, and must not previously have received any hepatitis B vaccine.

PROCEDURE: Patients are randomly assigned to one of 5 groups. Health care personnel constitute a sixth group.

Group	Vaccine/Dose/Regimen
1	Recombinant vaccine; 0.5 ml (10 mcg) at 0, 1 and 6 months
2	Recombinant vaccine; 1.0 ml (20 mcg) at 0, 1 and 6 months
3	Recombinant vaccine; 2x1.0 ml (40 mcg) at 0, 1 and 6 months
4	H-B-VAX; 1.0 ml (20 mcg) at 0, 1 and 6 months
5	H-B-VAX; 2x1.0 ml (40 mcg) at 0, 1 and 6 months
6	Recombinant vaccine; 0.5 ml (10 mcg) at 0, 1 and 6 months

All injections will be intramuscular. Patients in Groups 3 and 5 will have the vaccine administered in a divided dose (i.e., 2 injections - one injection in each of two contralateral limbs).

Vaccine recipients will be asked to record their temperature for 5 days after each injection and to note any local or systemic complaints. Study participants will be bled 1 to 10 days prior to vaccination to verify eligibility for the study.

Study 811

PROCEDURE (Cont.): Follow-up samples will be obtained at 1, 3, 6 and 8 months following the initial vaccine injection. Blood samples will also be obtained at 12 and 24 months from subjects who are positive for anti-HBs at 8 months. All serum samples will be assayed for anti-HBc, anti-HBs, HBsAg and ALT by the investigator, and may be assayed for yeast antibody at MSDRL. In addition, participants who show an anti-HBs titer $\geq$ 25 mIU/ml will have their serum tested to determine the proportions of anti-a and anti-d activity.

RESULTS:

PREDIALYSIS PATIENTS:

10 mcg Lot #974/C-K446 at 0, 1, and 6 months
20 mcg Lot #974/C-K446 at 0, 1, and 6 months
40 mcg Lot #974/C-K446 at 0, 1, and 6 months
20 mcg Lot #1510J at 0, 1, and 6 months
40 mcg Lot #1510J at 0, 1, and 6 months

1. Number Vaccinated:

Vaccine	Dose Level	Injection # 1	2	3
Recomb.	10 mcg	14	14	13
	20 mcg	14	14	13
	40 mcg	13	13	12
H-B-Vax	20 mcg	11	11	10
	40 mcg	11	11	10

2. Serologic Results:

Seven/eight month serology data are available for 13, 12, and 11 participants who received 10, 20 and 40 mcg injections of vaccine, respectively. Serology data for 7/8 months of follow-up are available for 8 subjects in each of the plasma-derived vaccine dose regimens.

Study #811

RESULTS: (Cont.)

Anti-HBs responses and GMTs for recipients of yeast recombinant and plasma-derived vaccine are summarized below:

Vaccine	Dose Level	% with Anti-HBs S/N ≥2.1	% with Anti-HBs mIU/ml ≥10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥2.1	GMT (mIU/ml) Responders mIU/ml ≥10
Recomb.	10 mcg	15 (2/13)	15 (2/13)	0.7	67.7	67.7
	20 mcg	58 (7/12)	58 (7/12)	13.8	213.7	213.7
	40 mcg	64 (7/11)	54 (6/11)	13.6	120.9	186.4
H-B-Vax	20 mcg	25 (2/8)	25 (2/8)	1.3	101.2	101.2
	40 mcg	50 (4/8)	38 (3/8)	8.7	251.0	791.5

Refer to Tables 1 and 2 for anti-HBs responses and GMTs through 12 months of follow-up

3. Clinical Complaints:

Clinical follow-up data are available for at least 12 participants, after each injection, who were enrolled in the 10 mcg dose regimen, 13 participants who received 20 mcg injections, and at least 10 subjects who received 40 mcg injections of yeast recombinant vaccine.

At least 5 participants in each of the plasma-derived vaccine dose groups have clinical follow-up data after each injection.

The overall frequencies of complaints among vaccinees who received yeast recombinant or plasma-derived vaccine are presented below:

Study 811

RESULTS: (Cont.)

Type of Complaint	Vaccine	Dose Level	Frequency in % by Injection # 1	2	3
Injection Site	Recomb.	10 mcg	0(0/14)	0(0/14)	0(0/12)
		20 mcg	0(0/14)	7(1/14)	0(0/13)
		40 mcg	0(0/12)	0(0/11)	0(0/10)
	H-B-Vax	20 mcg	10(1/10)	0(0/8)	0(0/5)
		40 mcg	0(0/10)	0(0/10)	0(0/5)
Systemic	Recomb.	10 mcg	0(0/14)	0(0/14)	8(1/12)
		20 mcg	7(1/14)	0(0/14)	0(0/13)
		40 mcg	0(0/12)	0(0/11)	0(0/10)
	H-B-Vax	20 mcg	14(1/10)	0(0/8)	0(0/5)
		40 mcg	0(0/10)	0(0/10)	0(0/5)

No serious or alarming adverse experiences attributable to vaccine have been reported.

HBV MARKERS (Anti-HBc)

One subject in the 10 mcg yeast recombinant vaccine group was positive for anti-HBc at 1 and 3 months after the first injection of vaccine. The sera of this participant retested negative for anti-HBc. All samples were negative for HBsAg and ALT levels were normal.

Two subjects in the 20 mcg yeast recombinant vaccine group were positive for anti-HBc at 8 months post the first injection of vaccine. The patients were negative for HBsAg and ALT levels were normal. In both cases, the 12 month follow-up serum samples were negative for anti-HBc.

A predialysis patient in the 40 mcg yeast recombinant vaccine group was positive for anti-HBc IgG and negative for anti-HBc IgM at 6, 8, and 12 months post the initial vaccine injection. Serum samples were negative HBsAg and ALT levels were normal.

Study 811

RESULTS: (Cont.)

A subject in the 20 mcg plasma-derived vaccine group was positive for anti-HBc at 1 month after the first injection. The participant was negative for anti-HBc at 3 months. Serum samples were negative for HBsAg and ALT levels were within normal limits.

One participant in the 40 mcg plasma-derived vaccine group tested positive for anti-HBc at 1 month. The 3 and 6 month serum samples were negative for anti-HBc. The subject was negative HBsAg and ALT levels were normal.

There have been no reports of clinical hepatitis in any of the above vaccine recipients.

Reactions Reported to the OoBRR

A 28 year-old male (Case (b) (6) with underlying renal disease and recently initiated hemodialysis, died approximately one month after administration of the first injections of vaccine. The investigator reported death was due to vasculitis.

Table 1

Antibody Responses Among Predialysis Patients Following Vaccination with 10, 20, and 40 mcg Injections of Yeast Recombinant Hepatitis B Vaccine Lot # 974/C-K446 at 0, 1, and 6 Months in Study #811

	10 mcg					20 mcg					40 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Mos.)	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	0 (0/14)	0 (0/14)	0.3	---	---	0 (0/14)	0 (0/14)	0.3	---	---	0 (0/13)	0 (0/13)	0.3	---	---
3	0 (0/14)	0 (0/14)	0.3	---	---	7 (1/14)	7 (1/14)	0.5	90.0	90.0	0 (0/12)	0 (0/12)	0.3	---	---
6	0 (0/13)	0 (0/13)	0.3	---	---	28 (4/14)	28 (4/14)	1.0	23.6	23.6	42 (5/12)	42 (5/12)	1.7	19.4	19.4
7/8	15 (2/13)	15 (2/13)	0.7	67.7	67.7	58 (7/12)	58 (7/12)	13.8	213.7	213.7	64 (7/11)	54 (6/11)	23.6	120.9	186.4
12	8 (1/12)	0 (0/12)	0.4	6.0	---	60 (6/10)	60 (6/10)	8.5	78.5	78.5	40 (4/10)	40 (4/10)	3.3	117.3	117.3

25151-B
1/13/86

Table 2

Antibody Responses Among Predialysis Patients Following Vaccination with
20 and 40 mcg Injections of Plasma Derived Hepatitis B Vaccine
Lot # 1510J at 0, 1, and 6 Months in Study 811

Time (Months)	20 mcg					40 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	Responders S/N ≥ 2.1	Responders mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	Responders S/N ≥ 2.1	Responders mIU/ml ≥ 10
1	0(0/11)	0(0/11)	0.3	---	---	0(0/11)	0(0/11)	0.3	---	---
3	10(1/10)	10(1/10)	0.5	29.0	29.0	10(1/10)	0(0/10)	0.4	6.0	---
6	22(2/9)	11(1/9)	0.6	8.1	13.0	50(5/10)	40(4/10)	3.7	45.2	78.5
7/8	25(2/8)	25(2/8)	1.3	101.2	101.2	50(4/8)	38(3/8)	8.7	251.0	191.5
12	0(0/3)	0(0/3)	0.3	---	---	50(3/6)	50(3/6)	13.7	93.0	220.1

* One responder who received the third injection of vaccine at 3 months was excluded from the summary.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 816
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among: 1. adult dialysis patients negative for hepatitis B serologic markers. 2. health care personnel negative for hepatitis B serologic markers. 3. adult dialysis patients negative for hepatitis B serologic markers, who previously received plasma-derived hepatitis B vaccine and were nonresponders (anti-HBs negative).
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 974/C-K446 (20 mcg HBsAg/ml) Lot 986/C-K733 (20 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Stanley Plotkin, M.D./Stuart Starr, M.D. Division of Preventive Medicine Joseph Stokes, Jr. Research Institute Children's Hospital of Philadelphia 34 Street and Civic Center Boulevard Philadelphia, Pennsylvania 19104
STUDY LOCATION:	Biomedical Applications of Lehigh Valley 2015 Hamilton Avenue Allentown, Pennsylvania 18104 Dialysis, Inc. 1230 Burmont Road Drexel Hill, Pennsylvania The Kidney Center of Delaware Count 15th Street and Upland Avenue Chester, Pennsylvania 19013 The Kidney Center of Chester County 960 East Lincoln Highway Downington, Pennsylvania 19335

Study 816

DATE STUDY INITIATED: May 14, 1984

DATE STUDY COMPLETED: In progress

STUDY POPULATION: The study population consists of 40-50 adult dialysis patients (including previous nonresponders to plasma-derived vaccine), and 20-25 health care personnel, of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, and have a normal ALT level. Dialysis patients (excluding nonresponders to plasma-derived vaccine) and health care personnel have not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Dialysis patients are assigned to one of two groups, stratified by sex and age, to assure that patients in the two groups are similar. Health care personnel constitute a third group.

Dialysis patients receive 1.0 ml (20 mcg HBsAg) or 2 x 1.0 ml (40 mcg HBsAg) intramuscular injections of vaccine at 0, 1, and 6 months. Health care personnel receive 0.5 ml (10 mcg HBsAg) intramuscular injections of vaccine according to the same regimen. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 3, 6, 8, 12 and 24 months.

All serum samples are assayed for HBsAg, anti-HBs, anti-HBc, and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested to determine anti-a and anti-d subtype specificity.

Study 816

RESULTS:

DIALYSIS PATIENTS

20 mcg Lot 974/C-K446 at 0, 1, and 6 months *
40 mcg Lot 974/C-K446 at 0, 1, and 6 months *

1. Number Vaccinated:

Dose (mcg)	Injection No. 1	2	3
20	39	34	33
40	36	34	25

One dialysis patient who was initially anti-HBc positive received vaccine. The patient has remained anti-HBc positive through 12 months. The subject has not developed HBsAg or elevated ALT levels. At one month, the patient became anti-HBs positive.

Four dialysis patients (40 mcg dose) received 1.0 ml vaccine in the deltoid and 1.0 ml in the buttock.

* Two patients received a third 20 or 40 mcg dose of Lot 986/C-K733.

2. Serologic Results:

Serologic data at 7/8 months are available for 29 dialysis patients who received a 20 mcg dose and 21 dialysis patients who received a 40 mcg dose of vaccine.

Study 816

RESULTS: (Contd)

At 7/8 and 12 months, anti-HBs responses are as follows:

Time (Months)	Dose (mcg)	% Anti-HBs Positive S/N ≥2.1	% Anti-HBs Positive mIU/ml ≥10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥2.1	GMT (mIU/ml) Responders mIU/ml ≥10
7/8	20	59(17/29)	48(14/29)	7.8	69.1	118.6
	* 40	94(16/17)	88(15/17)	219.7	331.8	445.5
12	20	52(15/19)	41(12/29)	5.1	49.2	79.9
	* 40	81(17/21)	71(15/21)	41.6	107.9	165.6

* Serologic results included in the above summary do not include 4 dialysis patients (40 mcg dose) who received 1.0 ml vaccine in the deltoid and 1.0 ml in the buttock.

Anti-HBs responses at 1 through 12 months are included in Table 1.

3. Clinical Results:

Clinical follow-up data are available for 74, 68, and 56 dialysis patients following the first, second and third injections of vaccine, respectively. Clinical complaints and maximum temperatures reported following each injection are provided in Tables 2-5. In summary:

Clinical Complaint	Dose (mcg)	% Frequency by Injection No. 1	2	3
Injection Site	20	8(3/38)	0(0/34)	0(0/33)
	40	11(4/36)	3(1/34)	0(0/25)
Systemic	20	24(9/38)	3(1/34)	12(4/33)
	40	22(8/36)	0(0/34)	8(2/25)

No serious or alarming adverse reactions attributable to vaccination have been reported.

Study 816

RESULTS: (Contd)

Events reported to DoBRR

Seven deaths have occurred among dialysis patients who received recombinant hepatitis B vaccine Lot 974/C-K446. The investigator does not consider any of the deaths to be related to vaccination.

1. Case no. (b) (6) a 57 year-old female, died approximately six months after receiving athird 40 mcg dose of vaccine. The cause of death was cardiac arrest.

2. Case no. (b) (6) a 57 year-old male, died approximately one month after receiving a third 20 mcg dose of vaccine. The cause of death was attributed to a myocardial infarction and end-stage renal disease.

3. Case no. (b) (6) a 49 year-old male, died approximately four months after receiving a second 40 mcg dose of vaccine. Death was due to respiratory arrest, aspiration asphyxia, end-stage renal and coronary artery disease.

4. Case no. (b) (6) a 79 year-old male, died approximately four months after receiving a second 40 mcg dose of vaccine. Death was caused by cardiac arrest, atherosclerosis, end-stage renal disease and multiple myeloma.

5. Case no. (b) (6) a 71 year-old female, died approximately one month after receiving one 20 mcg dose of vaccine. Death was due to cardio-pulmonary arrest, uremia, chronic renal failure and abdominal aortic aneurysm without rupture.

6. Case no. (b) (6) a 49 year-old male, died approximately four months after receiving a second 40 mcg dose of vaccine. The death was due to cardiac arrest, pulmonary edema, and end-stage kidney disease.

7. Case no. (b) (6) a 37 year-old female, died approximately two months after receiving a second 40 mcg dose of vaccine. The death was caused by sepsis, end-stage renal disease, acute respiratory distress syndrome, infected dialysis graft, and diabetes mellitus.

Table 1

Antibody Responses Among Dialysis Patients Following Vaccination with
20 or 40 mcg Doses of Yeast Recombinant Hepatitis B Vaccine
Lot 974/C-K446 * at 0, 1, and 6 Months in Study 816

Time (Months)	Dialysis Patients									
	20 mcg					40 mcg **				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	Responders S/N ≥ 2.1	Responders mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥ 10	All Vaccinees	Responders S/N ≥ 2.1	Responders mIU/ml ≥ 10
1	8(2/26)	4(1/26)	0.4	5.4	18.5	15(4/26)	8(2/26)	0.6	8.1	17.9
3	21(5/24)	4(1/24)	0.6	6.5	76.1	52(13/25)	28(7/25)	2.3	15.0	32.9
6	33(8/24)	13(3/24)	1.0	6.4	21.7	81(13/16)	63(10/16)	10.8	21.5	35.2
7/8	59(17/29)	48(14/29)	7.8	69.1	118.6	94(16/17)	88(15/17)	219.7	331.8	445.5
12	52(15/29)	41(12/29)	5.1	49.2	79.9	81(17/21)	71(15/21)	41.6	107.9	165.6

* Two dialysis patients received a third 20 or 40 mcg dose of Lot 986/C-K733.

** Four dialysis patients (40 mcg dose) received 1.0 ml vaccine in the deltoid and 1.0 ml in the buttock. At 7/8 months, 25% (1/4) seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). These four subjects are not included in the above summary.

25381-11
1/22/86

00756

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK496
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (39 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	3 (7.9%)
PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
SORENESS	1 (2.6%)	1 (2.6%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.9%)
STIFFNESS/TIGHTNESS	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
SYSTEMIC	4 (10.5%)	3 (7.9%)	4 (10.5%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	9 (23.7%)
WHOLE BODY/GENERAL	1 (2.6%)	3 (7.9%)	3 (7.9%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	6 (15.8%)
CHILLS	0 (0.0%)	2 (5.3%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	3 (7.9%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.3%)
HEADACHE	1 (2.6%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.3%)
DIGESTIVE SYSTEM	1 (2.6%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	2 (5.3%)
DIARRHEA	1 (2.6%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	1 (2.6%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (39 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	6	5		
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)		1 (2.6%)
NERVOUS SYSTEM	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.6%)
VERTIGO/DIZZINESS	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.6%)
PSYCHIATRIC/BEHAVIORAL	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.6%)
INSOMNIA/DISTURBED SLEEP	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.6%)
PERSONS WITH COMPLAINTS	4 (10.5%)	4 (10.5%)	5 (13.2%)	2 (5.3%)	1 (2.6%)	1 (2.6%)		11 (28.9%)
PERSONS WITH NO COMPLAINTS	34 (89.5%)	34 (89.5%)	33 (86.8%)	36 (94.7%)	37 (97.4%)	37 (97.4%)		27 (71.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00758

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (34 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.9%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.9%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.9%)
PERSONS WITH NO COMPLAINTS	34 (100.0%)	34 (100.0%)	34 (100.0%)	34 (100.0%)	33 (97.1%)	34 (100.0%)	33 (97.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
SYSTEMIC	1 (3.1%)	2 (6.3%)	3 (9.4%)	3 (9.4%)	1 (3.1%)	3 (9.4%)		4 (12.5%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)		1 (3.1%)
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)		1 (3.1%)
RESPIRATORY	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	2 (6.3%)		2 (6.3%)
UPPER RESPIRATORY INFECT., NOS	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)		1 (3.1%)
BRONCHITIS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)		1 (3.1%)
NERVOUS SYSTEM	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
TREMOR	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
PERSONS WITH COMPLAINTS	1 (3.1%)	2 (6.3%)	3 (9.4%)	3 (9.4%)	1 (3.1%)	3 (9.4%)		4 (12.5%)
PERSONS WITH NO COMPLAINTS	31 (96.9%)	30 (93.8%)	29 (90.6%)	29 (90.6%)	31 (96.9%)	29 (90.6%)		28 (87.5%)

00760

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00761

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (1 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)		1 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00762

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (39 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
NORMAL	11 (29.7%)	11 (29.7%)	11 (29.7%)	11 (29.7%)	11 (31.4%)	11 (34.4%)			11 (29.7%)
< 99	14 (37.8%)	18 (48.6%)	19 (51.4%)	18 (48.6%)	16 (45.7%)	16 (50.0%)			8 (21.6%)
99 - 99.9	12 (32.4%)	7 (18.9%)	7 (18.9%)	7 (18.9%)	7 (20.0%)	4 (12.5%)			16 (43.2%)
100 - 100.9	0 (0.0%)	1 (2.7%)	0 (0.0%)	1 (2.7%)	1 (2.9%)	1 (3.1%)			2 (5.4%)
TEMPERATURE TAKEN	37 (94.9%)	37 (94.9%)	37 (94.9%)	37 (94.9%)	35 (89.7%)	32 (82.1%)			37 (94.9%)
TEMPERATURE NOT TAKEN	2 (5.1%)	2 (5.1%)	2 (5.1%)	2 (5.1%)	4 (10.3%)	7 (17.9%)			2 (5.1%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (34 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	15 (46.9%)	15 (45.5%)	15 (44.1%)	15 (45.5%)	15 (45.5%)	15 (46.9%)			15 (44.1%)
< 99	11 (34.4%)	15 (45.5%)	16 (47.1%)	16 (48.5%)	13 (39.4%)	16 (50.0%)			10 (29.4%)
99 - 99.9	6 (18.8%)	3 (9.1%)	3 (8.8%)	2 (6.1%)	5 (15.2%)	1 (3.1%)			9 (26.5%)
TEMPERATURE TAKEN	32 (94.1%)	33 (97.1%)	34 (100.0%)	33 (97.1%)	33 (97.1%)	32 (94.1%)			34 (100.0%)
TEMPERATURE NOT TAKEN	2 (5.9%)	1 (2.9%)	0 (0.0%)	1 (2.9%)	1 (2.9%)	2 (5.9%)			0 (0.0%)

00764

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0016
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (32 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	15 (50.0%)	15 (48.4%)	15 (50.0%)	15 (50.0%)	14 (45.2%)	14 (46.7%)		14 (45.2%)
< 99	11 (36.7%)	14 (45.2%)	11 (36.7%)	12 (40.0%)	13 (41.9%)	13 (43.3%)		7 (22.6%)
99 - 99.9	3 (10.0%)	2 (6.5%)	3 (10.0%)	2 (6.7%)	3 (9.7%)	2 (6.7%)		7 (22.6%)
100 - 100.9	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (3.2%)	0 (0.0%)		1 (3.2%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (3.3%)		2 (6.5%)
TEMPERATURE TAKEN	30 (93.8%)	31 (96.9%)	30 (93.8%)	30 (93.8%)	31 (96.9%)	30 (93.8%)		31 (96.9%)
TEMPERATURE NOT TAKEN	2 (6.3%)	1 (3.1%)	2 (6.3%)	2 (6.3%)	1 (3.1%)	2 (6.3%)		1 (3.1%)

00765

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (1 PATIENTS) - DOSE 3 — DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
NORMAL	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)		1 (100.0%)
TEMPERATURE TAKEN	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)		1 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00766

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 1 DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	3 (8.3%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (11.1%)
SORENESS	2 (5.6%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (8.3%)
STIFFNESS/TIGHTNESS	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
ECCHYMOSIS	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
SYSTEMIC	2 (5.6%)	3 (8.3%)	5 (13.9%)	2 (5.6%)	4 (11.1%)	2 (5.6%)		8 (22.2%)
WHOLE BODY/GENERAL	2 (5.6%)	2 (5.6%)	3 (8.3%)	2 (5.6%)	3 (8.3%)	1 (2.8%)		6 (16.7%)
SENSATION OF WARMTH, GENERAL	1 (2.8%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
FATIGUE/WEAKNESS	1 (2.8%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	2 (5.6%)	0 (0.0%)		3 (8.3%)
MALAISE	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
HEADACHE	1 (2.8%)	2 (5.6%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	0 (0.0%)		2 (5.6%)
LIGHTHEADED	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
ILLNESS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)		1 (2.8%)

00767

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RESPIRATORY	0 (0.0%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	2 (5.6%)
MUSCLE CRAMPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
ARM PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)	1 (2.8%)	2 (5.6%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	1 (2.8%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)	1 (2.8%)
APPETITE INCREASED	0 (0.0%)	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
PERSONS WITH COMPLAINTS	5 (13.9%)	4 (11.1%)	6 (16.7%)	2 (5.6%)	4 (11.1%)	2 (5.6%)	9 (25.0%)
PERSONS WITH NO COMPLAINTS	31 (86.1%)	32 (88.9%)	30 (83.3%)	34 (94.4%)	32 (88.9%)	34 (94.4%)	27 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00768

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0616
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (34 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)		1 (2.9%)
ECCHYMOSIS	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)		1 (2.9%)
PERSONS WITH COMPLAINTS	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)		1 (2.9%)
PERSONS WITH NO COMPLAINTS	33 (97.1%)	33 (97.1%)	33 (97.1%)	33 (97.1%)	33 (97.1%)	33 (97.1%)		33 (97.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (24 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	1 (4.2%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.3%)
WHOLE BODY/GENERAL	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
HEADACHE	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
HAND CRAMPS	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)
PERSONS WITH COMPLAINTS	1 (4.2%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.3%)
PERSONS WITH NO COMPLAINTS	23 (95.8%)	24 (100.0%)	23 (95.8%)	24 (100.0%)	24 (100.0%)	24 (100.0%)	22 (91.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (1 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)		1 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (36 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
NORMAL	11 (33.3%)	11 (32.4%)	11 (31.4%)	11 (30.6%)	11 (31.4%)	11 (31.4%)		11 (30.6%)
< 99	17 (51.5%)	17 (50.0%)	17 (48.6%)	18 (50.0%)	21 (60.0%)	18 (51.4%)		12 (33.3%)
99 - 99.9	4 (12.1%)	4 (11.8%)	5 (14.3%)	6 (16.7%)	1 (2.9%)	5 (14.3%)		9 (25.0%)
100 - 100.9	1 (3.0%)	2 (5.9%)	2 (5.7%)	1 (2.8%)	2 (5.7%)	0 (0.0%)		3 (8.3%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)		1 (2.8%)
TEMPERATURE TAKEN	33 (91.7%)	34 (94.4%)	35 (97.2%)	36 (100.0%)	35 (97.2%)	35 (97.2%)		36 (100.0%)
TEMPERATURE NOT TAKEN	3 (8.3%)	2 (5.6%)	1 (2.8%)	0 (0.0%)	1 (2.8%)	1 (2.8%)		0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (34 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
NORMAL	13 (43.3%)	13 (40.6%)	13 (40.6%)	13 (39.4%)	13 (43.3%)	13 (40.6%)		13 (39.4%)
< 99	10 (33.3%)	14 (43.8%)	15 (46.9%)	16 (48.5%)	16 (53.3%)	16 (50.0%)		11 (33.3%)
99 - 99.9	6 (20.0%)	4 (12.5%)	4 (12.5%)	4 (12.1%)	1 (3.3%)	3 (9.4%)		8 (24.2%)
100 - 100.9	1 (3.3%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
TEMPERATURE TAKEN	30 (88.2%)	32 (94.1%)	32 (94.1%)	33 (97.1%)	30 (88.2%)	32 (94.1%)		33 (97.1%)
TEMPERATURE NOT TAKEN	4 (11.8%)	2 (5.9%)	2 (5.9%)	1 (2.9%)	4 (11.8%)	2 (5.9%)		1 (2.9%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (24 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	14 (58.3%)	14 (60.9%)	14 (60.9%)	14 (60.9%)	14 (60.9%)	14 (58.3%)			14 (58.3%)
< 99	8 (33.3%)	8 (34.8%)	7 (30.4%)	6 (26.1%)	7 (30.4%)	9 (37.5%)			5 (20.8%)
99 - 99.9	2 (8.3%)	1 (4.3%)	2 (8.7%)	3 (13.0%)	2 (8.7%)	1 (4.2%)			5 (20.8%)
TEMPERATURE TAKEN	24 (100.0%)	23 (95.8%)	23 (95.8%)	23 (95.8%)	23 (95.8%)	24 (100.0%)			24 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (4.2%)	1 (4.2%)	1 (4.2%)	1 (4.2%)	0 (0.0%)			0 (0.0%)

00774

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0616
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (1 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	1 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)			0 (0.0%)
99 - 99.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)	0 (0.0%)			1 (100.0%)
TEMPERATURE TAKEN	1 (100.0%)	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)			1 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

00775

STUDY 825

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 825
PURPOSE:	To evaluate antibody and clinical responses to a high dose (100 mcg) level of yeast recombinant hepatitis B vaccine among adult hemodialysis patients.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #1005/C-L915 (100 mcg/ml)
PRIMARY INVESTIGATOR:	Harvey J. Alter, M.D. Chief, Immunology Section Clinical Center Blood Bank National Institutes of Health Bethesda, Maryland 20205
SECONDARY INVESTIGATOR:	Beverly Elder, R.N. Clinical Center Blood Bank National Institutes of Health Bethesda, Maryland 20205 Barry Strauch, M.D. Fairfax Dialysis Unit 8316 Arlington Blvd. Fairfax, Virginia 23022 James Shih, Ph.D. Clinical Center Blood Bank National Institutes of Health Bethesda, Maryland 20205
STUDY LOCATION:	Fairfax Dialysis Unit 8316 Arlington Boulevard Fairfax, Virginia 23022 Bio-Medical Applications of Annapolis 203 Ridgely Avenue Annapolis, Maryland 21401 Bio-Medical Applications of Washington 4905 Del Ray Avenue Bethesda, Maryland 10105

Study 825

DATE INITIATED: April 10, 1985

DATE COMPLETED: In progress

STUDY POPULATION: The study population consists of 75 - 100 adult hemodialysis patients of either sex (excluding pregnant women) who are negative for HBsAg, anti-HBs, anti-HBc and who have a normal ALT. Patients who have been shown to be nonresponders to three or more doses of plasma derived vaccine may be eligible for participation in the study. Dialysis patients must not be receiving any immunosuppressive therapy or be allergic to yeast.

PROCEDURE: Participants receive intramuscular injections of vaccine (100 mcg) on Day 0, 1 and 6 months. Study subjects are asked to record their temperature for five days after each injection and note any local or systemic complaints.

Blood specimens are obtained prior to vaccination, monthly for three months and at 6, 9, 12 and 24 months post initial injection. All specimens are assayed for anti-HBs, anti-HBc, HBsAg and ALT by Dr. Alter. Samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested to determine anti-a and anti-d activity. Samples may be tested for yeast antibody at MSDRL.

RESULTS: DIALYSIS PATIENTS:

100 mcg #Lot #1005/C-L915 at 0, 1 and 6 months.

1. Number Vaccinated:

Injection Number		
1	2	3
44	41	0

Study B25

RESULTS: (Cont.)

2. Serologic Results:

Serologic data are available for 28 study participants at 3 months. At that time, 68% (19/28) seroconverted (S/N ≥2.1) while 25% (7/28) developed protective levels of antibody. The GMT for all vaccinees was 4.4. Table 1 shows seroconversion rates and GMT's through 3 months of follow-up.

3. Clinical Complaints:

Clinical follow-up data is available for 44 and 39 participants following injections one and two, respectively. Specific complaints and maximum temperatures reported during the 5 days following these injections are provided in Tables 2 and 3.

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	100 mcg	9(4/44)	8(3/39)	
Systemic	100 mcg	7(3/44)	0(0/39)	

There have been no serious or alarming adverse reactions attributable to vaccine.

ALT Elevations

Three subjects have had elevations of ALT ranging from 3-5 times the upper limit of normal. One of these elevations occurred one month after receiving the first dose of vaccine, was transient, and returned to normal within a month. The other two elevations occurred one to two months after receiving the first dose of vaccine. Both have remained elevated through three months of follow-up. No reason for these elevations have been discovered. The subjects have not shown any clinical or serologic signs (HBsAg or anti-HBc) of hepatitis B.

Study 825

RESULTS: (Cont.)

HBV Markers (anti-HBc)

Two subjects whose prevaccination sera were negative for anti-HBc had one or more positive serum samples post-vaccination. In the first case the positive anti-HBc occurred at 3 months and was transient. A 4-month sample was negative for anti-HBc. The subject has remained negative for anti-HBc through 6 months and has shown no other serologic or clinical signs of illness.

In the second case the positive anti-HBc occurred at 3 months. Samples taken at 4 and 6 months continued to be anti-HBc positive. The patient has been anti-HBs positive since 3 months. He has remained HBsAg negative and there has been no report of clinical illness. He continues to be closely monitored.

Reactions Reported to DoBRR

Case (b) (6) a 31 year old male hemodialysis patient with ESRD, diabetes mellitus and hypertension, died (b) (6) days after administration of his first injection of vaccine (100 mcg Lot 1005/C-L915) on (b) (6) No adverse effects due to vaccination were noted. The cause of death was reported as cardiac arrthymia secondary to end stage renal disease. The death was not related to vaccine.

Case (b) (6) a 73-year-old female, died on (b) (6) from cerebral vascular accident secondary to diabetes mellitus associated vascular disease. She had received two doses of 100 mc lot 1005/C-L915 on (b) (6). On (b) (6) the patient came for scheduled dialysis. While on dialysis, she complained of weakness on her left side. She was hospitalized until her death on (b) (6) The death is not considered to be vaccine related.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0825
POPULATION : DIALYSIS PATIENTS
DOSE : 100 MCG
LOT : CL915
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (S/N)			
						RESPONDERS		
	S/N >= 2.1		S/N >= 10		ALL VACCINEES	S/N >= 2.1	S/N >= 10	
1 MONTH	13%	(5/38)	0%	(0/38)	1.3	3.0		
2 MONTHS	37%	(14/38)	18%	(7/38)	2.5	10.2	26.9	
3 MONTHS	68%	(19/28)	25%	(7/28)	4.4	8.4	33.3	

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0825
TREATMENT :
LOT NUMBER : CL915
DOSE : 100 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (44 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (2.3%)	2 (4.5%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	2 (4.5%)	4 (9.1%)
SORENESS	1 (2.3%)	2 (4.5%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	2 (4.5%)	4 (9.1%)
STIFFNESS/TIGHTNESS	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
SYSTEMIC	1 (2.3%)	2 (4.5%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	3 (6.8%)
WHOLE BODY/GENERAL	1 (2.3%)	2 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.5%)
FATIGUE/WEAKNESS	1 (2.3%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
OTHER	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (2.3%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (2.3%)
COUGH	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (2.3%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
ARTHRALGIA (OTHER)	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0825
TREATMENT :
LOT NUMBER : CL915
DOSE : 100 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (44 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	2 (4.5%)	4 (9.1%)	2 (4.5%)	1 (2.3%)	1 (2.3%)	3 (6.8%)	7 (15.9%)
PERSONS WITH NO COMPLAINTS	42 (95.5%)	40 (90.9%)	42 (95.5%)	43 (97.7%)	43 (97.7%)	41 (93.2%)	37 (84.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00782

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0825
TREATMENT :
LOT NUMBER : CL915
DOSE : 100 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (41 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	3 (7.7%)
INFLAMMATION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)
SORENESS	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	2 (5.1%)
ERYTHEMA (REDNESS)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	1 (2.6%)
PERSONS WITH COMPLAINTS	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	1 (2.6%)	3 (7.7%)
PERSONS WITH NO COMPLAINTS	38 (97.4%)	38 (97.4%)	38 (97.4%)	38 (97.4%)	38 (97.4%)	38 (97.4%)	36 (92.3%)
PERSONS WITH NO DATA	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0825
TREATMENT :
LOT NUMBER : CL915
DOSE : 100 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (44 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
NORMAL	1 (2.4%)	1 (2.7%)	1 (2.4%)	1 (2.6%)	1 (2.4%)	1 (2.8%)			1 (2.3%)
< 99	34 (81.0%)	31 (83.8%)	39 (92.9%)	31 (81.6%)	37 (90.2%)	29 (80.6%)			27 (62.8%)
99 - 99.9	7 (16.7%)	5 (13.5%)	2 (4.8%)	4 (10.5%)	3 (7.3%)	5 (13.9%)			12 (27.9%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.3%)	0 (0.0%)	1 (2.8%)			3 (7.0%)
TEMPERATURE TAKEN	42 (95.5%)	37 (84.1%)	42 (95.5%)	38 (86.4%)	41 (93.2%)	36 (81.8%)			43 (97.7%)
TEMPERATURE NOT TAKEN	2 (4.5%)	7 (15.9%)	2 (4.5%)	6 (13.6%)	3 (6.8%)	8 (18.2%)			1 (2.3%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0825
TREATMENT :
LOT NUMBER : CL915
DOSE : 100 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (41 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	0 (0.0%)	1 (2.9%)	1 (2.9%)	1 (3.0%)	1 (2.9%)	1 (2.9%)		0 (0.0%)
< 99	23 (74.2%)	29 (85.3%)	30 (85.7%)	30 (90.9%)	29 (82.9%)	33 (94.3%)		25 (64.1%)
99 - 99.9	7 (22.6%)	4 (11.8%)	4 (11.4%)	2 (6.1%)	5 (14.3%)	1 (2.9%)		13 (33.3%)
100 - 100.9	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.6%)
TEMPERATURE TAKEN	31 (75.6%)	34 (82.9%)	35 (85.4%)	33 (80.5%)	35 (85.4%)	35 (85.4%)		39 (95.1%)
TEMPERATURE NOT TAKEN	10 (24.4%)	7 (17.1%)	6 (14.6%)	8 (19.5%)	6 (14.6%)	6 (14.6%)		2 (4.9%)

STUDY 838

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 838.
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine in the following, initially seronegative, adult populations: 1. Dialysis Patients 2. Predialysis Patients 3. Health Care Personnel
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot # 986/C-K733 (20 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Professor Dr. Friedrich Deinhardt Director Max v. Pettenkofer Institute Pettenkoferstr. 9a 8000 Muenchen 2 West Germany
SECONDARY INVESTIGATORS:	Dr. Wolfgang Jilg Max v. Pettenkofer Institute Pettenkoferstr. 9a 8000 Muenchen 2 West Germany Professor Dr. Juergen Bommer Medizinische Universitatsklinik Bergheimer Str. 56 6900 Heidelberg 1 West Germany Professor Dr. R. Mueller Medizinische Hochschule Hannover Abt. f. Innere Medizin Karl-Wiechert-Allee 9 D-3000 Hannover-Kleefeld West Germany Professor Dr. Horst Braas Staedtische Krankenanstalten Medizinische Klinik II Bremserstr. 79 D-6700 Ludwigshafen West Germany

Study 838

SECONDARY INVESTIGATORS: (Cont.)

Dr. Bernhard Weinel
Staedtische Krankenanstalten
Medizinische Klinik II
Bremserstr. 79
D-6700 Ludwigshafen
West Germany

STUDY LOCATIONS: Munich, Heidelberg, Hannover, and Ludwigshafen, West Germany

DATE INITIATED: June 7, 1984

DATE COMPLETED: In progress

STUDY POPULATIONS: Under the original protocol and subsequent addenda, the following groups are enrolled in the study. Participants may be of either sex, but pregnant women are excluded. Prospective vaccine recipients must be negative for hepatitis B serologic markers, have a normal ALT level and may not have received any hepatitis B vaccine (except as noted under addendum #2).

Protocol/ Addendum #	Population	Approx. Number	Regimen
Initial protocol	Health Care Personnel	25	10 mcg (0.5 ml) at 0, 1, and 6 months
Initial protocol	Dialysis Patients	50	40 mcg (2 x 1.0 ml) at 0, 1 and 6 months
Add. #1	Dialysis Patients	20	20 mcg (1.0 ml) at 0, 1, 2, 3, 4, and 6 months
Add. #1	Dialysis Patients	20	40 mcg (2 x 1.0 ml) at 0, 1, 2, 3, 4, and 6 months

Study 838

STUDY POPULATIONS: (CONT.)

Protocol/ Addendum #	Population	Approx. Number	Regimen
Add. #2	Initial protocol subjects who do not form anti-HBs after 3 doses of vaccine		10 mcg (0.5 ml) for health care personnel; 40 mcg (2 x 1.0 ml) for dialysis patients
Add. #3	Predialysis patients	10	10 mcg (2 x 1.0 ml) at 0, 1, and 6 months

PROCEDURE:

Participants receive intramuscular injections of vaccine according to the regimens outlined above under STUDY POPULATIONS.

Study participants will be asked to record their temperature for five days after each injection and to note any local or systemic complaints.

Serum samples will be obtained prior to and on the day of vaccination. Follow-up blood specimens will be obtained 1, 2, 3, 6, 8, 12 and 24 months post the initial injection of vaccine. Nonresponders who receive a fourth injection of vaccine under addendum #2 will have a blood sample taken one month after this injection. Serum samples will be assayed for HBsAg, anti-HBs, anti-HBc and ALT by Dr. Deinhardt's laboratory. Samples may also be assayed at MSDRL for yeast antibody. Those that are positive for anti-HBs with a titer of $\geq$25 mIU/ml may be assayed for anti-a and anti-d subtype specificity.

Study 838

RESULTS:

DIALYSIS PATIENTS:

40 mcg Lot #986/C-K733 at 0, 1, and 6 months
40 mcg Lot #986/C-K733 at 0, 1, 2, 3, 4, and 6 months
20 mcg Lot #986/C-K733 at 0, 1, 2, 3, 4, and 6 months

1. Number Vaccinated:

Regimen	Injection No. 1	2	3	4	5	6
3 x 40 mcg	51	51	48			
6 x 40 mcg	20	20	20	19	19	17
6 x 20 mcg	20	20	20	20	20	17

Note: All vaccine was administered into the buttock.

2. Serologic Results:

Serologic data are available for 36 participants at 7/8 months who received three 40 mcg injections of vaccine at 0, 1, and 6 months. Seroconversion (S/N $\geq$2.1) for anti-HBs at that time was 64% (23/36). Fifty-eight percent (21/36) of the patients developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT at 7/8 months for all vaccinees was 12.3 mIU/ml and 115.5 for responders (mIU/ml $\geq$10).

Serology data are available for 15 patients at 10 months who received six 40 mcg injections of vaccine at 0, 1, 2, 3, 4, and 6 months. Seroconversion (S/N $\geq$2.1) for anti-HBs at that time was 67% (10/15). Sixty percent (9/15) developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT at ten months for all vaccinees was 6.7 mIU/ml and 27.7 for responders(mIU/ml $\geq$10).

Eighteen subjects who received six 20 mcg injections of vaccine at 0, 1, 2, 3, 4, and 6 months, have serology data available for the ten month follow-up interval. Fifty percent (9/18) of the patients seroconverted for anti-HBs (S/N $\geq$2.1)

RESULTS (CONT.):

at that time. Forty-four percent (8/18) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at ten months for all vaccinees was 4.7 mIU/ml and 55.0 for responders(mIU/ml ≥10).

Refer to Table 1 for anti-HBs responses and GMTs, by dose regimen, for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for at least 38, 16, and 17 participants after each injection in the 3 x 40 mcg, 6 x 40 mcg, and 6 x 20 mcg dose regimens, respectively. The overall frequencies of complaints are presented below.

Type of Complaint	Regimen	Frequency in % by Injection					
		1	2	3	4	5	6
Injection Site	3 x 40 mcg	0(0/51)	0(0/49)	0(0/38)			
	6 x 40 mcg	0(0/20)	0(0/20)	0(0/20)	0(0/19)	0(0/19)	0(0/16)
	6 x 20 mcg	0(0/20)	0(0/20)	5(1/20)	0(0/20)	0(0/20)	0(0/17)
Systemic	3 x 40 mcg	8(4/51)	0(0/49)	3(1/38)			
	6 x 40 mcg	15(3/20)	10(2/20)	15(3/20)	16(3/19)	0(0/19)	0(0/16)
	6 x 20 mcg	5(1/20)	10(2/20)	5(1/20)	5(1/20)	0(0/20)	0(0/17)

Refer to Tables 2 through 4 for listings of specific clinical complaints by dose regimen and injection number. Maximum temperature data are provided in Tables 5 through 7.

HBV Markers (Anti-HBc)

One patient enrolled in the 3 x 40 mcg group was anti-HBc positive and had an ALT level approximately 1.5 times the upper limit of normal prior to vaccination. He has remained anti-HBc positive post-vaccination. Post-vaccination ALT levels have not been ascertained. All pre- and post-vaccination samples were negative for HBsAg. There has been no report of illness in this subject. The patient has not developed protective levels of anti-HBs (mIU/ml ≥10).

Study 838

RESULTS (CONT.):

A patient in the 3 x 40 mcg group was anti-HBc positive prior to vaccination. In all subsequent post-vaccination samples, she was negative for anti-HBc. The subject developed protective levels of anti-HBs (mIU/ml ≥10) at two months after the second injection.

A male dialysis patient in the 6 x 20 mcg group became positive for anti-HBc one month after the sixth injection of vaccine. He was HBsAg negative. The subject had developed protective levels of anti-HBs (mIU/ml ≥10) at the time of his fourth injection with a titer of 29 mIU/ml. One month after the sixth injection his anti-HBs titer was 438 mIU/ml. There has been no report of illness in this patient.

Reactions Reported to the OoBRR

A 70-year old male with a history of coronary artery disease and end stage renal disease died of a myocardial infarction (b) (6) days after receiving the fifth injection of vaccine (6 x 40 mcg group). His death was not considered to be vaccine related.

A 46-year old male dialysis patient with a history of diabetes mellitus and diabetic nephropathy, died two months after administration of his third injection of vaccine (3 x 40 mcg group). Death was due to cardiac arrest secondary to hyperkalemia and was not considered vaccine related.

PUBLICATIONS:

Mueller R, Bommer J, Braas H, Deinhardt A, Jilg W, Kuttler G, et al. Erste erfahrungen mit rekombinanter hepatitis B-vaccine bei patienten unter chronischer haemodialyse-behandlung. Gastroenterol 1985; 23: 297.

Study 838

RESULTS (CONT.): PREDIALYSIS PATIENTS:

40 mcg Lot #986/C-K733 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
8	8	0

2. Serologic Results:

One month serology data are available for all eight vaccinees. Anti-HBs responses at that time are summarized below:

% with Anti-HBs		GMT (mIU/ml)		
			Responders	
S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10
13(1/8)	0(0/8)	0.7	4.6	—

3. Clinical Complaints:

Clinical follow-up data are available for eight participants after the first injection. There were no clinical complaints or temperature elevations. No serious or alarming adverse experiences attributable to vaccine have been reported.

Table 1

Antibody Responses Among Dialysis Patients Following Vaccination with
Yeast Recombinant Hepatitis B Vaccine Lot # 986/C-K733 in Study #838

	40 mcg at 0, 1, and 6 Months					40 mcg at 0, 1, 2, 3, 4, and 6 Months*					20 mcg at 0, 1, 2, 3, 4, and 6 Months*				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Mos.)	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	0 (0/48)	0 (0/48)	0.3	---	---	0 (0/20)	0 (0/20)	0.3	---	---	0 (0/20)	0 (0/20)	0.3	---	---
2	30 (14/46)	13 (6/46)	0.9	---	---	21 (4/19)	5 (1/19)	0.6	10.0	50.0	15 (3/20)	10 (2/20)	0.5	16.5	25.0
3	35 (16/46)	22 (10/46)	1.3	16.5	31.0	35 (7/20)	20 (4/20)	1.2	17.4	33.5	32 (6/19)	26 (5/19)	1.2	23.6	31.4
6	34 (12/35)	29 (10/35)	1.4	26.1	33.8	69 (11/16)	69 (11/16)	32.2	189.8	189.8	56 (9/16)	44 (7/16)	9.7	87.3	190.0
7/8	64 (23/36)	58 (21/36)	12.3	90.2	115.5	---	---	----	-----	-----	---	---	---	----	-----
10	65 (24/37)	54 (20/37)	12.8	73.8	117.6	67 (10/15)	60 (9/15)	6.7	24.5	27.7	50 (9/18)	44 (8/18)	4.7	45.0	55.0

*Dose scheduled at 6 months was actually administered at 5 months in most cases.

NOTE: All injections were into the buttock.

2514I-9
1/3/86

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG *
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (51 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
SYSTEMIC	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)		4 (7.8%)
WHOLE BODY/GENERAL	1 (2.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.9%)
CHILLS	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.0%)
LIGHTHEADED	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.0%)
CARDIOVASCULAR	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.0%)
OTHER	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.0%)
NERVOUS SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)		1 (2.0%)
VERTIGO/DIZZINESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)		1 (2.0%)
PERSONS WITH COMPLAINTS	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	1 (2.0%)	0 (0.0%)		4 (7.8%)
PERSONS WITH NO COMPLAINTS	50 (98.0%)	50 (98.0%)	50 (98.0%)	50 (98.0%)	50 (98.0%)	51 (100.0%)		47 (92.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

* Three injection regimen

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (51 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	49 (100.0%)	49 (100.0%)	49 (100.0%)	49 (100.0%)	49 (100.0%)	49 (100.0%)		49 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (48 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1		3	4	5	
SYSTEMIC	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
CARDIOVASCULAR	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
HYPERTENSION	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
DIGESTIVE SYSTEM	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
NAUSEA	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
PERSONS WITH COMPLAINTS	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)
PERSONS WITH NO COMPLAINTS	37 (97.4%)	38 (100.0%)	38 (100.0%)	38 (100.0%)	38 (100.0%)	38 (100.0%)	37 (97.4%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG *
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
SYSTEMIC	2 (10.0%)	2 (10.0%)	2 (10.0%)	1 (5.0%)	2 (10.0%)	1 (5.0%)		3 (15.0%)
WHOLE BODY/GENERAL	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)	1 (5.0%)		3 (15.0%)
FATIGUE/WEAKNESS	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)	1 (5.0%)		3 (15.0%)
CARDIOVASCULAR	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
OTHER	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
MUSCULOSKELETAL	0 (0.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
ARTHRALGIA (OTHER)	0 (0.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
PERSONS WITH COMPLAINTS	2 (10.0%)	2 (10.0%)	2 (10.0%)	1 (5.0%)	2 (10.0%)	1 (5.0%)		3 (15.0%)
PERSONS WITH NO COMPLAINTS	18 (90.0%)	18 (90.0%)	18 (90.0%)	19 (95.0%)	18 (90.0%)	19 (95.0%)		17 (85.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

* Six injection regimen

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	2 (10.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	2 (10.0%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (5.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	2 (10.0%)
HEADACHE	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	2 (10.0%)
PERSONS WITH NO COMPLAINTS	20 (100.0%)	19 (95.0%)	19 (95.0%)	18 (90.0%)	20 (100.0%)	20 (100.0%)	18 (90.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	1 (5.0%)	1 (5.0%)	2 (10.0%)	3 (15.0%)	2 (10.0%)	1 (5.0%)	3 (15.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (5.0%)	2 (10.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	3 (15.0%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
HEADACHE	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
ILLNESS, NOS	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)
ARTHRALGIA (OTHER)	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)
DIGESTIVE SYSTEM	1 (5.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	3 (15.0%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
NAUSEA	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)
PERSONS WITH COMPLAINTS	1 (5.0%)	1 (5.0%)	2 (10.0%)	3 (15.0%)	2 (10.0%)	1 (5.0%)	3 (15.0%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	19 (95.0%)	19 (95.0%)	18 (90.0%)	17 (85.0%)	18 (90.0%)	19 (95.0%)	17 (85.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (19 PATIENTS) - DOSE 4							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
SYSTEMIC	1 (5.3%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	2 (10.5%)		3 (15.8%)
WHOLE BODY/GENERAL	1 (5.3%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	2 (10.5%)		3 (15.8%)
CHILLS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)		1 (5.3%)
FATIGUE/WEAKNESS	1 (5.3%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	1 (5.3%)		2 (10.5%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)		1 (5.3%)
COUGH	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)		1 (5.3%)
PERSONS WITH COMPLAINTS	1 (5.3%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	2 (10.5%)		3 (15.8%)
PERSONS WITH NO COMPLAINTS	18 (94.7%)	19 (100.0%)	18 (94.7%)	18 (94.7%)	18 (94.7%)	17 (89.5%)		16 (84.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (19 PATIENTS) - DOSE 5						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	19 (100.0%)	19 (100.0%)	19 (100.0%)	19 (100.0%)	19 (100.0%)	19 (100.0%)	19 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (17 PATIENTS) - DOSE 6						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	16 (100.0%)	16 (100.0%)	16 (100.0%)	16 (100.0%)	16 (100.0%)	16 (100.0%)	16 (100.0%)
PERSONS WITH NO DATA	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG *
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
SYSTEMIC	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)		1 (5.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)		1 (5.0%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)		1 (5.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)		1 (5.0%)
PERSONS WITH NO COMPLAINTS	20 (100.0%)	19 (95.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	19 (95.0%)		19 (95.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

* Six injection regimen

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
SYSTEMIC	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)		2 (10.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
HEADACHE	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
LIGHTHEADED	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)		2 (10.0%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)		1 (5.0%)
NAUSEA	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)		2 (10.0%)
PERSONS WITH NO COMPLAINTS	20 (100.0%)	19 (95.0%)	20 (100.0%)	20 (100.0%)	19 (95.0%)	20 (100.0%)		18 (90.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
PRURITIS (ITCHING)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)		1 (5.0%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
CARDIOVASCULAR	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
HYPOTENSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)		1 (5.0%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)		1 (5.0%)
PERSONS WITH COMPLAINTS	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)		2 (10.0%)
PERSONS WITH NO COMPLAINTS	19 (95.0%)	20 (100.0%)	20 (100.0%)	19 (95.0%)	20 (100.0%)	19 (95.0%)		18 (90.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 4						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
MUSCULOSKELETAL	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
ARTHRALGIA (OTHER)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
DIMINISHED APPETITE	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
DEPRESSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
PERSONS WITH COMPLAINTS	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (5.0%)
PERSONS WITH NO COMPLAINTS	19 (95.0%)	19 (95.0%)	19 (95.0%)	19 (95.0%)	20 (100.0%)	20 (100.0%)	19 (95.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (20 PATIENTS) - DOSE 5						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00808

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (17 PATIENTS) - DOSE 6						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG *
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (51 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
< 99	47 (92.2%)	46 (90.2%)	48 (94.1%)	48 (94.1%)	46 (92.0%)	43 (95.6%)		39 (76.5%)
99 - 99.9	3 (5.9%)	3 (5.9%)	3 (5.9%)	1 (2.0%)	4 (8.0%)	2 (4.4%)		10 (19.6%)
100 - 100.9	1 (2.0%)	2 (3.9%)	0 (0.0%)	2 (3.9%)	0 (0.0%)	0 (0.0%)		2 (3.9%)
TEMPERATURE TAKEN	51 (100.0%)	51 (100.0%)	51 (100.0%)	51 (100.0%)	50 (98.0%)	45 (88.2%)		51 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	6 (11.8%)		0 (0.0%)

* Three injection regimen

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (51 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	46 (95.8%)	46 (95.8%)	45 (93.8%)	42 (87.5%)	48 (100.0%)	45 (100.0%)		40 (83.3%)
99 - 99.9	2 (4.2%)	2 (4.2%)	3 (6.3%)	6 (12.5%)	0 (0.0%)	0 (0.0%)		8 (16.7%)
TEMPERATURE TAKEN	48 (94.1%)	48 (94.1%)	48 (94.1%)	48 (94.1%)	48 (94.1%)	45 (88.2%)		48 (94.1%)
TEMPERATURE NOT TAKEN	3 (5.9%)	3 (5.9%)	3 (5.9%)	3 (5.9%)	3 (5.9%)	6 (11.8%)		3 (5.9%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (48 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	35 (92.1%)	36 (94.7%)	38 (100.0%)	38 (100.0%)	38 (100.0%)	38 (100.0%)		33 (86.8%)
99 - 99.9	2 (5.3%)	2 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (10.5%)
101 - 101.9	1 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.6%)
TEMPERATURE TAKEN	38 (79.2%)	38 (79.2%)	38 (79.2%)	38 (79.2%)	38 (79.2%)	38 (79.2%)		38 (79.2%)
TEMPERATURE NOT TAKEN	10 (20.8%)	10 (20.8%)	10 (20.8%)	10 (20.8%)	10 (20.8%)	10 (20.8%)		10 (20.8%)

Table 6

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0836
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG *
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (20 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	17 (85.0%)	18 (90.0%)	18 (90.0%)	17 (85.0%)	17 (85.0%)	18 (90.0%)		13 (65.0%)
99 - 99.9	3 (15.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)	3 (15.0%)	1 (5.0%)		5 (25.0%)
100 - 100.9	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)	1 (5.0%)		2 (10.0%)
TEMPERATURE TAKEN	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)		20 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

* Six injection regimen

Table 6 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (20 PATIENTS) - DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	17 (89.5%)	15 (78.9%)	16 (88.9%)	14 (82.4%)	16 (88.9%)	17 (100.0%)			13 (68.4%)
99 - 99.9	2 (10.5%)	3 (15.8%)	1 (5.6%)	3 (17.6%)	2 (11.1%)	0 (0.0%)			5 (26.3%)
100 - 100.9	0 (0.0%)	1 (5.3%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (5.3%)
TEMPERATURE TAKEN	19 (95.0%)	19 (95.0%)	18 (90.0%)	17 (85.0%)	18 (90.0%)	17 (85.0%)			19 (95.0%)
TEMPERATURE NOT TAKEN	1 (5.0%)	1 (5.0%)	2 (10.0%)	3 (15.0%)	2 (10.0%)	3 (15.0%)			1 (5.0%)

Table 6 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (20 PATIENTS) - DOSE 3 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	17 (89.5%)	16 (84.2%)	18 (94.7%)	18 (94.7%)	17 (94.4%)	17 (94.4%)			16 (84.2%)
99 - 99.9	2 (10.5%)	3 (15.8%)	1 (5.3%)	1 (5.3%)	1 (5.6%)	0 (0.0%)			2 (10.5%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)			1 (5.3%)
TEMPERATURE TAKEN	19 (95.0%)	19 (95.0%)	19 (95.0%)	19 (95.0%)	18 (90.0%)	18 (90.0%)			19 (95.0%)
TEMPERATURE NOT TAKEN	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)	2 (10.0%)			1 (5.0%)

00815

Table 6 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (19 PATIENTS) - DOSE 4								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	18 (100.0%)	16 (88.9%)	18 (100.0%)	15 (83.3%)	16 (88.9%)	17 (94.4%)			15 (83.3%)
99 - 99.9	0 (0.0%)	2 (11.1%)	0 (0.0%)	3 (16.7%)	2 (11.1%)	1 (5.6%)			3 (16.7%)
TEMPERATURE TAKEN	18 (94.7%)	18 (94.7%)	18 (94.7%)	18 (94.7%)	18 (94.7%)	18 (94.7%)			18 (94.7%)
TEMPERATURE NOT TAKEN	1 (5.3%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	1 (5.3%)			1 (5.3%)

Table 6 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (19 PATIENTS) - DOSE 5								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	16 (94.1%)	16 (88.9%)	17 (100.0%)	17 (100.0%)	17 (100.0%)	17 (100.0%)			16 (88.9%)
99 - 99.9	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (5.6%)
100 - 100.9	1 (5.9%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (5.6%)
TEMPERATURE TAKEN	17 (89.5%)	18 (94.7%)	17 (89.5%)	17 (89.5%)	17 (89.5%)	17 (89.5%)			18 (94.7%)
TEMPERATURE NOT TAKEN	2 (10.5%)	1 (5.3%)	2 (10.5%)	2 (10.5%)	2 (10.5%)	2 (10.5%)			1 (5.3%)

Table 6 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 40 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (17 PATIENTS) - DOSE 6 — DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
< 99	13 (86.7%)	14 (93.3%)	15 (100.0%)	14 (93.3%)	14 (93.3%)	14 (100.0%)			13 (86.7%)
99 - 99.9	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)			1 (6.7%)
100 - 100.9	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (6.7%)
TEMPERATURE TAKEN	15 (88.2%)	15 (88.2%)	15 (88.2%)	15 (88.2%)	15 (88.2%)	14 (82.4%)			15 (88.2%)
TEMPERATURE NOT TAKEN	2 (11.8%)	2 (11.8%)	2 (11.8%)	2 (11.8%)	2 (11.8%)	3 (17.6%)			2 (11.8%)

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG *
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (20 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	15 (83.3%)	16 (88.9%)	16 (88.9%)	17 (94.4%)	17 (94.4%)	16 (88.9%)			14 (77.8%)
99 - 99.9	3 (16.7%)	2 (11.1%)	2 (11.1%)	1 (5.6%)	1 (5.6%)	1 (5.6%)			3 (16.7%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)			1 (5.6%)
TEMPERATURE TAKEN	18 (90.0%)	18 (90.0%)	18 (90.0%)	18 (90.0%)	18 (90.0%)	18 (90.0%)			18 (90.0%)
TEMPERATURE NOT TAKEN	2 (10.0%)	2 (10.0%)	2 (10.0%)	2 (10.0%)	2 (10.0%)	2 (10.0%)			2 (10.0%)

* Six injection regimen

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (20 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
< 99	18 (94.7%)	19 (100.0%)	19 (100.0%)	18 (100.0%)	19 (100.0%)	19 (100.0%)		18 (94.7%)
99 - 99.9	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.3%)
TEMPERATURE TAKEN	19 (95.0%)	19 (95.0%)	19 (95.0%)	18 (90.0%)	19 (95.0%)	19 (95.0%)		19 (95.0%)
TEMPERATURE NOT TAKEN	1 (5.0%)	1 (5.0%)	1 (5.0%)	2 (10.0%)	1 (5.0%)	1 (5.0%)		1 (5.0%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (20 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	18 (90.0%)	19 (95.0%)	17 (85.0%)	19 (95.0%)	19 (95.0%)	19 (95.0%)		15 (75.0%)
99 - 99.9	2 (10.0%)	1 (5.0%)	3 (15.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)		5 (25.0%)
TEMPERATURE TAKEN	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)		20 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0836
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (20 PATIENTS) - DOSE 4 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	19 (95.0%)	19 (95.0%)	19 (95.0%)	18 (90.0%)	20 (100.0%)	20 (100.0%)			16 (80.0%)
99 - 99.9	1 (5.0%)	0 (0.0%)	1 (5.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)			3 (15.0%)
100 - 100.9	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (5.0%)
TEMPERATURE TAKEN	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)			20 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (20 PATIENTS) - DOSE 5								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	20 (100.0%)	20 (100.0%)	19 (95.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)			19 (95.0%)
99 - 99.9	0 (0.0%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (5.0%)
TEMPERATURE TAKEN	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)	20 (100.0%)			20 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 7 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0838
TREATMENT :
LOT NUMBER : CK733
DOSE : 20 MCG
PATIENT CLASS: DIALYSIS PATIENTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (17 PATIENTS) - DOSE 6								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	15 (93.8%)	15 (93.8%)	16 (100.0%)	16 (100.0%)	16 (100.0%)	15 (93.8%)			13 (81.3%)
99 - 99.9	1 (6.3%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)			3 (18.8%)
TEMPERATURE TAKEN	16 (94.1%)	16 (94.1%)	16 (94.1%)	16 (94.1%)	16 (94.1%)	16 (94.1%)			16 (94.1%)
TEMPERATURE NOT TAKEN	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (5.9%)			1 (5.9%)

Erste Erfahrungen mit rekombinanter Hepatitis B-Vaccine bei Patienten unter chronischer Haemodialyse-Behandlung.

R. Müller[1], J. Bommer[2], H. Brass[3], F. Deinhardt[4], A. Feuerhake[5], W. Jilg[4], G. Küttler[1], B. Weinel[1], Abteilung für Gastroenterologie und Hepatologie, Medizinische Hochschule Hannover[1]; Sektion Nephrologie, Medizinische Klinik Universität Heidelberg[2]; Medizinische Klinik II, Städt. Krankenanstalten Ludwigshafen[3]; Max von Pettenkofer Institut der Ludwig-Maximilian-Universität München[4].

Die Immunogenität natürlicher, aus Humanplasma gewonnener Hepatitis B-Vaccine hat sich bei endogen oder exogen immunsupprimierten Patienten beträchtlich schwächer erwiesen als bei gesunden Personen. Es erschien daher interessant zu prüfen, ob nach Impfung mit einer gentechnologisch gewonnenen HB-Vaccine bei chronischen Haemodialyse-Patienten höhere Seronkonversionsraten für anti-HB_s erzielt werden können als mit natürlichem HB-Impfstoff. 51 HBV empfängliche Patienten unter chronischer Haemodialyse-Behandlung erhielten 3 Impfungen mit je 40 ug Hb_sAg Protein, das in einem DNS-rekombiniertem Stamm der Hefe Saccharomyces cerovisiae hergestellt wurde (Hepatitis B-Vaccine [recombinant] MSD, Westpoint USA; Lot 934/C-J625). Die zweite und dritte Impfung erfolgten einen bzw. 6 Monate nach der ersten Impfung. Einen Monat nach der 2. Impfung hatten 20 von 48 (42%) der Patienten anti-HB_s gebildet. Der mittlere Antikörper-Gehalt betrug 24,7 IU/ml. Bei 21 Patienten ist das Impfprogramm abgeschlossen, 13 von ihnen wiesen im 7. Monat nach Impfbeginn eine Serokonversion nach anti-HB_s auf. Der mittlere anti-HB_s-Gehalt war auf 151 IU/ml angestiegen. Danach lassen sich bei Dialyse-Patienten mit rekombinat hergestellter HB-Vaccine ähnliche Serokonversionsraten erzielen wie mit HB-Impfstoff, der aus Humanplasma gewonnen wurde.

Muller R, Bommer J, Brass H, Deinhardt A, Jilg W, Kuttler G, et al. Erste erfahrungen mit rekombinanter hepatitis B-vaccine bei patienten unter chronischer haemodialyse-behandlung. Gastroenterol 1985; 23:297.

NOTE: There is no missing material. There was an error in numbering.

Janurary 1986

REPORT NO. 3
in Support for a License Application for

RECOMBIVAX
(Yeast Recombinant Hepatitis B Vaccine, MSD)
CLINICAL DATA*
VOLUME 3 OF 3

Merck Sharp & Dohme Research Laboratories

MENTALLY RETARDED

SUMMARY - MENTALLY RETARDED INDIVIDUALS

Two studies (Study 815 and 889) are being conducted to evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among institutionalized mentally retarded individuals who are negative for hepatitis B virus serologic markers. Mentally retarded individuals receive three 10 or 20 mcg doses of yeast recombinant vaccine (Study 815 and 889) or three 20 mcg doses of plasma-derived vaccine (Study 815) at 0, 1, and 6 months.

A total of 200 mentally retarded individuals have completed a three injection regimen of vaccination. No serious or alarming adverse reactions attributable to vaccine have been reported.

Serologic data after one injection of vaccine are available for 201 individuals. At one month 19-20% of vaccine recipients who received either one 10 or 20 mcg dose had detectable antibody (S/N $\geq$2.1). Titers of at least 10 mIU/ml occurred in 8% (10 mcg dose) and 11% (20 mcg dose) of vaccine recipients at this time. Among mentally retarded individuals with a minimum titer of S/N $\geq$2.1, the geometric mean titers were 8.7 mIU/ml (10 mcg dose) and 13.7 mIU/ml (20 mcg dose). Geometric mean titers for responders with antibody levels of mIU/ml $\geq$10 were 19.9 mIU/ml (10 mcg dose) and 38.7 mIU/ml (20 mcg dose).

Clinical data are available on 201 mentally retarded individuals after two injections of vaccine. The vaccine has been very well tolerated in this population with very few clinical complaints reported. No injection site reactions were reported following either the first or second injection. Systemic complaints were reported in 2% of vaccine recipients following the initial 10 mcg dose and 1% vaccine recipients following the initial 20 mcg dose of vaccine. No systemic complaints were reported after the second injection.

MENTALLY RETARDED INDIVIDUALS

Study 815 - The Netherlands - Dr. S. Schalm

The study population consists of institutionalized mentally retarded individuals and health care personnel. Mentally retarded individuals and health care personnel receive either three 10 or 20 mcg doses of yeast recombinant hepatitis B vaccine lot 993/C-K937 or three 20 mcg doses of plasma-derived vaccine lot 2277K at 0, 1, and 6 months. Vaccination and clinical follow-up continues in progress.

Study 889 - St. Louis, MO - Dr. R. Perrillo

The study population consists of institutionalized mentally retarded individuals and health care personnel. Mentally retarded individuals receive three 10 or 20 mcg doses of yeast recombinant hepatitis B vaccine lot 993/C-K937 at 0, 1, and 6 months. Health care personnel receive 10 mcg doses of vaccine according to the same regimen.

One hundred mentally retarded individuals have received three 10 mcg doses of vaccine. At one month 19% (19/101) participants seroconverted (S/N $\geq$2.1) and 8% (8/101) developed protective levels of antibody (mIU/ml $\geq$10). The geometric mean titer for responders with antibody $\geq$10 mIU/ml was 19.9 mIU/ml.

One hundred mentally retarded individuals have received three 20 mcg doses of vaccine. At one month the seroconversion rate (S/N $\geq$2.1) was 20% (20/100) with 11% (11/100) developing protective levels of antibody (mIU/ml $\geq$10). Responders with titers of at least 10 mIU/ml had a geometric mean titer of 38.7 mIU/ml.

No serious or alarming adverse reactions attributable to vaccine have been reported. The study continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 815
PURPOSE:	To compare antibody and clinical responses to yeast recombinant and plasma-derived hepatitis B vaccine among: 1 Mentally retarded individuals who are negative for hepatitis B virus serologic markers. 2. Health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	1. Yeast Recombinant Hepatitis B Vaccine Lot 993/C-K937 (20 mcg/HBsAg/ml) 2. Plasma-Derived Hepatitis B Vaccine Lot 2277K (20 mcg HBsAg/ml
PRIMARY INVESTIGATOR:	Solko W. Schalm, M.D. Department of Internal Medicine and Gastroenterology University Hospital Dijkzigt Rotterdam, The Netherlands
SECONDARY INVESTIGATORS:	Dr. Rudolf A. Heijtink Department of Virology Erasmus University Rotterdam, The Netherlands Dr. Maria Alida van de Velde Dr. Mr. Willem van den Bergh - Stichting Noordwijk, The Netherlands
STUDY LOCATION:	Dr. Mr. Willem van den Bergh-Stichting Noordwijk, The Netherlands University Hospital Dijkzigt Rotterdam, The Netherlands
DATE STUDY INITIATED:	December, 1985
DATE STUDY COMPLETED:	In progress

Study 815

STUDY POPULATION: The study population consists of approximately 90 mentally retarded individuals. and 90 health care personnel, who are negative for HBsAg, anti-HBc, anti-HBs, have a normal ALT and have not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Mentally retarded individuals and health care personnel are randomly assigned to receive either yeast recombinant or plasma-derived hepatitis B vaccine, stratified by sex and age.

Mentally retarded individuals and health care personnel receive a 0.5 ml (10 mcg HBsAg) or a 1.0 ml (20 mcg HBsAg) intramuscular injection of yeast recombinant vaccine or a 1.0 ml (20 mcg HBsAg) intramuscular injection of plasma-derived vaccine at 0, 1, and 6 months.

The temperature of each vaccine recipient and any local or systemic complaints are recorded for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately three weeks before the first injection of vaccine. Post-vaccination blood samples are obtained from mentally retarded individuals at 3, 7, and 12 months and from health care personnel at 1, 2, 3, 6, 7, 9 and 12 months. Blood samples are obtained at 24 months from those participants who have seroconverted.

All serum samples are assayed for HBsAg, anti-HBc, anti-HBs and ALT. Samples may be assayed for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested for anti-a and anti-d subtype specificity.

RESULTS: Clinical follow-up data and serologic results are not yet available. The study continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 889
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among: 1. Mentally retarded individuals who are negative for hepatitis B virus serologic markers. 2. Health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 993/C-K937 (20 mcg/HBsAg/ml)
PRIMARY INVESTIGATOR:	Robert P. Perrillo, M.D. Director, Gastroenterology Veterans Administration Medical Center St. Louis, Missouri 63125
SECONDARY INVESTIGATOR:	Oliver H. Lowry, M.D. Department of Pharmacology Washington Univ. School of Medicine St. Louis, Missouri 63110
STUDY LOCATION:	Beverly Farms Foundation Godfrey, Illinois 62035 Veterans Administration Medical Center St. Louis, Missouri 63125
DATE STUDY INITIATED:	June 19, 1985
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of approximately 250 mentally retarded individuals, above 5 years of age, and 50 health care personnel, who are negative for HBsAg, anti-HBc, anti-HBs, have a normal ALT and have not previously received any hepatitis B vaccine.

Study 889

STUDY PROCEDURE:

Mentally retarded individuals are randomly assigned to one of two groups, stratified by sex and age. Health care personnel constitute a third group.

Mentally retarded individuals receive a 0.5 ml (10 mcg HBsAg) or a 1.0 ml (20 mcg HBsAg) intramuscular injection of vaccine at 0, 1, and 6 months. Health care personnel receive a 0.5 ml (10 mcg HBsAg) intramuscular injection of vaccine according to the same regimen.

The temperature of each vaccine recipient and any local or systemic complaints are recorded for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 3, 6, 10 and 24 months.

All serum samples are assayed for HBsAg, anti-HBc and anti-HBs. The pre-vaccination and 3 month post-vaccination samples are also tested for ALT. Samples may be assayed for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested for anti-a and anti-d subtype specificity.

RESULTS:

MENTALLY RETARDED INDIVIDUALS

10 mcg Lot 993/C-K937 at 0, 1, and 6 months
20 mcg Lot 993/C-K937 at 0, 1, and 6 months

1. Number Vaccinated:

Dose (mcg)	Injection No. 1	2	3
10	101	101	100
20	101	100	100

Study 889

RESULTS: (Contd)

2. Serologic Results:

Serologic data at 1 month are available for 101 mentally retarded individuals who received a 10 mcg dose and 100 mentally retarded individuals who received a 20 mcg dose of vaccine.

At 1 month, anti-HBs responses among mentally retarded individuals are as follows:

Dose (mcg)	% Anti-HBs Positive S/N ≥2.1	% Anti-HBs Positive mIU/ml ≥10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥2.1	GMT (mIU/ml) Responders mIU/ml ≥10
10	19 (19/101)	8 (8/101)	0.5	8.7	19.9
20	20 (20/100)	11 (11/100)	0.6	13.7	38.7

3. Clinical Results:

Clinical follow-up data are available for 101 (10 mcg dose) and 101 (20 mcg dose) mentally retarded individuals following the first injection of vaccine and 101 (10 mcg dose) and 100 (20 mcg dose) individuals following the second injection. Clinical complaints and maximum temperatures reported following each injection are provided in Tables 1-4. In summary:

Clinical Complaint	Dose (mcg)	% Frequency by Injection No. 1	2	3
Injection Site	10	0 (0/101)	0 (0/101)	NA
	20	0 (0/101)	0 (0/100)	NA
Systemic	10	2 (2/101)	0 (0/101)	NA
	20	1 (1/101)	0 (0/100)	NA

No serious or alarming adverse reactions attributable to vaccination have been reported.

Table 1

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: RETARDED

CLINICAL COMPLAINTS	TOTAL VACCINEES (101 PATIENTS) - DOSE 1 — DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	2 (2.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
HEADACHE	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
RESPIRATORY	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	2 (2.0%)
RHINITIS	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	2 (2.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	2 (2.0%)
PERSONS WITH NO COMPLAINTS	101 (100.0%)	100 (99.0%)	101 (100.0%)	100 (99.0%)	101 (100.0%)	101 (100.0%)	99 (98.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 1 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: RETARDED

CLINICAL COMPLAINTS	TOTAL VACCINEES (101 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	101 (100.0%)	101 (100.0%)	101 (100.0%)	101 (100.0%)	101 (100.0%)	100 (100.0%)		101 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: RETARDED

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (101 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	82 (81.2%)	84 (83.2%)	90 (89.1%)	81 (81.8%)	88 (88.0%)	89 (88.1%)			56 (55.4%)
99 - 99.9	15 (14.9%)	16 (15.8%)	11 (10.9%)	16 (16.2%)	11 (11.0%)	12 (11.9%)			38 (37.6%)
100 - 100.9	4 (4.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)			6 (5.9%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)			1 (1.0%)
TEMPERATURE TAKEN	101 (100.0%)	101 (100.0%)	101 (100.0%)	99 (98.0%)	100 (99.0%)	101 (100.0%)			101 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.0%)	1 (1.0%)	0 (0.0%)			0 (0.0%)

Table 2 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 10 MCG
PATIENT CLASS: RETARDED

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (101 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	88 (88.0%)	96 (95.0%)	93 (92.1%)	85 (84.2%)	86 (86.0%)	90 (90.0%)			69 (68.3%)
99 - 99.9	10 (10.0%)	5 (5.0%)	6 (5.9%)	14 (13.9%)	13 (13.0%)	10 (10.0%)			28 (27.7%)
100 - 100.9	1 (1.0%)	0 (0.0%)	2 (2.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)			3 (3.0%)
101 - 101.9	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)
102 - 102.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)			1 (1.0%)
TEMPERATURE TAKEN	100 (99.0%)	101 (100.0%)	101 (100.0%)	101 (100.0%)	100 (99.0%)	100 (99.0%)			101 (100.0%)
TEMPERATURE NOT TAKEN	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)			0 (0.0%)

00837

Table 3

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 20 MCG
PATIENT CLASS: RETARDED

CLINICAL COMPLAINTS	TOTAL VACCINEES (101 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
PERSONS WITH NO COMPLAINTS	101 (100.0%)	101 (100.0%)	100 (99.0%)	101 (100.0%)	101 (100.0%)	101 (100.0%)		100 (99.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0869
TREATMENT :
LOT NUMBER : CK937
DOSE : 20 MCG
PATIENT CLASS: RETARDED

CLINICAL COMPLAINTS	TOTAL VACCINEES (100 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	100 (100.0%)	100 (100.0%)	100 (100.0%)	100 (100.0%)	100 (100.0%)	100 (100.0%)		100 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 20 MCG
PATIENT CLASS: RETARDED

	TOTAL VACCINEES (101 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
MAX TEMPERATURE (DEG F, ORAL)	0	1	2	3	4	5		
< 99	88 (88.0%)	93 (92.1%)	89 (88.1%)	83 (82.2%)	85 (84.2%)	86 (86.0%)		62 (61.4%)
99 - 99.9	11 (11.0%)	8 (7.9%)	11 (10.9%)	17 (16.8%)	14 (13.9%)	13 (13.0%)		33 (32.7%)
100 - 100.9	1 (1.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	2 (2.0%)	1 (1.0%)		6 (5.9%)
TEMPERATURE TAKEN	100 (99.0%)	101 (100.0%)	101 (100.0%)	101 (100.0%)	101 (100.0%)	100 (99.0%)		101 (100.0%)
TEMPERATURE NOT TAKEN	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)		0 (0.0%)

Table 4 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0889
TREATMENT :
LOT NUMBER : CK937
DOSE : 20 MCG
PATIENT CLASS: RETARDED

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (100 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	93 (93.0%)	94 (94.9%)	87 (87.0%)	87 (87.9%)	89 (91.8%)	86 (87.8%)		67 (67.0%)
99 - 99.9	5 (5.0%)	5 (5.1%)	13 (13.0%)	11 (11.1%)	8 (8.2%)	10 (10.2%)		29 (29.0%)
100 - 100.9	2 (2.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	2 (2.0%)		4 (4.0%)
TEMPERATURE TAKEN	100 (100.0%)	99 (99.0%)	100 (100.0%)	99 (99.0%)	97 (97.0%)	98 (98.0%)		100 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	3 (3.0%)	2 (2.0%)		0 (0.0%)

THALASSEMICS/
HEMOPHILIACS

Hemophiliacs and Thalassemics

Two studies have been initiated to assess antibody and clinical responses to recombinant hepatitis B vaccine in persons with hemophilia or thalassemia.

Study 799 - New York, New York - Dr. C. Stevens

Thirty-one thalassemic children, less than 16 years of age, who are negative for hepatitis B serologic markers, are receiving either 5 mcg doses or 2.5 mcg doses of vaccine lot 972/C-K444 at 0, 1, and 6 months. The vaccine is administered intramuscularly.

Fifteen children have received three 5 mcg injections. At 7 months, seroconversion was 89% (8/9) (S/N $\geq$2.1) with a GMT for all vaccinees of 88 S/N. When the cut-off was S/N $\geq$10, the seroconversion rate was 78% (7/9).

Sixteen children have received two 2.5 mcg injections of vaccine and 12 of these have received the third injection. The seroconversion rate at 7 months was 100% (5/5) whether the cut-ff was S/N $\geq$2.1 or S/N $\geq$10. The GMT for all vaccinees at 7 months was 200.0 S/N.

Twenty of the children enrolled in the study had pre-vaccination elevated ALT levels which is characteristic of the clinical disease process of thalassemia. One recipient of 5 mcg doses who had a normal pre-vaccination ALT level developed an elevation of ALT which was approximately 2.5 times the upper limit of normal one month after receiving the first injection of vaccine. This elevation was transient and returned to normal within a month. No serious adverse experiences attributable to vaccine have been reported.

Study 861 - Milwaukee, Wisconsin - Dr. S. Gill

The study population consists of persons with hemophilia who are negative for hepatitis B serologic markers. Participants under 20 years of age are receiving 5 mcg doses while those who are 20 years of age or older are receiving 10 mcg doses of vaccine at 0, 1, and 6 months from lot 979/C-K564. The vaccine is administered subcutaneously in this population.

Twelve hemophiliacs <20 years of age have received two 5 mcg injections and 5 of these have received the third injection. At three months, seroconversion by either cut-off (S/N $\geq$2.1 or mIU/ml $\geq$10) was 100% (8/8). The geometric mean titer was 143.2 mIU/ml.

Three hemophiliacs $\geq$20 years of age have received two 10 mcg doses of vaccine and one has received all three injections. Serologic data at 3 months are available for two vaccine recipients. Both participants seroconverted (S/N $\geq$2.1) at three months. Neither developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The geometric mean titer was 6.7 mIU/ml. No serious or alarming adverse experiences attributable to vaccine (either dose regimen) have been reported.

wva/3137I
1/21/86

Study 799

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 799
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among thalassemic children who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #972/C-K444 (10 mcg/ml)
PRIMARY INVESTIGATOR:	Cladd Stevens, M.D. Lindsley F. Kimball Research Institute New York Blood Center 310 East 67th Street New York, New York 10021
SECONDARY INVESTIGATOR:	Patricia Giardina, M.D. New York Hospital - Cornell Medical Center 525 East 68th Street New York, New York 10021 Margaret W. Hilgartner, M.D. New York Hospital - Cornell Medical Center 525 East 68th Street New York, New York 10021 Patricia E. Taylor, Ph.D. Lindsley F. Kimball Research Institute New York Blood Center 310 East 67th Street New York, New York 10021
STUDY LOCATION:	Lindsley F. Kimball Research Institute New York Blood Center 310 East 67th Street New York, New York 10021 New York Hospital - Cornell Medical Center 525 East 68th Street New York, New York 10021
DATE INITIATED:	August 1984
DATE COMPLETED:	In progress.

Study 799

DATE COMPLETED: In progress

STUDY POPULATION: The study population consists of 31 thalassemic children, 16 years of age or less, who are negative for HBsAg, anti-HBc and anti-HBs, and have not previously received any hepatitis B vaccine.

PROCEDURE: Study participants are allocated to one of two groups and receive the vaccine at 0, 1 and 6 months. Group 1 receives 0.5 ml (5 mcg) doses and Group 2 0.25 ml (2.5 mcg) doses. All injections intramuscular. The parent or guardian are asked to record the child's temperature for 5 days after each injection and note any local or systemic complaints. Medically significant events and therapies relating to the child's pre-existing thalassemia will be recorded.

Blood specimens are obtained prior to vaccination, monthly for 3 months and at 6, 7, 9, 12 and 24 months post initial injection.

All samples are assayed for HBsAg, anti-HBs, anti-HBc and ALT by Dr. Steven's laboratory. Samples may also be assayed for yeast antibody at MSDRL.

RESULTS: THALASSEMIC CHILDREN:

5 mcg Lot #972/C-K444 at 0, 1 and 6 months.

2.5 mcg Lot #972/C-K444 at 0, 1 and 6 months.

1. Number Vaccinated:

Dose Level	Injection Number		
	1	2	3
5 mcg	15	15	15
2.5 mcg	16	16	12

Study 799

RESULTS (CONT.):

2. Serologic Results:

Serologic data at 7/8 months are available for 9 and 5 recipients of 5 and 2.5 mcg injections respectively.

Seroconversion was 89% (8/9) when the cutoff was S/N ≥2.1 among those receiving 5 mcg doses, with a GMT of 88.0 for all vaccinees. When the cutoff was S/N ≥10, seroconversion was 78% (7/9).

Among the recipients of 2.5 mcg doses, seroconversion was 100% (5/5) whether the cutoff was S/N ≥2.1 or S/N ≥10. The GMT for all vaccinees was 200.0. Table 1 shows seroconversion rates and GMT's for up to 9 months of follow-up.

3. Clinical Complaints:

Clinical follow-up data are available for 14, 14, and 3 participants following the first, second and third injections of 5 mcg doses; and for 16, 16, and 2 participants following the first, second and third injections of 2.5 mcg doses.

Specific complaints and maximum temperatures reported during the 5 days following each injection are provided in Tables 2 through 5.

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	5 mcg	14 (2/14)	21 (3/14)	33 (1/3)
	2.5 mcg	19 (3/16)	19 (3/16)	0 (0/2)
Systemic	5 mcg	36 (5/14)	14 (2/14)	0 (0/3)
	2.5 mcg	6 (1/16)	13 (2/16)	0 (0/2)

There were no serious or alarming adverse reactions attributable to vaccine.

ALT Elevations

Twenty of the 31 children enrolled in this study had prevaccination ALT levels ranging from 1.5-9

Study 799

RESULTS (CONT.):

times the upper limit of normal. Most of these remained at an elevated level during the course of follow-up. Thalassemia is characterized by increased serum alanine aminotransferase, reflecting hepatic damage secondary to hemosiderosis.

One recipient of 5 mcg doses who had a normal prevaccination ALT level developed an elevation of ALT which was approximately 2.5 times the upper limit of normal one month after receiving the first injection. This elevation was transient and returned to normal within a month.

Adverse Experiences:

Two of the children enrolled in this study experienced episodes of vomiting accompanied by fever within a day of receiving their first dose of recombinant vaccine. One of the children was a two-year-old who received a 5 mcg dose. His temperature was 104°F the day following the injection. The child was examined by the investigator who diagnosed a possible viral infection. The second child was a one-year-old who received a 2.5 mcg dose. A fever of 100.2°F was recorded on the day of injection. A diagnosis was made of a probable concurrent respiratory infection.

TABLE 1

Antibody Responses Among Thalassemic Children Following Vaccination with 5 or 2.5 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot # 972/C-K444 at 0, 1, and 6 Months in Study # 799.

	5 mcg					2.5 mcg				
Time (Months)	% with Anti-HBs		GMT (S/N)			% Anti-HBs		GMT (S/N)		
				Responders					Responders	
	S/N ≥ 2.1	S/N ≥ 10	All Vaccinees	S/N ≥ 2.1	S/N ≥ 10	S/N ≥ 2.1	S/N ≥ 10	All Vaccinees	S/N ≥ 2.1	S/N ≥ 10
1	25 (4/16)	6 (1/16)	1.5	4.7	11.5	33 (5/15)	13 (2/15)	2.2	12.4	42.8
2	93 (13/14)	71 (10/14)	21.6	27.8	45.2	78 (7/9)	67 (6/9)	13.2	29.4	45.7
3	93 (14/15)	73 (11/15)	24.2	29.2	46.4	83 (10/12)	67 (8/12)	16.1	29.7	48.7
6	75 (9/12)	58 (7/12)	13.6	35.5	64.6	82 (9/11)	64 (7/11)	13.8	25.2	46.5
7	89 (8/9)	78 (7/9)	88.0	144.0	248.1	100 (5/5)	100 (5/5)	200.0	200.0	200.0
9	90 (9/10)	90 (9/10)	91.4	146.5	146.5	100 (5/5)	100 (5/5)	150.1	150.1	150.1

24721-5/cfs
12/20/85

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: THALASSEMICS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	1 (7.1%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
SORENESS	1 (7.1%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
SYSTEMIC	1 (7.1%)	2 (14.3%)	0 (0.0%)	1 (7.1%)	2 (15.4%)	0 (0.0%)	5 (35.7%)
INTEGUMENTARY SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	2 (14.3%)
RASH, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	2 (14.3%)
RESPIRATORY	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	1 (7.1%)
ARM PAIN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	1 (7.1%)
DIGESTIVE SYSTEM	1 (7.1%)	1 (7.1%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
NAUSEA	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	2 (14.3%)
VOMITING	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: THALASSEMICS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	1 (7.1%)
EARACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	1 (7.1%)
PERSONS WITH COMPLAINTS	2 (14.3%)	4 (28.6%)	0 (0.0%)	1 (7.1%)	2 (15.4%)	0 (0.0%)	7 (50.0%)
PERSONS WITH NO COMPLAINTS	12 (85.7%)	10 (71.4%)	14 (100.0%)	13 (92.9%)	11 (84.6%)	1 (100.0%)	7 (50.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: THALASSEMICS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (14.3%)	2 (14.3%)	2 (14.3%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	3 (21.4%)
SORENESS	2 (14.3%)	2 (14.3%)	2 (14.3%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	3 (21.4%)
ECCHYMOSIS	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
SYSTEMIC	1 (7.1%)	1 (7.1%)	2 (14.3%)	2 (14.3%)	1 (7.7%)	0 (0.0%)	2 (14.3%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (7.1%)	2 (14.3%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	2 (14.3%)
RASH, NOS	0 (0.0%)	1 (7.1%)	2 (14.3%)	1 (7.1%)	1 (7.7%)	0 (0.0%)	2 (14.3%)
DIGESTIVE SYSTEM	1 (7.1%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
DIARRHEA	1 (7.1%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
PERSONS WITH COMPLAINTS	3 (21.4%)	3 (21.4%)	3 (21.4%)	2 (14.3%)	2 (15.4%)	0 (0.0%)	4 (28.6%)
PERSONS WITH NO COMPLAINTS	11 (78.6%)	11 (78.6%)	11 (78.6%)	12 (85.7%)	11 (84.6%)	1 (100.0%)	10 (71.4%)

00850

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: THALASSEMICS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT - :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: THALASSEMICS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)		1 (33.3%)
SORENESS	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)		1 (33.3%)
PERSONS WITH COMPLAINTS	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)		1 (33.3%)
PERSONS WITH NO COMPLAINTS	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	0 (0.0%)		2 (66.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: THALASSEMICS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	4 (28.6%)	4 (28.6%)	4 (28.6%)	4 (28.6%)	4 (30.8%)	0 (0.0%)			4 (28.6%)
< 99	4 (28.6%)	4 (28.6%)	7 (50.0%)	5 (35.7%)	6 (46.2%)	1 (100.0%)			2 (14.3%)
99 - 99.9	4 (28.6%)	6 (28.6%)	1 (7.1%)	6 (28.6%)	2 (15.4%)	0 (0.0%)			6 (28.6%)
100 - 100.9	2 (14.3%)	1 (7.1%)	2 (14.3%)	1 (7.1%)	1 (7.7%)	0 (0.0%)			3 (21.4%)
103 - 103.9	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (7.1%)
TEMPERATURE TAKEN	14 (93.3%)	14 (93.3%)	14 (93.3%)	14 (93.3%)	13 (86.7%)	1 (6.7%)			14 (93.3%)
TEMPERATURE NOT TAKEN	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	2 (13.3%)	14 (93.3%)			1 (6.7%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: THALASSEMICS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	6 (46.2%)	6 (42.9%)	6 (50.0%)	6 (42.9%)	6 (46.2%)	0 (0.0%)		6 (42.9%)
< 99	4 (30.8%)	3 (21.4%)	5 (41.7%)	5 (35.7%)	5 (38.5%)	1 (100.0%)		3 (21.4%)
99 - 99.9	3 (23.1%)	3 (21.4%)	1 (8.3%)	3 (21.4%)	1 (7.7%)	0 (0.0%)		3 (21.4%)
100 - 100.9	0 (0.0%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)		2 (14.3%)
TEMPERATURE TAKEN	13 (86.7%)	14 (93.3%)	12 (80.0%)	14 (93.3%)	13 (86.7%)	1 (6.7%)		14 (93.3%)
TEMPERATURE NOT TAKEN	2 (13.3%)	1 (6.7%)	3 (20.0%)	1 (6.7%)	2 (13.3%)	14 (93.3%)		1 (6.7%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: THALASSEMICS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)		1 (33.3%)
< 99	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	0 (0.0%)		2 (66.7%)
TEMPERATURE TAKEN	3 (20.0%)	3 (20.0%)	3 (20.0%)	3 (20.0%)	3 (20.0%)	0 (0.0%)		3 (20.0%)
TEMPERATURE NOT TAKEN	12 (80.0%)	12 (80.0%)	12 (80.0%)	12 (80.0%)	12 (80.0%)	15 (100.0%)		12 (80.0%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 2.5 MCG
PATIENT CLASS: THALASSEMICS

CLINICAL COMPLAINTS	TOTAL VACCINEES (16 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (20.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (18.8%)
SORENESS	2 (20.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (18.8%)
SYSTEMIC	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
RESPIRATORY	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
RHINITIS	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
PHARYNGITIS (SORE THROAT)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
PERSONS WITH COMPLAINTS	3 (30.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (25.0%)
PERSONS WITH NO COMPLAINTS	7 (70.0%)	15 (93.8%)	16 (100.0%)	16 (100.0%)	16 (100.0%)	6 (100.0%)	12 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 2.5 MCG
PATIENT CLASS: THALASSEMICS

CLINICAL COMPLAINTS	TOTAL VACCINEES (16 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	3 (23.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (18.8%)
SORENESS	3 (23.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (18.8%)
SYSTEMIC	2 (15.4%)	1 (6.7%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (12.5%)
ORGANS OF SPECIAL SENSE	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
OTHER	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
PSYCHIATRIC/BEHAVIORAL	1 (7.7%)	1 (6.7%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
IRRITABILITY	1 (7.7%)	1 (6.7%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
PERSONS WITH COMPLAINTS	4 (30.8%)	1 (6.7%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (25.0%)
PERSONS WITH NO COMPLAINTS	9 (69.2%)	14 (93.3%)	15 (93.8%)	16 (100.0%)	15 (100.0%)	3 (100.0%)	12 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 2.5 MCG
PATIENT CLASS: THALASSEMICS

CLINICAL COMPLAINTS	TOTAL VACCINEES (12 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	1 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	1 (100.0%)		2 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 2.5 MCG
PATIENT CLASS: THALASSEMICS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (16 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (10.0%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	0 (0.0%)			1 (6.3%)
< 99	4 (40.0%)	10 (62.5%)	8 (50.0%)	10 (62.5%)	11 (68.8%)	5 (83.3%)			8 (50.0%)
99 - 99.9	4 (40.0%)	4 (25.0%)	6 (37.5%)	4 (25.0%)	4 (25.0%)	1 (16.7%)			6 (37.5%)
100 - 100.9	1 (10.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)
101 - 101.9	0 (0.0%)	1 (6.3%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)			1 (6.3%)
TEMPERATURE TAKEN	10 (62.5%)	16 (100.0%)	16 (100.0%)	16 (100.0%)	16 (100.0%)	6 (37.5%)			16 (100.0%)
TEMPERATURE NOT TAKEN	6 (37.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (62.5%)			0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 2.5 MCG
PATIENT CLASS: THALASSEMICS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (16 PATIENTS) - DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
NORMAL	6 (46.2%)	6 (40.0%)	6 (37.5%)	6 (37.5%)	6 (40.0%)	0 (0.0%)			6 (37.5%)
< 99	4 (30.8%)	6 (40.0%)	6 (37.5%)	6 (37.5%)	6 (40.0%)	3 (100.0%)			5 (31.3%)
99 - 99.9	3 (23.1%)	2 (13.3%)	3 (18.8%)	3 (18.8%)	2 (13.3%)	0 (0.0%)			2 (12.5%)
100 - 100.9	0 (0.0%)	1 (6.7%)	1 (6.3%)	1 (6.3%)	1 (6.7%)	0 (0.0%)			3 (18.8%)
TEMPERATURE TAKEN	13 (81.3%)	15 (93.8%)	16 (100.0%)	16 (100.0%)	15 (93.8%)	3 (18.8%)			16 (100.0%)
TEMPERATURE NOT TAKEN	3 (18.8%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	13 (81.3%)			0 (0.0%)

00860

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0799
TREATMENT :
LOT NUMBER : CK444
DOSE : 2.5 MCG
PATIENT CLASS: THALASSEMICS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (12 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	1 (100.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	2 (100.0%)	1 (100.0%)		0 (0.0%)
99 - 99.9	0 (0.0%)	2 (100.0%)	1 (50.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)		2 (100.0%)
TEMPERATURE TAKEN	1 (8.3%)	2 (16.7%)	2 (16.7%)	2 (16.7%)	2 (16.7%)	1 (8.3%)		2 (16.7%)
TEMPERATURE NOT TAKEN	11 (91.7%)	10 (83.3%)	10 (83.3%)	10 (83.3%)	10 (83.3%)	11 (91.7%)		10 (83.3%)

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 861.
PURPOSE:	To assess antibody and clinical responses to vaccine in persons with hemophilia or homozygous sickle cell disease who are negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #979/C-K564 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Joan Gill, M.D., Medical Director Great Lakes Hemophilia Foundation 1701 W. Wisconsin Avenue Milwaukee, WI 53233
SECONDARY INVESTIGATORS:	Robert R. Montgomery, M.D. Great Lakes Hemophilia Foundation 1701 W. Wisconsin Avenue Milwaukee, WI 53233 Kathleen M. Marquardt, R.N. Great Lakes Hemophilia Foundation 1701 W. Wisconsin Avenue Milwaukee, WI 53233 Denise Lockhart, R.N. Nurse Coordinator, Sickle Cell Clinic Milwaukee Children's Hospital 1701 W. Wisconsin Avenue Milwaukee, WI 53233
STUDY LOCATION:	Great Lakes Hemophilia Foundation Milwaukee Children's Hospital 1701 West Wisconsin Avenue Milwaukee, WI 53233
DATE INITIATED:	November 8, 1984
DATE COMPLETED:	In progress

Study 861

STUDY POPULATION:

The study population will consist of 25-30 hemophiliacs of any age and either sex (pregnant women excluded), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

Under an addendum to the study, an additional population of approximately 10 persons (< 20 years of age) with homozygous sickle cell disease, who are undergoing chronic blood transfusion, and are negative for hepatitis B serologic markers, will also be included in the study.

PROCEDURE:

Each participant receives an injection of vaccine at 0, 1, and 6 months. The vaccine is administered subcutaneously to the hemophiliacs and intramuscularly to the subjects with homozygous sickle cell disease. Persons under 20 years of age are given a 0.5 ml (5 mcg HBsAg) injection of vaccine, while those 20 years of age and older receive a 1.0 ml (10 mcg HBsAg) injection of vaccine. Vaccine recipients (or their parents/guardians in the case of minors) will be asked to record their temperature for 5 days after each injection and to note any local or systemic complaints.

Blood specimens will be obtained prior to vaccination and 1, 3, 6, and 8 months post-initial injection. Samples will be assayed for HBsAg, anti-HBc, anti-HBs and ALT at MSDRL. Samples with an anti-HBs titer ≥25 mIU/ml will be further tested to determine the relative proportions of anti-a and anti-d activity. Samples may be assayed for yeast antibody.

RESULTS:

HEMOPHILIACS:

5 mcg (<20 years of age)
Lot #979/C-K564 at 0, 1, and 6 Months

10 mcg (≥20 years of age)
Lot #979/C-K564 at 0, 1, and 6 Months

Study 861

RESULTS: (Cont.)

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
5 mcg	9	9	0
10 mcg	2	2	0

2. Serologic Results:

Serologic data are available for 8 participants at 3 months who received 5 mcg injections and 2 participants who received 10 mcg injections. 7/8 month data are available for one participant from each dose level.

At three months, all eight participants (100%) who received 5 mcg injections seroconverted (S/N $\geq$ 2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$ 10). The GMT for those responders was 143.2 mIU/ml.

Both participants who received 10 mcg injections seroconverted for anti-HBs (S/N $\geq$2.1) at three months. Neither developed protective levels of anti-HBs (mIU/ml $\geq$ 10) at that time. The GMT for those participants was 6.7 mIU/ml.

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical complaints:

Clinical follow-up data for participants who received 5 mcg injections are available for 10, 8, and 5 vaccinees after injection 1,, 2, and 3, respectively. Among vaccinees who received 10 mcg injections, clinical follow-up data are available for 3, 2, and 1 participants after injection 1, 2 and 3, respectively.

Study 861

RESULTS (CONT.): The overall frequencies of complaints are presented below.

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	5 mcg	9 (1/11)	13 (1/8)	0 (0/5)
	10 mcg	33 (1/3)	50 (1/2)	0 (0/1)
Systemic	5 mcg	9 (1/11)	13 (1/8)	0 (0/5)
	10 mcg	33 (1/3)	0 (0/2)	100 (1/1)

Refer to Tables 2 and 3 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Tables 4 and 5.

There were no serious or alarming reactions attributable to vaccine.

HBV Markers (anti-HBc)

One subject with hemophilia (case (b)(6) became seropositive for anti-HBc 2 months after the third injection of yeast recombinant hepatitis B vaccine. At the time the subject was also seropositive for anti-HBs with reported titers of 42769.8 S/N and 118121.4 mIU/ml. The vaccinee was well; serum samples were negative for HBsAg and ALT levels were normal. Attempts will be made to obtain additional serum samples.

Reactions Reported to the OOBRR

One patient (case (b)(6)) was hospitalized for a bleeding telangiectasic site in the distal atrum of the stomach (b)(6) after administration of the third injection of vaccine. This 42 year old male with hemophilia had a medical history significant for recurrent GI bleeding, duodenal and antral gastric ulcer, and hemarthroses. The patient was adminstered whole blood and cryoprecipitate and was discharged after 5 days in stable condition. The investigator stated the patient's experience was not related to vaccination with yeast recombinant hepatitis B vaccine.

Study B61

RESULTS (CONT.): PATIENTS WITH SICKLE CELL ANEMIA

5 mcg Lot #979/C-K564 at 0, 1, and 6 months

1. Number vaccinated:

Injection No.		
1	2	3
4	4	0

2. Serologic Results:

Serologic results are not yet available.

3. Clinical Complaints:

There have been no serious or alarming reactions attributed to vaccination. Detailed data on clinical complaints and temperatures following vaccination are not yet available.

Table 1

Antibody Responses Among Hemophiliacs Following Vaccination with
5 mcg (Hemophiliacs < 20 years) or 10 mcg (Hemophiliacs ≥ 20 years) Injections of
Yeast Recombinant Hepatitis B Vaccine Lot # 979/C-K564 at 0, 1, and 6 Months in Study #861

Time (Months)	5 mcg (Hemophiliacs < 20 Years of Age)					10 mcg (Hemophiliacs > 20 Years of Age)				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders				All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1	18 (2/11)	18 (2/11)	0.9	15.9	15.9	0 (0/3)	0 (0/3)	0.3	---	---
3	100 (8/8)	100 (8/8)	143.2	143.2	143.2	100 (2/2)	0 (0/2)	6.7	6.7	---
6	100 (2/2)	100 (2/2)	223.7	223.7	223.7	0 (0/1)	0 (0/1)	1.3	---	---
7/8	100 (1/1)	100 (1/1)	3878.3	3878.3	3878.3	0 (0/1)	0 (0/1)	1.6	---	---

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 5 MCG
PATIENT CLASS: HEMOPHILIACS

CLINICAL COMPLAINTS	TOTAL VACCINEES (12 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	1 (9.1%)	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (9.1%)
SORENESS	1 (9.1%)	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (9.1%)
SWELLING	1 (9.1%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (9.1%)
SYSTEMIC	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)		1 (9.1%)
WHOLE BODY/GENERAL	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)		1 (9.1%)
SWEATING	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (9.1%)
FATIGUE/WEAKNESS	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)		1 (9.1%)
PERSONS WITH COMPLAINTS	2 (18.2%)	2 (18.2%)	2 (18.2%)	1 (9.1%)	1 (9.1%)	1 (9.1%)		2 (18.2%)
PERSONS WITH NO COMPLAINTS	9 (81.8%)	9 (81.8%)	9 (81.8%)	10 (90.9%)	10 (90.9%)	10 (90.9%)		9 (81.8%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 5 MCG
PATIENT CLASS: HEMOPHILIACS

CLINICAL COMPLAINTS	TOTAL VACCINEES (12 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
SORENESS	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)
PERSONS WITH COMPLAINTS	1 (12.5%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	2 (25.0%)
PERSONS WITH NO COMPLAINTS	7 (87.5%)	8 (100.0%)	7 (87.5%)	7 (87.5%)	7 (87.5%)	7 (87.5%)	6 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 5 MCG
PATIENT CLASS: HEMOPHILIACS

CLINICAL COMPLAINTS	TOTAL VACCINEES (5 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)		5 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEMOPHILIACS

CLINICAL COMPLAINTS	TOTAL VACCINEES (3 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (33.3%)
SORENESS	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (33.3%)
SYSTEMIC	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (33.3%)
WHOLE BODY/GENERAL	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (33.3%)
SWEATING	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (33.3%)
PERSONS WITH COMPLAINTS	2 (66.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (66.7%)
PERSONS WITH NO COMPLAINTS	1 (33.3%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)		1 (33.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEMOPHILIACS

CLINICAL COMPLAINTS	TOTAL VACCINEES (3 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (50.0%)
SORENESS	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (50.0%)
PERSONS WITH COMPLAINTS	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (50.0%)
PERSONS WITH NO COMPLAINTS	1 (50.0%)	1 (50.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)		1 (50.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00872

Table 3 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEMOPHILIACS

CLINICAL COMPLAINTS	TOTAL VACCINEES (1 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)
GI BLEEDING	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)
PERSONS WITH NO COMPLAINTS	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00873

Table 4

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 5 MCG
PATIENT CLASS: HEMOPHILIACS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (12 PATIENTS) - DOSE 1 — DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
< 99	8 (100.0%)	6 (75.0%)	7 (87.5%)	7 (87.5%)	7 (87.5%)	7 (87.5%)			6 (75.0%)
99 - 99.9	0 (0.0%)	2 (25.0%)	1 (12.5%)	1 (12.5%)	1 (12.5%)	1 (12.5%)			2 (25.0%)
TEMPERATURE TAKEN	8 (66.7%)	8 (66.7%)	8 (66.7%)	8 (66.7%)	8 (66.7%)	8 (66.7%)			8 (66.7%)
TEMPERATURE NOT TAKEN	4 (33.3%)	4 (33.3%)	4 (33.3%)	4 (33.3%)	4 (33.3%)	4 (33.3%)			4 (33.3%)

00874

Table 4 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 5 MCG
PATIENT CLASS: HEMOPHILIACS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (12 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	4 (80.0%)	4 (100.0%)	3 (60.0%)	3 (75.0%)	4 (80.0%)	4 (80.0%)		2 (40.0%)
99 - 99.9	1 (20.0%)	0 (0.0%)	2 (40.0%)	1 (25.0%)	1 (20.0%)	1 (20.0%)		3 (60.0%)
TEMPERATURE TAKEN	5 (41.7%)	4 (33.3%)	5 (41.7%)	4 (33.3%)	5 (41.7%)	5 (41.7%)		5 (41.7%)
TEMPERATURE NOT TAKEN	7 (58.3%)	8 (66.7%)	7 (58.3%)	8 (66.7%)	7 (58.3%)	7 (58.3%)		7 (58.3%)

Table 4 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 5 MCG
PATIENT CLASS: HEMOPHILIACS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (5 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)	1 (100.0%)		1 (100.0%)
TEMPERATURE TAKEN	1 (20.0%)	1 (20.0%)	1 (20.0%)	1 (20.0%)	1 (20.0%)	1 (20.0%)		1 (20.0%)
TEMPERATURE NOT TAKEN	4 (80.0%)	4 (80.0%)	4 (80.0%)	4 (80.0%)	4 (80.0%)	4 (80.0%)		4 (80.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEMOPHILIACS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (3 PATIENTS) - DOSE 1								DAYS POST VACCINATION	NUMBER WITH MAX TEMP
	0	1	2	3	4	5				
< 99	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	1 (100.0%)				2 (100.0%)
TEMPERATURE TAKEN	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	1 (33.3%)				2 (66.7%)
TEMPERATURE NOT TAKEN	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	2 (66.7%)				1 (33.3%)

Table 5 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0861
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEMOPHILIACS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (3 PATIENTS) - DOSE 2 — DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
< 99	1 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)			2 (100.0%)
TEMPERATURE TAKEN	1 (33.3%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)			2 (66.7%)
TEMPERATURE NOT TAKEN	2 (66.7%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)			1 (33.3%)

NONRESPONDERS/
HYPORESPONDERS

SUMMARY - NONRESPONDERS, HYPORESPONDERS AND TRANSIENT RESPONDERS

Nonresponders

A total of 81 persons, all of whom failed to develop antibody after receiving three injections of plasma-derived hepatitis B vaccine, have received one or more injections of yeast recombinant vaccine in six studies. This population includes both healthy adults and patients with chronic renal insufficiency who are receiving dialysis treatment (dialysis patients) . Healthy adults receive three 10 mcg doses and dialysis patients receive three 20 mcg or 40 mcg doses of yeast recombinant vaccine at 0, 1, and 6 months.

Fifty-five healthy adults have received one or more 10 mcg doses of yeast recombinant vaccine. Twenty-four persons have completed the three injection regimen. At 7-9 months, 79% (11/14) seroconverted (S/N $\geq$2.1) and 50% (7/14) developed protective levels of antibody (mIU/ml $\geq$10). Geometric mean titers among responders with a titer of S/N $\geq$10 or mIU/ml $\geq$10 were 39.3 S/N and 245.1 mIU/ml in each of the two studies where such data are available.

Twenty-six dialysis patients have received an initial injection of vaccine. Twenty-one of these received a 40 mcg dose and five received a 20 mcg dose. Six participants have received three injections of vaccine. At 2-3 months, 25% (1/4) and 35% (6/17) have titers of S/N $\geq$2.1 after two 20 or 40 mcg doses of vaccine, respectively. Protective levels of antibody developed in 25% (20 mcg dose) and 18% (40 mcg dose). Geometric mean titers among responders with an antibody level of mIU/ml $\geq$10 were 53.0 mIU/ml (20 mcg dose) and 43.2 mIU/ml (40 mcg dose). At 7-8 months the single individual measured after three 20 mcg doses and one of three persons monitored after three 40 mcg doses have protective levels of antibody (mIU/ml $\geq$10). These two responders had titers of 136.9 mIU/ml (20 mcg dose) and 49.4 mIU/ml (40 mcg dose).

Two hemodialysis patients withdrew from a study due to clinical complaints which were considered possibly related to vaccine. A 32-year old subject developed a swollen, stiff and sore left arm after administration of vaccine. The symptoms persisted for one week and then subsided. A 72-year old male subject developed generalized achiness and a headache three days after administration of the first injection of vaccine. Forty-eight hours after onset of these symptoms, he developed a flu-like syndrome with a temperature of 100°F. He did not receive any further vaccine injections.

Hyporesponders and Transient Responders

Two hyporesponders and three transient responders to plasma-derived hepatitis B vaccine have received a single 10 mcg dose of yeast recombinant vaccine. No serious or alarming adverse reactions attributable to vaccine have been reported.

Hyporesponders and Transient Responders (Cont.)

At one month post-vaccination, one hyporesponder displayed a marked boost in HBs antibody. A protective level of antibody has been maintained over 6 months of follow-up in this individual. The other individual has not responded to the vaccine. One month after vaccination, 100% (2/2) of transient responders have protective levels of antibody with a geometric mean titer of 67.9 mIU/ml.

NONRESPONDERS, HYPORESPONDERS AND TRANSIENT RESPONDERS

Study 794 - Bethesda, MD - Dr. H. Alter

The study population consists of seronegative nonresponders to plasma-derived vaccine and health care personnel who have not previously received any hepatitis B vaccine. Health care personnel receive either 5 mcg of 10 mcg injections of vaccine and nonresponders receive 10 mcg injections. All participants are administered vaccine lot C-K444 at 0, 1, and 6 months.

Eleven nonresponders have received two 10 mcg injections of vaccine and eight of these have received the third dose. At 7/8 months, 88% (7/8) of the participants seroconverted (S/N $\geq$2.1) and 63% (5/8) developed protective levels of anti-HBs (S/N $\geq$10). The GMT at that time for all vaccinees was 25.0 S/N and 95.9 for responders (S/N $\geq$10).

No serious or alarming adverse reactions attributable to vaccine have been reported. The study continues in progress. Refer to the summary on health care personnel/healthy adults for data regarding other subjects vaccinated in this study.

Study 816 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

The study population consists of three groups of adults negative for hepatitis B serologic markers: hemodialysis patients, health care personnel, and hemodialysis patients who were nonresponders to plasma-derived vaccine. Nonresponders receive 20 mcg or 40 mcg injections of vaccine lot C-K444 at 0, 1, and 6 months.

Five nonresponders have received two 20 mcg injections of vaccine and three of these have received the third injection. Serology data at 7/8 months is available for one vaccinee only. This subject seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10) with a titer of 136.9 mIU/ml.

Four nonresponders have received two 40 mcg injections of vaccine. Three of these have received the third injection. Seven/eight month serology data are available for three vaccine recipients. One (33%) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml) at that time. The GMT for all vaccinees was 2.1 mIU/ml and 49.4 for responders (mIU/ml $\geq$10).

No serious or alarming reactions attributable to vaccine have been reported. The study continues in progress. Refer to the summaries on health care personnel/healthy adults and dialysis patients for data regarding other subjects vaccinated in this study.

Study 817 - West Point, PA - Dr. R. Bishop

Preimmune healthy adults and nonresponders to plasma-derived vaccine are enrolled in Study 817. Preimmune adults receive a single 10 mcg injection of

Study 817 - West Point, PA - Dr. R. Bishop (Cont.)

vaccine. Nonresponders receive 10 mcg injections of vaccine lot C-K444 at 0, 1, and 6 months.

Four nonresponders have received two 10 mcg injections of vaccine and three of these have received the third injection. Serology data are available for two of the vaccinees at 7/8 months. Neither participant seroconverted for anti-HBs at that time.

No serious or alarming adverse experiences related to vaccine have been reported. The study continues in progress. Refer to the summary on preimmune adults for data regarding other subjects vaccinated in this study.

Study 854 - Boston, MA - Dr. J. Dienstag

The population of Study 854 consists of four groups: chronic carriers of HBsAg, and healthy hyporesponders, nonresponders, and transient responders to plasma-derived hepatitis B vaccine. Hyporesponders and transient responders receive a single 10 mcg injection of vaccine lot C-K564. Nonresponders receive 10 mcg injections of the same vaccine lot at 0, 1, and 6 months.

Two hyporesponders have received a 10 mcg injection of vaccine. One of the vaccinees displayed a marked boost in anti-HBs titer one month after receiving vaccine. The other participant has not responded.

Three transient responders have received a 10 mcg injection of vaccine. At one month, two out of the three (67%) transient responders who were seronegative for anti-HBs prior to vaccination, seroconverted for anti-HBs. The GMT for the two responders was 67.9 mIU/ml.

Fourteen nonresponders have received one 10 mcg injection of vaccine and thirteen of these have been administered the second and third injections. At 6 months, 58% (7/12) of the subjects seroconverted for anti-HBs (S/N $\geq$2.1) and 25% (3/12) developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees at 6 months was 3.2 mIU/ml and 45.8 for responders (mIU/ml $\geq$10).

No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress. Refer to the summary on chronic carriers for data regarding other subjects vaccinated in this study.

Study 874 - Pasadena, CA - Dr. M. Tong

Healthy adults who were nonresponders or hyporesponders to plasma-derived hepatitis B vaccine are enrolled in the study. All participants receive 10 mcg injections of vaccine lot C-K563 at 0, 1, and 6 months.

Twenty-six nonresponders and hyporesponders have received two 10 mcg injections of vaccine. None have received the third injection. At one month, 36% (9/25) of the vaccinees seroconverted for anti-HBs (S/N $\geq$2.1). Further serologic data are not currently available.

Study 874 - Pasadena, CA - Dr. M. Tong (Cont.)

No serious or alarming adverse events attributable to vaccine have been reported. The study continues in progress.

Study 875 - Duluth, MN - Dr. T. Johnson

The study population consists of adult hemodialysis patients who were nonresponders to plasma-derived hepatitis B vaccine. Participants received 40 mcg injections of either yeast recombinant vaccine lot C-K937 or plasma-derived vaccine lot 2277K at 0, 1, and 6 months.

Seventeen nonresponders have received one 40 mcg injection of yeast recombinant vaccine and fifteen of these have been administered the second injection. None have yet received the third injection. Two month serology data are available for 13 recipients of yeast recombinant vaccine. Thirty-eight percent (5/13) seroconverted for anti-HBs (S/N $\geq$2.1) and 15% (2/13) developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for responders was 70.7 (mIU/ml $\geq$10).

Eighteen nonresponders have received one 40 mcg injection of plasma-derived vaccine. Seventeen of these have received the second injection and none have received the third. At 2 months, 40% (7/15) of the plasma-derived vaccine recipients seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for responders was 131.6 (mIU/ml $\geq$10).

Two subjects experienced adverse experiences which were considered possibly related to vaccine. A 32-year old male hemodialysis patient received a 20 mcg intramuscular injection of vaccine into each deltoid (total dose 40 mcg). The patient's left arm subsequently became swollen, stiff and sore. These symptoms persisted for one week and then subsided. The patient did not receive any further vaccine injections. A 72-year old male hemodialysis patient developed generalized achiness and a headache three days after administration of the first injection of vaccine. Forty-eight hours after onset of these symptoms, he developed a flu-like syndrome with a temperature of 100°F. The patient did not receive any further vaccine injections.

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 794
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among: 1. Health care personnel immunized with plasma derived vaccine who were nonresponders (anti-HBs negative). 2. Health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine: Lot #972/C-K444 (10 mcg/HBsAg ml)
PRIMARY INVESTIGATOR:	Harvey J. Alter, M.D. Chief, Immunology Section Clinical Center Blood Bank National Institutes of Health Bethesda, Maryland
SECONDARY INVESTIGATORS:	David Henderson, M.D. James Schmitt, M.D. Ms. Deloris Koziol Ms. Beverly Elder
STUDY LOCATION:	Clinical Center Blood Bank National Institute of Health Bethesda, Maryland 20205
DATE INITIATED:	April 12, 1984
DATE COMPLETED:	In progress.
STUDY POPULATION:	The study population consists of 71 health care personnel of either sex (excluding pregnant women) who are negative for HBsAG, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine. It also includes 11 nonresponders to plasma-derived vaccine.

Study 794

PROCEDURE:

Health care workers receive either 5 mcg or 10 mcg doses of vaccine at 0, 1 and 6 months. Nonresponders receive 10 mcg doses at 0, 1 and 6 months. All injections are intramuscular. Participants are asked to record their temperature for 5 days after each injection and note any local or systemic reactions.

Blood specimens are obtained prior to vaccination, and monthly for 7 months and at 9, 12 and 24 months post initial injection. All samples are assayed for anti-HBs, anti-HBc, and HBsAg and ALT by Dr. Alter. Samples with anti-HBs titers ≥25 mIU/ml may be tested for anti-a and anti-d activity at MSDRL.

RESULTS:

NONRESPONDERS TO PLASMA VACCINE

10 mcg Lot 972/C-K444 at 0, 1 and 6 months

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
10 mcg	11	11	8

2. Serologic Results:

Serologic data are available for 8 study participants at 7/8 months. Seroconversion was 88% (7/8) when the cutoff was S/N ≥2.1. When the cutoff was S/N ≥10, seroconversion was 63% (5/8). The GMT for all vaccinees was 25.0. Table 1 shows anti-HBs responses through 12 months of follow-up.

Study 794

RESULTS: (Contd)

3. Clinical Complaints:

Clinical follow-up data are available for 11, 10, and 8 vaccinees following injections one, two and three, respectively. Listings of specific complaints and maximum temperatures reported during the five days of follow-up after each injection are provided in Tables 2 and 3.

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	10 mcg	9(1/11)	0(0/10)	25(2/8)
Systemic	10 mcg	18(2/11)	10(1/10)	0(0/8)

There were no serious or alarming adverse reactions attributable to vaccination.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
POPULATION : NONRESPONDERS (H)
DOSE : 10 MCG
LOT : CK444
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (S/N)		
						RESPONDERS	
	S/N >= 2.1		S/N >= 10		ALL VACCINEES	S/N >= 2.1	S/N >= 10
1 MONTH	45%	(5/11)	18%	(2/11)	3.1	11.1	52.6
2 MONTHS	55%	(6/11)	18%	(2/11)	4.7	15.8	114.2
3 MONTHS	78%	(7/9)	33%	(3/9)	8.0	14.1	60.3
6 MONTHS	60%	(3/5)	60%	(3/5)	12.3	61.5	61.5
7/8 MONTHS	88%	(7/8)	63%	(5/8)	25.0	39.0	95.9
9 MONTHS	80%	(4/5)	60%	(3/5)	12.9	23.8	39.3
12 MONTHS	60%	(3/5)	40%	(2/5)	8.2	31.3	55.9

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

CLINICAL COMPLAINTS	TOTAL VACCINEES (11 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
SORENESS	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
SYSTEMIC	0 (0.0%)	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (18.2%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
MUSCULOSKELETAL	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
ARTHRALGIA, MONOARTICULAR	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
PERSONS WITH COMPLAINTS	1 (9.1%)	1 (9.1%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (27.3%)
PERSONS WITH NO COMPLAINTS	10 (90.9%)	10 (90.9%)	10 (90.9%)	11 (100.0%)	11 (100.0%)	11 (100.0%)	8 (72.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

CLINICAL COMPLAINTS	TOTAL VACCINEES (11 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
CHILLS	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
NAUSEA	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)
PERSONS WITH NO COMPLAINTS	10 (100.0%)	9 (90.0%)	10 (100.0%)	10 (100.0%)	10 (100.0%)	9 (100.0%)	9 (90.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (H)

CLINICAL COMPLAINTS	TOTAL VACCINEES (8 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (25.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
SORENESS	2 (25.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
PERSONS WITH COMPLAINTS	2 (25.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
PERSONS WITH NO COMPLAINTS	6 (75.0%)	7 (87.5%)	7 (87.5%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	6 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0790
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (11 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
NORMAL	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (10.0%)	1 (11.1%)	1 (11.1%)		1 (9.1%)
< 99	8 (72.7%)	8 (72.7%)	8 (72.7%)	8 (80.0%)	6 (66.7%)	7 (77.8%)		7 (63.6%)
99 - 99.9	1 (9.1%)	2 (18.2%)	2 (18.2%)	0 (0.0%)	2 (22.2%)	1 (11.1%)		2 (18.2%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
102 - 102.9	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (9.1%)
TEMPERATURE TAKEN	11 (100.0%)	11 (100.0%)	11 (100.0%)	10 (90.9%)	9 (81.8%)	9 (81.8%)		11 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	2 (18.2%)	2 (18.2%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

	TOTAL VACCINEES (11 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER
MAX TEMPERATURE (DEG F, ORAL)	0	1	2	3	4	5		WITH MAX TEMP
NORMAL	1 (11.1%)	1 (10.0%)	1 (10.0%)	1 (11.1%)	1 (14.3%)	1 (14.3%)		1 (10.0%)
< 99	7 (77.8%)	7 (70.0%)	8 (80.0%)	7 (77.8%)	5 (71.4%)	5 (71.4%)		7 (70.0%)
99 - 99.9	0 (0.0%)	2 (20.0%)	1 (10.0%)	1 (11.1%)	1 (14.3%)	1 (14.3%)		1 (10.0%)
100 - 100.9	1 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (10.0%)
TEMPERATURE TAKEN	9 (81.8%)	10 (90.9%)	10 (90.9%)	9 (81.8%)	7 (63.6%)	7 (63.6%)		10 (90.9%)
TEMPERATURE NOT TAKEN	2 (18.2%)	1 (9.1%)	1 (9.1%)	2 (18.2%)	4 (36.4%)	4 (36.4%)		1 (9.1%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (8 PATIENTS) - DOSE 3 DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
NORMAL	3 (37.5%)	4 (50.0%)	4 (50.0%)	5 (62.5%)	5 (62.5%)	5 (62.5%)			3 (37.5%)
< 99	5 (62.5%)	4 (50.0%)	4 (50.0%)	3 (37.5%)	3 (37.5%)	3 (37.5%)			5 (62.5%)
TEMPERATURE TAKEN	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)	8 (100.0%)			8 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

PROGRAM: Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 816

PURPOSE: To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among:

1. adult dialysis patients negative for hepatitis B serologic markers.
2. health care personnel negative for hepatitis B serologic markers.
3. adult dialysis patients negative for hepatitis B serologic markers, who previously received plasma-derived hepatitis B vaccine and were nonresponders (anti-HBs negative).

VACCINE: Yeast Recombinant Hepatitis B Vaccine
Lot 974/C-K446 (20 mcg HBsAg/ml)
Lot 986/C-K733 (20 mcg HBsAg/ml)

PRIMARY INVESTIGATOR: Stanley Plotkin, M.D./Stuart Starr, M.D.
Division of Preventive Medicine
Joseph Stokes, Jr. Research Institute
Children's Hospital of Philadelphia
34 Street and Civic Center Boulevard
Philadelphia, Pennsylvania 19104

STUDY LOCATION: Biomedical Applications of Lehigh Valley
2015 Hamilton Avenue
Allentown, Pennsylvania 18104

Dialysis, Inc.
1230 Burmont Road
Drexel Hill, Pennsylvania

The Kidney Center of Delaware Count
15th Street and Upland Avenue
Chester, Pennsylvania 19013

The Kidney Center of Chester County
960 East Lincoln Highway
Downingtown, Pennsylvania 19335

Study 816

DATE STUDY INITIATED: May 14, 1984

DATE STUDY COMPLETED: In progress

STUDY POPULATION: The study population consists of 40-50 adult dialysis patients (including previous nonresponders to plasma-derived vaccine), and 20-25 health care personnel, of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, and have a normal ALT level. Dialysis patients (excluding nonresponders to plasma-derived vaccine) and health care personnel have not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Dialysis patients are assigned to one of two groups, stratified by sex and age, to assure that patients in the two groups are similar. Health care personnel constitute a third group.

Dialysis patients receive 1.0 ml (20 mcg HBsAg) or 2 x 1.0 ml (40 mcg HBsAg) intramuscular injections of vaccine at 0, 1, and 6 months. Health care personnel receive 0.5 ml (10 mcg HBsAg) intramuscular injections of vaccine according to the same regimen. Vaccine recipients record their temperature and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each study participant approximately two weeks before the first injection of vaccine. Post-vaccination blood samples are obtained at 1, 3, 6, 8, 12 and 24 months.

All serum samples are assayed for HBsAg, anti-HBs, anti-HBc, and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer $\geq$ 25 mIU/ml may be tested to determine anti-a and anti-d subtype specificity.

Study B16

RESULTS:

NONRESPONDERS (DIALYSIS PATIENTS)

20 mcg Lot 974/C-K446 at 0, 1, and 6 months
40 mcg Lot 974/C-K446 at 0, 1, and 6 months

1. Number Vaccinated:

Dose (mcg)	Injection Number 1	2	3
20	5	5	3
40	4	4	3

2. Serologic Results:

Serologic data at 7/8 months are available for four dialysis patients who were nonresponders to the plasma-derived vaccine.

At 7/8 and 12 months, anti-HBs responses are as follows:

Time (Months)	Dose (mcg)	Positive anti-HBs S/N ≥2.1	Positive anti-HBs mIU/ml ≥10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥2.1	GMT (mIU/ml) Responders mIU/ml ≥10
7/8	20	100(1/1)	100(1/1)	136.9	136.9	136.9
	40	33(1/3)	33(1/3)	2.1	49.4	49.4
12	20	50(1/2)	50(1/2)	3.4	38.5	38.5
	40	67(2/3)	33(1/3)	3.0	9.3	22.3

Anti-HBs responses at 1 through 12 months are included in Table 1.

3. Clinical Results:

Clinical follow-up data are available for 3 (20 mcg dose) and 4 (40 mcg dose) dialysis patients who

Study 816

RESULTS (CONT.): were nonresponders to the plasma-derived vaccine following the first injection of vaccine; for 4 dialysis patients following the second 20 or 40 mcg dose and for 3 dialysis patients following the third 20 or 40 mcg dose of vaccine.

Clinical complaints and maximum temperatures reported following each injection are provided in Tables 2-5. In summary:

Clinical Complaint	Dose (mcg)	% Frequency by Injection Number 1	2	3
Injection Site	20	0 (0/3)	0 (0/4)	0 (0/3)
	40	0 (0/4)	0 (0/4)	0 (0/3)
Systemic	20	0 (0/3)	0 (0/4)	0 (0/3)
	40	0 (0/4)	0 (0/4)	0 (0/3)

No serious or alarming adverse reactions attributable to vaccination have been reported.

Events Reported to OoBRR

1. A 53-year old female subject, case no. (b)(6) had a history of hypertension, diabetes mellitus, cirrhosis, severe renal osteodystrophy and end-stage renal disease (3x/week hemodialysis). Approximately five months after receiving a second 20 mcg dose of recombinant hepatitis B vaccine lot 974/C-K446, she died due to congestive heart failure, renal failure, and severe arteriosclerosis. The investigator does not consider the death to be related to vaccination.

2. A 63-year old male dialysis patient, case no. (b)(6) with ESRD and severe peripheral vascular disease, was hospitalized for a left femoral-popliteal bypass and lumbar sympathectomy approximately 2 months after administration of a third injection of recombinant hepatitis B vaccine lot 974/C-K446. His hospital course was complicated by postoperative blood loss, hypotension and hyperkalemia. He subsequently experienced a respiratory arrest requiring resuscitative measures. Post resuscitation, the patient was comatose and decerebrate. His condition further deteriorated and he died (b)(6) days after admission to the hospital.

Table 1

Antibody Responses Among Initially Seronegative Nonresponders to Plasma-Derived Hepatitis B Vaccine (Dialysis Patients) Following Vaccination with 20 or 40 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot 974/C-K446 at 0, 1, and 6 Months in Study 816

Time (Months)	20 mcg					40 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders				All Vaccinees	Responders	
	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1	0(0/4)	0(0/4)	0.3	---	---	0(0/3)	0(0/3)	0.3	---	---
3	25(1/4)	25(1/4)	1.1	53.0	53.0	25(1/4)	25(1/4)	0.8	16.1	16.1
6	0(0/2)	0(0/2)	0.3	---	---	33(1/3)	0(0/3)	0.9	9.5	---
7/8	100(1/1)	100(1/1)	136.9	136.9	136.9	33(1/3)	33(1/3)	2.1	49.4	49.4
12	50(1/2)	50(1/2)	3.4	38.5	38.5	67(2/3)	33(1/3)	3.0	9.3	22.3

2539I-5/cfs
12/16/85

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: NONRESPONDERS (D)

CLINICAL COMPLAINTS	TOTAL VACCINEES (5 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)		3 (100.0%)
PERSONS WITH NO DATA	2 (40.0%)	2 (40.0%)	2 (40.0%)	2 (40.0%)	2 (40.0%)	2 (40.0%)		2 (40.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: NONRESPONDERS (0)

CLINICAL COMPLAINTS	TOTAL VACCINEES (5 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)
PERSONS WITH NO DATA	1 (20.0%)	1 (20.0%)	1 (20.0%)	1 (20.0%)	1 (20.0%)	1 (20.0%)	1 (20.0%)

00600

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: NONRESPONDERS (0)

CLINICAL COMPLAINTS	TOTAL VACCINEES (3 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
PERSONS WITH NO COMPLAINTS	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)		3 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: NONRESPONDERS (D)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (5 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (33.3%)	1 (50.0%)	1 (33.3%)	1 (33.3%)	1 (50.0%)	1 (50.0%)			1 (33.3%)
< 99	2 (66.7%)	1 (50.0%)	2 (66.7%)	2 (66.7%)	1 (50.0%)	1 (50.0%)			2 (66.7%)
TEMPERATURE TAKEN	3 (60.0%)	2 (40.0%)	3 (60.0%)	3 (60.0%)	2 (40.0%)	2 (40.0%)			3 (60.0%)
TEMPERATURE NOT TAKEN	2 (40.0%)	3 (60.0%)	2 (40.0%)	2 (40.0%)	3 (60.0%)	3 (60.0%)			2 (40.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: NONRESPONDERS (D)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (5 PATIENTS) - DOSE 2								
	DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
NORMAL	2 (50.0%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)			2 (50.0%)
< 99	2 (50.0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)			2 (50.0%)
TEMPERATURE TAKEN	4 (80.0%)	3 (60.0%)	3 (60.0%)	3 (60.0%)	3 (60.0%)	3 (60.0%)			4 (80.0%)
TEMPERATURE NOT TAKEN	1 (20.0%)	2 (40.0%)	2 (40.0%)	2 (40.0%)	2 (40.0%)	2 (40.0%)			1 (20.0%)

00903

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 20 MCG
PATIENT CLASS: NONRESPONDERS (D)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (3 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)			2 (100.0%)
TEMPERATURE TAKEN	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)			2 (66.7%)
TEMPERATURE NOT TAKEN	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)			1 (33.3%)

00904

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0616
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

CLINICAL COMPLAINTS	TOTAL VACCINEES (4 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

CLINICAL COMPLAINTS	TOTAL VACCINEES (4 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (0)

CLINICAL COMPLAINTS	TOTAL VACCINEES (3 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (4 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)			1 (25.0%)
< 99	3 (75.0%)	2 (50.0%)	1 (25.0%)	3 (75.0%)	2 (50.0%)	3 (75.0%)			1 (25.0%)
99 - 99.9	0 (0.0%)	1 (25.0%)	2 (50.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)			2 (50.0%)
TEMPERATURE TAKEN	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)			4 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0616
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (4 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)			1 (25.0%)
< 99	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)			1 (25.0%)
99 - 99.9	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)			2 (50.0%)
TEMPERATURE TAKEN	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)			4 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

60600

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0816
TREATMENT :
LOT NUMBER : CK446
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

	TOTAL VACCINEES (3 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER
MAX TEMPERATURE (DEG F, ORAL)	0	1	2	3	4	5		WITH MAX TEMP
< 99	2 (66.7%)	2 (66.7%)	2 (66.7%)	3 (100.0%)	3 (100.0%)	3 (100.0%)		2 (66.7%)
99 - 99.9	1 (33.3%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (33.3%)
TEMPERATURE TAKEN	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (100.0%)		3 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 817
PURPOSE:	To evaluate antibody and clinical responses to 10 mcg doses of yeast recombinant vaccine among: 1. healthy adults immunized previously with plasma-derived vaccine who were nonresponders (anti-HBs negative) 2. preimmune healthy adults
VACCINE:	Hepatitis B Vaccine (Recombinant) - Alum Adsorbed: Lot #972/C-K444 (10 mcg/ml)
PRIMARY INVESTIGATOR:	Robert P. Bishop, M.D. Director, Health Services Merck & Co., Inc. West Point, PA 19486
SECONDARY INVESTIGATOR(S):	Edgardo P. Avancena, M.D. Joseph C. Rogers, M.D. Joseph P. Romano, M.D. Merck & Co., Inc. West Point, PA & Rahway, NJ
STUDY LOCATION:	Merck & Co., Inc. West Point, PA 19486 Merck & Co., Inc. Rahway, NJ 07065
DATE INITIATED:	March 21, 1984
DATE COMPLETED:	In progress

Study 817

STUDY POPULATION: The study population will consist of 40-50 healthy adults of either sex (excluding pregnant females), who are employees of Merck & Co., Inc. Half of the population will consist of persons with pre-existing hepatitis B antibody which may be either naturally acquired or plasma vaccine induced. The other half will consist of persons who have been vaccinated with plasma vaccine but failed to develop detectable antibody to hepatitis B. All participants must be negative for anti-HBc and HBsAg, and have a normal ALT level.

PROCEDURE: Study participants are allocated to one of two regimens as shown below. All injections are intramuscular.

Group	No.	Dose	Time of Vaccination
1. Preimmune	5	1.0 ml (10 mcg)	0
2. Nonresponders	4	1.0 ml (10 mcg)	0, 1 & 6 mos.

Vaccinees are asked to record their temperature daily for five days after each injection and also to record any local or systemic complaints they may have during this period.

A blood specimen (10-15 ml) is obtained from each participant approximately 2 weeks before the first vaccination. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12 and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, yeast antibody and ALT. Those with anti-HBs titers $\geq$ 25 mIU/ml may be tested for the proportions of anti-a and anti-d activity.

Study 817

RESULTS:

NONRESPONDERS TO PLASMA VACCINE:

10 mcg Lot #972/C-K444 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
4	4	3

2. Serologic Results:

Serologic data are avilable for two study participants at 7/8 months.

At seven months neither of the two vaccinees tested had seroconverted. Table 1 shows seroconversion rates and GMT's for up to 7/8 months of follow-up.

3. Clinical Complaints:

Clinical follow-up data are available for four participants following the first two injections and for three after the third injection. Specific complaints and maximum temperatures reported during the five days of follow-up following each injection are provided in Table 2.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	25(1/4)	0 (0/4)	0 (0/3)
Systemic	25(1/4)	0 (0/4)	0 (0/3)

There were no serious or alarming adverse reactions attributable to vaccine.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
POPULATION : NONRESPONDERS (H)
DOSE : 10 MCG
LOT : CK444
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	RESPONDERS S/N >= 2.1	RESPONDERS MIU/ML >= 10
PRE VAC	0%	(0/4)	0%	(0/4)	0.4		
1 MONTH	0%	(0/3)	0%	(0/3)	0.3		
2 MONTHS	0%	(0/1)	0%	(0/1)	0.3		
3 MONTHS	0%	(0/2)	0%	(0/2)	0.3		
6 MONTHS	0%	(0/1)	0%	(0/1)	1.9		
7/8 MONTHS	0%	(0/2)	0%	(0/2)	0.7		

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

CLINICAL COMPLAINTS	TOTAL VACCINEES (4 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (25.0%)
SORENESS	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (25.0%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (25.0%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (25.0%)
SHOULDER PAIN	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (25.0%)
PERSONS WITH COMPLAINTS	1 (25.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (50.0%)
PERSONS WITH NO COMPLAINTS	3 (75.0%)	4 (100.0%)	3 (75.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)		2 (50.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

CLINICAL COMPLAINTS	TOTAL VACCINEES (4 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (H)

CLINICAL COMPLAINTS	TOTAL VACCINEES (3 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PERSONS WITH NO COMPLAINTS	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (4 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)		4 (100.0%)
TEMPERATURE TAKEN	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)		4 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (H)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (4 PATIENTS) - DOSE 2								DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5											
NORMAL	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)											1 (25.0%)
< 99	3 (75.0%)	3 (75.0%)	3 (75.0%)	3 (75.0%)	3 (75.0%)	3 (75.0%)											3 (75.0%)
TEMPERATURE TAKEN	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)	4 (100.0%)											4 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)											0 (0.0%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (3 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)			2 (100.0%)
TEMPERATURE TAKEN	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)			2 (66.7%)
TEMPERATURE NOT TAKEN	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)			1 (33.3%)

Study 854

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 854.
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine in the following adult populations: 1. Chronic Carriers of HBsAg 2. Healthy Hyporesponders to Plasma-Derived Vaccine. 3. Healthy Nonresponders to Plasma-Derived Vaccine. 4. Healthy Transient Responders to Plasma-Derived Vaccine.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #979/C-K564 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Jules Dienstag, M.D. Associate Professor of Medicine Gastrointestinal Unit Massachusetts Gen. Hosp. Boston, MA 02114
SECONDARY INVESTIGATOR:	Eloise Watkins, R.N., M.P.H. Gastrointestinal Unit Mass. General Hosp. Fruit Street Boston, MA 02114 Lynn F. Butterly, M.D. Clinical & Research Fellow Gastrointestinal Unit Mass. General Hosp. Boston, MA 02114
STUDY LOCATION:	Massachusetts General Hospital Fruit Street Boston, MA 02114
DATE INITIATED:	October 14, 1984
DATE COMPLETED:	In progress

Study 854

STUDY POPULATIONS: The study population will consist of adults of either sex (excluding pregnant women) who can be classified into one of the following groups:

Group	Number of Subjects	Qualifications
Carriers	10-15	Chronic carrier of HBsAg for at least one year, with no signs or symptoms of chronic liver disease, and a stable ALT level less than 3 times the upper limit of normal.
Hyporesponders	15-20	Healthy adults who have had only a low level anti-HBs response (positive titer obtained in at least 2 successive bleedings) to a complete 3 injection regimen of plasma derived hepatitis B vaccine. [maximum antibody titer 8-36 when measured in (b) (4) RIA units, 2.1-9.9 when measured in terms of S/N ratio, or <10 mIU/ml]
Nonresponders	15-20	Healthy adults who had a single post-vaccination blood sample with an anti-HBs titer in the range S/N = 2.1-9.9 followed by additional samples all with S/N less than 2.1 as well as persons whose post-vaccination blood samples all had anti-HBs titers of S/N less than 2.1 after receiving a three injection series of plasma-derived hepatitis B vaccine.
Transient Responders	10-15	Healthy adults who had at least one blood sample with an anti-HBs titer of S/N $\geq$10 following a 3 injection series of plasma derived hepatitis B vaccine but have subsequently lost antibody (S/N <2.1).

Study 854

PROCEDURE:

Prior to vaccination, each participant will be screened for HBsAg, anti-HBc, anti-HBs and ALT level. A serum pregnancy test will also be performed for all women of childbearing age. Vaccine is administered intramuscularly according to the following schedule.

Group	Vaccination Regimen
Carriers	1.0 ml (10 mcg HBsAg) at time 0, 1, 2, 3, 4 and 5 months.
Hyporesponders	1.0 ml (10 mcg HBsAg) at time 0
Nonresponders	1.0 ml (10 mcg HBsAg) at time 0, 1 and 6 months.
Transient Responders	1.0 ml (10 mcg HBsAg) at time 0.

The vaccine recipients are asked to record their temperature for 5 days after each injection and to note any local or systemic complaints. Unexpected or serious reactions will be reported to the study physician immediately.

Follow-up blood samples will be obtained from carriers monthly for 6 months and at 9 and 12 months; from hyporesponders and transient responders at 1, 3, 6, 9, 12 and 24 months and; from nonresponders at 1, 2, 3, 6, 9 months, and at 12 and 24 months from those who have seroconverted by 9 months. Samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT by Dr. Dienstag. Samples may also be assayed at MSDRL for yeast antibody and for the proportions of anti-HBs specific for the a and d determinants of HBsAg.

RESULTS:

HYPORESPONDERS:

10 mcg Lot #979/C-K564 at time 0.

1. Number Vaccinated: 2

Study B54

RESULTS: (Cont.)

2. Serologic Results:

One of the vaccine recipients displayed a marked boost in anti-HBs titer one month after receiving one injection of vaccine (10 mcg HBsAg). The other vaccine recipient has not responded. The anti-HBs titers for these two subjects are presented below.

Case #	Pre-vaccination anti-HBs Titer	Anti-HBs Titer (mIU/ml) 1 Month	3 Months	6 Months
(b) (6)	6.2	186.8	123.0	39.0
	2.4	1.5	0.1	0.2

3. Clinical Complaints:

Clinical follow-up data are available for both vaccinees. One participant had an injection site complaint and one participant had a systemic complaint. Refer to Table 2 for a listing of specific clinical complaints. Temperature data are provided in Table 3.

There were no serious or alarming reactions attributable to vaccine.

NONRESPONDERS

10 mcg Lot #979/C-K564 at 0, 1, and 6 months.

1. Number Vaccinated:

Injection No.		
1	2	3
14	13	13

Study 854

RESULTS (CONT.):

2. Serologic Results:

Serologic data are available for 12 participants at six months. Fifty-eight percent (7/12) of the subjects seroconverted (S/N ≥2.1) for anti-HBs. Twenty-five percent (3/12) of the vaccinees developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 6 months for all vaccinees was 3.2 mIU/ml and 45.8 for responders (mIU/ml ≥10).

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for at least thirteen participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	----Frequency in % by Injection----- 1	2	3
Injection Site	21 (3/14)	8 (1/13)	15 (2/13)
Systemic	14 (2/14)	8 (1/13)	0 (0/13)

Refer to Table 4 for listings of specific complaints by injection number. Maximum temperature data are provided in Table 5.

There were no serious or alarming adverse reactions attributable to vaccine.

TRANSIENT RESPONDERS

10 mcg Lot #979/C-K564 at time 0

1. Number Vaccinated: 3

2. Serologic Results:

At one month, two of the transient responders who were seronegative for anti-HBs prior to vaccination,

Study 854

RESULTS (CONT.): seroconverted for anti-HBs. The GMT for the two responders was 67.9 mIU/ml. The anti-HBs titers for the three subjects are presented below.

Case #	Pre-vaccination anti-HBs Titer	Anti-HBs Titer (mIU/ml) 1 Month
(b) (6)	0.2	14.8
	0	311.7
	0.4	—

3. Clinical Complaints:

Clinical follow-up data are available for all the participants. No vaccinee had an injection site complaint. One subject had a systemic complaint (Table 6). The maximum reported temperature was 99.9°F (Table 7).

No serious or alarming adverse experiences attributable to vaccine have been reported.

PUBLICATIONS: Butterly L, Watkins E, Hinkle CA, Dienstag JL. Response to recombinant yeast hepatitis B vaccine in nonresponders to plasma-derived hepatitis B vaccine. Hepatology 1985; 5:1007 (Abstract).

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
POPULATION : NONRESPONDERS (H)
DOSE : 10 MCG
LOT : CK564
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	RESPONDERS S/N >= 2.1	RESPONDERS MIU/ML >= 10
1 MONTH	38%	(5/13)	15%	(2/13)	3.3	17.2	76.5
2 MONTHS	67%	(8/12)	58%	(7/12)	18.5	38.9	59.5
3 MONTHS	64%	(7/11)	45%	(5/11)	10.9	35.8	86.2
6 MONTHS	58%	(7/12)	25%	(3/12)	3.2	7.7	45.8
9 MONTHS	100%	(4/4)	50%	(2/4)	36.0	36.0	245.1

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HYPORESPONDERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (2 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
SORENESS	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
SYSTEMIC	1 (50.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
RESPIRATORY	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
RHINITIS	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
PERSONS WITH COMPLAINTS	2 (100.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)
PERSONS WITH NO COMPLAINTS	0 (0.0%)	1 (50.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	0 (0.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HYPORESPONDERS

	TOTAL VACCINEES (2 PATIENTS) - DOSE 1							
	DAYS POST VACCINATION							
MAX TEMPERATURE (DEG F, ORAL)	0	1	2	3	4	5		NUMBER WITH MAX TEMP
< 99	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)		2 (100.0%)
TEMPERATURE TAKEN	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)		2 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

62600

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

CLINICAL COMPLAINTS	TOTAL VACCINEES (14 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (7.1%)	2 (14.3%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
INFLAMMATION	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
SORENESS	1 (7.1%)	2 (14.3%)	2 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	1 (7.1%)	2 (14.3%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (7.1%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.1%)
PERSONS WITH COMPLAINTS	1 (7.1%)	2 (14.3%)	2 (14.3%)	1 (7.1%)	0 (0.0%)	1 (7.1%)	5 (35.7%)
PERSONS WITH NO COMPLAINTS	13 (92.9%)	12 (85.7%)	12 (85.7%)	13 (92.9%)	14 (100.0%)	13 (92.9%)	9 (64.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (H)

CLINICAL COMPLAINTS	TOTAL VACCINEES (13 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	1 (7.7%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
SORENESS	0 (0.0%)	1 (7.7%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (7.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (7.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (7.7%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (7.7%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (7.7%)	1 (7.7%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	2 (15.4%)
PERSONS WITH NO COMPLAINTS	13 (100.0%)	12 (92.3%)	12 (92.3%)	13 (100.0%)	12 (92.3%)	13 (100.0%)	11 (84.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

CLINICAL COMPLAINTS	TOTAL VACCINEES (13 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (7.7%)	2 (15.4%)	1 (7.7%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	2 (15.4%)
SORENESS	0 (0.0%)	1 (7.7%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
OTHER	1 (7.7%)	1 (7.7%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
PERSONS WITH COMPLAINTS	1 (7.7%)	2 (15.4%)	1 (7.7%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	2 (15.4%)
PERSONS WITH NO COMPLAINTS	12 (92.3%)	11 (84.6%)	12 (92.3%)	12 (92.3%)	13 (100.0%)	13 (100.0%)	11 (84.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00932

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (14 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	13 (92.9%)	11 (78.6%)	11 (84.6%)	13 (92.9%)	14 (100.0%)	14 (100.0%)			9 (64.3%)
99 - 99.9	1 (7.1%)	3 (21.4%)	2 (15.4%)	1 (7.1%)	0 (0.0%)	0 (0.0%)			5 (35.7%)
TEMPERATURE TAKEN	14 (100.0%)	14 (100.0%)	13 (92.9%)	14 (100.0%)	14 (100.0%)	14 (100.0%)			14 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

00933

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (N)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (13 PATIENTS) - DOSE 2 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
< 99	9 (81.8%)	12 (100.0%)	11 (91.7%)	8 (66.7%)	9 (75.0%)	10 (83.3%)		6 (50.0%)
99 - 99.9	2 (18.2%)	0 (0.0%)	1 (8.3%)	4 (33.3%)	3 (25.0%)	2 (16.7%)		6 (50.0%)
TEMPERATURE TAKEN	11 (84.6%)	12 (92.3%)	12 (92.3%)	12 (92.3%)	12 (92.3%)	12 (92.3%)		12 (92.3%)
TEMPERATURE NOT TAKEN	2 (15.4%)	1 (7.7%)	1 (7.7%)	1 (7.7%)	1 (7.7%)	1 (7.7%)		1 (7.7%)

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: NONRESPONDERS (H)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (13 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	10 (76.9%)	12 (92.3%)	11 (91.7%)	12 (92.3%)	12 (92.3%)	11 (91.7%)		9 (69.2%)
99 - 99.9	2 (15.4%)	1 (7.7%)	1 (8.3%)	1 (7.7%)	1 (7.7%)	1 (8.3%)		3 (23.1%)
100 - 100.9	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.7%)
TEMPERATURE TAKEN	13 (100.0%)	13 (100.0%)	12 (92.3%)	13 (100.0%)	13 (100.0%)	12 (92.3%)		13 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	1 (7.7%)		0 (0.0%)

Table 6 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: TRANSIENT RESPONDERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (3 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
HIP PAIN	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)
PERSONS WITH NO COMPLAINTS	3 (100.0%)	3 (100.0%)	2 (66.7%)	3 (100.0%)	3 (100.0%)	3 (100.0%)	2 (66.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00936

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: TRANSIENT RESPONDERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (3 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	2 (66.7%)	3 (100.0%)	3 (100.0%)	2 (100.0%)	3 (100.0%)	3 (100.0%)			2 (66.7%)
99 - 99.9	1 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (33.3%)
TEMPERATURE TAKEN	3 (100.0%)	3 (100.0%)	3 (100.0%)	2 (66.7%)	3 (100.0%)	3 (100.0%)			3 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

244 RESPONSE TO RECOMBINANT YEAST HEPATITIS B VACCINE IN NONRESPONDERS TO PLASMA-DERIVED HEPATITIS B VACCINE

L Butterly, E Watkins, CA Hinkle and JL Dienstag. Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

Preliminary reports suggested that recombinant yeast hepatitis B vaccine (R-HBvac) might be more immunogenic than the triply inactivated plasma-derived hepatitis B vaccine (P-HBvac) (Hepatology 1984;4:1077). Therefore, to test this hypothesis, we administered three 10 µg doses of R-HBvac (Merck Sharp & Dohme Research Laboratories) at time 0, 1, and 6 months to 14 normal adults who had failed to respond to one or more courses (3-6 doses) of P-HBvac. The frequency [# positive/# vaccinated] (%) and geometric mean titer (mIU/ml) of anti-HBs responses were as follows:

Month	1	2	3	6
anti-HBs+	5/13 (39)	8/14 (57)	7/14 (50)	7/13 (54)
GMT ± SD	17 ± 7	39 ± 10	36 ± 23	8 ± 7

For comparison, the same data are charted below for 65 seronegative health workers, never previously vaccinated, after receiving R-HBvac:

Month	1	2	3	6
anti-HBs+	26/65 (38)	53/62 (86)	61/65 (94)	60/62 (97)
GMT ± SD	7 ± 4	38 ± 4	50 ± 4	72 ± 4

The mean ± SD ages of the 8 initial nonresponders who ultimately did respond and the 6 who did not were indistinguishable, 38 ± 8 and 41 ± 15. The response to R-HBvac in almost 60% of nonresponders to P-HBvac appeared promising, especially when compared with a 40% rate of low-level, poorly sustained anti-HBs responses in P-HBvac nonresponders given a second course of P-HBvac (Hepatology 1984;4:1077); however, the level of antibody fell substantially by six months, when measured just prior to the booster injection. Additional follow-up will be necessary to determine whether the antibody response to R-HBvac in nonresponders to P-HBvac increases and is sustained after booster immunization.

Butterly L, Watkins E, Hinkle CH, Dienstag JL. Response to recombinant hepatitis B vaccine in nonresponders to plasma-derived hepatitis B vaccine. Hepatology 1985; 5:1007 (abstract).

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 874.
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine in healthy adults who failed to develop antibody (nonresponders) or developed only low levels of antibody (hyporesponders) in response to three or four injections of plasma-derived hepatitis B vaccine.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 978/C-K 563 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Myron Tong, M.D., Ph.D. Department of Medical Education Huntington Memorial Hospital 100 Congress Street P.O. Box 7013 Pasadena, CA 91105 - 7013
SECONDARY INVESTIGATORS:	Deborah Roskamp, R.N. Liver Center Huntington Memorial Hospital 100 Congress Street P.O. Box 7013 Pasadena, CA 91105 - 7013
STUDY LOCATION:	Liver Center Huntington Memorial Hospital 100 Congress Street P.O. Box 7013 Pasadena, CA 91105 - 7013
DATE INITIATED:	September 1985.
DATE COMPLETED:	In progress.
STUDY POPULATION:	Participants in the study will be healthy adults of either sex (pregnant women excluded) who failed to develop antibody (S/N <2.1) or had very minimal antibody development (S/N 2.1-9.9) after receiving three or four injections of plasma-derived hepatitis B vaccine. Approximately 40 persons will be enrolled.

Study 874

PROCEDURE: Each participant will receive a 1 ml injection of vaccine in the deltoid muscle at 0, 1, and 6 months. Study participants will be asked to take and record their body temperature for five days after each injection of vaccine and to record any local or systemic complaints. They will also be asked to notify the study investigator immediately if an unexpected or serious reaction occurs.

Blood specimens will be obtained prior to vaccination and at 1, 2, 3, 6, and 8 months postvaccination. Additional samples will be obtained at 12 and 24 months from those who have seroconverted by eight months.

All blood samples will be assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Testing will be performed at Huntington Memorial Hospital and the Medical Laboratory Network. Some samples may be assayed for yeast antibody and anti-HBs subtype specificity at MSDRL.

RESULTS: NONRESPONDERS/HYPORESPONDERS TO PLASMA-DERIVED VACCINE

10 mcg lot #978/C-K563 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
26	26	0

2. Serologic Results:

At one month, 36% (9/25) of the vaccinees seroconverted for anti-HBs (S/N $\geq$2.1). Further serologic data are not available.

3. Clinical Complaints

A summary of frequencies of clinical complaints is not yet available. However, no serious or alarming adverse events attributable to vaccine have been reported. Vaccination and follow-up continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 875
PURPOSE:	To evaluate antibody and clinical responses to licensed hepatitis B vaccine (Heptavax-B) and yeast recombinant hepatitis B vaccine in renal dialysis patients who have already failed to develop antibody after receiving three injections of HEPTAVAX-B.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #993/C-K937 (20 mcg HBsAg/ml) Licensed Vaccine (Heptavax-B) Lot #2277K (20 mcg HBsAg/ml)
PRINCIPAL INVESTIGATORS:	Theodore L. Johnson, M.D. The Duluth Clinic, Ltd. 400 E. Third Street Duluth, MN 55805 Richard N. Hellman, M.D. The Duluth Clinic, Ltd. 400 E. Third Street Duluth, MN 55805 Mark R. Eckman, M.D. The Duluth Clinic, Ltd. 400 East Third Street Duluth, MN 55805
SECONDARY INVESTIGATORS:	Pamela Elde, R.N. Miller-Dwan Medical Center 502 East Second Street Duluth, MN 55805 Gayle Gilmore, R.N. Miller-Dwan Medical Center 502 East Second Street Duluth, MN 55805
STUDY LOCATION:	Miller-Dwan Medical Center 502 East Second Street Duluth, MN 55805

Study 875

DATE INITIATED: June, 1985

DATE COMPLETED: In progress.

STUDY POPULATION: Adult patients who are receiving dialysis treatments for end stage renal disease and have failed to develop anti-HBs following administration of plasma-derived hepatitis B vaccine (HEPTAVAX-B) are eligible for the study. Prospective subjects must not be pregnant, must be negative for HBsAg, anti-HBc, and anti-HBs, and must have a normal ALT. Approximately 40 patients will be enrolled in the study.

PROCEDURE: Prior to administration of the 1st injection of vaccine, participants will have a blood specimen obtained and tested for HBsAg, anti-HBc, anti-HBs and ALT.

Participants will be assigned to one of the following groups:

Group	Vaccine
1	Plasma vaccine (HEPTAVAX-B)
2	Yeast Recombinant vaccine

Participants will also be distributed between the groups with respect to sex and 10 year age strata (i.e., 30-39, 40-49, etc.).

Each subject will receive 2 - 1.0 ml (40 mcg HBsAg) intramuscular injections of HEPTAVAX-B (Group 1) or the yeast recombinant vaccine (Group 2) at 0, 1, and 6 months. Vaccinees will be asked to take and record their temperatures for 5 days after each injection and record any local or systemic complaints that they have.

Follow-up blood samples will be obtained at 1, 2, 3, 6 and 8 months following the first injection of vaccine. All samples will be tested for HBsAg, anti-HBc, anti-HBs, and ALT. Assays for ALT will be done in Duluth, Minnesota. All other assays will be

Study 875

PROCEDURE: (Cont.) done by the Merck Sharp and Dohme Research Laboratories (MSDRL).

RESULTS: DIALYSIS PATIENTS (Nonresponders to HEPTAVAX-B):

40 mcg Lot 993/C-K937 (Yeast Recombinant) at 0, 1, and 6 months

40 mcg Lot 2277K (Licensed) at 0, 1, and 6 months

1. Number Vaccinated:

Vaccine	Injection No. 1	2	3
Yeast Recombinant	17	15	0
Plasma-Derived	18	17	0

2. Serologic Results:

Two month serologic data are available for 13 participants who received yeast recombinant hepatitis B vaccine. Seroconversion for anti-HBs (S/N ≥2.1) at two months was 38% (5/13). Fifteen percent (2/13) of these vaccinees developed protective levels of anti-HBs (mIU/ml ≥10) at that time.

The GMT at two months for all subjects who received yeast recombinant vaccine subjects was 1.4 mIU/ml and 70.7 mIU/ml for responders with a titer of mIU/ml ≥10.

Two months serologic data are available for 15 subjects who received plasma-derived hepatitis B vaccine. Forty-seven percent (7/15) of the participants seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at two months.

The GMT at two months for all vaccinees was 5.1 mIU/ml and 131.6 mIU/ml for responders with a titer of mIU/ml ≥10..

Study 875

RESULTS (CONT.):

Refer to Table 1 for anti-HBs responses and GMTs through two months of follow-up.

Two participants who received yeast recombinant hepatitis-B vaccine and one participant who received plasma-derived vaccine were found to have low positive anti-HBs titers prior to vaccination. All three participants had a >4-fold rise in their anti-HBs titers one month after their first injection of vaccine.

3. Clinical Complaints:

Clinical follow-up data are available for at least 15 participants from each vaccine group after the first and second injections. The overall frequencies of complaints are presented below:

	Type of Complaint	Frequency in % by Injection No. 1	2	3
Yeast Recombinant	Injection Site	12(2/17)	0(0/15)	—
	Systemic	29(5/17)	13(2/15)	—
Plasma-Derived	Injection Site	13(2/16)	0(0/15)	—
	Systemic	31(5/16)	7(1/15)	—

Refer to Table 2 and 3 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Tables 4 and 5.

ALT Elevations:

Two participants had elevated ALT levels (1.5 to 2.0 times the upper limit of normal) prior to vaccination. They remained elevated at one and two months post the initial vaccine injection. Neither patient was seropositive for HBsAg or anti-HBc.

One subject developed an elevated ALT level (1.5 times the upper limit of normal) one month post the second injection of plasma-derived hepatitis-B vaccine. He was seronegative for anti-HBc, HBsAg and anti-HBs at that time. Additional serum samples are pending.

Study 875

RESULTS (CONT.):

Reactions Reported to the OoBRR:

Three participants withdrew from the study due to clinical complaints following one injection of vaccine.

1. A 32-year old male who received two 20 mcg injections of yeast recombinant vaccine (one injection into each deltoid) developed a swollen, sore and stiff left arm after administration of the vaccine. The swelling and soreness persisted for one week and then subsided. No treatment was necessary. The subject recovered.

2. A 70-year old male reported becoming "ill" after receiving two 20 mcg injections of Heptavax-B (one injection into each deltoid). The participant was hospitalized. The study investigator considered the illness unrelated to vaccine.

3. A 72-year old male developed generalized achiness and a headache three days after administration of his first injections of yeast recombinant vaccine. Forty-eight hours after onset of those symptoms, he developed a flu-like syndrome with a temperature of 100°F.

There have been two deaths among the study participants unrelated to vaccine administration.

1. A 53-year old female hemodialysis patient with an 18 month history of widely metastasized adenocarcinoma of the breast in addition to chronic obstructive pulmonary disease, hypertension, and uremic pericarditis, died (b) (6) days after administration of the second injections of Heptavax-B. Death was due to respiratory failure. The study investigator did not consider the death vaccine related.

2. (b) (6) days after administration of the second injections of yeast recombinant vaccine, a 66-year old female dialysis patient was hospitalized for an infarcted bowel. Exploratory surgery was performed and the (b) (6) the patient expired.

Table 1

Antibody Responses Among Dialysis Patients Following Vaccination with
40 mcg Injections of Yeast Recombinant Hepatitis B Vaccine
Lot #993/C-K937 or Plasma-Derived Hepatitis B Vaccine
Lot #2277K at 0, 1, and 6 Months in Study 875

	40 mcg (Yeast Recombinant)					40 mcg (Plasma-Derived)				
			GMT (mIU/ml)					GMT (mIU/ml)		
Time	% with Anti-HBs		All	Responders		% with Anti-HBs		All	Responders	
(Months)	S/N ≥ 2.1	mIU/ml ≥ 10	Vaccinees	S/N ≥ 2.1	mIU/ml ≥ 10	S/N ≥ 2.1	mIU/ml ≥ 10	Vaccinees	S/N ≥ 2.1	mIU/ml ≥ 10
1	7.7(1/13)	0(0/13)	0.4	7.0	----	50(7/14)	36(5/14)	3.4	37.4	103.5
2	38(5/13)	15(2/13)	1.4	12.0	70.1	47(7/15)	47(7/15)	5.1	131.6	131.6

24071/6
12/31/85

00946

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : CK037
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (0)

CLINICAL COMPLAINTS	TOTAL VACCINEES (17 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	2 (11.8%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)		2 (11.8%)
SORENESS	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)		2 (11.8%)
STIFFNESS/TIGHTNESS	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)		1 (5.9%)
SYSTEMIC	1 (5.9%)	0 (0.0%)	2 (11.8%)	3 (17.6%)	1 (5.9%)	2 (11.8%)		5 (29.4%)
WHOLE BODY/GENERAL	1 (5.9%)	0 (0.0%)	2 (11.8%)	3 (17.6%)	1 (5.9%)	2 (11.8%)		5 (29.4%)
CHILLS	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	0 (0.0%)		1 (5.9%)
HEADACHE	0 (0.0%)	0 (0.0%)	2 (11.8%)	1 (5.9%)	1 (5.9%)	0 (0.0%)		2 (11.8%)
ILLNESS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)		1 (5.9%)
ACHINESS	0 (0.0%)	0 (0.0%)	1 (5.9%)	2 (11.8%)	1 (5.9%)	1 (5.9%)		3 (17.6%)
PERSONS WITH COMPLAINTS	3 (17.6%)	1 (5.9%)	2 (11.8%)	3 (17.6%)	1 (5.9%)	3 (17.6%)		6 (35.3%)
PERSONS WITH NO COMPLAINTS	14 (82.4%)	16 (94.1%)	15 (88.2%)	14 (82.4%)	16 (94.1%)	14 (82.4%)		11 (64.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

00947

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : CK937
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
SYSTEMIC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	2 (13.3%)		2 (13.3%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.7%)		1 (6.7%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.7%)		1 (6.7%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)		1 (6.7%)
VOMITING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)		1 (6.7%)
PERSONS WITH COMPLAINTS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	2 (13.3%)		2 (13.3%)
PERSONS WITH NO COMPLAINTS	15 (100.0%)	15 (100.0%)	15 (100.0%)	14 (93.3%)	14 (93.3%)	13 (86.7%)		13 (86.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : 2277K
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (0)

CLINICAL COMPLAINTS	TOTAL VACCINEES (16 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (6.3%)	2 (12.5%)
SORENESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (6.3%)	1 (6.3%)
ECCHYMOSIS	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
SYSTEMIC	2 (12.5%)	0 (0.0%)	3 (18.8%)	1 (6.3%)	2 (12.5%)	2 (12.5%)	5 (31.3%)
WHOLE BODY/GENERAL	2 (12.5%)	0 (0.0%)	2 (12.5%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	4 (25.0%)
FATIGUE/WEAKNESS	2 (12.5%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (12.5%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	2 (12.5%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)
WRIST PAIN	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)	1 (6.3%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (6.3%)

Table 3 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : 2277K
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

	TOTAL VACCINEES (16 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
CLINICAL COMPLAINTS	0	1	2	3	4	5	
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (6.3%)
PERSONS WITH COMPLAINTS	2 (12.5%)	1 (6.3%)	3 (18.8%)	1 (6.3%)	3 (18.8%)	3 (18.8%)	6 (37.5%)
PERSONS WITH NO COMPLAINTS	14 (87.5%)	15 (93.8%)	13 (81.3%)	15 (93.8%)	13 (81.3%)	13 (81.3%)	10 (62.5%)
PERSONS WITH NO DATA	2 (11.1%)	2 (11.1%)	2 (11.1%)	2 (11.1%)	2 (11.1%)	2 (11.1%)	2 (11.1%)

00950

Table 3 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : 2277K
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

CLINICAL COMPLAINTS	TOTAL VACCINEES (17 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
SYSTEMIC	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
MUSCULOSKELETAL	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
MUSCLE STIFFNESS	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
PERSONS WITH NO COMPLAINTS	15 (100.0%)	14 (93.3%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)		14 (93.3%)
PERSONS WITH NO DATA	2 (11.8%)	2 (11.8%)	2 (11.8%)	2 (11.8%)	2 (11.8%)	2 (11.8%)		2 (11.8%)

00951

Table 4

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : CK937
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (17 PATIENTS) - DOSE 1 — DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
NORMAL	1 (5.9%)	1 (5.9%)	1 (5.9%)	1 (6.3%)	1 (5.9%)	2 (12.5%)		1 (5.9%)
< 99	10 (58.8%)	12 (70.6%)	13 (76.5%)	11 (68.8%)	10 (58.8%)	12 (75.0%)		6 (35.3%)
99 - 99.9	5 (29.4%)	4 (23.5%)	2 (11.8%)	4 (25.0%)	5 (29.4%)	1 (6.3%)		7 (41.2%)
100 - 100.9	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)		2 (11.8%)
102 - 102.9	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (5.9%)	0 (0.0%)		1 (5.9%)
TEMPERATURE TAKEN	17 (100.0%)	17 (100.0%)	17 (100.0%)	16 (94.1%)	17 (100.0%)	16 (94.1%)		17 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)	1 (5.9%)		0 (0.0%)

00952

Table 4 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : CK937
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	2 (14.3%)	2 (13.3%)	2 (13.3%)	2 (14.3%)	2 (15.4%)	2 (14.3%)		2 (13.3%)
< 99	9 (64.3%)	10 (66.7%)	9 (60.0%)	10 (71.4%)	10 (76.9%)	10 (71.4%)		7 (46.7%)
99 - 99.9	3 (21.4%)	3 (20.0%)	4 (26.7%)	1 (7.1%)	1 (7.7%)	2 (14.3%)		5 (33.3%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
TEMPERATURE TAKEN	14 (93.3%)	15 (100.0%)	15 (100.0%)	14 (93.3%)	13 (86.7%)	14 (93.3%)		15 (100.0%)
TEMPERATURE NOT TAKEN	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	2 (13.3%)	1 (6.7%)		0 (0.0%)

00953

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : 2277K
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (0)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (16 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	2 (12.5%)	2 (13.3%)	2 (12.5%)	2 (13.3%)	2 (13.3%)	2 (13.3%)		2 (12.5%)
< 99	13 (81.3%)	7 (46.7%)	9 (56.3%)	8 (53.3%)	9 (60.0%)	8 (53.3%)		5 (31.3%)
99 - 99.9	1 (6.3%)	5 (33.3%)	3 (18.8%)	4 (26.7%)	3 (20.0%)	3 (20.0%)		5 (31.3%)
100 - 100.9	0 (0.0%)	1 (6.7%)	2 (12.5%)	1 (6.7%)	1 (6.7%)	1 (6.7%)		3 (18.8%)
102 - 102.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)		1 (6.3%)
TEMPERATURE TAKEN	16 (88.9%)	15 (83.3%)	16 (88.9%)	15 (83.3%)	15 (83.3%)	15 (83.3%)		16 (88.9%)
TEMPERATURE NOT TAKEN	2 (11.1%)	3 (16.7%)	2 (11.1%)	3 (16.7%)	3 (16.7%)	3 (16.7%)		2 (11.1%)

Table 5 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
PLASMA-DERIVED HEPATITIS B VACCINE

STUDY : 0875
TREATMENT :
LOT NUMBER : 2277K
DOSE : 40 MCG
PATIENT CLASS: NONRESPONDERS (D)

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (17 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (7.1%)	1 (7.1%)	1 (7.7%)		1 (6.7%)
< 99	9 (60.0%)	10 (66.7%)	9 (60.0%)	10 (71.4%)	8 (57.1%)	10 (76.9%)		6 (40.0%)
99 - 99.9	4 (26.7%)	3 (20.0%)	4 (26.7%)	2 (14.3%)	5 (35.7%)	2 (15.4%)		7 (46.7%)
102 - 102.9	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
103 - 103.9	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (7.1%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
TEMPERATURE TAKEN	15 (88.2%)	15 (88.2%)	15 (88.2%)	14 (82.4%)	14 (82.4%)	13 (76.5%)		15 (88.2%)
TEMPERATURE NOT TAKEN	2 (11.8%)	2 (11.8%)	2 (11.8%)	3 (17.6%)	3 (17.6%)	4 (23.5%)		2 (11.8%)

PREIMMUNE ADULTS

PREIMMUNE ADULTS - POPULATION SUMMARY

Preimmune adults are included in the populations of two studies (Study 817 and Study 813, addendum 6 and 7). The pre-existing hepatitis B antibody in this population may be naturally acquired or due to previous administration of either plasma-derived or yeast recombinant hepatitis B vaccine. The studies are designed to assess antibody and clinical responses of preimmune adults to a single 10 or 5 mcg booster injection of hepatitis B yeast recombinant vaccine.

To date, 63 preimmune adults have received a 10 mcg dose of yeast recombinant vaccine. Anti-HBs responses 1-2 months after the booster injections have been measured in mIU/ml for 31 subjects. All 31 participants demonstrated a boost in anti-HBs titer at that time. The GMT at 1-2 months post-vaccination was 1110.6 mIU/ml versus a prevaccination GMT of 62.0 mIU/ml. Anti-HBs responses expressed in S/N ratio units are also available for an additional 31 subjects whose antibody response was measured 2-4 weeks after a single 10 mcg booster injection. Ninety-seven percent (30/31) of these participants demonstrated a boost in antibody titer at 2-4 weeks. One vaccinee who was seronegative at the time of vaccination but antibody positive at an earlier time failed to develop detectable antibody four weeks after vaccination.

Twenty-eight preimmune adults have received a single 5 mcg booster injection of vaccine. All 25 participants tested at 1-2 months after the booster injection demonstrated a boost in anti-HBs titer. The GMT 1-2 months post-vaccination was 1275.2 mIU/ml versus a pre-vaccination GMT of 59.9 mIU/ml.

The vaccine has been well tolerated in this population. No serious reactions attributable to vaccination have been reported.

PREIMMUNE ADULTS

Study 813 - New York, NY - Dr. M. Davidson

The population for study 811 addenda 6 and 7 consists of two groups of pre-immune health care personnel. Group 1 (addendum 6) includes personnel who received plasma-derived hepatitis B vaccine at 0, 1, 2, and 9 months, 5 to 7 years previously. These subjects receive a 10 mcg booster injection of yeast recombinant hepatitis B vaccine lot C-M126. Group 2 (addendum 7) includes subjects who previously received 2.5 mcg injections of yeast recombinant vaccine at 0, 1, and 6 months in study 813. These participants receive either a 5 mcg or 10 mcg booster injection of yeast recombinant vaccine lot C-M126.

Thirty-one group 1 participants have received a 10 mcg injection of vaccine. At one month post the booster injection, 21 of 30 (70%) subjects had a greater than four-fold rise in anti-HBs titer.

In group 2, 28 participants have received a 5 mcg injection and 28 have received a 10 mcg injection of vaccine. At 1-2 months after receipt of the booster injection, 21 of 25 (84%) subjects, who received a 5 mcg dose, had a greater than four-fold rise in anti-HBs titer. The GMT for all vaccinees was 59.9 mIU/ml prior to the booster dose and 1275.2 mIU/ml 1-2 months post the booster injection.

Twenty-three of 27 (85%) participants, who received a 10 mcg booster dose, had a greater than four-fold rise in anti-HBs titer 1-2 months post the vaccine injection. Prior to the booster injection, the GMT for all vaccinees was 96.5 mIU/ml. The GMT rose to 1337.0 mIU/ml 1-2 months after the booster dose.

No serious adverse experiences attributable to vaccine have been reported. Refer to the summary on health care personnel/healthy adults for data regarding other subjects vaccinated in this study.

Study 817 - West Point, PA - Dr. R. Bishop

The study population consists of 2 groups of healthy adults. Group 1 includes pre-immune adults (naturally acquired anti-HBs or plasma-derived vaccine induced) who receive a single 10 mcg dose of yeast recombinant vaccine lot C-K444. Group 2 includes healthy adults who were nonresponders to previously administered plasma-derived vaccine. These participants receive a 10 mcg injection of yeast recombinant hepatitis B vaccine lot C-K444 at 0, 1, and 6 months.

Five healthy pre-immune adults (group 1) have received a 10 mcg injection of vaccine. All five subjects showed a greater than four-fold rise in anti-HBs titer three months post the booster injection. The GMT for all the vaccinees prior to the booster dose was 5.7 mIU/ml. At three months after the booster injection, the GMT for all vaccinees was 402.5 mIU/ml.

Study 817 - West Point, PA - Dr. R. Bishop (Cont.)

There were no serious or alarming adverse experiences attributable to vaccine. Refer to the summary on non-responders/hyporesponders for data regarding other subjects vaccinated in this study.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 813
PURPOSE:	To evaluate antibody and clinical responses to several dose levels of yeast recombinant hepatitis B vaccine among the following populations: 1. Health Care Personnel (Seronegative) 2. Preimmune Adults
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 972/C-K444 (10 mcg HBsAg/ml) Lot 81954I/18071/C-L220 (10 mcg HBsAg/0.5 ml) Lot 85860/22123/C-M125 (20 mcg HBsAg/ml) Lot 85861/22124/C-M126 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Morton Davidson, M.D. New York University Medical Center University Hospital 560 First Avenue New York, NY 10016
SECONDARY INVESTIGATOR:	Saul Krugman, M.D. Professor Department of Pediatrics New York University Medical Center 550 First Avenue New York, NY 10016
STUDY LOCATION:	New York University Medical Center University Hospital 560 First Avenue New York, NY 10016
DATE INITIATED:	February 1, 1984
DATE COMPLETED:	In progress.

Study 813

STUDY POPULATIONS: Under the original protocol and subsequent addenda, the following groups of health care personnel are included in the study. Participants may be of either sex, but pregnant women are excluded. Initially seronegative subjects have not previously received any hepatitis B vaccine.

Addendum No.	Characteristics	Number	Vaccine Lot No.#	Regimen
Initial protocol	Initially seronegative	50	972/C-K444	10 mcg (1.0 ml) at 0, 1, and 6 months
Add. #1	Initially seronegative	50	972/C-K444	5 mcg (0.5 ml) at 0, 1, and 6 months
Add. #2	Initially seronegative	50	972/C-K444	2.5 mcg (0.25 ml) at 0, 1, and 6 months
Add. #3	Initially seronegative	50	81954I/18071/ C-L220	10 mcg (0.5 ml) at 0, 1, and 6 months
Add. #4	Initially seronegative	50	81954I/18071/ C-L220	5 mcg (0.25 ml) at 0, 1, and 6 months
Add. #5	Initially seronegative; ≥40 years of age	50	85860/22123/ C-M125	20 mcg (1.0 ml) at 0, 1, and 6 months
Add. #5	Initially seronegative; ≥40 years of age	50	85861/22124/ C-M126	10 mcg (1.0 ml) at 0, 1, and 6 months
Add. #6	Vaccinated 3-5 yrs previously with plasma derived hepatitis B vaccine (HEPTAVAX-B)	100	85861/22124/ C-M126	10 mcg (1.0 ml) at time 0
Add. #7	Vaccinated previously with three 2.5 mcg doses of recombinant vaccine under Add. #2.	50	85861/22124/ C-M126	5 mcg (0.5 ml) or 10 mcg (1.0 ml) at time 0

Study 813

PROCEDURE:

Participants receive intramuscular injections of vaccine according to the regimens outlined above under STUDY POPULATIONS. Those enrolled under addendum #5 who fail to develop antibody following 3 injections of vaccine or have only a transient response that becomes negative by 12 months after the first dose may receive a fourth injection of vaccine.

Participants will be asked to record their temperature for 5 days after each injection of vaccine and to note any local or systemic complaints. Unexpected or serious reactions are to be reported immediately to the study physician.

Blood samples will be obtained from the initially seronegative groups prior to and on the day of the first vaccination. Follow-up samples will be obtained 1, 2, 3, 6, 8, 12 and 24 months after the initial injection of vaccine (initial protocol and addenda #1-5). Follow-up samples from persons vaccinated under addendum #6 are only taken 1 month after vaccination while persons enrolled under addendum #7 have blood samples taken 2 weeks, 4 weeks, and 6 months after vaccination.

Blood samples will be assayed for HBsAg, anti-HBc, anti-HBs and ALT by Dr. Krugman's laboratory and may be assayed for yeast antibody by the Merck Sharp and Dohme Research Laboratories. Samples with an anti-HBs titer $\geq$25 mIU/ml may be tested to determine the relative proportions of anti-a and anti-d activity.

RESULTS:

PREIMMUNE ADULTS (Previously Vaccinated with plasma-derived hepatitis B vaccine):

10 mcg lot 85861/22124/C-M126 at time 0

1. Number Vaccinated: 31

2. Serologic Results:

   At one month following administration of the booster injection of yeast recombinant vaccine, 21 of 30 (70%) participants had a greater than 4-fold rise in anti-HBs titer.

Study 813

RESULTS: (Contd)

Refer to Table 1 for anti-HBs titers prior to and post the booster injection.

3. Clinical Complaints:

Clinical follow-up data are available for 19 participants after the booster injection of vaccine. The overall frequencies of complaints are presented below:

	Frequency in %
Injection Site	32 (6/19)
Systemic	21 (4/19)

Refer to Table 4 for listing of specific complaints. Temperature data are provided in Table 5.

No serious or alarming reactions attributable to vaccine have been reported.

PREIMMUNE ADULTS (Previously Vaccinated with Yeast Recombinant Hepatitis B Vaccine:

5 mcg lot 85861/22124/C-M126 at time 0
10 mcg lot 85861/22124/C-M126 at time 0

1. Number Vaccinated:

Dose Level	
5 mcg	28
10 mcg	28

2. Serologic Results:

Serologic data are available for 25 participants who received a 5 mcg injection of vaccine and 27 participants who received a 10 mcg injection.

Study 813

RESULTS: (Contd)

At 1-2 months after administration of the booster injection, 21 of 25 (84%) participants who received a 5 mcg dose had a greater than 4-fold rise in anti-HBs titer. The GMT for all vaccinees was 59.9 mIU/ml prior to receipt of the booster injection and 1275.2 mIU/ml 1-2 months after the booster dose.

Refer to Table 2 for a listing of anti-HBs titers prior to and post the booster injection.

Twenty-three of 27 (85%) participants who received a 10 mcg booster dose of vaccine, had a greater than 4-fold rise in anti-HBs titer at 1-2 months post the injection. The GMT for all vaccinees was 96.5 mIU/ml prior to receipt of the booster injection and 1337.0 mIU/ml 1-2 months after the booster dose.

Refer to Table 3 for a listing of anti-HBs titers prior to and post the booster injection.

3. Clinical Complaints:

Clinical follow-up data are available for 11 participants who received a 5 mcg injection and 14 participants who received a 10 mcg injection of vaccine. The overall frequencies of complaints are presented below:

Type of Complaint	Dose Level	Frequency in %
Injection site	5 mcg	40 (4/10)
Systemic		10 (1/10)
Injection site	10 mcg	21 (3/14)
Systemic		0 (0/14)

Refer to Table 6 for a listing of specific clinical complaints by dose level. Maximum temperature data are provided in Table 7.

There were no serious or alarming adverse reactions attributable to vaccine.

Study 813

PUBLICATIONS:

Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985; 1:108-9.

Davidson M, Krugman S. Recombinant yeast hepatitis B vaccine: Side effects and immunogenicity compared with plasma-derived hepatitis B vaccine. Submitted for publication to Hepatitis Scientific Memoranda.

Table 1

Anti-HBs Response Following Primary Immunization with
Plasma-Derived Hepatitis B Vaccine* and a
Subsequent Booster Dose (10 mcg) of
Yeast Recombinant Hepatitis B Vaccine**
5 to 7 Years Later

No.	Age	Sex	Anti-HBs Response S/N					
			Years After Initial Immunization				Weeks after Booster	
			1	5	6	7	2	4
(b) (6)								
	51	M	69			<2.1	101	101
	45	F	72			<2.1	22	12
	37	F	3.2			<2.1	5	6.5
	36	M	26			<2.1	165	115
	28	M	27			<2.1	22	16
	74	M	23			<2.1	<2.1	<2.1
	47	M	93			2.3	82	95
	54	M	34			2.6	226	165
	44	M	103			4	165	78
	59	M	24			4	60	33
	39	M	40			6	40	28
	64	F	160			9	179	179
	46	F	73			9	225	158
	49	M	145			12	157	99
	41	F	177			13	192	183
	45	F	144			18	205	250
	74	F	214			20	177	238
	49	F	205			38	288	209
	43	F	100			41	168	145
	31	F	64			49	146	173
	34	M	206			87	154	151
	35	M	266			192	195	144
	52	F	128		2.8		106	83
	41	M	10		<2.1		14	88
	34	M	8		13		118	120
	30	M	125		22		112	
	35	M	168		36		190	203
	33	F	217		66		147	167
	28	F	28	3.4			112	153
	34	M	101	29			138	98
	34	M	204	112			173	160

* Plasma-derived vaccine: Lot #C-E575, 20 mcg dose at 0,1,2, and 9 months.
** Yeast recombinant vaccine: Lot #C-M126, 10 mcg dose.

2340I-16
1/13/86

Table 2

Antibody Responses to a 5 mcg Booster Injection of Yeast Recombinant Hepatitis B Vaccine Lot C-M126 in Health Care Personnel Who Previously Received 2.5 mcg Injections of Yeast Recombinant Vaccine at 0, 1, and 6 Months

	Anti-HBs Titer in mIU/ml	
Case #	Prior to Booster Injection	1-2 Months After Booster Injection
(b) (6)	142	9275
	115	2473
	157	944
	33	2145
	5.5	153
	318	4140
	Neg.	218
	13	940
	19	832
	6.9	244
	25	274
	7.6	301
	489	811
**	20	1100
	70	1662
	59	228
	241	3645
	90	6360
	551	7278
	19	1553
	3390	4116
	23	277
***	1559	2876
	394	5192
	45	2865
GMT in mIU/ml	59.9	1275.2

* Subject was antibody positive at an earlier time.
** Titer determined 4 months after booster injection.
*** Titer determined 3 months after booster injection.

Table 3

Antibody Responses to a 10 mcg Booster Injection of Yeast Recombinant Hepatitis B Vaccine Lot C-M126 in Health Care Personnel Who Previously Received 2.5 mcg Injections of Yeast Recombinant Vaccine at 0, 1, and 6 Months

	Anti-HBs Titer in mIU/ml	
Case #	Prior to Booster Injection	1-2 Months After Booster Injection
(b) (6)	73	800
	812	5828
	150	651
	115	953
	55	3732
	3.6	18
	358	215
	1778	574
	86	2789
	94	2543
	7	1635
	231	3837
	128	2410
	104	3136
	212	9161
	288	490
	Neg.	245
	15	169
	2498	1837
	95	5716
	84	1784
	56	6188
	300	1611
	759	4514
	93	3508
	18	606
	145	948
GMT in mIU/ml	96.5	1337.0

* Subject was antibody positive at an earlier time.

2340I-18
1/13/86

Table 4
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
LOT NUMBER : CM126
DOSE : 10 MCG
PATIENT CLASS: PREIMMUNE ADULTS (Previously vaccinated with plasma-derived hepatitis B vaccine)

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	3 (15.8%)	2 (10.5%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (31.6%)
SORENESS	3 (15.8%)	2 (10.5%)	2 (10.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (31.6%)
STIFFNESS/TIGHTNESS	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
SYSTEMIC	1 (5.3%)	4 (21.1%)	2 (10.5%)	2 (10.5%)	3 (15.8%)	2 (10.5%)	4 (21.1%)
WHOLE BODY/GENERAL	1 (5.3%)	2 (10.5%)	2 (10.5%)	2 (10.5%)	1 (5.3%)	1 (5.3%)	2 (10.5%)
FLUSH	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
FATIGUE/WEAKNESS	1 (5.3%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	2 (10.5%)
MALAISE	1 (5.3%)	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (10.5%)
HEADACHE	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
ACHINESS	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	1 (5.3%)
INTEGUMENTARY SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (5.3%)
RASH, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (5.3%)

Table 4 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
LOT NUMBER : CH126
DOSE : 10 MCG
PATIENT CLASS: PREIMMUNE ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
CARDIOVASCULAR	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
ARRHYTHMIA, OTHER	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
MUSCULOSKELETAL	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	2 (10.5%)
ARTHRALGIA (OTHER)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	1 (5.3%)
MYALGIA	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	2 (10.5%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)	2 (10.5%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
CONJUNCTIVITIS	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
PERSONS WITH COMPLAINTS	4 (21.1%)	5 (26.3%)	4 (21.1%)	2 (10.5%)	3 (15.8%)	2 (10.5%)	8 (42.1%)
PERSONS WITH NO COMPLAINTS	15 (78.9%)	14 (73.7%)	15 (78.9%)	17 (89.5%)	16 (84.2%)	17 (89.5%)	11 (57.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
LOT NUMBER : CM126
DOSE : 10 MCG
PATIENT CLASS: PREIMMUNE ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (21 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	8 (42.1%)	8 (44.4%)	8 (42.1%)	8 (42.1%)	9 (47.4%)	11 (57.9%)			8 (42.1%)
< 99	9 (47.4%)	8 (44.4%)	9 (47.4%)	10 (52.6%)	9 (47.4%)	8 (42.1%)			7 (36.8%)
99 - 99.9	2 (10.5%)	1 (5.6%)	1 (5.3%)	0 (0.0%)	1 (5.3%)	0 (0.0%)			3 (15.8%)
100 - 100.9	0 (0.0%)	1 (5.6%)	1 (5.3%)	1 (5.3%)	0 (0.0%)	0 (0.0%)			1 (5.3%)
TEMPERATURE TAKEN	19 (90.5%)	18 (85.7%)	19 (90.5%)	19 (90.5%)	19 (90.5%)	19 (90.5%)			19 (90.5%)
TEMPERATURE NOT TAKEN	2 (9.5%)	3 (14.3%)	2 (9.5%)	2 (9.5%)	2 (9.5%)	2 (9.5%)			2 (9.5%)

Table 6
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
LOT NUMBER : CM126
DOSE : 5 MCG
PATIENT CLASS: PREIMMUNE ADULTS (Previously vaccinated with yeast recombinant hepatitis B vaccine)

CLINICAL COMPLAINTS	TOTAL VACCINEES (11 PATIENTS) - DOSE 1 DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	4 (40.0%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (40.0%)
SORENESS	4 (40.0%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (40.0%)
SYSTEMIC	0 (0.0%)	1 (10.0%)	1 (10.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)		1 (10.0%)
INTEGUMENTARY SYSTEM	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (10.0%)
PRURITIS/ITCHING	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (10.0%)
RESPIRATORY	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)		1 (10.0%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)		1 (10.0%)
PERSONS WITH COMPLAINTS	4 (40.0%)	2 (20.0%)	2 (20.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)		4 (40.0%)
PERSONS WITH NO COMPLAINTS	6 (60.0%)	8 (80.0%)	8 (80.0%)	10 (100.0%)	9 (90.0%)	10 (100.0%)		6 (60.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 6 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
LOT NUMBER : CM126
DOSE : 10 MCG
PATIENT CLASS: PREIMMUNE ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (14 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (14.3%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
SORENESS	2 (14.3%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
PERSONS WITH COMPLAINTS	2 (14.3%)	1 (7.1%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (21.4%)
PERSONS WITH NO COMPLAINTS	12 (85.7%)	13 (92.9%)	13 (92.9%)	14 (100.0%)	14 (100.0%)	14 (100.0%)	11 (78.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 7

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
LOT NUMBER : CH126
DOSE : 5 MCG
PATIENT CLASS: PREIMMUNE ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (11 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	7 (70.0%)	9 (90.0%)	10 (100.0%)	10 (100.0%)	10 (100.0%)	10 (100.0%)		7 (70.0%)
< 99	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (10.0%)
99 - 99.9	2 (20.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (20.0%)
TEMPERATURE TAKEN	10 (90.9%)	10 (90.9%)	10 (90.9%)	10 (90.9%)	10 (90.9%)	10 (90.9%)		10 (90.9%)
TEMPERATURE NOT TAKEN	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	1 (9.1%)		1 (9.1%)

Table 7 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0813
TREATMENT :
LOT NUMBER : CM126
DOSE : 10 MCG
PATIENT CLASS: PREIMMUNE ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (14 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	13 (92.9%)	13 (92.9%)	12 (85.7%)	12 (85.7%)	12 (85.7%)	12 (85.7%)		12 (85.7%)
< 99	1 (7.1%)	1 (7.1%)	1 (7.1%)	2 (14.3%)	2 (14.3%)	2 (14.3%)		1 (7.1%)
99 - 99.9	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (7.1%)
TEMPERATURE TAKEN	14 (100.0%)	14 (100.0%)	14 (100.0%)	14 (100.0%)	14 (100.0%)	14 (100.0%)		14 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

IMMUNOGENICITY OF RECOMBINANT YEAST HEPATITIS B VACCINE

SIR,—In Dr Jilg and colleagues' study (Nov 24, p 1174) in thirty recipients of recombinant hepatitis B vaccine "the immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels". They compared a 10 µg dose of recombinant vaccine with a 20 µg dose of plasma-derived vaccine.

As indicated in the table, our results in a similar study in one hundred and seven seronegative health professionals, 21–30 years of age, revealed essentially the same immune response in recipients of 5 µg and 10 µg doses of recombinant yeast hepatitis B vaccine when compared with a comparable group who received 20 µg doses of plasma-derived vaccine.

Valid conclusions cannot be drawn from studies in thirty or a hundred vaccinees. More extensive studies will be required to evaluate anti-HBs response and its persistence in recipients of recombinant hepatitis B vaccine. In the meantime, our initial results are encouraging.

NYU Medical Center,
New York, NY 10016, USA

MORTON DAVIDSON
SAUL KRUGMAN

SEROCONVERSION RATES AND GEOMETRIC MEAN TITRES (GMT) OF SERONEGATIVE INDIVIDUALS, ADULTS GIVEN RECOMBINANT OR PLASMA-DERIVED HEPATITIS B VACCINE

	Recombinant vaccine†						Plasma derived (20 µg)‡	
	10 µg			5 µg				
Time* (mo)	Anti-HBs response	mIU/ml (GMT)	S/N ratio (GMT)	Anti-HBs response	mIU/ml (GMT)	S/N ratio (GMT)	Anti-HBs response	S/N ratio (GMT)
0	..	..	..	..	..	..	..	..
1	22/51 (43%)	42	10	21/56 (37%)	95	35	18/47 (38%)	20
2	48/51 (94%)	88	37	51/56 (91%)	60	38	34/47 (72%)	37
3	50/51 (98%)	149	52	52/56 (93%)	120	51	45/47 (96%)	70
6	49/50 (98%)	321	63	53/56 (95%)	104	42	44/47 (94%)	84
7/8	45/46 (98%)	1011	104	49/50 (98%)	839	124	46/47 (98%)	141

*Vaccine given at 0, 1, and 6 months. Follow-up to 7 months (plasma derived) or 8 months (recombinant). †[illegible]. ‡[illegible] 751.

Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985; 1:108-9.

RECOMBINANT YEAST HEPATITIS B VACCINE: SIDE EFFECTS AND IMMUNOGENICITY COMPARED WITH PLASMA-DERIVED HEPATITIS B VACCINE.

Morton Davidson and Saul Krugman
NYU Medical Center, New York, N.Y.

A yeast recombinant hepatitis B vaccine (Merck Lot no. 972/C-K444) was evaluated in 107 seronegative health professionals, 21-30 years of age. The clinical and antibody responses were compared with the results of a previous similar study using a plasma-derived hepatitis B vaccine (Merck Lot no. 751).

The vaccine was administered at 0, 1 and 6 months to the following three groups: 1) 51 adults who received a 10 mcg dose of recombinant vaccine; 2) 56 adults who received a 5 mcg dose of recombinant vaccine, and 3) 47 adults who received a 20 mcg dose of plasma-derived vaccine. The three groups included medical students, house staff, and nurses who were of comparable age and sex.

Results

Side effects were negligible in all three groups. They consisted of transient, local soreness at the site of the inoculation in about 25% of the vaccinees in each group. No systemic reactions were observed.

The seroconversion rates and geometric mean titers are summarized in the Table. The results are essentially the same for all three groups. Under the conditions of this study the 5 mcg and 10 mcg doses of recombinant hepatitis B vaccine were just as immunogenic as a 20 mcg dose of plasma-derived hepatitis B vaccine.

Comment

A recent report by Jilg et al (Lancet 1984; 2:1174-75) described a similar study in 30 seronegative medical students and laboratory workers whose age and sex were comparable to those in our groups. They stated that "the immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels." Our results in 107 similar recipients of the recombinant hepatitis B vaccine do not support this conclusion.

It is obvious that valid conclusions cannot be drawn from studies involving either 30 or 100 vaccinees. More extensive studies will be required to determine anti-HBs response and its persistence in recipients of recombinant hepatitis B vaccines.

Davidson M, Krugman S. Recombinant yeast hepatitis B vaccine: Side effects and immunogenicity compared with plasma-derived hepatitis B vaccine. Submitted for publication to Hepatitis Scientific Memoranda.

TABLE

Seroconversion Rates and Geometric Mean Titers of Seronegative Adults Who Received Recombinant Yeast Hepatitis B Vaccine (Merck Lot No. 972/C-K444) or Plasma-Derived Hepatitis B Vaccine (Merck Lot No. 751).

Time Interval (Months)	Recombinant Hepatitis B Vaccine					
	10 mcg dose			5 mcg dose		
	anti-HBs response	mIU/ml GMT	S/N Ratio GMT	anti-HBs response	mIU/ml GMT	S/N Ratio GMT
0	-	-	-	-	-	-
1	22/51 (43%)	42	19	21/56 (37%)	55	25
2	48/51 (94%)	88	37	51/56 (91%)	69	38
3	50/51 (98%)	145	52	52/56 (93%)	128	51
6	49/50 (98%)	321	63	53/56 (95%)	184	42
8	45/46 (98%)	1911	164	49/50 (98%)	839	124

Vaccine given at 0, 1 and 6 months.
Age Range: 21 - 30 years

Time Interval (Months)	Plasma-Derived Hepatitis B Vaccine 20 mcg dose	
	anti-HBs response	S/N Ratio GMT
0	-	-
1	18/47 (38%)	20
2	34/47 (79%)	37
3	45/47 (96%)	79
6	44/47 (94%)	94
7	46/47 (98%)	141

Vaccine given at 0, 1 and 6 months.
Age range: 21 - 30 years

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 817
PURPOSE:	To evaluate antibody and clinical responses to 10 mcg doses of yeast recombinant vaccine among: 1. preimmune healthy adults 2. healthy adults immunized previously with plasma-derived vaccine who were nonresponders (anti-HBs negative.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #972/C-K444 (10 mcg/ml)
PRIMARY INVESTIGATOR:	Robert P. Bishop, M.D. Director, Health Services Merck & Co., Inc. West Point, PA 19486
SECONDARY INVESTIGATOR(S):	Edgardo P. Avancena, M.D. Joseph C. Rogers, M.D. Joseph P. Romano, M.D. Merck & Co., Inc. West Point, PA & Rahway, NJ
STUDY LOCATION:	Merck & Co., Inc. West Point, PA 19486 Merck & Co., Inc. Rahway, NJ 07065
DATE INITIATED:	March 21, 1984
DATE COMPLETED:	In progress

2547I/cfs
12/20/85

Study B17

STUDY POPULATION: The study population will consist of 40-50 healthy adults of either sex (excluding pregnant females), who are employees of Merck & Co., Inc. Half of the population will consist of persons with pre-existing hepatitis B antibody which may be either naturally acquired or plasma vaccine induced. The other half will consist of persons who have been vaccinated with plasma vaccine but failed to develop detectable antibody to hepatitis B. All participants must be negative for anti-HBc and HBsAg, and have a normal ALT level.

PROCEDURE: Study participants are allocated to one of two regimens as shown below. All injections are intramuscular.

Group	No.	Dose	Time of Vaccination
1. Preimmune	5	1.0 ml (10 mcg)	0
2. Nonresponders	4	1.0 ml (10 mcg)	0, 1 & 6 mos.

Vaccinees are asked to record their temperature daily for five days after each injection and also to record any local or systemic complaints they may have during this period.

A blood specimen (10-15 ml) is obtained from each participant approximately 2 weeks before the first vaccination. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12 and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, yeast antibody and ALT. Those with anti-HBs titers $\geq$ mIU/ml may be tested for the proportions of anti-a and anti-d activity.

Study 817

RESULTS:

PREIMMUNE ADULTS:

10 mcg Lot #972/C-K444 at time 0

1. Number Vaccinated: 5

2. Serologic Results:

All five vaccinees showed a large boost in anti-HBs following vaccination. Table 1 shows individual anti-HBs responses for up to 12 months of follow-up.

3. Clinical Complaints:

Clinical follow-up data are available for all 5 vaccinees for the five days of follow-up following vaccination. Specific complaints and maximum temperatures reported during that time are provided in Tables 2 and 3.

Type of Complaint	Frequency in %
Injection Site	20 (1/5)
Systemic	0 (0/5)

There were no serious or alarming adverse reactions attributable to vaccine.

Study 817

Table 1

Antibody Responses Among Preimunne Adults Following Vaccination with a Single 10 mcg Dose of Yeast Recombinant Hepatitis B Vaccine Lot #972/C-K444 in Study 817

Case #	Pre	Anti-HBs (mIU/ml) 1 Mo.	3 mo.	6 mo.	12 mo.
(b) (6)	4*	15.2	105.7	150.0	26.5
	4*	810.9	404.3	99.5	52.5
	8*	475	456.1	355.72	62.3
	11.5	---	350.3	50.7**	
	4*	1734.4	2063.4	1119.3	318.6
GMT (mIU/ml)	5.7	317.4	402.5	197.6	72.5

*Approximate mIU/ml (b) (4) titer ÷ 4)
**Late bleeding at 8 months.

2547I-4/cfs
12/20/85

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: PREIMMUNE ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (5 PATIENTS) - DOSE 1 — DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	1 (20.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (20.0%)
SORENESS	1 (20.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (20.0%)
PERSONS WITH COMPLAINTS	1 (20.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (20.0%)
PERSONS WITH NO COMPLAINTS	4 (80.0%)	4 (80.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)		4 (80.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0817
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: PREIMMUNE ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (5 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	5 (100.0%)	5 (100.0%)	5 (100.0%)	4 (100.0%)	5 (100.0%)	5 (100.0%)		5 (100.0%)
TEMPERATURE TAKEN	5 (100.0%)	5 (100.0%)	5 (100.0%)	4 (80.0%)	5 (100.0%)	5 (100.0%)		5 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

CHRONIC CARRIERS

Chronic Carriers - Population Summary

One study (#854) has been initiated to determine the safety of the vaccine for persons who are chronic carriers of HBsAg and to determine whether vaccination can eliminate the carrier state in these persons. Eighteen adult chronic carriers (positive for HBsAg for at least one year) have been scheduled to receive six 10 mcg injections of yeast recombinant hepatitis B vaccine at monthly intervals. Three participants have received all six injections; eighteen have received at least four injections. The study continues in progress.

To date, none of the chronic carriers has become negative for HBsAg. The vaccine has been well tolerated. No serious adverse experiences attributable to vaccine have been reported.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 854.
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine in the following adult populations: 1. Chronic Carriers of HBsAg 2. Healthy Hyporesponders to Plasma-Derived Vaccine. 3. Healthy Nonresponders to Plasma-Derived Vaccine. 4. Healthy Transient Responders to Plasma-Derived Vaccine.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #979/C-K564 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Jules Dienstag, M.D. Associate Professor of Medicine Gastrointestinal Unit Massachusetts Gen. Hosp. Boston, MA 02114
SECONDARY INVESTIGATOR:	Eloise Watkins, R.N., M.P.H. Gastrointestinal Unit Mass. General Hosp. Fruit Street Boston, MA 02114 Lynn F. Butterly, M.D. Clinical & Research Fellow Gastrointestinal Unit Mass. General Hosp. Boston, MA 02114
STUDY LOCATION:	Massachusetts General Hospital Fruit Street Boston, MA 02114
DATE INITIATED:	October 14, 1984
DATE COMPLETED:	In progress

Study 854

STUDY POPULATIONS: The study population will consist of adults of either sex (excluding pregnant women) who can be classified into one of the following groups:

Group	Number of Subjects	Qualifications
Carriers	10-15	Chronic carrier of HBsAg for at least one year, with no signs or symptoms of chronic liver disease, and a stable ALT level less than 3 times the upper limit of normal.
Hypo-responders	15-20	Healthy adults who have had only a low level anti-HBs response (positive titer obtained in at least 2 successive bleedings) to a complete 3 injection regimen of plasma derived hepatitis B vaccine. [maximum antibody titer 8-36 when measured in (b) (4) RIA units, 2.1-9.9 when measured in terms of S/N ratio, or <10 mIU/ml]
Non-responders	15-20	Healthy adults who had a single post-vaccination blood sample with an anti-HBs titer in the range S/N = 2.1-9.9 followed by additional samples all with S/N less than 2.1 as well as persons whose post-vaccination blood samples all had anti-HBs titers of S/N less than 2.1 after receiving a 3 injection series of plasma derived hepatitis B vaccine.
Transient Responders	10-15	Healthy adults who had at least one blood sample with an anti-HBs titer of S/N $\geq$10 following a 3 injection series of plasma derived hepatitis B vaccine but have subsequently lost antibody (S/N <2.1).

Study 854

PROCEDURE:

Prior to vaccination, each participant will be screened for HBsAg, anti-HBc, anti-HBs and ALT level. A serum pregnancy test will also be performed for all women of childbearing age. Vaccine is administered intramuscularly according to the following schedule.

Group	Vaccination Regimen
Carriers	1.0 ml (10 mcg HBsAg) at time 0, 1, 2, 3, 4 and 5 months.
Hyporesponders	1.0 ml (10 mcg HBsAg) at time 0
Nonresponders	1.0 ml (10 mcg HBsAg) at time 0, 1 and 6 months.
Transient Responders	1.0 ml (10 mcg HBsAg) at time 0.

The vaccine recipients are asked to record their temperature for 5 days after each injection and to note any local or systemic complaints. Unexpected or serious reactions will be reported to the study physician immediately.

Follow-up blood samples will be obtained from carriers monthly for 6 months and at 9 and 12 months; from hyporesponders and transient responders at 1, 3, 6, 9, 12 and 24 months and; from nonresponders at 1, 2, 3, 6, 9 months, and at 12 and 24 months from those who have seroconverted by 9 months. Samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT by Dr. Dienstag. Samples may also be assayed at MSDRL for yeast antibody and for the proportions of anti-HBs specific for the a and d determinants of HBsAg.

Study 854

RESULTS:

CARRIERS

10 mcg Lot #979/C-K564 at 0, 1, 2, 3, 4, and 5 months.

1. Number Vaccinated:

Injection No.					
1	2	3	4	5	6
18	18	18	18	12	3

2. Serologic Results:

None of the carriers has yet become negative for HBsAg.

3. Clinical Complaints:

Clinical follow-up data are available for 18 participants after injections one through four, 12 participants after injection five, and for 2 subjects after injection six. The overall frequencies of complaints are presented below:

Complaint	Frequency in % by Injection					
	1	2	3	4	5	6
Injection Site	22(4/18)	17(3/18)	22(4/18)	22(4/18)	8(1/12)	0(0/2)
Systemic	17(3/18)	11(2/18)	17(3/18)	11(2/18)	17(2/12)	50(1/2)

Refer to Table 1 for listings of specific complaints by injection number. Maximum temperature data are provided in Table 2.

There were no serious or alarming reactions attributable to vaccine.

Table 1

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	3 (16.7%)	2 (11.1%)	2 (11.1%)	2 (11.1%)	0 (0.0%)	0 (0.0%)		4 (22.2%)
SORENESS	3 (16.7%)	2 (11.1%)	2 (11.1%)	2 (11.1%)	0 (0.0%)	0 (0.0%)		4 (22.2%)
HEMATOMA	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
SYSTEMIC	1 (5.6%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.6%)		3 (16.7%)
WHOLE BODY/GENERAL	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
FATIGUE/WEAKNESS	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.6%)		2 (11.1%)
DIARRHEA	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	1 (5.6%)		1 (5.6%)
DIMINISHED APPETITE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.9%)	0 (0.0%)		1 (5.6%)
PERSONS WITH COMPLAINTS	4 (22.2%)	4 (22.2%)	2 (11.1%)	2 (11.1%)	1 (5.9%)	1 (5.6%)		7 (38.9%)
PERSONS WITH NO COMPLAINTS	14 (77.8%)	14 (77.8%)	16 (88.9%)	16 (88.9%)	16 (94.1%)	17 (94.4%)		11 (61.1%)

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	2 (11.1%)	3 (16.7%)	2 (11.1%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	3 (16.7%)
SORENESS	1 (5.6%)	2 (11.1%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
TENDERNESS	1 (5.6%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
SWELLING	2 (11.1%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
SYSTEMIC	1 (5.6%)	2 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	2 (11.1%)
WHOLE BODY/GENERAL	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
SWEATING	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (5.6%)
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	1 (5.6%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
OTHER	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
NERVOUS SYSTEM	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
VERTIGO/DIZZINESS	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
PERSONS WITH COMPLAINTS	3 (16.7%)	5 (27.8%)	2 (11.1%)	1 (5.6%)	0 (0.0%)	1 (5.6%)		5 (27.8%)
PERSONS WITH NO COMPLAINTS	15 (83.3%)	13 (72.2%)	16 (88.9%)	17 (94.4%)	18 (100.0%)	17 (94.4%)		13 (72.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	3 (16.7%)	2 (11.1%)	2 (11.1%)	1 (5.6%)	0 (0.0%)	0 (0.0%)		4 (22.2%)
SORENESS	2 (11.1%)	1 (5.6%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)		3 (16.7%)
TENDERNESS	1 (5.6%)	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
NODULE FORMATION	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
SYSTEMIC	2 (11.1%)	1 (5.6%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	1 (5.6%)		3 (16.7%)
WHOLE BODY/GENERAL	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)		2 (11.1%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
HEADACHE	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
INFECTIOUS SYNDROMES	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
INFLUENZA, NOS	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.6%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)		1 (5.6%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)		1 (5.6%)

00993

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
NAUSEA	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
OTHER	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
PERSONS WITH COMPLAINTS	5 (27.8%)	3 (16.7%)	2 (11.1%)	2 (11.1%)	0 (0.0%)	1 (5.6%)	5 (27.8%)
PERSONS WITH NO COMPLAINTS	13 (72.2%)	15 (83.3%)	16 (88.9%)	16 (88.9%)	18 (100.0%)	17 (94.4%)	13 (72.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 4						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	3 (16.7%)	4 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (22.2%)
SORENESS	2 (11.1%)	3 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (16.7%)
TENDERNESS	1 (5.6%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
SYSTEMIC	1 (5.6%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
WHOLE BODY/GENERAL	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
FATIGUE/WEAKNESS	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
ITCHING, FACIAL	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
OTHER	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
NERVOUS SYSTEM	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
VERTIGO/DIZZINESS	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)
PERSONS WITH COMPLAINTS	4 (22.2%)	4 (22.2%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (27.8%)

56600

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (18 PATIENTS) - DOSE 4						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	14 (77.8%)	14 (77.8%)	17 (94.4%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	13 (72.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (12 PATIENTS) - DOSE 5						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
SORENESS	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
SYSTEMIC	1 (8.3%)	2 (16.7%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	2 (16.7%)
WHOLE BODY/GENERAL	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
FATIGUE/WEAKNESS	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
INFECTIOUS SYNDROMES	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
INFLUENZA, NOS	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	1 (8.3%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (8.3%)
OTHER	0 (0.0%)	1 (8.3%)	1 (8.3%)	0 (0.0%)	1 (8.3%)	1 (8.3%)	1 (8.3%)
PERSONS WITH COMPLAINTS	1 (8.3%)	2 (16.7%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	2 (16.7%)
PERSONS WITH NO COMPLAINTS	11 (91.7%)	10 (83.3%)	11 (91.7%)	11 (91.7%)	11 (91.7%)	11 (91.7%)	10 (83.3%)

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (12 PATIENTS) - DOSE 5						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 1 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

CLINICAL COMPLAINTS	TOTAL VACCINEES (3 PATIENTS) - DOSE 6						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
SYSTEMIC	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)
RESPIRATORY	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
EARACHE	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
PERSONS WITH COMPLAINTS	0 (0.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)
PERSONS WITH NO COMPLAINTS	2 (100.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	1 (50.0%)	2 (100.0%)	1 (50.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (18 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	15 (83.3%)	17 (94.4%)	18 (100.0%)	16 (88.9%)	17 (94.4%)	18 (100.0%)		12 (66.7%)
99 - 99.9	3 (16.7%)	1 (5.6%)	0 (0.0%)	2 (11.1%)	0 (0.0%)	0 (0.0%)		5 (27.8%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)		1 (5.6%)
TEMPERATURE TAKEN	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)		18 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (18 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	16 (88.9%)	18 (100.0%)	16 (88.9%)	17 (94.4%)	18 (100.0%)	17 (94.4%)			13 (72.2%)
99 - 99.9	2 (11.1%)	0 (0.0%)	2 (11.1%)	1 (5.6%)	0 (0.0%)	1 (5.6%)			5 (27.8%)
TEMPERATURE TAKEN	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)			18 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 2 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (18 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	15 (83.3%)	16 (88.9%)	15 (83.3%)	15 (83.3%)	17 (94.4%)	15 (83.3%)			9 (50.0%)
99 - 99.9	3 (16.7%)	2 (11.1%)	2 (11.1%)	3 (16.7%)	1 (5.6%)	3 (16.7%)			8 (44.4%)
100 - 100.9	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (5.6%)
TEMPERATURE TAKEN	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)			18 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0 (0.0%)

Table 2 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (18 PATIENTS) - DOSE 4							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	0 (0.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
< 99	17 (94.4%)	16 (88.9%)	15 (83.3%)	17 (94.4%)	17 (94.4%)	18 (100.0%)		14 (77.8%)
99 - 99.9	1 (5.6%)	2 (11.1%)	2 (11.1%)	1 (5.6%)	1 (5.6%)	0 (0.0%)		4 (22.2%)
TEMPERATURE TAKEN	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)	18 (100.0%)		18 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0859
TREATMENT :
LOT NUMBER : CR564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (12 PATIENTS) - DOSE 5							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	9 (75.0%)	10 (83.3%)	9 (75.0%)	9 (81.8%)	10 (83.3%)	9 (75.0%)		6 (50.0%)
99 - 99.9	3 (25.0%)	1 (8.3%)	2 (16.7%)	1 (9.1%)	1 (8.3%)	3 (25.0%)		4 (33.3%)
100 - 100.9	0 (0.0%)	1 (8.3%)	1 (8.3%)	1 (9.1%)	0 (0.0%)	0 (0.0%)		1 (8.3%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)		1 (8.3%)
TEMPERATURE TAKEN	12 (100.0%)	12 (100.0%)	12 (100.0%)	11 (91.7%)	12 (100.0%)	12 (100.0%)		12 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0854
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: CHRONIC CARRIERS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (3 PATIENTS) - DOSE 6							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)		2 (100.0%)
TEMPERATURE TAKEN	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)		2 (66.7%)
TEMPERATURE NOT TAKEN	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)		1 (33.3%)

EFFICACY

EFFICACY SUMMARY

Hepatitis B vaccine derived from the plasma of chronically infected individuals was previously shown to be effective in preventing hepatitis B infection among adult male homosexuals and staff members in dialysis units. This vaccine also proved to be effective in preventing chronic hepatitis B infection among infants born to mothers who are positive for both HBsAg and HBeAg.

The efficacy studies involving plasma-derived hepatitis B vaccine demonstrated that the presence of anti-HBs equated with protection against hepatitis B. Consequently, the high seroconversion rates observed for recipients of the yeast recombinant hepatitis B vaccine (e.g. 96% of healthy adult vaccinees develop anti-HBs titers of mIU/ml $\geq$10) suggest that these individuals should be protected against hepatitis B. Ongoing in vitro studies to demonstrate the equivalence of anti-HBs raised to yeast recombinant hepatitis B vaccine and plasma-derived hepatitis B vaccine are described in Appendix 1.

The feasibility of conducting efficacy studies of the yeast recombinant hepatitis B vaccine in various populations was considered. Such studies are reasonable only in populations known to experience relatively high rates of infection. Control groups are also a problem. Since a proven preventive therapy (plasma-derived hepatitis B vaccine) is now available in most parts of the world, it is no longer ethical to conduct a study with untreated controls. In some instances, notably with infants of Asian mothers who are positive for HBsAg and HBeAg, there have been very high rates of infection documented among untreated individuals, and it is reasonable to use these rates as a basis for estimating protective efficacy in contemporary studies lacking untreated controls. However, historical data on the incidence of infection in various candidate adult population are no longer applicable. Rates of hepatitis B infection are probably declining among homosexuals, due to changed sexual practices since the AIDS epidemic. The incidence of hepatitis B infection has also been declining for a number of years in dialysis units. We have concluded that an efficacy study of the yeast recombinant hepatitis B vaccine in an adult population is not feasible. However, studies involving infants born to mothers who are carriers of the hepatitis B virus are feasible.

Four studies have been initiated to evaluate the efficacy of yeast recombinant hepatitis B vaccine in preventing chronic hepatitis B infection in infants born to mothers who carry the virus:

Study	Study Population/Regimen
862	Healthy infants born to mothers who are positive for HBsAg and either positive or negative for HBeAg receive a single 0.5 ml injection of HBIG at birth following by 5 mcg doses of yeast recombinant hepatitis B vaccine or 10 mcg doses of plasma-derived hepatitis B vaccine at 0, 1, and 6 months. The study is being conducted in Hong Kong.

Study	Study Population/Regimen
864	Healthy infants born to mothers of Asian descent, who are positive for both HBsAg and HBeAg, receive a single 0.5 ml injection of HBIG at birth following by 5 mcg doses of the yeast recombinant hepatitis B vaccine at 0 (within the first few days of birth), 1, and 6 months. The study is being conducted in the United States.
878	Healthy infants born to mothers who are positive for both HBsAg and HBeAg receive either a single 0.5 ml injection of HBIG at birth followed by 5 mcg doses of the yeast recombinant hepatitis B vaccine at 0 (within 12 hours of birth), 1, and 6 months, or vaccine alone. The study is being conducted in China.
892	Healthy infants born to mothers who are positive for both HBsAg and HBeAg receiving yeast recombinant hepatitis B vaccine (5 or 10 mcg dose) or plasma-derived hepatitis B vaccine (10 or 20 mcg dose) at 0 (within 12 hours of birth), 1, and 6 months. This study is being conducted in China.

A total of 412 infants have been enrolled to date in the four studies, 289 of these in groups receiving the yeast recombinant hepatitis B vaccine. Postvaccination follow-up data are currently available from studies 862 and 864 only. Comments regarding efficacy will be restricted to infants of mothers positive for both HBsAg and HBeAg who are receiving passive-active prophylaxis (HBIG at birth plus 5 mcg doses of yeast recombinant hepatitis B vaccine at 0, 1, and 6 months). The numbers of infants who have received the first, second, and third injections of vaccine together with their antigen status at various times are tabulated below:

Number Vaccinated	Study 862	Study 864	Both Studies
First Injection	40	134	174
Second Injection	37	120	157
Third Injection	12	61	73

Proportion HBsAg Positive	Study 862	Study 864	Both Studies
Birth	4/40	4/134	8/174
3 Months	1/25	3/85	4/110
6 Months	0/12	1/47	1/59
9 Months	---	0/19	0/19

Eight (8) infants were positive for HBsAg at birth. Four (4) of the eight have been tested at 3 months and all were still positive for HBsAg. One of these infants has been followed through 6 months, is still HBsAg positive, and is now classified as a chronic carrier. The infants who are positive for

HBsAg at birth may have been infected in utero and such infections cannot be prevented through postnatal vaccination. To date, there have been no persistent infections appearing after birth.

The efficacy of HBIG and yeast recombinant vaccine in preventing chronic hepatitis B infection may be estimated with the following formula:

$$\% \text{ Efficacy} = \left[1 - \left(\frac{\text{Incidence of infection in vaccinated}}{\text{Incidence of infection in unvaccinated}}\right)\right] \times 100$$

The single chronic carrier among the vaccinated infants followed for six months represents an incidence of 1.7%. A number of previous studies have estimated the incidence of chronic infection among untreated infants born to Asian mothers positive for HBsAg and HBeAg at 60-92%.[1-10] In addition, the investigators in Study 864 have recently obtained follow-up serology on 13 children born in the United States during the past several years to mothers positive for HBsAg and HBeAg who did not receive HBIG or hepatitis B vaccine. Nine of the 13 children (69.2%) had become positive for HBsAg. This rate is similar to those cited above and was used as our estimate for the incidence of chronic infection in unvaccinated infants. Estimates of the efficacy of the HBIG-yeast recombinant vaccine regimen at 6 and 9 months are tabulated below:

Efficacy in %	Study 862	Study 864	Both Studies
6 Months	100	97	98
9 Months	---	100	--

No serious adverse experiences related to vaccine have been reported. These data suggest that passive-active prophylaxis involving a single dose of HBIG and three 5 mcg doses of yeast recombinant hepatitis B vaccine is safe and will provide a high level of protection against chronic hepatitis B virus infection.

References:

1. Beasley, R.P., Trepo, C., Stevens, C.E., et al.: The e Antigen and Vertical Transmission of Hepatitis B Surface Antigen. Am. J. Epidemiol. 105:94-98, 1977.

2. Beasley, R.P., Lee, G. C-Y., Roan, C-H., et al.: Prevention of Perinatally Transmitted Hepatitis B Virus Infections with Hepatitis B Immune Globulin and Hepatitis B Vaccine. Lancet 2:1099-1102, 1983.

3. Chung, W.K., Yoo, J.Y., Sun, H.S., et al.: Prevention of Perinatal Transmission of Hepatitis B Virus: A Comparison Between the Efficacy of Passive and Passive-Active Immunization in Korea. J. Infect. Dis. 151:280-286, 1985.

4. Dr. M. Kane, CDC, personal communication.

5. Lo, K.J., Tsai, Y.T., Lee, S.D., et al.: Combined Passive and Active Immunization for Interruption of Perinatal Transmission of Hepatitis B Virus in Taiwan (Abst.), In Vyas, G.N., Dienstag, J.L., and Hoofnagle, J.H. (eds.), Viral Hepatitis and Liver Disease, Grune and Stratton. Orlando, 1984, pp. 679-680.

6. Oon, C.J., Chan, L., Goh, K.T., et al.: Epidemiology of Viral Hepatitis B in Singapore (Abst.), In Vyas, G.N., Dienstag, J.L., and Hoofnagle, J.H. (eds.), Viral Hepatitis and Liver Disease, Grune and Stratton. Orlando, 1984, p. 642.

7. Pongpipat, D., Suvatte, V., and Assateerawatts, A.: Hepatitis B Immune Globulin (HBIG): Efficacy in the Interruption of Vertical Transmission of Hepatitis B Virus (HBV) Carrier State. J. Med. Assoc. Thailand 66:49-53, 1983.

8. Shikata, T., Yano, M., Shiraki, K., et al.: Efficacy Trial of HBIG and Hepatitis B Vaccine for the Prevention of Perinatal HBV Transmission, In Vyas, G.N., Dienstag, J.L., and Hoofnagle, J.H. (eds.), Viral Hepatitis and Liver Disease, Grune and Stratton. Orlando, 1984, pp. 593-597.

9. Wong, V.C.W., Reesink, H.W., Reerink-Brongers, E.E., et al.: Prevention of the HBsAg Carrier State in Newborn Infants of Mothers Who Are Chronic Carriers of HBsAg and HBeAg by Administration of Hepatitis B Vaccine and Hepatitis-B Immunoglobulin. Lancet 1:921-926, 1984.

10. Xu, Z-Y., Liu, C-B., Francis, D.P., et al.: Prevention of Perinatal Acquisition of Hepatitis B Virus Carriage Using Vaccine: Preliminary Report of a Randomized, Double-Blind Placebo-Controlled and Comparative Trial. Pediatrics. 76:713-718, 1985.

EFFICACY

Study 862 - Hong King - Dr. E. K. Yeoh

The study population consists of two groups of healthy infants. Group 1 includes infants born to mothers positive for HBsAg and HBeAg. The infants receive HBIG at birth and then either 5 mcg injections of yeast recombinant hepatitis B vaccine lot C-K734 or 10 mcg injections of plasma-derived vaccine at 0, 1, and 6 months. Group 2 includes infants born to mothers positive for HBsAg and negative for HBeAg. These infants also receive HBIG at birth and then either yeast recombinant or plasma-derived vaccine according to the same dose and schedule as the infants in group 1. The initial injection of vaccine is administered within 12 hours after birth.

Twenty-eight infants in group 1 (HBeAg positive mothers) have received one dose of HBIG and the first injection of plasma-derived vaccine. Twenty-seven and eight of these infants have received the second and third injections of vaccine, respectively. Forty infants in group 1 have received one dose of HBIG and the first injection of yeast recombinant vaccine. Thirty-seven and five of these participants have been administered the second and third injections of vaccine, respectively.

At three months, 100% (19/19) of the infants (group 1) who received plasma-derived vaccine and 100% (24/24) of the infants who received yeast recombinant vaccine developed protective levels (mIU/ml $\geq$10) of anti-HBs (excludes infants HBsAg positive at birth).

Two infants (group 1) who received plasma-derived vaccine were HBsAg positive at birth. Both infants were negative for HBsAg at one month of follow-up. One infant, who was HBsAg negative at one and three months, tested HBsAg positive at six months. Her serum was anti-HBc IgM negative. Four infants who received yeast recombinant vaccine were HBsAg positive at birth. At one month, two of these were negative for HBsAg and two of the infants remained positive. Three month serology data is available for one of the HBsAg positive infants. This subject remained positive at that time.

Eighty-five infants in group 2 (HBeAg negative mothers) have received one dose of HBIG and the first injection of plasma-derived vaccine. Seventy-nine and 18 of these have received the second and third injections, respectively. Seventy-five infants in group 2 have received one dose of HBIG and the first injection of yeast recombinant vaccine. Seventy-three and 15 of these infants have been administered the second and third injections, respectively.

At three months, 100% (42/42) of the infants (group 2) who received plasma-derived vaccine and 100% (41/41) of the infants who received yeast recombinant vaccine developed protective levels (mIU/ml $\geq$10) of anti-HBs (excludes infants HBsAg positive at birth).

Two infants who received plasma-derived vaccine were HBsAg positive at birth. They tested negative at one month. Another infant was positive for HBsAg at one month. Additional serology data are not available for this

Study 862 - Hong King - Dr. E. K. Yeoh (Cont.)

infant. Three additional infants, who were negative for HBsAg at one and three months, tested positive for HBsAg at six months. In two of these cases, the six month sera were anti-HBc IgM negative. All three infants seroconverted for anti-HBs by three months post-entry into the study.

Two infants (group 2) who received yeast recombinant vaccine were HBsAg positive at birth. Both infants were negative at one month. An additional infant, who was HBsAg negative at one and three months, tested HBsAg positive at six months. The six month serum was anti-HBc IgM negative. The infant seroconverted for anti-HBs by three months post-entry into the study.

No serious or alarming adverse experiences related to vaccine have been reported. The study continues in progress.

Study 864 - New York, NY - Dr. C. Stevens

Healthy infants born to women of Asian descent who are positive for HBsAg and HBeAg, are enrolled in Study 864. The study is designed to evaluate rates of chronic hepatitis B antigenemia in infants at extremely high risk of infection. The infants are scheduled to receive one dose of HBIG within the first few hours of birth. Yeast recombinant vaccine (5 mcg injections) lot C-K732 is administered within the first few days after birth and at one and six months of age.

One hundred thirty-four infants have received one dose of HBIG and the first injection of vaccine. One hundred twenty and 61 infants have been administered the second and third injections of vaccine, respectively. All of 46 antigen negative infants followed for 6 months had developed anti-HBs (S/N $\geq$2.1).

Four infants were positive for HBsAg at birth. One of these has been followed for 1 month only and remains positive. Three of the infants have been followed for at least 3 months and were still antigen positive. One of the three has been followed for 6 months and is still positive.

No serious or alarming adverse experiences related to vaccine have been reported. Vaccination and follow-up continues in progress.

Study 878 - China - Dr. T. Sun

Healthy infants, born to women who are positive for HBsAg and HBeAg, are enrolled in Study 878. The first 30 infants entered in the study receive one dose of HBIG and a 5 mcg injection of vaccine lot C-K564 at birth. Subsequent 5 mcg injections of vaccine are administered at one and six months of age. All additional infants enrolled in the study receive no HBIG at birth and 5 mcg injections of vaccine according to the same schedule (0, 1 and 6 months).

Study 878 - China - Dr. T. Sun (Cont.)

Thirty infants have received one dose of HBIG and their first 5 mcg injection of vaccine. Serologic data are not yet available. There have been no reports of serious or alarming adverse experiences related to vaccine. Vaccination and follow-up continues in progress.

Study 892 - China - Dr. Z. H. Hu

The study population consists of healthy infants born to mothers who are positive for HBsAg and HBeAg. The study is designed to compare the efficacy of yeast recombinant vaccine and plasma-derived vaccine in preventing chronic hepatitis B antigenemia among infants at high risk for infection. Infants are randomly assigned to receive either 5 mcg or 10 mcg injections of recombinant vaccine lot C-K564 or 10 mcg or 20 mcg injections of plasma-derived vaccine lot 0027L. All injections are administered within 12 hours after birth and at one and six months of age.

Five infants have receive the first injection of vaccine in each dose and vaccine regimen. Serology data are not yet available. No serious adverse experiences related to vaccine have been reported. Vaccination and follow-up continues in progress.

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 862
PURPOSE:	To evaluate the efficacy of 5 mcg doses of the yeast recombinant hepatitis B vaccine, as compared with 10 mcg doses of plasma derived vaccine H-B-VAX, both given in conjunction with HBIG at birth in preventing chronic hepatitis B infection among: 1. Infants born to mothers positive for HBsAg and HBeAg. 2. Infants born to mothers positive for HBsAg and Negative for HBeAg.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 987/C-K734 H-B-VAX, Plasma Derived Hepatitis B Vaccine Lot 1032K Lot 2455J Lot 0027L Lot 1507J Hep-B-Gammagee Lot 0031L Lot 1120K
PRIMARY INVESTIGATOR:	E. K. Yeoh, M.D., B.S., M.R.C.P. Consultant Physician Medical "A" Unit Queen Elizabeth Hospital Kowloon, Hong Kong
SECONDARY INVESTIGATORS:	W. K. Chang, M.P., B.S., F.R.C. Path. Consultant Microbiologist Queen Mary Hospital Hong Kong Patricia Ip, M.B., B.S., M.R.C.P. Consultant Pediatrician United Christian Hospital Kowloon, Hong Kong

Study B62

SECONDARY INVESTIGATORS: (Contd)	Enid Chan, M.B., B.S., F.R.C.O.G. Consultant Obstetrician United Christian Hospital Kowloon, Hong Kong K. H. Chan, M.B., B.S., M.R.C.P. Consultant Pediatrician Caritas Medical Centre Kowloon, Hong Kong Charles Fung, M.D., B.S., M.R.C.O.G. Consultant Obstetrician Caritas Medical Center Kowloon, Hong Kong
STUDY LOCATION:	United Christin Hospital Hip Wo Street Kowloon, Hong Kong Caritas Medical Centre Wing Hong Street Kowloon, Hong Kong Queen Mary Hospital Pokfulam Road Hong Kong
DATE INITIATED:	February, 1985
DATE COMPLETED:	In progress.
STUDY POPULATION:	The 300 population consists of approximately 150 infants born to mothers who are positive for HBsAg and HBeAg and 150 infants born to mothers who are HBsAg positive and HBeAg negative. Other criteria for eligibility of the infants include the following: 1) Birth weight $\geq$2000 grams. 2) Apgar score $\geq$7 (taken at 5 mins.) 3) Good health

Study 862

PROCEDURE:

At the first prenatal visit, a blood specimen is obtained from prospective mothers and assayed for HBsAg. Women who are detected to be positive for HBsAg are recruited into the study. A second prenatal blood specimen will be obtained from women who wish to participate and assayed for HBsAg. A third blood specimen will be obtained from the women at parturition and assayed for HBsAg and HBeAg. Eligible infants born to HBsAg, HBeAg positive women will be randomized into Groups 1 and 2. Infants of HBsAg positive and HBeAg negative women will be randomized into Groups 3 and 4.

Infants in all four groups receive HBig and hepatitis B vaccine within 12 hours after birth in different sites (anterior thighs). The second and third doses of vaccine are administered one and six months after birth. Infants in Groups 1 and 3 receive recombinant vaccine (5 mcg) and those in Groups 2 and 4 received plasma-derived vaccine (10 mcg).

Blood specimens are obtained ffrom the infants prior to vaccination and 1, 3, 6, 9, 12, 18 and 24 months post initial injection. All specimens are assayed for HBsAg, and anti-HBs. Anti-HBc is also tested in the infants' sera at 18 months. A follow-up blood sample is also obtained from the mother at six months. Assays are performed by W. K. Chang using RIA kits.

RESULTS:

<u>HEALTHY INFANTS</u>

HEP-B-GAMMAGEE Lot #0031L or 1120K at time 0
5 mcg Lot 987/C-K734 at 0, 1, and 6 months
10 mcg H-B-VAX Lot #1032K, 2455J, 0027L or 1507J at 0, 1, and 6 months

A. HEALTHY INFANTS BORN TO HBsAg-POSITIVE and HBeAg-POSITIVE MOTHERS

1. <u>Number Vaccinated</u>:

Dose Level	Injection No. 1	2	3
5 mcg Recombinant	40	37	12
10 mcg Plasma	28	27	10

Study B62

RESULTS (Contd)

B. HEALTHY INFANTS BORN TO HBsAg-POSITIVE, HBeAg-NEGATIVE MOTHERS:

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
5 mcg Recombinant	75	73	30
10 mcg Plasma	85	79	25

2. Serologic Results:

A. Healthy Infants Born to HBsAg-Positive and HBeAg-Positive Mothers

At three months, 100% (24/24) of the infants who received yeast recombinant vaccine and 100% (19/19) of the infants who received plasma-derived vaccine developed protective levels (mIU/ml ≥10) of anti-HBs (excludes infants who were HBsAg-positive at birth). Table 1 gives the range of antibody titers observed at 1 and 3 months.

Four infants who received yeast recombinant vaccine were HBsAg-positive at birth. At one month, two of these were negative for HBsAg. Of the two who remained positive for HBsAg, one has been followed through three months and has remained positive at that time.

Two infants who received plasma-derived vaccine were HBsAg-positive at birth. Both were negative for HBsAg at one onth. One infant, who was negative for HBsAg at one and three months became positive at six months. The serum sample at that time was anti-HBc IgM-negative.

Refer to Figure 1 for a summary of HBsAg positivity in these infants.

RESULTS (Contd)

B. Healthy Infants Born to HBsAg-Positive, HBeAg-Negative Mothers

At three months, 100% (41/41) of the infants who received yeast recombinant vaccine and 100% (42/42) of those who received plasma-derived vaccine developed protective levels (mIU/ml $\geq$10) of anti-HBs (excluding infants HBsAg positive at birth). Table 2 gives the range of antibody titers observed at 1 and 3 months.

Two infants who received yeast recombinant vaccine were HBsAg-positive at birth. Both were negative at one month. An additional infant, who was HBsAg-negative at one and three months was HBsAg-positive at six months. The six month serum was anti-HBc IgM-negative. This infant seroconverted for anti-HBs by three months.

Two infants who received plasma-derived vaccine were HBsAg positive at birth. Both were negative at one month. Another infant tested positive for HBsAg at one month. Additional serology is not yet available for this infant. Three additional infants, who were negative for HBsAg at one and three months, were positive at six months. In two of these, the six month sera were anti-HBc IgM-negative. All three of these had seroconverted for anti-HBs at three months.

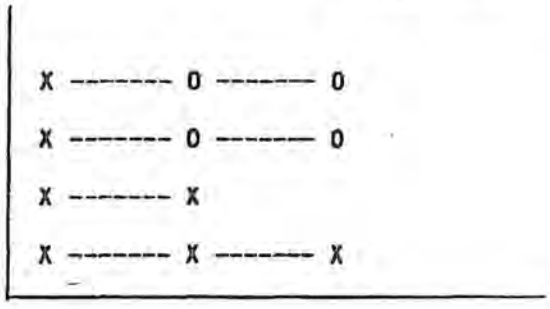
Figure 1 presents a summary of HBsAg positivity in these infants.

3. Clinical Complaints:

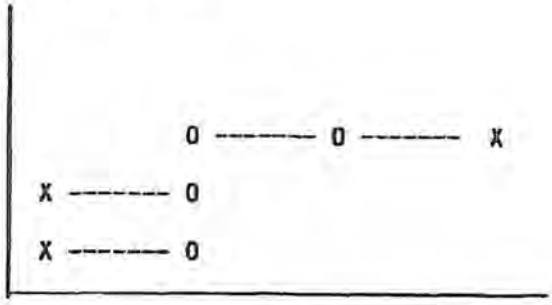
Currently, only a preliminary summary of clinical complaint data is available. The investigator has reported that there have been no clinical complaints among the recipients of either vaccine other than one infant who had a fever of 37.8°C on the day following the first injection. This infant received yeast recombinant vaccine.

Figure 1

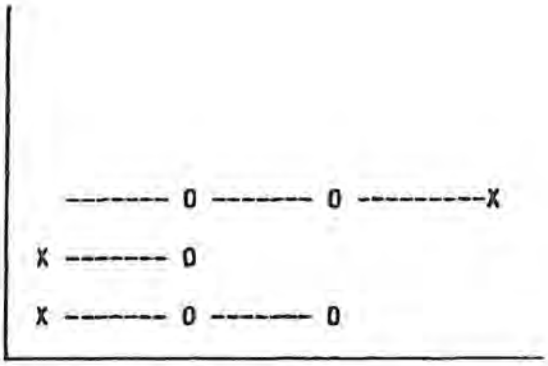
HBsAg Positive Infants in Study 862



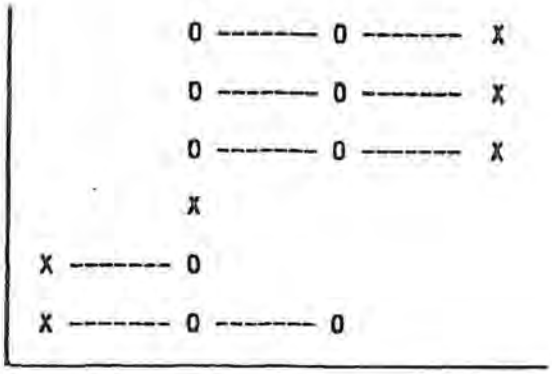
Infants born to HBeAg Positive Mothers who Received Yeast Recombinant Vaccine



Infants born to HBeAg Positive Mothers who Received Plasma-Derived Vaccine



Infants born to HBeAg Negative Mothers who Received Yeast Recombinant Vaccine



Infants born to HBeAg Negative Mothers who Received Plasma-Derived Vaccine

X = HBsAg positive
O = HBsAg negative

3246I/1
1/23/86

Table 1

Anti-HBs in HBsAg Negative Infants* Born to HBeAg Positive Mothers
Who Received Yeast Recombinant Vaccine

Infants Age at Testing	Number Tested	% (Proportion) Anti-HBs mIU/ml			
		2.1-10	11-49	50-99	≥100
1 month	31			3.2 (1/31)	96.7 (30/31)
3 months	24		41.7 (10/24)	41.7 (10/24)	16.7 (4/24)

*Excludes four who were HBsAg positive at birth

Anti-HBs in HBsAg Negative Infants* Born to HBeAg Positive Mothers
Who Received Plasma-Derived Vaccine

Infants Age at Testing	Number Tested	% (Proportion) Anti-HBs mIU/ml			
		2.1-10	11-49	50-99	≥100
1 month	25			12.0 (3/25)	88.0 (22/25)
3 months	19		52.6 (10/19)	15.8 (3/19)	31.6 (6/19)

*Excludes two infants who were HBsAg positive at birth

3246I/2
1/23/86

Table 2

Anti-HBs in HBsAg Negative Infants* Born to HBeAg Negative Mothers
Who Received Yeast Recombinant Vaccine

Infants Age at Testing	Number Tested	% (Proportion) Anti-HBs mIU/ml			
		2.1-10	11-49	50-99	≥100
1 month	68		1.5 (1/68)	4.4 (3/68)	94.1 (64/68)
3 months	41		41.5 (17/41)	36.6 (15/41)	21.9 (9/41)

*Excludes two who were HBsAg positive at birth

Anti-HBs in HBsAg Negative Infants* Born to HBeAg Negative Mothers
Who Received Plasma-Derived Vaccine

Infants Age at Testing	Number Tested	% (Proportion) Anti-HBs mIU/ml			
		2.1-10	11-49	50-99	≥100
1 month	76			2.6 (2/76)	97.4 (74/76)
3 months	42		40.5 (17/42)	23.8 (10/42)	35.7 (15/42)

*Excludes two infants who were HBsAg positive at birth

3246I/3
1/23/86

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 864
PURPOSE:	This study is designed to evaluate rates of chronic hepatitis B antigenemia in infants at extremely high risk of infection who are treated with a combination of HBIG and yeast recombinant hepatitis B vaccine.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot # 985/C-K732 (5 mcg HBsAg/ml) Lot # 987/C-K734 (5 mcg HBsAg/ml) Hep-B-GAMMAGEE Lot # 1120K 2745J 2660J 0031L
PRINCIPAL INVESTIGATOR:	Cladd E. Stevens, M.D. The Lindsley F. Kimball Research Institute New York Blood Center New York, New York 10021
SECONDARY INVESTIGATORS:	Rita H. Fisher, M.D. Chief of Neonatology St. Vincent's Hospital New York, New York 10011 Myron Tong, M.D. Director, Liver Research Center Huntington Memorial Hosp. Pasadena, CA 91109 Pearl Toy, M.D. San Francisco General Hosp. San Francisco, CA 94110
STUDY LOCATIONS:	New York University Hospital 550 First Avenue New York, NY 10016 Beekman Downtown Hospital- New York Infirmary 170 William Street New York, NY 10038

Study 864

STUDY LOCATIONS:
(Contd)

Huntington Memorial Hospital
100 Congress Street
Pasadena, CA 91105

French Hospital
532 W. College St.
Los Angeles, CA 90012

University of California S.F.
Medical Center
Parnassus Avenue
San Francisco, CA 94143

St. Mary's Hospital Medical Center
450 Stanyan
San Francisco, CA 94117

Columbia Presbyterian Medical Center
622 West 168th Street
New York, NY

Saint Vincent's Hospital
153 West 11th Street
New York, NY 10011

California Hospital
1414 S. Hopr St.
Los Angeles, CA 90015

Garfield Hospital
150 Hampton
Monterey Park, CA 91754

San Francisco General Hospital
1001 Portrero Avenue
San Francisco, CA 94110

Santa Clara Valley Medical Center
751 South Bascom Avenue
San Jose, CA 95128

Highland General Hospital
1411 E. 31st Street
Oakland, CA 94553

Kaiser Foundation Hospital
2425 Geary Blvd.
San Francisco, CA 94115

Study 864

STUDY LOCATIONS: (Contd)

Children Hospital, S.F.
3700 California St.
San Francisco, CA 94118

Contra Costa County Health Services
2500 Alhambra Avenue
Martinez, CA 94553

Kaiser Permanente Hospital
280 West MacArthur Blvd.
Oakland, CA 94611

DATE INITIATED: September 1, 1984.

DATE COMPLETED: In progress.

STUDY POPULATION: The study population consists of healthy infants (i.e., weigh $\geq$ 2000 gms at birth and have an apgar score $\geq$ 7 at 5 minutes) born to mothers of Asian descent who are positive for both HBsAg and HBeAg. Enrollment of at least 80 infants is planned.

STUDY PROCEDURE: Infants, whose parents consent to their enrollment in the study, receive a single intramuscular injection of HBIG (0.5 cc) within the first few hours after birth. Pregnant women of Asian descent are screened for hepatitis infection prior to delivery to identify potential study candidates within the first few hours of birth (infants). The initial 1.0 ml (5 mcg HBsAg) intramuscular injection of recombinant hepatitis B vaccine is given in the first few days after birth. The second injection of vaccine is administered at one month of age, and the third injection is received at six months. If an infant becomes HBsAg positive prior to completing the immunization schedule, no further vaccine injections will be administered.

A cord blood specimen is obtained at the time of delivery and just prior to administration of the HBIG. A venous blood sample is also to be taken from the infant at this time. The cord sample is tested for HBsAg and the venous sample for HBsAg and ALT (SGPT).

Study 864

STUDY PROCEDURE: (Contd)

Follow-up venous blood samples are obtained from the infant at 1, 3, 6, 9, 12, and 18 months of age. These sera are tested for HBsAg, anti-HBc, anti-HBs and ALT. A follow-up blood sample is also obtained from the mother at or near the time of delivery to verify her HBsAg and HBeAg positive status.

Sera are being tested at the New York Blood Center by radioimmunoassay using (b) (4) kits. Some sera may be tested for yeast antibody at MSDRL.

RESULTS:

INFANTS OF HBsAg$^+$/HBeAg$^+$ MOTHERS

5 mcg Lot 985/C-K732 at 0, 1, and 6 months

1. Number Vaccinated:

Injection #		
1	2	3
134	120	61

2. Serologic Results:

Four infants were positive for HBsAg at birth. One of these has been followed for 1 month only and remains positive. Three of the infants have been followed for at least 3 months and were still antigen positive. One of the three has been followed for 6 months and is still positive. This infant is now classified as a chronic carrier (Figure 1).

At present, only a preliminary summary of antibody response data is available. According to the study investigator, all of 46 antigen negative infants followed for 6 months had developed anti-HBs (S/N $\geq$2.1). Refer to Table 1 for anti-HBs responses through 9 months of follow-up.

Study 864

RESULTS: (Contd)

3. Clinical Complaints:

Currently, only a preliminary summary of clinical complaint data is available. The study investigator has reported the following overall frequencies of complaints:

Type of Complaint	Frequency in % by Injection # 1	2	3
Fever ≥100°F	3.2 (3/95)	1.3 (1/77)	9.7 (3/31)
Local redness or swelling	2.1 (2/95)	1.3 (1/77)	19.4 (6/31)
Rash	1.1 (1/95)	5.2 (4/77)	3.2 (1/31)
Other	3.2 (3/95)	2.6 (2/77)	0 (0/31)

There have been no serious or alarming reactions attributable to vaccine.

Reactions Reported to the OoBRR:

A neonatal male received HBIG and his first injection of vaccine at birth (b)(6). On the fifth and sixth days post-vaccination he had a temperature of 38°C. The infant received Tylenol and his temperature returned to normal. He received his second and third injections of vaccine without temperature elevation.

A male neonate received 1 dose of HBIG at birth (b)(6). He developed physiologic jaundice on day 4 (b)(6) after birth. The jaundice resolved by day 7. The first injection of vaccine was administered on (b)(6) The infant received the second and third injections of vaccine without local or systemic complaints.

On the first day of life, a female neonate had a fever of 101.7°F. The child received one dose of HBIG at birth. The following day her temperature was normal and she received her first injection of vaccine. Her temperature remained within normal limits after the first, second, or third injections of vaccine.

Study 864

RESULTS: (Contd)

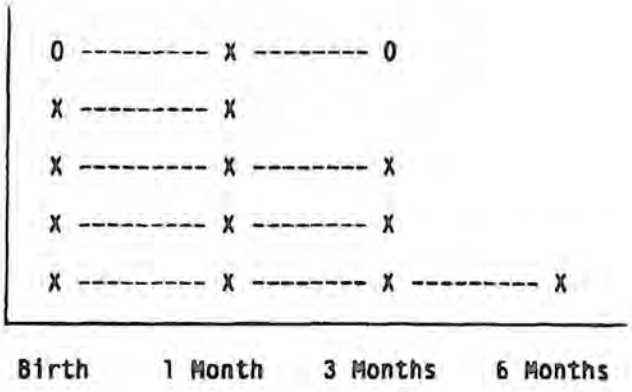
A male neonate was reported to have developed jaundice during the post-natal period. He had received one dose of HBIG at birth (b) (6) and his first injection of vaccine three days later. The second injection of vaccine was administered on (b) (6)

There has been one death among study participants unrelated to vaccine.

A one-day old full term male infant with Apgar scores of 9 at both 1 and 5 minutes was entered into the study. He received one dose of Hep-B-Gammagee on the day of birth and his first dose of vaccine on the following day. The infant did well until 2 days post delivery when poor feeding was noted. A cardiac evaluation revealed a murmur and possible atrial septal defect. His clinical condition deteriorated requiring intubation and administration of pressor and diuretic agents. The infant died 7 days after birth after circulatory collapse and the onset of arrhythmias. An autopsy revealed intracranial, renal and hepatic hemorrhage, hypoplasia of the left auricle and ventricle, a patent foramen ovale, an atrial septal defect, and aspiration pneumonia.

Figure 1

HBsAg Positive Infants in Study 864



X = HBsAg^{+}

O = HBsAg^{-}

Table 1

Yeast Recombinant Hepatitis B Vaccine in
Perinatal Transmission: Anti-HBs Response in HBsAg Negative Infants
Study 864

Infant's Age at Testing	Number Tested	% Anti-HBs (Titer in S/N)		
		2.1-19.9	20-49.9	≥50
3 Months	82	36	43	21
6 Months	46	7	29	64
9 Months	19	0	16	84

wva/2382I/8
1/13/86

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 878
PURPOSE:	To evaluate the efficacy of yeast recombinant hepatitis B vaccine, given in conjunction with hepatitis B immune globulin at birth, or alone, in preventing chronic hepatitis B infection among infants born to mothers positive for HBsAG and HBeAg.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 979/C-K564 (10 mcg HBsAg/ml)
IMMUNE GLOBULIN:	Hepatitis B Immune Globulin HEP-B-GAMMAGEE Lot 0031L
PRIMARY INVESTIGATOR:	Sun Tsung-tang, M.D. Chairman, Department of Immunology Cancer Institute (Hospital) Chinese Academy of Medical Sciences Panjiaynan, Beijing People's Republic of China
SECONDARY INVESTIGATOR:	Dr. Chu Yuan Yun Qidong Liver Institute Qidong People's Republic of China
STUDY LOCATION:	Qidong Liver Institute Qidong, Jiangsu Province People's Republic of China
DATE STUDY INITIATED:	July, 1985
DATE STUDY COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 70-150 healthy infants born to mothers who are positive for HBsAg and HBeAg.

Study 878

STUDY PROCEDURE:

Prior to enrollment of an infant in this study, a prenatal blood sample is obtained from each prospective mother. A follow-up blood sample is also obtained from the mother at the time of delivery to verify the eligibility of infants for the study.

Eligible infants receive a single 0.5 ml intramuscular injecton of hepatitis B immune globulin in the anterior thigh within 12 hours of birth, followed by a 0.5 ml (5 mcg HBsAg) intramuscular injection of yeast recombinant hepatitis B vaccine in the contralateral anterior thigh at 0 (within 12 hours of birth), 1 and 6 months, or vaccine alone according to the same regimen.

The parent or guardian will be asked to record the child's temperature and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each infant prior to vaccination and, if possible, at 3, 6, 12, and 24 months.

All serum samples obtained from each mother are assayed for HBsAg, anti-HBs, anti-HBc, and ALT.

All serum samples obtained from each infant are assayed for HBsAg, anti-HBs, and when indicated for anti-HBc and ALT. Samples may be tested for yeast antibody. In addition, samples with an anti-HBs titer $\geq$25 mIU/ml may be tested to determine anti-a and anti-d subtype specificity.

RESULTS:

To date, 20 infants have received one injection of vaccine in conjunction with HBIG. No serious or alarming reactions attributable to vaccination have been reported. Clinical follow-up data and serologic results are not yet available. The study continues in progress.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 892
PURPOSE:	To compare the efficacy of yeast recombinant hepatitis B vaccine and plasma-derived hepatitis B vaccine in preventing chronic hepatitis B infection among infants born to mothers positive for HBsAg and for HBeAg.
VACCINE:	1. Yeast Recombinant Hepatitis B Vaccine Lot 819541/18071/C-L220 (10 mcg HBsAg/ml) 2. Plasma-Derived Hepatitis B Vaccine Lot 0027L (20 mcg HBsAg/ml)
PRIMARY INVESTIGATOR:	Dr. Hu Zong-Han Department of Biological Products Inspection Bureau of Pharmaceutical and Biological Inspection Ministry of Health Temple of Heaven, West Gate Beijing, People's Republic of China
SECONDARY INVESTIGATOR:	Dr. Meng Lingxian
STUDY LOCATIONS:	The Third Hospital Chinese Medical University Shen Yang, People's Republic of China Shen Yang Municipal Anti-Epidemic Station Shen Yang, People's Republic of China Fujian Provincial Anti-Epidemic Station Fujian, People's Republic of China Guang Dong Provincial Anti-Epidemic Station Guang Dong, People's Republic of China Si Chuan Provincial Anti-Epidemic Station Si Chaun, People's Republic of China
DATE STUDY INITIATED:	December, 1985
DATE STUDY COMPLETED:	In progress

3206I/1
1/16/86

Study 892

STUDY POPULATION: The study population consists of 200 healthy infants of either sex, born to mothers who are positive for HBsAg and for HBeAg.

STUDY PROCEDURE: Prior to enrollment of an infant in this study, a prenatal blood sample is obtained from each prospective mother. A follow-up blood sample is also obtained from the mother at the time of delivery to verify the eligibility of infants for the study.

Infants are randomly assigned to receive yeast recombinant or plasma-derived hepatitis B vaccine as follows:

Group	Vaccine	Dose	Number	Regimen
1	Recombinant	5 mcg	50	0.5 ml intramuscular injection of vaccine within 12 hours of birth and at 1 and 6 months
		10 mcg	50	1.0 ml intramuscular injection of vaccine within 12 hours of birth and at 1 and 6 months
2	Plasma	10 mcg	50	0.5 ml intramuscular injection of vaccine within 12 hours of birth and at 1 and 6 months
		20 mcg	50	1.0 ml intramuscular injection of vaccine within 12 hours of birth and at 1 and 6 months

The parent or guardian will be asked to record the child's temperature and any local or systemic complaints for five days after each injection of vaccine.

A blood sample is obtained from each infant prior to vaccination and at 1, 3, 6, 7 or 8, 12, and 24 months of age.

Study B92

STUDY PROCEDURE: (Contd)

All serum samples obtained from each mother are assayed for HBsAg, HBeAg, anti-HBe and ALT.

All serum samples obtained from each infant are assayed for HBsAg and anti-HBs, and when indicated for anti-HBc and ALT.

RESULTS:

To date, 20 infants have received one injection of yeast recombinant or plasma-derived hepatitis B vaccine. No serious or alarming reactions attributable to vaccination have been reported. Clinical follow-up data and serologic results are not yet available. The study continues in progress.

APPENDIX 1

EQIVALENCE OF ANTIBODY RAISED TO YEAST RECOMBINANT HEPATITIS B VACCINE AND TO PLASMA-DERIVED HEPATITIS B VACCINE

Antibodies and Protective Efficacy

Clinical studies with the plasma-derived vaccine established the relationship between antibody to the hepatitis B surface antigen (anti-HBs) and protection against hepatitis B infection.

To support the protective efficacy studies that have been done in chimpanzees (with yeast-derived hepatitis B vaccine) and those ongoing in neonates, serological studies designed to demonstrate the equivalence of anti-HBs antibodies raised to yeast-derived hepatitis B vaccine and to plasma-derived hepatitis B vaccine are being carried out.

These are:

A. Cross-Adsorption of Antibodies Raised to Plasma-Derived Vaccine and to Yeast-Derived Vaccine

(b) (4) assays (b) (4) showed that anti-HBs raised in plasma vaccinees completely reacted with yeast-derived vaccine antigen and, conversely, antibodies raised to the yeast-derived vaccine were completely cross-reactive with plasma-derived vaccine antigen (see Table 1). This demonstrates that both vaccines raise essentially identical antibodies. Had either vaccine raised substantially different antibodies, incomplete cross-reactivity would have been observed with the converse antigens. This did not occur.

B. Binding of Anti-HBs to Synthetic Peptide (affinity constants)*

An important common antibody is elicited in recipients of both vaccines as demonstrated by (b) (4) (b) (4) (an important amino acid sequence in HBsAg). Binding of this antibody to this peptide can be used to derive affinity constants by (b) (4)

(b) (4)

Affinity constants are shown in Table 2. It will be noted that the average affinity constant for antibodies induced in plasma vaccinees is 4 X 10^{7} and that in the yeast vaccinees is also 4 X 10^{7}.

* Affinity constant defines the binding strength of the antibody to its respective antigen.

C. Inhibition Assay with "Protective" Monoclonal anti-HBs Antibody

Using the "protective" monoclonal antibody (b) (4) (b) (4) in an inhibition assay, the presence of antibodies to the identical HBsAg epitope can be detected and quantitated in the sera of plasma and yeast vaccinees (see Table 3). It has been clearly shown that recipients of our plasma and yeast hepatitis B vaccines make such antibodies in equivalent amounts.

D. Avidity Constants

If the assay described under Affinity Constants is used with the entire hepatitis B surface antigen against sera from plasma and yeast vaccinees, a property can be derived which is called the avidity constant (see Table 4). The similarity of these constants for the anti-HBs antibodies in plasma and yeast vaccinees further demonstrates the qualitative similarity of antibodies elicited in recipients of both vaccines.

E. IgM/IgG Antibody Pattern

Comparisons of IgM and IgG anti-HBs in plasma and yeast vaccinees revealed similar patterns; i.e., initial production of IgM anti-HBs changes over to IgG anti-HBs as the vaccination regimen progresses in recipients of each vaccine (see Table 5).

F. D Antibody, A Antibody Pattern

The plasma and yeast vaccinees sera show similar patterns with respect to the formation of antibody specific for the subtype determinants of HBsAg (type ad HBsAg used as immunogen). D antibody is initially high and as the vaccine regimen progresses, this converts to A antibody and is nearly 100% A at the completion of the 3-dose regimen (see Table 6). [A is the broadly reactive and protective antibody in anti-HBs.]

TABLE 1

CROSS NEUTRALIZATION OF ANTIBODIES

YEAST HBsAB (CL934)	(b) (4)	% NEUTRALIZATION WITH AY PLASMA	AD PLASMA	AD YEAST
(b) (6) (4 MOS.)		98	100	100
(4 MOS.)		98	100	100
(4 MOS.)		98	100	99
(4 MOS.)		94	100	99
(4 MOS.)		97	100	99
(4 MOS.)		87	100	100

PLASMA HBSAB (LOT 820)	(b) (4)	% NEUTRALIZATION WITH AY PLASMA	AD PLASMA	AD YEAST
(b) (6) (3 MOS.)		86	100	99
(3 MOS.)		97	99	95
(3 MOS.)		94	100	97
(3 MOS.)		50	100	93
(3 MOS.)		86	100	97
(3 MOS.)		87	100	87

ASSAYS PERFORMED AT MSDRL BY W. MILLER ET AL.

TABLE 2

AFFINITY CONSTANTS OF HBsAb IN HUMANS RECEIVING
RECOMBINANT OR PLASMA DERIVED VACCINE

(b) (4)

TABLE 3

INHIBITION OF THE PROTECTIVE MONOCLONAL HBsAb BY HUMAN HBsAb FROM RECOMBINANT OR PLASMA-DERIVED VACCINE

PLASMA VACCINEES

SAMPLE	(b) (4)	% INHIBITION (b) (4)	% INHIBITION MSDRL
(b) (6)		19	17
		18	--
		46	--
		77	74
		97	--
		23	--
		38	--
		99	97
		37	--
		86	79

YEAST VACCINEES

SAMPLE	(b) (4)	% INHIBITION (b) (4)	% INHIBITION MSDRL
(b) (6)		66	59
		19	--
		14	18
		65	--
		13	--
		38	44
		68	--
		13	--
		10	8
		69	--
		--	83
		--	79
		--	77
		--	81

METHOD (b) (4)

TABLE 4

AVIDITY CONSTANTS OF HBsAb

YEAST RECOMBINANT HBs VACCINEES

BLEEDING NUMBER		AVIDITY CONSTANT
(b) (6)	(4 MOS.)	(b) (4) 4×10^{10}
	(4 MOS.)	1×10^{10}
	(4 MOS.)	16×10^{10}
	(4 MOS.)	5×10^{10}
	(4 MOS.)	1×10^{10}
	(4 MOS.)	14×10^{10}

PLASMA DERIVED HBs VACCINEES

BLEEDING NUMBER		AVIDITY CONSTANT
(b) (6)	(3 MOS.)	(b) (4) 4×10^{10}
	(3 MOS.)	8×10^{10}
	(3 MOS.)	4×10^{10}
	(3 MOS.)	4×10^{10}
	(3 MOS.)	7×10^{10}
	(3 MOS.)	8×10^{10}

ASSAYS PERFORMED AT MSDRL BY W. MILLER ET AL.

TABLE 5

RELATIVE PROPORTIONS OF (b) (4) ANTI-HBs IN SERUM

STUDY	CASE	TYPE*	PERCENT OF TOTAL (b) (4) MONTHS POST INITIAL VACCINATION					
			PRE	1	2	3	4	6
779 (YEAST)	(b) (6)	(b) (4)	0	100	0	-	-	-
			0	0	100	-	-	-
			0	-	25	-	0	-
			0	-	75	-	100	-
			0	-	0	-	0	-
			0	-	100	-	100	-
			0	-	-	0	-	-
			0	-	-	100	-	-
			0	100	-	1	-	-
			0	0	-	99	-	-
542 (PLASMA)			0	-	0	-	4	-
			0	-	100	-	96	-
			0	-	37	-	-	0
			0	-	63	-	-	100
			0	-	8	-	12	-
			0	-	92	-	88	-
639 (PLASMA)			0	-	-	0	-	0
			0	-	-	100	-	100
			0	-	-	0	-	0
			0	-	-	100	-	100

ASSAY (b) (4) (b) (4)

TABLE 6

PERCENTAGES OF ANTI-HBs SPECIFIC FOR A AND D DETERMINANTS OF HBsAg IN POST-VACCINATION SERA

YEAST VACCINEES

Months After First Injection	Number of Samples	% Anti-A Range	% Anti-A Mean	% Anti-D Range	% Anti-D Mean
1	20	0-100	65	0-100	34
3	69	33-100	91	0-63	9
6	44	58-100	93	0-37	7
7	27	81-100	95	0-19	5
8	12	94-100	97	0-6	3

PLASMA VACCINEES

Months After First Injection	Number of Samples	% Anti-A Range	% Anti-A Mean	% Anti-D Range	% Anti-D Mean
1	0	-	-	-	-
3	3	87-89	88	9-13	12
6	6	79-95	89	5-18	10
7	8	74-97	93	2-26	7
12	7	87-96	94	4-13	6

ASSAYS PERFORMED AT MSDRL BY W. MILLER ET AL. (b) (4) METHOD (b) (4)

(b) (4)

REFERENCES

REFERENCES

Butterly L, Watkins E, Hinkle CH, Dienstag JL. Response to recombinant yeast hepatitis B vaccine in nonresponders to plasma-derived hepatitis B vaccine. Hepatology 1985; 5:1007 (Abstract).

Dandolos E, Roumeliotou-Karayannis A, Richardson SC, Papaevangelou G. Safety and immunogenicity of a recombinant hepatitis B vaccine. J Med Virology 1985; 17:57-62.

Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985; 1:108-9.

Davidson M, Krugman S. Recombinant yeast hepatitis B vaccine: Side effects and immunogenicity compared with plasma-derived hepatitis B vaccine. Submitted for publication to Hepatitis Scientific Memoranda.

Deinhardt F, Jilg W, Zoulek G, Lorbeer B, Wilske B. Clinical evaluation of a recombinant hepatitis B vaccine. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984:699 (Abstract).

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

Dienstag JL, Watkins E, Hinkle CA. Safety and immunogenicity of a recombinant hepatitis B vaccine (Abstract). In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984:710.

Heijtink RA, Kruining J, Bakker M, Schalm SW. Immune response after vaccination with recombinant hepatitis B vaccine as compared to that after plasma-derived vaccine. Antiviral Res 1985; Suppl. 1:273-9.

Heijtink RA, Schalm SW. Anti-HBs/a determination after hepatitis B vaccination. Submitted for publication to Lancet 1985.

Hilleman MR, Buynak ER, Markus HZ, Maigetter RZ, McAleer WJ, McLean AA, et.al. Control of Hepatitis B virus infection: Vaccines produced from Alexander cell line and from recombinant yeast cell cultures. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984:307-14.

Hilleman MR, Weibel RE, Scolnick EM. Recombinant yeast human hepatitis B vaccine. J Hong Kong Med Assoc 1985; 2:75-85.

Hollinger FB, Sanchez Y, Troisi C, Dreesman GR, Melnick JL. Immunogenicity and reactogenicity of new hepatitis B vaccines. Hepatology 1984; 4:1027(Abstract).

Hollinger FB, Troisi CL., Pepe PE. Anti-HBs responses to vaccination with a human hepatitis B vaccine made by recombinant DNA technology in yeast. J Infect Dis 1986; 1:156-9.

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2:1174-5.

Jilg W, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical comparison of a recombinant and a plasma-derived hepatitis B Vaccine (Abstract). Presented at the 24th Interscience conference on antimicrobial agents and chemotherapy, Washington, DC, October 1984

McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178-80.

Mueller R, Bommer J, Braas H, Deinhardt A, Jilg W, Kuttler G, et al. Erste erfahrungen mit rekombinanter hepatitis B-vaccine bei patienten unter chronischer haemodialyse-behandlung. Gastroenterol 1985; 23:297.

Papaevangelou G, Dandolos E, Roumeliotou-Karayannis A, Richardson SC. Immunogenicity of recombinant hepatitis B vaccine. Lancet 1985; 1:455-6.

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F, Jilg W. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

Zajac BA, West DJ, McAleer WJ, Scolnick EM. Overview of clinical studies with hepatitis B vaccine (recombinant). Presented at the fifth biennial scientific meeting, Asian Pacific Association for the Study of the Liver, Symposium on recent advances in the prevention of hepatitis B infection, January 1986 (Singapore).

244 RESPONSE TO RECOMBINANT YEAST HEPATITIS B VACCINE IN NONRESPONDERS TO PLASMA-DERIVED HEPATITIS B VACCINE

L Butterly, E Watkins, CA Hinkle and JL Dienstag.
Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

Preliminary reports suggested that recombinant yeast hepatitis B vaccine (R-HBvac) might be more immunogenic than the triply inactivated plasma-derived hepatitis B vaccine (P-HBvac) (Hepatology 1984;4:1077). Therefore, to test this hypothesis, we administered three 10 µg doses of R-HBvac (Merck Sharp & Dohme Research Laboratories) at time 0, 1, and 6 months to 14 normal adults who had failed to respond to one or more courses (3-6 doses) of P-HBvac. The frequency [# positive/# vaccinated] (%) and geometric mean titer (mIU/ml) of anti-HBs responses were as follows:

Month	1	2	3	6
anti-HBs+	5/13 (39)	8/14 (57)	7/14 (50)	7/13 (54)
GMT ± SD	17 ± 7	39 ± 10	36 ± 23	8 ± 7

For comparison, the same data are charted below for 65 seronegative health workers, never previously vaccinated, after receiving R-HBvac:

Month	1	2	3	6
anti-HBs+	26/65 (38)	53/62 (86)	61/65 (94)	60/62 (97)
GMT ± SD	7 ± 4	38 ± 4	50 ± 4	72 ± 4

The mean ± SD ages of the 8 initial nonresponders who ultimately did respond and the 6 who did not were indistinguishable, 38 ± 8 and 41 ± 15. The response to R-HBvac in almost 60% of nonresponders to P-HBvac appeared promising, especially when compared with a 40% rate of low-level, poorly sustained anti-HBs responses in P-HBvac nonresponders given a second course of P-HBvac (Hepatology 1984;4:1077); however, the level of antibody fell substantially by six months, when measured just prior to the booster injection. Additional follow-up will be necessary to determine whether the antibody response to R-HBvac in nonresponders to P-HBvac increases and is sustained after booster immunization.

Butterly L, Watkins E, Hinkle CH, Dienstag JL. Response to recombinant hepatitis B vaccine in nonresponders to plasma-derived hepatitis B vaccine. Hepatology 1985; 5:1007 (abstract).

Journal of Medical Virology 17:57–62 (1985)

Safety and Immunogenicity of a Recombinant Hepatitis B Vaccine

E. Dendolos, A. Roumeliotou-Karayannis, S.C. Richardson, and G. Papaevangelou

National Centre for Viral Hepatitis, Athens School of Hygiene, Athens, Greece

A hepatitis B vaccine produced in yeast by recombinant DNA technology was evaluated using 5-μg and 10-μg doses in a randomized trial lasting 7 months in 110 male armed forces recruits aged 17–19 years. Results were compared to those of an identical trial of a plasma-derived vaccine. No allergic reactions were observed, and the rate of mild side effects was similar to the plasma-derived vaccine. Seroconversion rates in the first month were 60% (33/55) and 67% (37/55) with the 5-μg and 10-μg doses of the recombinant vaccine, respectively. All participants seroconverted by 3 months, and none lost antibody. These results are very similar to those for plasma-derived vaccine. Comparison of titres of antibody to hepatitis B surface antigen (anti-HBs) showed a slightly higher level with the 10-μg than with the 5-μg dose of the recombinant vaccine. Geometric mean titres of anti-HBs after the booster dose were similar in the 5-μg and 10-μg dose recombinant vaccine groups (2,620 and 2,748 IU/l, respectively) and in the 5-μg plasma-derived vaccine group (3,591 IU/l) but significantly higher (9,227 IU/l) with the 10-μg dose of the plasma-derived vaccine. These results confirm the safety and immunogenicity of the recombinant vaccine, although further study is needed on the duration of immunity.

Key words: active immunoprophylaxis, hepatitis B, plasma-derived hepatitis B vaccine, recombinant hepatitis B vaccine

INTRODUCTION

The safety and immunogenicity of plasma-derived hepatitis B vaccines have been amply demonstrated by clinical trials in various high-risk groups in different parts of the world [Szmuness et al, 1980; Maupas et al, 1981; Beasley et al, 1983]. However, the high cost and limited availability have prevented widespread use of these vaccines, especially in the less developed areas where they are needed most. Vaccination programmes are at present generally limited to groups at high risk of infection, such as hospital personnel. Within these programmes, acceptance may have been affected by unfounded loss of confidence in the safety of the vaccine, following

Accepted for publication April 1, 1985.

Address reprint requests to Prof. G. Papaevangelou, National Centre for Viral Hepatitis, Athens School of Hygiene, P.O. Box 14085, Athens 115 21, Greece.

isons at each time point. All analyses were carried out after logarithmic transformation of anti-HBs titres.

RESULTS

The trial was completed in all but two recruits, both the losses being from the group receiving the 10-μg dose. One was lost from the study after receiving the second dose and the other after the booster dose. No participant developed either clinical or asymptomatic viral hepatitis, and neither anaphylactoid nor other allergic reactions were observed. Mild side effects were reported, but no case of fever above 37.5°C was noted, and no local discomfort or pain lasting for more than 1 day. The overall frequency of side effects was very similar to that reported for the plasma-derived vaccine in the earlier study (Table I).

The two groups receiving recombinant vaccine showed a similar and rapid immune response (Table II). Both of the recruits who did not complete follow-up had already seroconverted in the first month. All participants had seroconverted by 3 months, and none lost antibody. These rates are very similar to those recorded in the trial of the plasma-derived vaccine. Differences in seroconversion rates at 1 month between the four groups in Table II are not significant ($\chi^2_3 = 5.26$; $P = 0.15$).

Geometric mean titres (GMT) of anti-HBs are shown in Table III. Multivariate comparison between the two recombinant vaccine groups shows that they do not differ in rates of increase of anti-HBs ($F_{3,104} = 1.99$; $P > 0.1$). The 10-μg group had significantly higher GMT of antibody overall than the 5-μg group ($t_{106} = 2.08$; $P < 0.05$), although the difference appears to be small after the booster dose.

Multivariate comparisons of the anti-HBs profiles in the 5-μg and 10-μg recombinant vaccine groups against the corresponding plasma-derived vaccine groups show

TABLE I. Frequency of Side Effects by Type of Vaccine (Summed Over Administrations of Vaccine)

Side effect	Recombinant vaccine (%)	Plasma-derived vaccine (%)
Local pain	6.0	9.0
Fever < 37.5°C	16.3	11.1
Other	2.3	2.3
Total	24.6	22.4

TABLE II. Number (%) of Seroconverted (anti-HBs > 2.1 IU/l) by Month and Type of Vaccine

	Recombinant vaccine		Plasma-derived vaccine	
Month	5 μg (N = 55)	10 μg (N = 55)	5 μg (N = 50)	10 μg (N = 50)
1	33 (60)	37 (67)	40 (80)	32 (64)
3	55 (100)	54 (100)[a]	49 (98)	49 (98)
6	55 (100)	54 (100)[a]	49 (98)	49 (98)
7	55 (100)	53 (100)[b]	49 (98)	50 (100)

[a]One person lost to follow-up.
[b]Two persons lost.

population, with all participants in both the trials of recombinant and plasma-derived vaccines being males of similar age living under exactly similar conditions.

Comparison of the 5-μg and 10-μg doses of recombinant vaccine shows a small advantage to the 10-μg dose overall in terms of GMT anti-HBs, although any final difference is slight. Davidson and Krugman [1985], with older vaccinees of both sexes, reported a final (8 months) GMT anti-HBs in the 10-μg group more than double that in the 5-μg group, although the statistical significance is not stated. Irrespective of dose, all participants in our trial reached the 10 IU/l generally regarded as protective. Only five (4.6%; two from the 5-μg group and three from the 10-μg group) had titres lower than 100 IU/l.

Our results confirm reports of the safety and immunogenicity of the Merck Sharp and Dohme recombinant yeast hepatitis B vaccine [Jilg et al, 1984b; Davidson and Krugman, 1985]. The minor differences observed in the immune response stress the need for more extensive studies in various population groups under consideration for vaccination, before the appropriate dose and vaccination scheme are decided. Similarly, further follow-up is required to establish the duration of protective levels of antibody [Jilg et al, 1984a; Davidson and Krugman, 1985]. Finally, in assessing the efficacy of the vaccine, information concerning the quality of the anti-HBs induced should complement the data on the anti-HBs levels achieved [Brown et al, 1984].

ACKNOWLEDGMENTS

This study was supported by a grant from the Ministry of Health and Welfare of Greece.

REFERENCES

Beasley RP, Lee GC, Roan C, Hwang L, Lan C, Huang F, Chen C (1983): Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet ii:1099–1102.

Brown SE, Zuckerman AJ, Howard CR, Steward MW (1984): Affinity of antibody responses in man to hepatitis B vaccine determined with synthetic peptides. Lancet ii:184–187.

Davidson M, Krugman S (1985): Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet i:108–109.

Hollinger FB, Adam E, Heiberg D, Melnick JL (1982): Response to hepatitis B vaccine in a young adult population. In Szmuness W, Alter HJ, Maynard JE (eds): "Viral Hepatitis. 1981 International Symposium." Philadelphia: Franklin Institute Press, pp 451–466.

Jilg W, Schmidt M, Deinhardt F, Zachoval R (1984a): Hepatitis B vaccination: How long does protection last? Lancet ii:458.

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F (1984b): Clinical evaluation of a recombinant hepatitis B vaccine. Lancet ii:1174–1175.

Maupas P, Chiron JP, Barin F, Coursaget P, Goudeau A, Perrin J, Denis F, Diop Mar I (1981): Efficacy of hepatitis B vaccine in prevention of early HBsAg carrier state in children. Controlled trial in an endemic area (Senegal). Lancet i:289–292.

McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR (1984): Human hepatitis B vaccine from recombinant yeast. Nature 307:178–180.

Morrison DF (1976): "Multivariate Statistical Methods," (2nd ed). New York: McGraw-Hill.

Papaevangelou G, Roumeliotou-Karayannis A, Vissoulis C, Richardson SC, Krugman S (1985): Immunogenicity of a 5 μg dose hepatitis B vaccine. Journal of Medical Virology. 15:65–69.

Papaevangelou G, Roumeliotou-Karayannis A, Vissoulis C, Stathopoulou P, Kolaitis N, Krugman S (1983): Safety and immunogenicity of a further reduced dose (10 mcg) of the hepatitis B vaccine.

IMMUNOGENICITY OF RECOMBINANT YEAST HEPATITIS B VACCINE

SIR,—In Dr Jilg and colleagues' study (Nov 24, p 1174) in thirty recipients of recombinant hepatitis B vaccine "the immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels". They compared a 10 μg dose of recombinant vaccine with a 20 μg dose of plasma-derived vaccine.

As indicated in the table, our results in a similar study in one hundred and seven seronegative health professionals, 21–30 years of age, revealed essentially the same immune response in recipients of 5 μg and 10 μg doses of recombinant yeast hepatitis B vaccine when compared with a comparable group who received 20 μg doses of plasma-derived vaccine.

Valid conclusions cannot be drawn from studies in thirty or a hundred vaccinees. More extensive studies will be required to evaluate anti-HBs response and its persistence in recipients of recombinant hepatitis B vaccine. In the meantime, our initial results are encouraging.

NYU Medical Center,
New York, NY 10016, USA

MORTON DAVIDSON
SAUL KRUGMAN

SEROCONVERSION RATES AND GEOMETRIC MEAN TITRES (GMT) OF SERONEGATIVE INDIVIDUALS, ADULTS GIVEN RECOMBINANT OR PLASMA-DERIVED HEPATITIS B VACCINE

	Recombinant vaccine†						Plasma derived (20 μg)‡	
	10 μg			5 μg				
Time* (mo)	Anti-HBs response	mIU/ml (GMT)	S/N ratio (GMT)	Anti-HBs response	mIU/ml (GMT)	S/N ratio (GMT)	Anti-HBs response	S/N ratio (GMT)
0	..	..	..	..	..	..	..	..
1	22/51 (43%)	42	10	21/56 (37%)	95	25	10/47 (21%)	20
2	40/51 (78%)	88	37	51/54 (91%)	60	30	34/47 (72%)	37
3	50/51 (98%)	145	82	52/54 (93%)	120	51	45/47 (96%)	70
6	49/50 (98%)	321	83	53/56 (95%)	106	42	44/47 (94%)	94
7/8	45/46 (98%)	1011	364	49/50 (98%)	890	124	46/47 (98%)	141

*Vaccine given at 0, 1, and 6 months. Follow-up to 7 months (plasma derived) or 8 months (recombinant). †Above the 97.5% C.I. exceeded. ‡Above the 75th.

Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985; 1:108-9.

RECOMBINANT YEAST HEPATITIS B VACCINE: SIDE EFFECTS AND IMMUNOGENICITY COMPARED WITH PLASMA-DERIVED HEPATITIS B VACCINE.

Morton Davidson and Saul Krugman
NYU Medical Center, New York, N.Y.

A yeast recombinant hepatitis B vaccine (Merck Lot no. 972/C-K444) was evaluated in 107 seronegative health professionals, 21-30 years of age. The clinical and antibody responses were compared with the results of a previous similar study using a plasma-derived hepatitis B vaccine (Merck Lot no. 751).

The vaccine was administered at 0, 1 and 6 months to the following three groups: 1) 51 adults who received a 10 mcg dose of recombinant vaccine; 2) 56 adults who received a 5 mcg dose of recombinant vaccine, and 3) 47 adults who received a 20 mcg dose of plasma-derived vaccine. The three groups included medical students, house staff, and nurses who were of comparable age and sex.

Results

Side effects were negligible in all three groups. They consisted of transient, local soreness at the site of the inoculation in about 25% of the vaccinees in each group. No systemic reactions were observed.

The seroconversion rates and geometric mean titers are summarized in the Table. The results are essentially the same for all three groups. Under the conditions of this study the 5 mcg and 10 mcg doses of recombinant hepatitis B vaccine were just as immunogenic as a 20 mcg dose of plasma-derived hepatitis B vaccine.

Comment

A recent report by Jilg et al (Lancet 1984; 2:1174-75) described a similar study in 30 seronegative medical students and laboratory workers whose age and sex were comparable to those in our groups. They stated that "the immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels." Our results in 107 similar recipients of the recombinant hepatitis B vaccine do not support this conclusion.

It is obvious that valid conclusions cannot be drawn from studies involving either 30 or 100 vaccinees. More extensive studies will be required to determine anti-HBs response and its persistence in recipients of recombinant hepatitis B vaccines.

Davidson M, Krugman S. Recombinant yeast hepatitis B vaccine: Side effects and immunogenicity compared with plasma-derived hepatitis B vaccine. Submitted for publication to Hepatitis Scientific Memoranda.

TABLE

Seroconversion Rates and Geometric Mean Titers of Seronegative Adults Who Received Recombinant Yeast Hepatitis B Vaccine (Merck Lot No. 972/C-K444) or Plasma-Derived Hepatitis B Vaccine (Merck Lot No. 751).

Time Interval (Months)	Recombinant Hepatitis B Vaccine					
	10 mcg dose			5 mcg dose		
	anti-HBs response	mIU/ml GMT	S/N Ratio GMT	anti-HBs response	mIU/ml GMT	S/N Ratio GMT
0	-	-	-	-	-	-
1	22/51 (43%)	42	19	21/56 (37%)	55	25
2	48/51 (94%)	88	37	51/56 (91%)	69	38
3	50/51 (98%)	145	52	52/56 (93%)	128	51
6	49/50 (98%)	321	63	53/56 (95%)	184	42
8	45/46 (98%)	1911	164	49/50 (98%)	839	124

Vaccine given at 0, 1 and 6 months.
Age Range: 21 - 30 years

Time Interval (Months)	Plasma-Derived Hepatitis B Vaccine 20 mcg dose	
	anti-HBs response	S/N Ratio GMT
0	-	-
1	18/47 (38%)	20
2	34/47 (79%)	37
3	45/47 (96%)	79
6	44/47 (94%)	94
7	46/47 (98%)	141

Vaccine given at 0, 1 and 6 months.
Age range: 21 - 30 years

SAT-LA.10

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

F. Deinhardt*, W. Jilg, G. Zoulek, B. Lorbeer, and B. Wilske
Max von Pettenkofer-Institute, 8000 Munchen 2, Western Germany

Thirty healthy, young volunteers free of any HBV markers were vaccinated with a recombinant hepatitis B vaccine prepared by Merck, Sharp & Dohme, West Point, PA. Ten µg HBsAg were administered intramuscularly at time 0, and one month later. Seroconversion rates and geometric mean concentrations after 1, 2 and 3 months were compared with an age- and sex-matched control group vaccinated with 20 µg of plasma derived vaccine (Merck Sharp & Dohme) (Table 1).

Table 1: Comparison of immune response after recombinant vaccine and plasma derived vaccine.

month	seroconversion %		anti-HBs (geom. mean) mIU	
	recombinant vaccine	plasma vaccine	recombinant vaccine	plasma vaccine
1	27	44	8.6	15.2
2	70	95	37.8	52.5
3	97	95	27.4	164.4

In the recombinant vaccine group, 38% of the total anti-HBs at month 3 was directed against the determinant a of HBsAg, compared to 30% in the control group. No increase in antibody titers against candida albicans was found in recipients of the recombinant vaccine 4 weeks after the second injection as compared to prevaccination levels. No serious side effects were observed in any of the vaccinated individuals.

Deinhardt F, Jilg W, Zoulek G, Lorbeer B, Wilske B. Clinical evaluation of a recombinant hepatitis B vaccine. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Straton, 1984:699.

RECOMBINANT YEAST HEPATITIS B VACCINE: IMMUNOGENICITY AND SAFETY. JL Dienstag, E Watkins, and CA Hinkle, Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

Cumbersome to produce, expensive, and limited in supply, currently available human plasma-derived hepatitis B vaccines are likely to be replaced in the future by "genetically engineered" vaccines. Recently, a recombinant DNA vaccine was prepared in recombinant yeast Saccharomyces cerevisiae strain 2150-2-3 cells transformed with the plasmid pHBS 56-GAP347/33, containing the gene for hepatitis B surface antigen (HBsAg/ad) (Valenzuela et al. Nature 1982; 298:347-50). Purified by biochemical and biophysical methods from the yeast extract, the HBsAg particles synthesized by these yeast cells are not glycosylated but otherwise are indistinguishable from native 22 nm HBsAg particles. Treated with formalin and adsorbed to alum, the recombinant vaccine is immunogenic and protective in experimental animals. We administered three 10 µg doses of the recombinant hepatitis B vaccine (Merck Sharp & Dohme Research Laboratories) at time 0, 1, and 6 months to 60 seronegative adult health workers. The frequency and geometric mean titer (mIU/ml) of anti-HBs responses were as follows:

Month	1	2	3	4	5	6
Number	37	29	30	29	25	16
anti-HBs+	41%	83%	93%	97%	96%	94%
GMT ± SD	7 ± 2	33 ± 5	36 ± 4	46 ± 4	55 ± 4	79 ± 4

94 ± 5 (mean ± SD) % of the anti-HBs was specific for the a determinant of HBsAg. Changes in antibodies to yeast antigens were negligible. The most frequent adverse reaction was transient soreness at the injection site, occurring after 32% of first, 37% of second, and 55% of third injections. No serious adverse effects were encountered, and neither type B nor non-B hepatitis has occurred in any vaccinee. These preliminary results demonstrate that the recombinant yeast hepatitis B vaccine is safe and that 10 µg of the recombinant vaccine is equivalent in immunogenicity to 20 µg of the plasma-derived vaccine.

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

SAT-LA-50

SAFETY AND IMMUNOGENICITY OF A RECOMBINANT HEPATITIS B VACCINE

J.L. Dienstag*, E. Watkins, and C.A. Hinkle
Gastrointestinal Unit (Medical Services), Massachusetts General Hospital, and Department of Medicine, Harvard Medical School, Boston, Massachusetts 02114

Currently available, licensed hepatitis B vaccines are prepared from plasma obtained from hepatitis B surface antigen (HBsAg) carriers. Cumbersome to produce, expensive, and available in limited supply, the plasma vaccine is likely to be replaced in the future by one of a number of later generation vaccines. Recently, a recombinant DNA vaccine was prepared in recombinant yeast Saccharomyces cerevisiae strain 2150-2-3 cells transformed with plasmid pHBS56-GAP347/33, which contains the gene for HBsAg (Valenzuela et al, Nature 1982; 298:347-50). The HBsAg synthesized by these yeast cells was purified from the yeast extract by physical and chemical methods and was found to be indistinguishable from native 22 nm HBsAg particles, except that the HBsAg is not glycosylated. Treated with formalin and adsorbed to alum, the recombinant vaccine is comparable in purity to the plasma vaccine and is immunogenic and protective in experimental animals.

We studied the immunogenicity and safety of recombinant hepatitis B vaccine Lot 934, formulated to contain 10 micrograms of HBsAg per 1.0 ml dose (Merck Sharp & Dohme Research Laboratories). Thirty seronegative adult health care workers received three 1.0 ml doses of the recombinant vaccine at time 0, 1 and 6 months. Adverse effects were limited to soreness at the injection site, and immunogenicity was excellent, approximating 50% at one month. Three months of follow-up will be complete by the time of the International Meeting.

Dienstag JL, Watkins E, Hinkle CA. Safety and immunogenicity of a recombinant hepatitis B vaccine (Abstract). In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984:710.

Antiviral Research, Suppl. 1 (1985) 273–279
Proc. 1st Int. TNO Conf. Antiviral Res. 1985 Rotterdam
A. Billiau, E. De Clercq and H. Schellekens (eds.)

IMMUNE RESPONSE AFTER VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE AS COMPARED TO THAT AFTER PLASMA-DERIVED VACCINE

R.A.HEIJTINK, J.KRUINING, M.BAKKER, S.W.SCHALM*
Departments of Virology and Internal Medicine, Erasmus University Rotterdam, Rotterdam, The Netherlands

SUMMARY

Thirty-one individuals (health care workers) were vaccinated with recombinant hepatitis B vaccine (10 µg dose) and their immune response (anti-HBs) was compared to that of twenty-five health care workers after vaccination with plasma-derived vaccine (20 µg dose). Although the seroconversion rate and the percentage of anti-HBs/a antibodies at month 7 were comparable, the geometric mean titre of anti-HBs at month 7 was considerably lower for the recombinant vaccine group (857.4 vs. 6736.5 IU/l). However, vaccinees from the two groups showing seroconversion at month 1 had comparable titres at month 7. Raising the dose of HBsAg in the recombinant vaccine may favourably influence the seroconversion rate at month 1 and thereby the immune response after three injections.

INTRODUCTION

Only six years ago, a plasma-derived vaccine was introduced to overcome the worldwide problem of hepatitis B infections.[1] General acceptance of the vaccine, however, has been hampered by the high costs and in particular by doubts about the suitability of infectious plasma as its source. Public concern has waned considerably since the discovery of human T-cell leukaemia virus as a possible cause of the acquired immune deficiency syndrome and the possibility of investigating the efficacy of inactivation of this virus in vaccine preparation procedures.[2] Meanwhile, an alternative for the latter objective has been found in the preparation of hepatitis B surface antigen by recombinant DNA technology in the yeast *Saccharomyces cerevisiae*.[3] Although the yeast recombinant DNA produced HBsAg polypeptides, unlike the native HBsAg, are not glycosylated, the vaccine thus prepared has proven to induce protective antibodies during chimpanzee challenge studies.[4] Its safety and immunicity in man has been demonstrated by several groups of investigators.[5,6,7,8] One of these studies is presented here.

Soon after the introduction of the plasma-derived vaccine it was uncertain whether an HBsAg/adw vaccine would protect against HBsAg/ayw virus infections. Nowadays it is generally known from chimpanzee studies as well as experiments in man[7 9 10] that the antibodies directed against the main determinant a provide cross protection for infections with strains not incorporated in the vaccine.

However, in the plasma-derived vaccine studies[11 12] it was found that the relative proportion of anti-HBs antibodies is variable, which may partially account for hepatitis B infections in the first few months after vaccination. Therefore, the need to monitor the development of anti-HBs/a antibodies after vaccination is stressed.

MATERIAL AND METHODS

Population

The study population consisted of 56 health care workers. Recombinant vaccine was given to 31 individuals (17 female, 14 male; mean age 32 ± 2 yr, range 20-59); plasma-derived vaccine was given to 25 individuals (13 female, 12 male; mean age 30 ± 2 yr, range 22-53). Participants to this study were negative for HBsAg, anti-HBc, and anti-HBs and had a normal alanine transferase level at the entrance to the study.

Vaccine

Participants were vaccinated at 0, 1, and 6 months with either a 10 µg HBsAg/adw dose of the recombinant hepatitis B vaccine (Merck, Sharp and Dohme, lot 972/C-K444) or a 20 µg HBsAg/adw dose of the plasma-derived vaccine (Merck, Sharp and Dohme, lot 1510 J). Recombinant HBsAg used here was purified by hydrophobic interaction chromatography.[5 7]

Assays

HBsAg, anti-HBc, anti-HBs were measured in commercially available kits (Ausria II, Corab, and Ausab; Abbott Laboratories, North Chicago, USA). The concentration of anti-HBs was calculated by the method of Hollinger et al.[13] and expressed in IU/l after comparison with the WHO standard preparation (125 IU/l), obtained from the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands. Calculations were made for positive results in Ausab only (sample/negative control ratio ≥ 2.1). Samples containing more than 200 IU/l were diluted and retested. Dilutions were made in the negative control serum from Ausab. Estimation of the proportion of anti-HBs/a antibodies was performed according to the method of Hoofnagle et al.[14] In short, undiluted or diluted sera containing 1000-2000 cpm in Ausab were incubated for 2 h at room temperature with pooled HBsAg/ad, HBsAg/ay, and normal human serum, respectively. Pooled sera

included reference sera from Dr.A.M.Courouce-Pauty as mentioned in an earlier study.[13] Reduction of cpm after incubation with HBsAg/ay strains measured the anti-HBs/a proportion of the total amount of anti-HBs, since the vaccine consisted of HBsAg/adw only. The proportion of anti-HBs/d(w) antibodies was obtained by subtracting the reduction percentage after incubation with HBsAg/ay pooled serum from the reduction percentage after incubation with HBsAg/ad pooled serum.

RESULTS

Table I shows a delayed seroconversion rate for the recombinant vaccine group as compared to the plasma-derived vaccine group in the course of the vaccine study. Similar results were obtained for titres $\geq$ 10 IU/l, the supposed protective level of antibodies.

TABLE I

SEROCONVERSION RATE AFTER VACCINATION WITH RECOMBINANT (10 µg) AND PLASMA-DERIVED (20 µg) VACCINE IN HEALTH CARE WORKERS

Month	Recombinant vaccine	Plasma-derived vaccine	Recombinant vaccine	Plasma-derived vaccine
	Percentage seroconversion		Percentage anti-HBs $\geq$ 10 IU/l	
1	19(6/31)	56(14/25)	13(4/31)	40(10/25)
2	77(24/31)	96(22/23)	39(12/31)	74(17/23)
3	90(28/31)	100(25/25)	74(23/31)	96(24/25)
6	94(29/31)	100(25/25)	87(27/31)	100(25/25)
7	100(31/31)	100(22/22)	100(31/31)	100(22/22)

Geometric mean titres of anti-HBs were significantly lower in the recombinant vaccine group as compared to the plasma-derived vaccine group at month 2, 3, 6, and 7 (Table II).

After three injections females had significantly ($p < 0.05$) higher anti-HBs titres than males in the recombinant vaccine group (1412 vs. 468 IU/l) but not in the plasma-derived vaccine group (6036 vs. 7519 IU/l).

All vaccinees were negative for HBsAg and anti-HBc at 7 months and had normal alanine transferase levels in all sera obtained. Table III illustrates the increase of the relative proportion of anti-HBs/a antibodies from about 60% at month 1 to about 100% at month 7 following the first injection for both vaccine groups as measured by specific absorption. In any sample at

TABLE II

GEOMETRIC MEAN TITRES OF ANTI-HBs AFTER VACCINATION WITH RECOMBINANT VACCINE (10 µg) AND PLASMA-DERIVED VACCINE (20 µg)

Month	Recombinant vaccine GMT in IU/l	Plasma-derived vaccine GMT in IU/l
1	16.8(n= 6)*	19.7(n=14)
2	13.7(n=24)	61.8(n=22)°
3	34.8(n=28)	177.7(n=25)°
6	69.0(n=29)	291.1(n=25)°
7	857.4(n=31)	6736.5(n=22)°

* Responders only ° $p < 0.05$ Wilcoxon's rank sum test

TABLE III

DETERMINATION OF SUBDETERMINANT SPECIFIC ANTIBODIES AFTER VACCINATION WITH RECOMBINANT VACCINE (10 µg) AND PLASMA-DERIVED VACCINE (20 µg) AS DETERMINED BY SPECIFIC ABSORPTION

Month	Recombinant vaccine			Plasma-derived vaccine		
	No. samples	% anti-HBs/a (range)	% anti-HBs/d	No. samples	% anti-HBs/a (range)	% anti-HBs/d
1	4	60(19- 92)*	39	6	57(22- 99)	42
2	9	81(40- 98)	17	15	83(25- 99)	17
3	18	95(74-100)	5	23	88(26-100)	11
6	26	99(89-100)	1	24	94(43-100)	6
7	31	99(90-100)	1	22	97(91-100)	3

* Determination of anti-HBs/a and anti-HBs/d was limited by the minimum amount of 25 IU/l anti-HBs.

month 7 the proportion of anti-HBs/a antibodies was at least 90%. In sera with anti-HBs $\geq$ 10 IU/l at month 1, two out of four in the recombinant vaccine group and three out of six in the plasma-derived vaccine group had less than 50% anti-HBs/a. In only two cases, one in each group, the anti-HBs/a percentage at month 1 was above 90, suggesting an anamnestic response. Geometric mean titres for those vaccinees with a positive anti-HBs response

at month 1 increased to 11158 IU/l (n=6) in sera from the recombinant vaccine group and to 13748 IU/l (n=13) in sera from the plasma-derived vaccine group, both at month 7.

DISCUSSION

Table IV compares the results of the immunicity of recombinant hepatitis B vaccine of Merck, Sharp and Dohme in our study with results of others as recently published. [3 6 7 8] Several lots of vaccine with minor differences in the purification procedure were used. Comparison is made in some studies with earlier results using plasma-derived vaccine from the same manufacturer. In our study vaccination with recombinant vaccine and plasma-derived vaccine took place simultaneously. Serum samples could therefore be handled similarly and investigated with the same batch of reagents.

We found anti-HBs development during the first six months following the first injection very similar to Scolnick et al.[3] and Jilg et al.[6]. After the booster injection at month 6 we found a lower geometric mean titre than observed by others. The proportion of anti-HBs/a antibodies, however, was very similar for the two vaccine groups and increased from 60% at month 1 to about 100% at month 7.

Interestingly, we noted high titres of anti-HBs at month 7 for those vaccinees who had already shown seroconversion at month 1. Titres in this subgroup were comparable to those in early responders in the plasma-derived vaccine group. Since we had the lowest seroconversion rate at month 1 observed so far for recombinant vaccine (19%), this may explain the low geometric mean titre at month 7. The reason for the initial low conversion rate in our study is unknown. Sex and age differences with other study groups may have contributed. Sex and age effects may have their most pronounced influence on vaccination of weak responders.[16 17] The highest seroconversion rate (67%) and the highest geometric mean titre (2749 IU/l) at month 7 were observed by Papaevangelou et al.[8] in male recruits aged 17-19 years.

If our observations can be confirmed in more extended studies, equalizing the dose of HBsAg in the recombinant vaccine preparation to that of the plasma-derived vaccine may favourably influence the seroconversion rate at month 1 and the amount of anti-HBs produced after three injections.

ACKNOWLEDGEMENT

We thank Mrs. R.S.Engels-Bakker for preparation of the manuscript.

TABLE IV

IMMUNE RESPONSE AFTER VACCINATION WITH RECOMBINANT AND PLASMA-DERIVED HEPATITIS B VACCINE AS COMPARED FROM LITERATURE

Authors	Dose	Geometric mean titres in IU/l Month 1	3	6	7	No.	Mean age	No. of men	No. of women	Lot no.
Recombinant vaccine										
Scolnick et al.[5]	10 µg	8	56	68	1905	15	33,23-53	10	5	934
Jilg et al.[6]	10 µg	9	29	68	2135	30	25,21-34	13	17	934
Papaevangelou et al.[8]	10 µg	11	198	189	2749	55	17-19	55		979
Davidson and Krugman[7]	10 µg	42	145	321	1911	51	21-30			972
Present study	10 µg	17	35	69	857	31	32,20-59	14	17	972
Plasma-derived vaccine										
Jilg et al.[6]	20 µg	15	164	263	4299	41	25,21-32	18	23	
Present study	20 µg	20	177	291	6737	25	30,22-53	12	13	
Papaevangelou et al.[8]	10 µg	4	278	492	9227	50				

REFERENCES

1. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A (1981) Hepatology 1: 377-385
2. Stevens CE, Taylor PE, Rubinstein P, Ting RCY, Bodner AJ, Samgadharan MG, Gallo RC (1985) N Engl J Med 312: 375-376
3. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD (1982) Nature 298: 347-350
4. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR (1984) Nature 307: 178-180.
5. Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB (1984) J Am Med Ass 251: 2812-2815
6. Jilg W, Lorbeer B, Schmidt M, Wilske B, Zoulek G, Deinhardt F (1984) Lancet II: 1174-1175
7. Davidson M, Krugman S (1985) Lancet I: 108-109
8. Papaevangelou G, Dandolos E, Roumeliotou-Karayannis A, Richardson SC (1985) Lancet I: 455-456.
9. Barker LF, Maynard JE, Purcell RH, Hoofnagle JH, Berquist KR, London WT (1975) Am J Med Sci 270: 189-195
10. Szmuness W, Stevens CE, Harley EJ, Zang EA, Alter HJ, Taylor PE, De Vern A, Chen GTS, Kellner, The Dialysis Vaccine Trial Study Group (1982) N Engl J Med 307: 1481-1486
11. Legler K, Strohmeyer H, Ritter S, Gerlich WH, Thomssen R (1983) Develop Biol Standard 54: 179-189
12. Jilg W, Delhoune C, Deinhardt F, Roumeliotou-Karayannis AJ, Papaevangelou GJ, Mushahwar IK, Overby LR (1984) J Med Virol 13: 171-178
13. Hollinger FB, Adam E, Heiberg D, Melnick JL (1982) In: Szmuness W, Alter HJ, Maynard JE (eds) Viral Hepatitis. Philadelphia, Franklin Institute Press, pp. 451-466
14. Hoofnagle JH, Gerety RJ, Smallwood LA, Barker LF (1977) Gastroenterology 72: 290-296
15. Heijtink RA, Van Hattum J, Schalm SW, Masurel N (1982) J Med Virol 10: 83-90
16. Heijtink RA, De Jong P, Schalm SW, Masurel N (1984) Hepatology 4: 611-614
17. Stevens CE, Szmuness W, Goodman AI, Weseley SA, Fotino M (1980) Lancet II: 1211-1213

ANTI-HBs/a DETERMINATION AFTER HEPATITIS B VACCINATION

Sir, — The determination of antibodies against the a determinant from HBsAg after vaccination with HBsAg/adw is of interest, since anti-HBs/a antibodies are thought to be protective. Two methods for measurement of these antibodies are in use: 1) Specific absorption of serum anti-HBs with pooled HBsAg/ay.[1] The reduction of anti-HBs, as measured in direct tests for anti-HBs, reflects the proportion of anti-HBs/a antibodies. 2) A radioimmunoassay or ELISA using HBsAg/ay as solid phase antigen.

We applied methods 1 and 2 on sera from our comparative study on the immunogenicity of recombinant and plasma-derived vaccine. Thirty-one health care workers were vaccinated with recombinant vaccine and twenty-five with plasma derived-vaccine, both from Merck, Sharp & Dohme. All participants showed seroconversion at month 7. In all individual sera sampled at month 7 we found that the anti-HBs contained 90-100% anti-HBs/a antibodies by method 1 in both groups of vaccinees, as published elsewhere.[2] The percentage of anti-HBs/a according to method 2 was calculated from the geometric mean anti-HBs concentrations found in Ausab (Abbott Laboratories) using HBsAg/adw,ayw coated beads ($Ausab_t$) and in Ausab using HBsAg/ayw coated beads ($Ausab_{ay}$). All sera were prediluted until the concentration in $Ausab_t$ was less than 200 IU/l. For both assays, $Ausab_t$ and $Ausab_{ay}$, anti-HBs was determined by linear intrapolation of the results from the test samples in between the results from a twofold dilution series of the WHO reference serum. Results in the recombinant vaccine and the plasma-derived vaccine groups showed 80 and 40% anti-HBs/a, respectively. An ELISA (Organon Diagnostics Research Labs, Oss, The Netherlands) using microtitre plates coated with HBsAg/ayw, showed 60 and 45% anti-HBs/a in the recombinant vaccine and plasma-derived vaccine groups, respectively.

The specific absorption method confirmed the findings of Scolnick et al[3] (90-100% anti-HBs/a after recombinant vaccine administration), whereas our results with method 2 (anti-HBs/a "specific" tests) are in accordance with those of Jilg et al.[4] (49% anti-HBs/a after plasma-derived vaccine administration). Our results show, however, that the apparent differences in percentage anti-HBs/a as published by Scolnick

Heijtink RA, Schalm SW. Anti-HBs/a determination after hepatitis B vaccination. Submitted for publication to Lancet.

et al. and Jilg et al. are not primarily related to the differences in the vaccines but to the methodology applied to assess anti-HBs/a antibodies.

Which test system provides the most useful data? In method 1, anti-HBs antibodies are absorbed with an excess of pooled HBsAg/ay, which may contain other epitopes in addition to a- and y-related epitopes. High, but also low affinity antibodies[5] are removed and the reduction of anti-HBs will be optimal. This test will likely overestimate the percentage of neutralizing anti-HBs/a antibodies.

Problems with the determination of anti-HBs/a by method 2 are illustrated in the figure. Anti-HBs/a containing reagents (anti-a monoclonal antibody, positive control serum Ausab$_t$ test, the WHO reference standard containing 200 IU/1) and anti-d monoclonal antibody were tested in various dilutions simultaneously in Ausab$_t$ and Ausab$_{ay}$. Monoclonal anti-a gave almost identical results in both tests, and fitted the line of identity. About 10% (based on cpm) anti-d monoclonal antibody measured in Ausab$_t$ was detected in Ausab$_{ay}$, presumably as a result of non-specific absorption. The line obtained with the Ausab positive control serum was also linear, but not parallel to the line of identity. Results for the WHO reference serum showed a curved line. Quantitation of anti-HBs/a using the Ausab positive control and/or the WHO reference serum as a standard is therefore in fact impossible, although both standards contain more than 90% anti-HBs/a antibodies, according to specific absorption. In our opinion, antibodies with variable affinity and/or reacting with different epitopes must be present to explain the discrepancies.

Detailed description of the anti-HBs response after vaccination is important. The initial interest concerned the quantitative aspects. Many investigators are shifting their interest to the qualitative aspect of the anti-HBs evoked by vaccines.

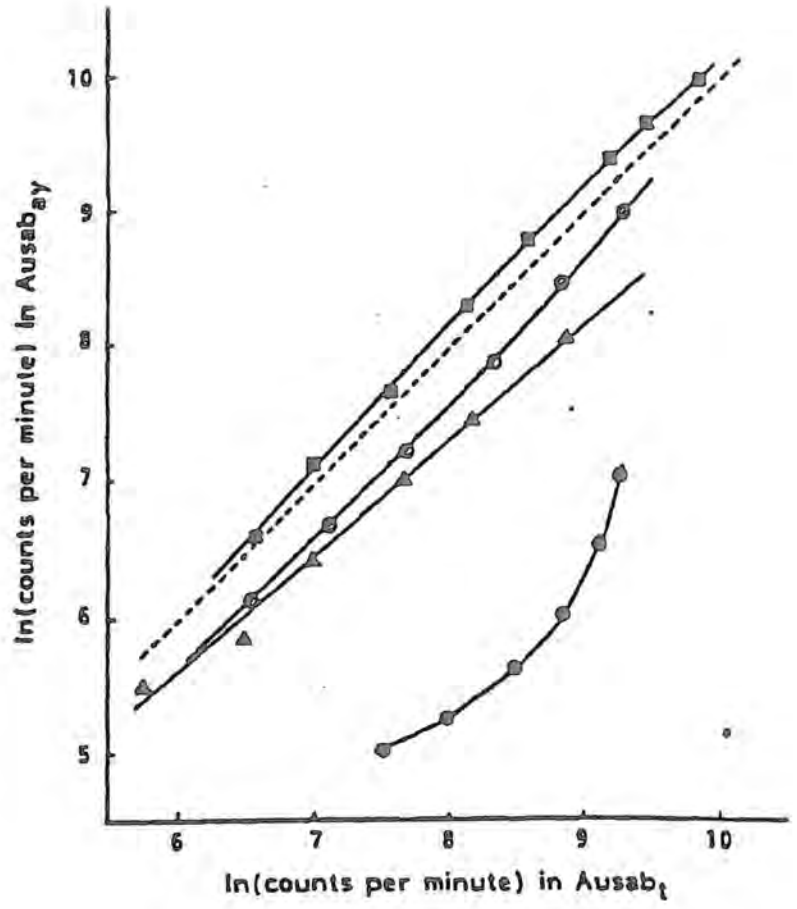
In our opinion, there is an urgent need for unambiguous test systems for vaccine evaluation, especially when results from vaccines with HBsAg from different sources (plasma, recombinant, synthetic) or with different compositions (with and without pre-s-polypeptides) are to be compared.

Departments of Virology and
Internal Medicine, Erasmus University,
P.O.Box 1738, 3000 DR Rotterdam,
The Netherlands

R.A.HEIJTINK
S.W.SCHALM

1. Hoofnagle JH, Gerety RJ, Smallwood LA, Barker LF. Subtyping of hepatitis B surface antigen and antibody by radioimmunoassay. Gastroenterology 1977; 72: 290-296.
2. Heijtink RA, Kruining J, Bakker M, Schalm SW. Immune response after vaccination with recombinant hepatitis B vaccine as compared to that after plasma-derived vaccine. Antiv Res (in press).
3. Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. J Am Med Ass 1984; 251: 2812-2815.
4. Jilg W, Delhoune C, Deinhardt F, Roumeliotou-Karayannis AJ, Papaevangelou GJ, Mushahwar IK, Overby LR. Hepatitis B surface antigen (HBsAg) subtype-specific antibodies in persons vaccinated against hepatitis B. J Med Virol 1984; 13: 171-178.
5. Brown SE, Howard CR, Zuckerman AJ, Steward MW. Affinity of antibody responses in man to hepatitis B vaccine determined with synthetic peptides. Lancet 1984; II: 184-187.

Figure: Comparison between counts per minute (natural logarithm) in $Ausab_{\varepsilon}$ (HBsAg/adw,ayw coated beads) and $Ausab_{ay}$ (HBsAg/ayw coated beads) in dilution series of monoclonal anti-a (■——■), monoclonal anti-d (●——●), the WHO standard reference serum (○——○), and the $Ausab_{\varepsilon}$ positive control serum (△——△). The dashed line represents identical results in $Ausab_{\varepsilon}$ and $Ausab_{ay}$.


10
9
8
7
6
5
6
7
8
9
10
ln(counts per minute) in Ausab$_{ay}$
ln(counts per minute) in Ausab$_{t}$

Maurice R. Hilleman, Eugene B. Buynak, Henry Z. Markus, Robert Z. Maigetter, William J. McAleer, Arlene A. McLean, William J. Miller, D. Eugene Wampler and Robert E. Weibel

22

Control of Hepatitis B Virus Infection: Vaccines Produced from Alexander Cell Line and from Recombinant Yeast Cell Cultures

Human hepatitis B virus has yet to be successfully grown in cell culture. Current vaccines *(1–5)* against hepatitis B virus employ hepatitis B surface antigen (HBsAg) that is obtained from the plasmas of human carriers of hepatitis B virus infection. The HBsAg stimulates antibody against the virus and prevents infection and illness caused by the agent. Available supply of suitable carrier plasma and the need to apply highly technical procedures to purify HBsAg and to render it safe limit the amount of plasma-derived vaccine that can be made and impose cost restrictions on its use. We have sought to explore alternative sources of HBsAg to prepare hepatitis B vaccine and have prepared and tested vaccines made from HBsAg secreted from carrier hepatocellular carcinoma (HCC) cells *(6)* and from yeast cells carrying an expression vector of HBsAg *(7)*. The properties of such vaccines are the subject of this report.

HEPATITIS B VACCINE DERIVED FROM A HEPATOCELLULAR CARCINOMA CELL LINE

Alexander and co-workers *(8)* recovered a continuous line of HCC cells (PLC/PRF/5: Alexander cell line) in culture from a cancer patient who was also an HBsAg carrier. These cells, grown in vitro, secrete HBsAg but no infectious virus *(9)*. The immortality of such cells offered an alternative source of HBsAg but the yields grown in conventional culture were too small to be considered feasible economically *(10–13)*. McAleer and colleagues *(6,14)*, in our laboratories, adapted the Alexander cells to growth in Vitafiber pseudocapillary units. In this system, the Alexander cells are propagated in the interstices of bundles of semipermeable membrane capillaries through which the growth medium is circulated. Maximal

VIRAL HEPATITIS and LIVER DISEASE
ISBN 0-8089-1678-5

Hilleman MR, Buynak ER, Markus HZ, Maigetter RZ, McAleer WJ, McLean AA, et.al. Control of Hepatitis B virus infection: Vaccines produced from alexander cell line and from recombinant yeast cell cultures. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Statton, 1984:307-14.

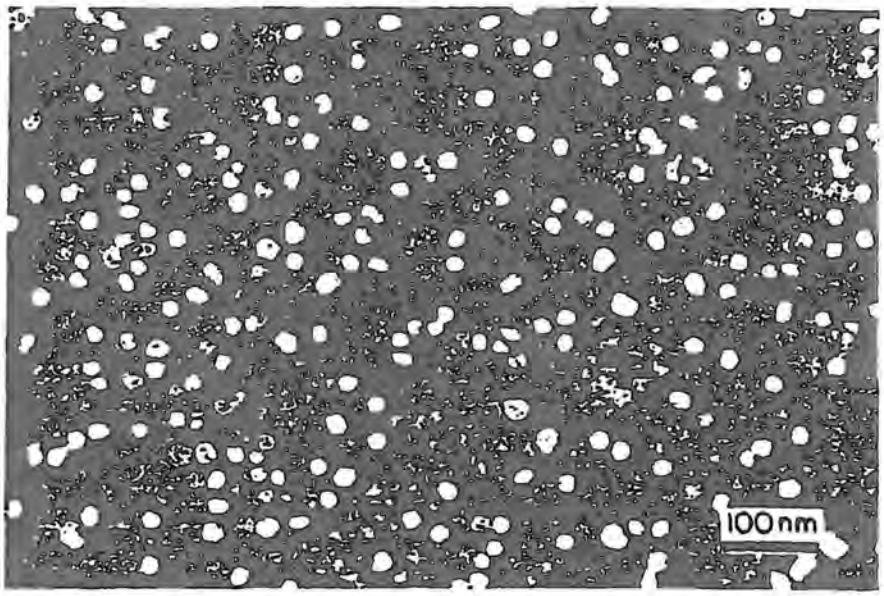


Fig. 22.1. Hepatitis B surface antigen particles purified from Alexander hepatocarcinoma cell culture fluid.

yields of HBsAg were obtained in the fiber bundle units under conditions that lowered cellular metabolism. This consisted of lowering the temperature of incubation to 32°C with the addition of 10^{-4} molar caffeine to the circulating medium. Such cells could be maintained for periods up to a year, with periodic harvest of fluid that contained an amount of HBsAg equal to that of some human plasmas. The HBsAg was readily purified from the cell culture fluid by immune affinity chromatography followed by digestion with pepsin and DNase.

Figure 22.1 shows purified HBsAg particles that were indistinguishable morphologically from those that were purified from human plasma. Particles obtained from plasma were essentially identical in all measurable aspects to those purified from Alexander cell fluids. The particles were 22 nm in diameter; the ultraviolet absorption spectra were the same; and the $E^{1\%}$ and the HBsAg to protein ratios were alike.

Purified HBsAg derived from Alexander cells was treated with formaldehyde and was formulated into vaccine *(6)* by absorbing 20 μg of HBsAg to each ml of aluminum hydroxide suspension containing 0.5 mg of aluminum and adding 1:20,000 concentration of thimerosal as preservative. The vaccine was proved safe in tests in four chimpanzees that were given aqueous material by the intravenous route.

The vaccine was assayed for immunizing potency in mice by a standardized extinction dilution assay and was compared with plasma-derived vaccine. Table 22.1 shows that the 50% extinction dose, ED_{50}, was nearly the same for both vaccines and the geometric mean titers were comparable. It is evident that the HBsAg produced in HCC cells is indistinguishable in potency from that derived from plasma.

Table 22.1
Mouse Potency of HBsAg Vaccine Prepared in Alexander Cell Culture Compared with That Prepared from Human Plasma

	Alexander Cell Vaccine		Plasma Vaccine Lot 799-2	
Vaccine (μg)	No. mice positive/total	G.M. Titer*	No. mice positive/total	G.M. Titer
10	8/10	1431	8/10	1729
2.5	8/10	504	9/10	1204
0.625	7/10	74	4/10	8
0.156	0/9	<8	0/10	<8
ED_{50}†	0.79		0.81	

*Geometric mean titer.
†Dose required to seroconvert 50% of mice.

Two persons who were initially seronegative for hepatitis B virus markers and who had advanced central nervous system cancer were given two primary doses of vaccine a month apart and a booster dose 6 months after the initial injection. The findings shown in Table 22.2 revealed that both patients developed antibody to HBsAg (anti-HBs) in low titer. Three persons, two of whom were given only the primary doses and one of whom was given all three doses of vaccine, but were lost to follow-up, demonstrated no anti-HBs response. The slow and relatively low antibody responses to the HCC cell-derived vaccine were similar to those in other immunosuppressed persons who were given vaccine of human plasma origin. The vaccine was well tolerated in all the subjects.

Table 22.2
Findings in Two Cancer Patients who Received Alexander Cell-Produced Hepatitis B Vaccine at Time 0, 1, and 6 Months

		Titer*					
			Months after Vaccination				
Observation	Patient	Pre-vaccine†	1	2	3	6	7
Anti-HBs	717-4	< 8	< 8	8	16	16	36
	-6	< 8	< 8	< 8	ND	< 8	36
HBsA	717-4	–	–	–	–	–	–
	-6	–	–	–	–	–	–
Anti-HBc	717-4	–	–	–	–	–	–
	-6	–	–	–	–	–	–
AST	717-4	18	25	16	24	16	14
	-6	9	7	8	ND	9	6
ALT	717-4	19	23	24	21	22	18
	-6	24	20	20	ND	17	12

*Titer is expressed in units. ND = no determination; – = below the limit of detection.
†7 days prior to starting vaccination.

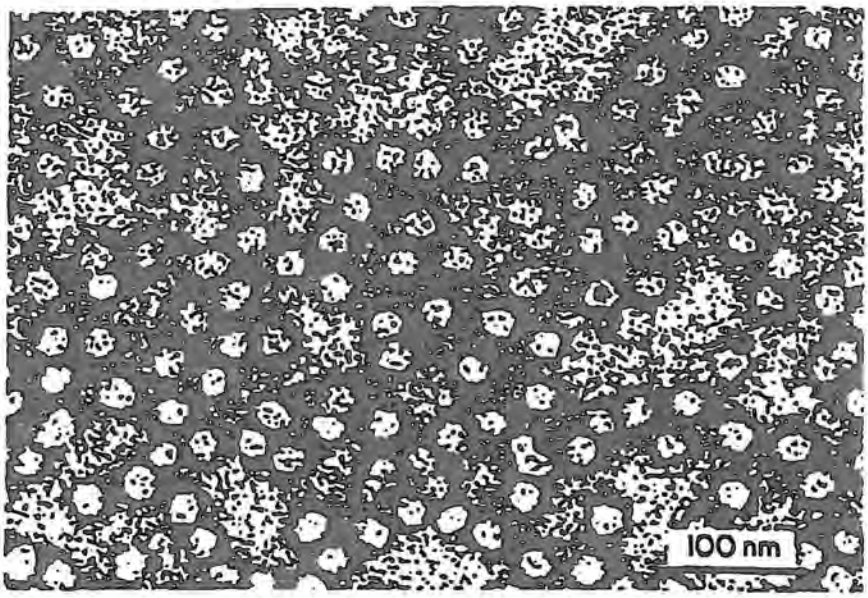


Fig. 22.2. Hepatitis B surface antigen particles purified from recombinant yeast cell culture.

Careful attention was given to the matter of safety of the vaccine, considering its origin from human liver cancer cells. The methods used for treatment in purifying the HBsAg and the DNA-destructive processes aimed at viral and cellular nucleic acids that were used to prepare the vaccine were of such efficiency as to delete any possible oncogenic DNA that might have been theoretically present in the starting fluid.

RECOMBINANT HEPATITIS B VACCINE

Joint efforts between our laboratories and those of W. Rutter and B. Hall led to the preparation of vectors carrying the DNA sequence for HBsAg *(7,15)*. The HBsAg was of subtype *adw* and was produced in fermentation cultures of *Saccharomyces cerevisiae* carrying the vector and employing yeast alcohol dehydrogenase I as the promoter. HBsAg was released from the cells by homogenization and was purified by immune affinity chromatography *(16)*.

Electron microscopy of yeast-derived HBsAg, as shown in Figure 22.2, revealed a homogeneous array of particles free of extraneous morphologic entities. The ultraviolet absorption spectrum was the same as for plasma-derived HBsAg with an $E^{1\%}$ of 45. The SDS-polyacrylamide gel electrophoretic pattern under reducing conditions shown in Figure 22.3 revealed a single band at 23,000 daltons (23K) corresponding to the nonglycosylated polypeptide of HBsAg derived from plasma.

The purified HBsAg was formulated into vaccine by adsorbing to aluminum hydroxide adjuvant to contain 40 μg of HBsAg protein and 0.5 mg aluminum per

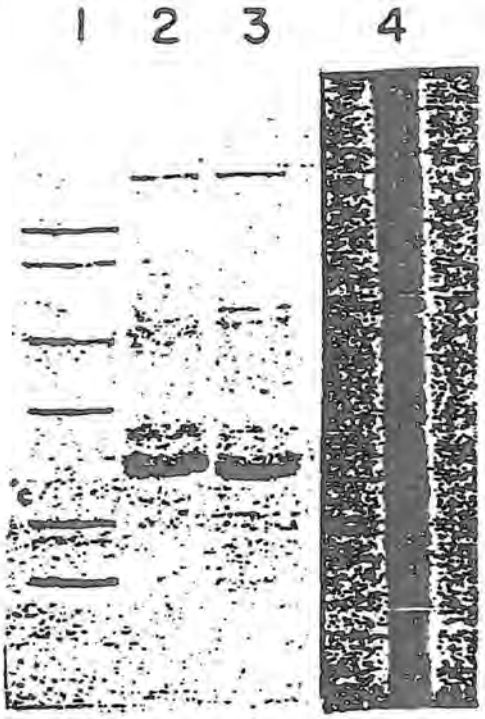


Fig. 22.3. SDS-polyacrylamide gel electrophoresis of purified Alexander cell (lane 2) and yeast-derived (lane 3) hepatitis B surface antigen. Lane 1 contains molecular weight standards and lane 4 contains clarified yeast extract before purification.

dose. The standardized extinction mouse potency test, shown in Table 22.3, demonstrated that the yeast-derived HBsAg was at least as potent as plasma-derived antigen based on the 50% extinction dose (ED_{50}) and the geometric mean titers.

Table 22.4 shows that grivet monkeys also developed antibody following vaccination with the yeast-derived antigen. A single injection at all dose levels resulted in seroconversion of all the animals in both yeast and plasma vaccine groups. High antibody titers were maintained for more than a year.

Protective efficacy was tested in challenge experiments with susceptible chimpanzees. In the tests shown in Table 22.5, four chimpanzees were given three 1-ml injections of the *adw* subtype yeast-derived vaccine 1 month apart and four animals were held as unvaccinated controls. One month after the third dose of vaccine was given, two vaccinated and two control animals were challenged intravenously with *adr* subtype virus and the other four vaccinated or unvaccinated animals were challenged with *ayw* subtype virus. All the vaccinated animals developed antibody following immunization and all were solidly protected against the virus with all serologic and histopathologic markers remaining negative. Protection

Table 22.3
Antigenic Potency in Mice of HBsAg Purified from Yeast and from Human Plasma

Vaccine Source	HBsAg dose per injection (μg protein)	Anti-HBs response after vaccination	
		No. pos./Total	GMT
Human Plasma	10	9/10	563
Lot 799-2	2.5	10/10	2235
	0.625	4/9	32
	0.156	0/10	4
ED_{50}	0.639		
Yeast	40	10/10	5432
Lot 81-4	10	10/10	3400
	2.5	8/10	673
	0.625	8/10	967
ED_{50}	< 0.625		

was afforded irrespective of HBsAg subtype. The finding of subtype cross-protection is consistent with the presence of the common *a* antigen determinant present in all hepatitis B virus subtypes *(17,18)*. That this common *a* antigen suffices to protect against all subtypes was confirmed recently in clinical studies *(19)* in which HBsAg/*ad* vaccine protected renal dialysis staff against type HBsAg/*ay* exposures.

Clinical studies of the yeast cell-derived vaccine have been initiated by our group. The early findings indicate most favorable antibody responses in man that are being reported elsewhere in this symposium (Abstr. SAT. LA 50 and chapter 23).

CONCLUSION

The evolution in our laboratories of a fiber bundle-engineered culture system for production of HBsAg by Alexander HCC cells presents a simple and practical means for hepatitis B vaccine preparation. However, the more recent develop-

Table 22.4
Antigenic Potency in Grivet Monkeys of HBsAg Purified from Yeast and from Human Plasma*

Vaccine Source	HBsAg dose per injection (μg protein)	Anti-HBs response after initial vaccine dose (Geometric mean titer)			
		Week 4	Week 8	Week 12	Week 52
Human plasma	10	36	213	170	127
Lot 86016	2.5	343	6227	17348	9924
	0.625	53	4642	3164	5688
	0.156	15	128	83	358
Yeast	40	88	1078	7103	11554
Lot 81-4	10	184	877	8489	4984
	2.5	225	1168	6361	10868
	0.625	109	925	518	313

*Vaccine given at time 0 and 4 weeks.

Table 22.5
Protective Efficacy of Purified Yeast HBsAg Vaccine

				Challenge Result			
Vaccine	Chimp	Anti-HBs Titers	HBsAg Subtype	HBsAg	Anti-HBc	AST & ALT Elevations	Liver Pathology
Yeast Vaccine	1	1830	*adr*	0	0	0	0
	2	540	*adr*	0	0	0	0
	3	18300	*ayw*	0	0	0	0
	4	7200	*ayw*	0	0	0	0
Controls	5	< 8	*adr*	+	+	+	+
	6	< 8	*adr*	+	+	+	+
	7	< 8	*ayw*	+	+	+	+
	8	< 8	*ayw*	+	+	+	+

ment, by our group, of HBsAg production in recombinant yeast cells appears to offer advantages that exceed those of the Alexander cell system. The most important advantages of the recombinant vaccine relate to simpler HBsAg production by yeast cells in fermentation tanks and removal of any lingering apprehensions about safety of vaccine derived from a human cancer cell source.

Human plasma-derived hepatitis B virus vaccine is limited by the supply of plasma and the technical complexity of the process to assure safety and efficacy. Alternative technologies developed in our laboratories include production from (a) hepatocellular carcinoma cells (Alexander cell line: PLC/PRF/5) cells in culture, and (b) from recombinant yeast carrying a high expression vector for hepatitis B surface antigen (HBsAg) gene subtype *adw*. HBsAg was purified mainly by affinity chromatography and formulated on alum adjuvant. The polypeptide dimer of HBsAg produced in Alexander cells was identical to that from plasma; the yeast-derived dimer was not glycosylated but was otherwise the same. Both vaccines were as potent as plasma vaccine in mice and both were highly immunogenic when tested in humans. The subtype *adw* yeast vaccine was also highly immunogenic for monkeys and gave solid protection in chimpanzees against challenge with heterologous subtype *adr* and *ayw* viruses. Vaccine prepared from yeast offers a means for simplified production of HBsAg in fermentation tank culture and does not bear the stigma of cancer cell origin of Alexander cell vaccine. Recombinant yeast-derived HBsAg shows great promise for simplified mass production of hepatitis B vaccine.

REFERENCES

1. Hilleman MR, Berland AU, Buynak EB, et al. Clinical and laboratory studies of HBsAg vaccine. In Vyas GN, Cohen SN, Schmid R eds. Viral Hepatitis. Philadelphia, Franklin Institute Press, 1978:525–537.
2. Hilleman MR, Buynak EB, McAleer WJ, et al. Hepatitis A and hepatitis B vaccines. In Szmuness W, Alter H, Maynard J eds. Viral Hepatitis. 1981 International Symposium. Philadelphia, Franklin Institute Press, 1982:385–397.

3. Buynak EB, Roehm RR, Tytell AA, et al. Vaccine against human hepatitis B. JAMA 1976; 235:2832–2834.
4. Adamowicz P, Gerfaux G, Platel A, et al. Large scale production of an hepatitis B vaccine. In Maupas P, Guesry P eds. Hepatitis B Vaccine. INSERM Symposium No. 18. Amsterdam, Elsevier/North-Holland Biomedical Press, 1981:37–49.
5. Coutinho RA, Lelie N, Albrecht-Van Lent P, et al. Efficacy of a heat inactivated hepatitis B vaccine in male homosexuals: outcome of a placebo controlled double blind trial. Br Med J 1983; 286:1305–1308.
6. McAleer WJ, Markus HZ, Wampler DE, et al. Vaccine against human hepatitis B virus prepared from antigen derived from human hepatoma cells in culture. Proc Soc Exp Biol Med 1984; 175:314–319.
7. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.
8. Alexander J, Macnab G, Saunders R. Studies on *in vitro* production of hepatitis B surface antigen by a human hepatoma cell line. In Pollard M ed. Perspectives in Virology. New York, Raven Press, 1978:103–120.
9. Tabor E, Copeland JA, Mann GF, et al. Nondetection of infectious hepatitis B virus in a human hepatoma cell line producing hepatitis B surface antigen. Intervirology 1981; 15:82–86.
10. Macnab GM, Alexander JJ, Lecatsas G, et al. Hepatitis B surface antigen produced by a human hepatoma cell line. Br J Cancer 1976; 34:509–515.
11. Skelly J, Copeland JA, Howard CR, et al. Hepatitis B surface antigen produced by a human hepatoma cell line. Nature 1979; 282:617–618.
12. Copeland JA, Skelly J, Mann GF, et al. Hepatitis B surface antigen production as a growth cycle-related terminal event in PLC/PRF/5 hepatoma cells. J Med Virol 1980; 5:257–264.
13. Daemer RJ, Feinstone SM, Alexander JJ, et al. PLC/PRF/5 (Alexander) hepatoma cell line: further characterization and studies of infectivity. Infect Immun 1980; 30:607–611.
14. McAleer WJ, Markus HZ, Bailey FJ, et al. Production of purified hepatitis B surface antigen from Alexander hepatoma cells grown in artificial capillary units. J Virol Meth 1983; 7:263–271.
15. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
16. Wampler DE, Buynak EB, Harder BJ, et al. Hepatitis B vaccine purification by immune affinity chromatography. In Chanock R, Lerner R eds. Modern Approaches to Vaccines. Cold Spring Harbor, Cold Spring Harbor Laboratory, 1984, in press.
17. Purcell RH, Gerin JL. Hepatitis B subunit vaccine: a preliminary report of safety and efficacy tests in chimpanzees. Am J Med Sci 1975; 270:395–399.
18. Barker LF, Maynard JE, Purcell RH, et al. Viral hepatitis, type B, in experimental animals. Am J Med Sci 1975; 270:189–195.
19. Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine in medical staff of hemodialysis units. N Engl J Med 1982; 307:1481–1486.

Journal of the Hong Kong Medical Association, Vol. 37, No. 2, 1985.

Recombinant Yeast Human Hepatitis B Vaccine

MAURICE R. HILLEMAN, ROBERT E. WEIBEL & EDWARD M. SCOLNICK

ABSTRACT

The human hepatitis B vaccine of plasma origin prepared by our laboratories has performed well with respect to safety, immunogenicity and protective efficacy. The vaccine has now been used in about 2 million persons worldwide. The recent demonstration of HTLV-III or LAV virus' putative role in AIDS and its ready inactivation by the steps used in vaccine production has removed the last lingering doubts about safety from the standpoints of AIDS in relation to plasma-derived vaccine.

The limit in supply of human hepatitis B carrier plasma and the need to apply highly technical procedures for purification and inactivation stimulated the seeking of an alternative source of antigen from yeast bearing the surface antigen gene. Preliminary data indicate that the recombinant vaccine prepared by our laboratories has shown at least equivalent immunogenicity for animals as well as human adults and children compared with plasma-derived vaccine. The antigen in the vaccine is highly purified and causes no clinically important reactions. Eighteen lots of vaccine have been prepared to date and licensure is expected during late 1985.

Keywords: *Recombinant Hepatitis B vaccine — yeast — immunogenicity — reactions*

PLASMA VACCINE

Human hepatitis B can be readily controlled by prophylactic vaccination. Licensed "first generation" vaccines prepared using surface antigen purified from the plasma of hepatitis B carriers have been produced in several countries (1-5).

Vaccine prepared in our laboratories (see Table 1) was licensed for general distribution in 1981. This vaccine has performed very well. The vaccine consists of essentially pure surface antigen that is treated by 3 different inactivation procedures which are sequentially applied and which are designed to destroy all microbial life forms. The vaccine incorporated into alum adjuvant induces hepatitis B antibody in more than 95% of recipients, overall, and affords more than 95% protection against hepatitis B in exposed normal persons (6). As may be expected, the vaccine is less effective in persons whose immune systems are immunodeficient or are immunosuppressed. Less than expected antibody responses have been reported in some situations of use (7,8). Investigation has revealed that such lower antibody responses may occur in persons in whom the vaccine was injected into the buttocks rather than into the arm. Vaccine given in the buttocks may fail frequently to reach muscle and be deposited instead into fat where it may not be well mobilized (9).

Table 1

Present: Plasma-derived human hepatitis B vaccine	
Antigen source:	Plasma of human hepatitis B carriers.
Preparation:	Essentially pure surface antigen.
	Inactivation by 3 different methods, applied sequentially.
	Incorporated in alum adjuvant.
Efficacy:	>95% of normal children and adults develop antibody after 3 doses.
	>95% protection in normal persons.
	Less effective in immunodeficient or immunosuppressed persons.
	Duration of immunity is not known. It is also unknown when late booster doses of vaccine might be needed.
Targets:	Persons of defined high risk. Especially infants born to carrier mothers in high prevalence areas.
	Eventually all persons.
Safety and Extent of Use:	>4,500,000 doses distributed.
	>2,000,000 persons received vaccine to date.
	The vaccine is safe, including AIDS concerns.

Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486, U.S.A.
Maurice R. Hilleman, Ph. D., D. Sc.
Edward M. Scolnick, M.D.

Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, U.S.A.
Edward M. Scolnick, M.D.
Correspondence to: Dr. Maurice R. Hilleman

Presented at: Hong Kong Society of Gastroenterology
1985 Annual Scientific Conference: Hepatitis — New Horizons
March 24, 1985

The duration of protective efficacy following vaccination is not known but, as shown in Figure 1, the great majority of persons (39/44) retain antibody for at least 4-5 years (see 6). The 3-dose regimen for immunization, giving the booster dose at 6 months after the initial dose, is highly effective in priming the immune system for rapid anamnestic immune recall on later contact with viral antigen on revaccination (10) or on contact in nature (11) as well as in providing resident active immunity. Because immunity against hepatitis B infection may be present at antibody levels less than detectable in the laboratory, and because of the phenomenon of anamnestic recall, it may be premature (12) to project when late booster immunizations might be needed.

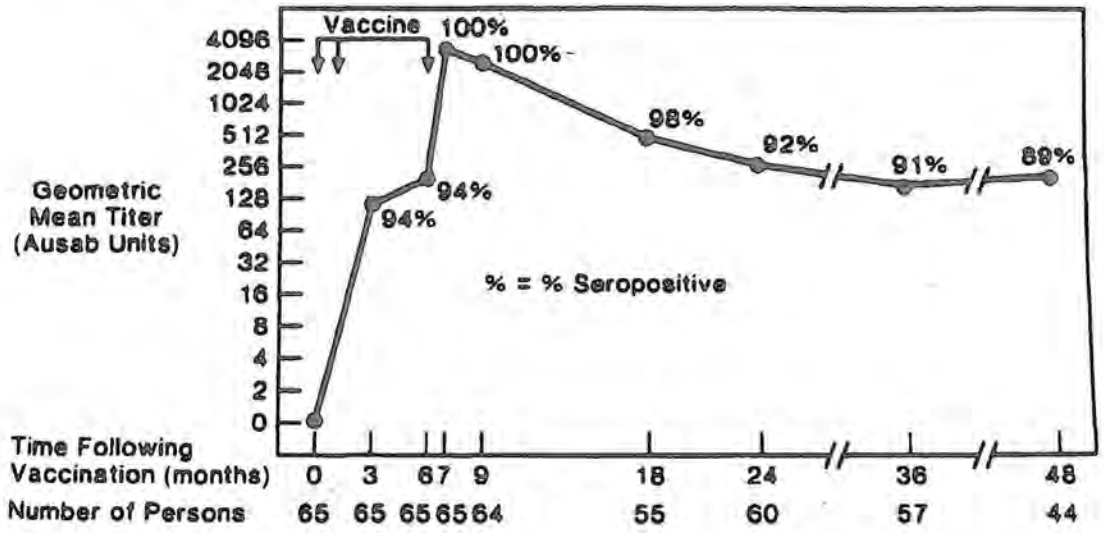


Figure 1
Antibody development and persistence in adults who received 3 doses of hepatitis B vaccine (study 555).

The vaccine has been targeted mainly for use in special groups at high risk to hepatitis B. Presently, added emphasis is being given to preventing infection in newborn infants born to carrier mothers in highly endemic populations such as in Eastern Asia and Africa. Eventually, all susceptible persons may be vaccinated. More than 4.5 million doses of the vaccine have been distributed and more than 2 million persons have received one or more doses of the vaccine to date.

Concern has been expressed for possible transmission of acquired immune deficiency disease (AIDS) by improperly prepared hepatitis B vaccines since the antigen is obtained from human plasma. Retroviruses of the HTLV-III or LAV group have now been shown (13-17) to be the likely cause for this blood and body secretion-transmitted disease. These agents are readily inactivated and destroyed by the process used to prepare the vaccine (18), giving direct evidential proof for the safety of the vaccine from the standpoint of "AIDS virus".

RECOMBINANT YEAST VACCINE

The production of human hepatitis B vaccine from the human plasma source is limited by the available supply of infected plasma and by the need to apply highly technical procedures for purification and inactivation of possible infectious agents that might be present in such plasma. Because of this, alternative sources of antigen were sought and two genetic recombinant antigens have been used in our laboratories (19-21). One of these, the carrier Alexander hepatocarcinoma cell (22) is a recombinant of nature. The other, obtained by cloning the gene of hepatitis B surface antigen into yeast (23), is quite unnatural.

Alexander hepatocarcinoma cell. Vaccine (19) prepared from antigen secreted from the hepatocarcinoma cells grown in culture initially proved very attractive from the standpoint of yield and immunizing potency, but it was evident that a vaccine derived from a non-cancer source would be more acceptable. Hepatitis B vaccine prepared using antigen obtained from either transformed or frankly neoplastic human or animal cells are not likely to be accepted by licensing authorities and the medical profession, especially since the antigens can be made efficiently in recombinant yeast cells.

Hepatitis B surface antigen preparation in recombined yeast. Joint efforts between our laboratories and those of Drs.

Journal of the Hong Kong Medical Association, Vol. 37, No. 2, 1985.

Rutter and Hall of the Universities of California and Washington led to the preparation of a recombinant yeast cell system for producing hepatitis B antigen (23). Figure 2 shows the principal defined areas of the hepatitis B genome The gene region that encodes the hepatitis B surface antigen, but not the "pre-S" (24) or the core antigen, was inserted into a suitable vector and was implanted into ordinary Baker's yeast or *Saccharomyces cerevisiae*. The plasmid construct, shown in Figure 3, consists of the hepatitis B surface antigen gene flanked on one side by a promoter (glyceraldehyde 3-P dehydrogenase I, ADH-I), both being essential to proper translation of the surface antigen. The rest of the nucleic acid in the plasmid is needed to achieve its functions in the yeast cell system and to serve as a marker (yeast leucine gene) for presence of the plasmid in yeast cells. The construct employed subtype Adw surface antigen gene.

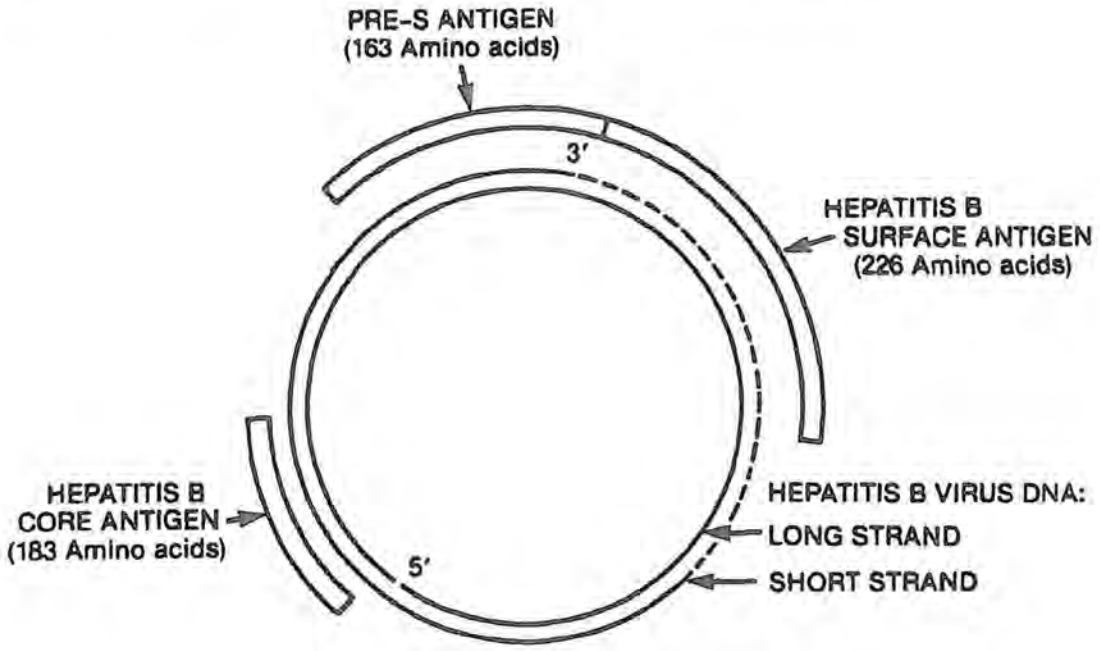


Figure 2
Hepatitis B virus genome and defined antigens that are produced

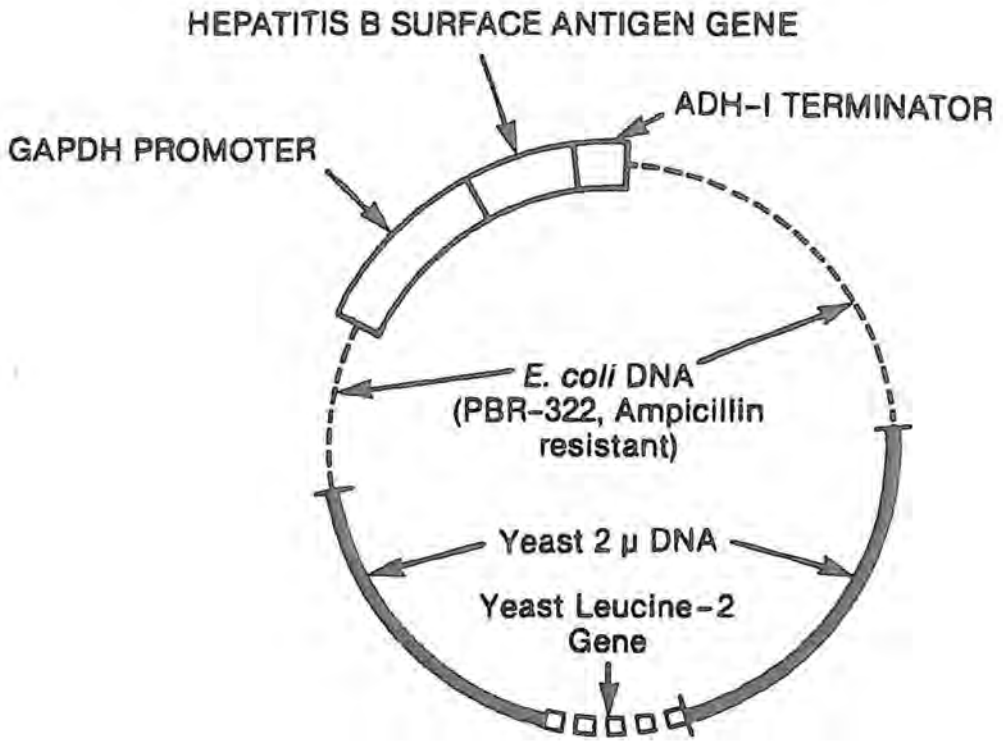


Figure 3
Construct of plasmid (pHBS56-GAP347/33) used to produce hepatitis B surface antigen in yeast.

The hepatitis B surface antigen produced in yeast is cell-associated. Surface antigen was released from the yeast cells by homogenization, the purification was achieved mainly by silica, hydrophobic interaction (butyl agarose) and gel exclusion chromatographies. The hepatitis B surface antigen used in the vaccine consists of polypeptides that are identical in amino acid sequence to those of human plasma source but lacking glycosylation. The glycosyl groups are not required for immunogenicity. Other measurable physical, chemical, and immunological attributes of the yeast-derived vaccine are substantially the same as those of the antigen prepared from human plasma.

As stated above, the recombinant hepatitis B surface antigen vaccine does not contain core antigen, *e* antigen, or antigen from the so-called "pre-S" region (see Figure 2). Antibody against core antigen and perhaps against *e* antigen may provide at least partial protection against hepatitis B virus infection (25-27). Antibody has been demonstrated in infected individuals that reacts with antigen encoded in the pre-S region (28-30) but it is not known whether such antibody may play a role in protective immunization. Though suggestions of the importance of pre-S region in generating full immunity to hepatitis B have been made (31), this statement is not supported by the known scientific evidence and the published literature (32). Indeed, vaccines without pre-S antigen have been proved highly effective in inducing immunity against hepatitis B in the extensive clinical and field studies carried out during the past several years (6,33-34). It is quite clear that there are many immunologic determinants or epitopes within the collection of viral antigens produced under the total of the viral genetic code. The question might be raised of how many different epitopes are needed or ought to be included in the vaccine. The *a* antigen epitopes of the surface antigen are quite adequate to afford solid and lasting protection against hepatitis B and there is presently no evident need or benefit to be derived from increasing the cost or complexity of the vaccine by adding antigens such as those from the pre-S region.

Journal of the Hong Kong Medical Association, Vol. 37, No. 2, 1985.

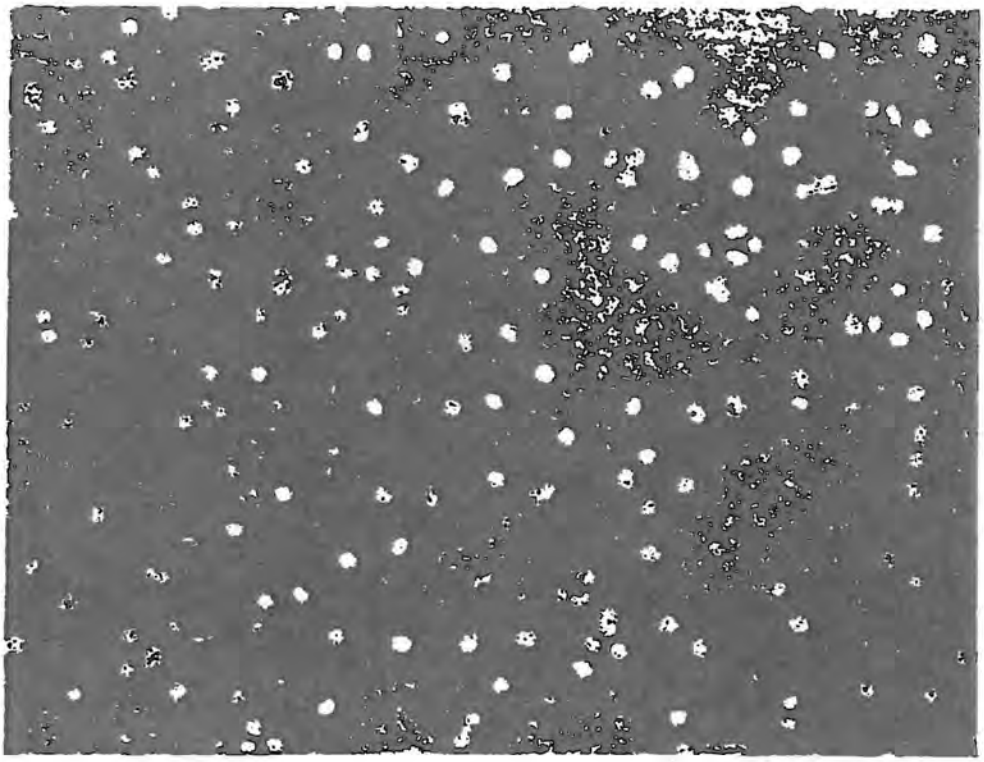


Figure 4
Electron micrograph of purified hepatitis B surface antigen derived from yeast recombinant cells (Lot CL-Y52-1, magnification 156, 750X)

The hepatitis B surface antigen particles produced in yeast cells, shown in Figure 4, are morphologically similar to those isolated from human plasma though the mean particle size of the former may be slightly smaller.

Hepatitis B vaccine prepared from recombinant yeast-derived surface antigen.

The purified antigen was formulated into vaccine by adsorbing to aluminum hydroxide adjuvant to contain 10 μg of antigen and 0.5 mg aluminum per 1 ml vaccine dose. Potency assay by the standard extinction mouse potency assay, as shown in Table 2, showed the yeast-derived vaccine to be at least as potent as plasma-derived antigen based on comparison of the 50% extinction dose (ED_{50}) and the geometric mean titers.

Table 2

Antigenic potency in mice of HBsAg purified from yeast and from human plasma

Vaccine Source	Antigen Dose per injection (μg protein)	Anti-HBsAg response after vaccination	
		no. pos./total	GMT
Human plasma	10	9/10	563
Lot 799-2	2.5	10/10	2,235
	0.625	4/9	32
	0.156	0/10	4
ED_{50}	0.639		
Yeast	40	10/10	5,432
Lot 81-4	10	10/10	3,400
	2.5	8/10	673
	0.625	8/10	967
ED_{50}	<0.625		

Chimpanzees given yeast recombinant hepatitis B vaccine in suitable regimen develop antibodies and are protected against infection on challenge with live hepatitis B virus. In the tests summarized in Table 3, four chimpanzees were given three intramuscular injections of vaccine containing 40 μg of antigen per ml dose at monthly intervals. One month after the third dose was given, 2 vaccinated and 2 control animals were challenged intravenously with heterologous *adr* subtype virus and a similar group of animals were challenged with heterologous *ayw* subtype virus. All the vaccinated animals developed antibody following immunization and all were solidly protected against the virus with all serologic and histopathologic markers remaining negative. The hepatitis B surface antigen contains the *a* antigen common to all subtypes plus the *d* and *w* subtype determinants. Protection was given against heterologous subtypes *adr* and *ayw*, showing the adequacy of the broad spectrum *a* epitopes in the recombinant antigen to protect against the heterologous subtypes. The finding of heterologous subtype protection with recombinant-derived vaccine is consistent with the findings with plasm-derived vaccines obtained in studies in animals (35-36) and in clinical studies (34) in which subtype *ad* vaccine protected renal dialysis staff workers against subtype *ay* challenge.

Table 3

Protective efficacy of purified yeast antigen vaccine

Vaccine	Chimp	Antibody Response to HBsAg	Challenge				
			Subtype	Result			
				Antigenemic (HBsAg)	Anti-HBcAg	Enzyme Elevations	Liver Pathology
Yeast Vaccine	1	1,830	Adr	0	0	0	0
	2	540	Adr	0	0	0	0
	3	18,300	Ayw	0	0	0	0
	4	7,200	Ayw	0	0	0	0
Controls	5	<8	Adr	+	+	+	+
	6	<8	Adr	+	+	+	+
	7	<8	Ayw	+	+	+	+
	8	<8	Ayw	+	+	+	+

Journal of the Hong Kong Medical Association, Vol. 37, No. 2, 1985.

Clinical tests in human beings. Studies in human subjects of the recombinant yeast vaccine have been initiated for purpose of measuring antibody responses and for demonstrating protective efficacy. About 1500 persons of diverse age, sex, and health status, and geographic residence have received vaccine to date. There were no important clinical reactions attributed to vaccination. Mild soreness at the injection site has been reported in 19% of recipients and other minor complaints such as headache, fatigue and malaise have been stated by a small percentage of vaccinees.

Prior studies established (6,33-34) the relationship between antibody response to vaccination and immunity to hepatitis B. Though any new vaccine must stand on its own merits, it is instructive to compare the serologic responses in human beings to the widely used plasma-derived vaccine prepared in our laboratories with those to the new recombinant preparation.

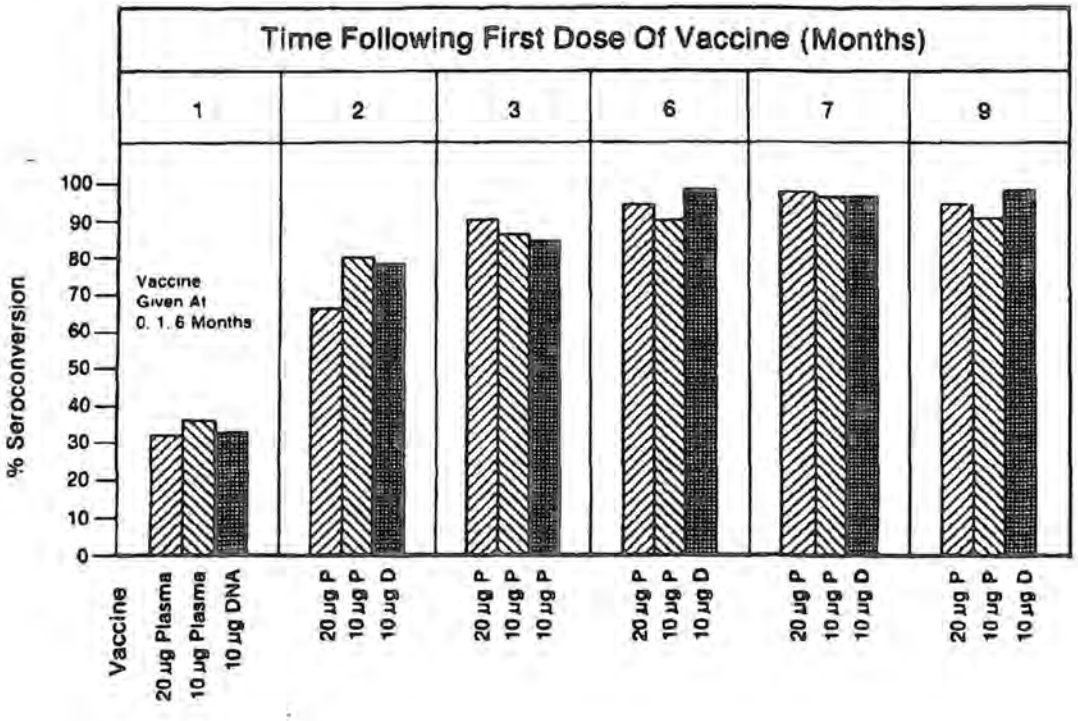


Figure 5
Serologic responses to 3 doses of plasma (20 µg or 10 µg) compared with recombinant (10 µg) vaccine in adults

Figure 5 shows the serologic findings in a composite of studies carried out by our laboratories to compare the antibody responses in adult persons to 3 doses of plasma-derived vaccine at 20 or 10 µg antigen per dose with that of the recombinant vaccine at 10 µg per dose. Data were from 400 to 800 subjects per vaccine group. All vaccines were given intramuscularly by the same regimen at time 0, 1 and 6 months. The rate and rapidity of antibody seroconversion in persons given 10 µg yeast vaccine compared with 10 µg or 20 µg plasma vaccine per dose were nearly alike. Most important, 87% of the subjects had developed antibody within 1 month following injection of the second dose of yeast-derived vaccine (3-month bleeding) and this was increased to 96-99% by 1 or 2 months following the booster dose given at 6 months.

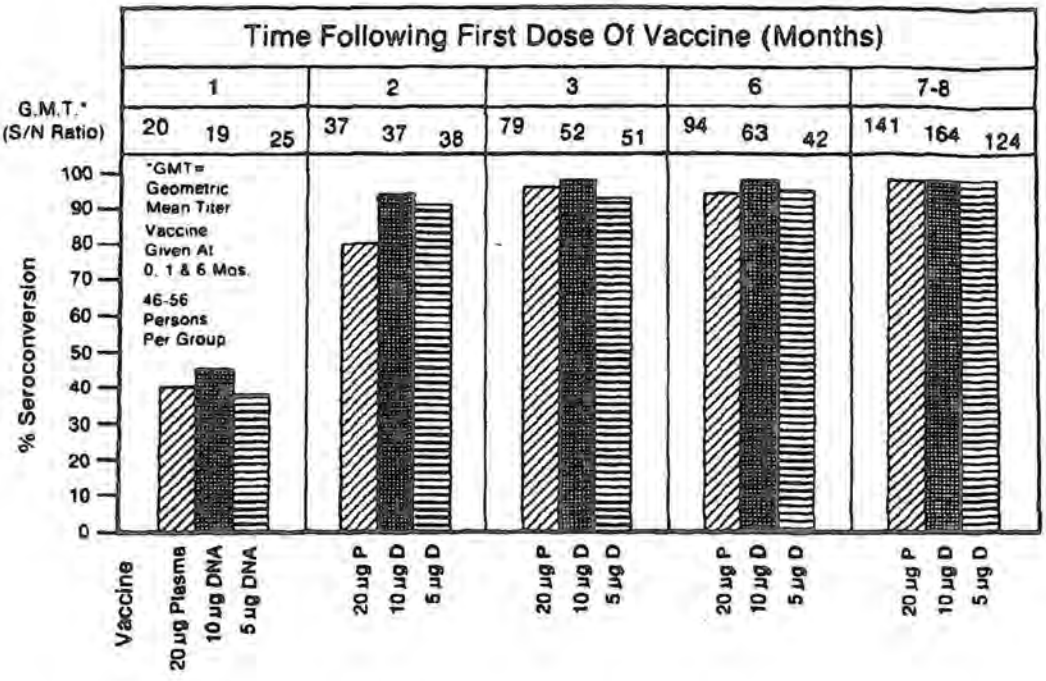


Figure 6
Serologic responses to 3 doses of plasma (20 µg) compared with recombinant (10 µg or 5 µg) vaccines in 21-30 year-old persons (adapted from Davidson and Krugman, Lancet 1: 108, 1985).

Similar findings, summarized in Figure 6, were obtained in studies carried out in 21-30 year old adults by Davidson and Krugman (37) in which rates for seroconversion, and heights of antibody following 20 µg dose plasma vaccine were compared with 10 µg or 5 µg dose yeast vaccine. These authors suggested that the lesser antibody responses to yeast recombinant vaccine reported by Jilg *et al.* (38) might have been related to the small numbers of individuals included in that study.

Journal of the Hong Kong Medical Association, Vol. 37, No. 2, 1985.

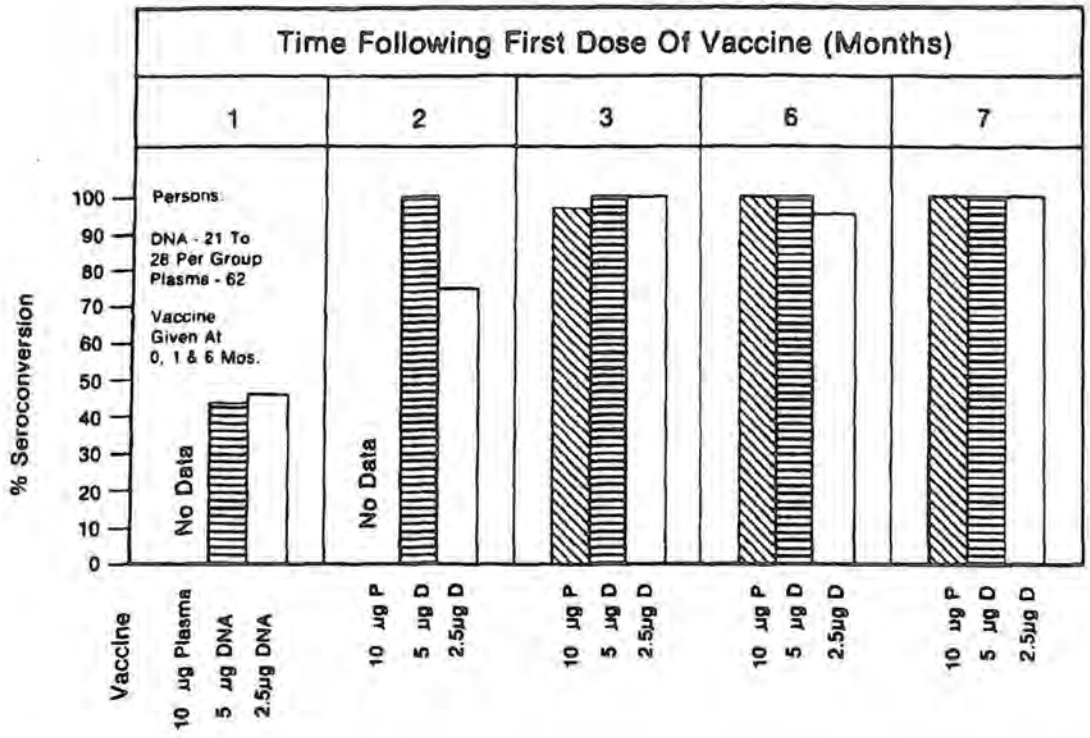


Figure 7
Serologic responses to 3 doses of plasma (10 µg) compared with recombinant (5 µg or 2.5 µg) vaccines in children 1-11 years of age.

Studies to measure antibody responses in children and infants are in progress. Only limited findings are available to date and these are from studies carried out by our group in 1- to 11-year old children. Figure 7 shows the serologic responses in these children, to 3 doses of plasma-derived vaccine given in 10 µg dose (62 children) compared with yeast recombinant vaccine given in 5.0 µg or 2.5 µg dose (21 and 28 children per group, respectively). The responses were essentially equivalent in all groups, though it must be noted that the numbers of individuals given vaccine are small.

CONCLUDING REMARKS

It is clear, we believe, that the plasma-derived hepatitis B vaccine has performed in an exemplary way and has provided a means for inducing immunity, with safety, against human hepatitis B virus infection. The necessity for developing a substitute but equally satisfactory vaccine, free from the need for human plasma and technologically simpler to produce, has been accomplished by the application of yeast recombinant technology. It is anticipated that the yeast vaccine will be licensed in the U.S.A. and other countries by late 1985 and that the vaccine will be available for general distribution in early 1986. In anticipation of the development of such recombinant vaccines, the World Health Organization convened a group of experts during November of 1984 who wrote the provisional requirements for the standardization and control of hepatitis B vaccine made by recombinant DNA techniques in yeast. These requirements should be made final before the end of 1985 and should provide a basis for worldwide regulatory control of hepatitis B vaccine produced in recombinant yeast cells.

Acknowledgement:

The authors are indebted to Dr. David J. West, Ph. D., M.P.H. and to Dr. Barbara A. Zajac, M.D., Ph. D. for the clinical response data.

REFERENCES

1. Buynak, EB; Roehm, RR; Tytell, AA et al: Vaccine against human hepatitis B. Journal of the American Medical Association 1976; 235: 2832-2834.
2. Hilleman, MR; Bertland, AU; Buynak, EB et al: Clinical and laboratory studies of HBsAg vaccine; in: Vyas, GN; Cohen, SN and Schmid, R (Eds) Viral Hepatitis, pp. 525-537 (The Franklin Institute Press, Philadelphia 1978).
3. Adamowicz, P; Gerlaux, G; Flatel, A et al: Larger scale production of an hepatitis B vaccine; in: Maupas, P and Guesry, P (Eds) Hepatitis B Vaccine. INSERM Symposium No 18, pp. 37-49 (Elsevier/North-Holland Biomedical Press, New York 1981).
4. Hilleman, MR; Buynak, EB; McAleer, WJ et al: Hepatitis A and hepatitis B vaccines; in: Szmuness, W; Alter, H and Maynard, J (Eds) Viral Hepatitis. 1981 International Symposium, pp. 385-397 (The Franklin Institute Press, Philadelphia 1982).
5. Coutinho, RA; Lelie, N; Albrecht-Van Lent, P et al: Efficacy of a heat inactivated hepatitis B vaccine in male homosexuals: outcome of a placebo controlled double blind trial. British Medical Journal 1983; 286: 1305-1308.
6. Szmuness, W; Stevens, CE; Zang, EA et al: A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. Hepatology 1981; 1: 377-385.
7. Schaaff, DM; Lender, M; Snedeker, P et al: Hepatitis B vaccine in a hospital. Annals of Internal Medicine 1984; 101: 702-721.
8. Strickler, AC; Kibsey, PC and Vellend, H: Seroconversion rates with hepatitis B vaccine. Annals of Internal Medicine 1984; 101: 564.
9. CDC: Suboptimal response to hepatitis B vaccine given by injection into the buttock. Morbidity and Mortality Weekly Report 1985; 34: 105-108, 113.
10. Hilleman, MR: Vaccines against viral hepatitis. International Review of the Army, Navy and Air Force Medical Services 1984; 57: 11-24.
11. Stevens, CE; Taylor, PE; Tong, MJ et al: Hepatitis B vaccine: an overview; in: Vyas, GN; Dienstag, JL and Hoofnagle, JH (Eds) Viral Hepatitis and Liver Disease, pp. 275-291 (Grune & Stratton, Orlando 1984).
12. Jilg, W; Schmidt, M; Deinhardt, F et al: Hepatitis B vaccination: How long does protection last? Lancet 1984; 2: 458.
13. Vilmer, E; Rouzioux, C; Vezinet Brun, F et al: Isolation of new lymphotropic retrovirus from two siblings with haemophilia B, one with AIDS. Lancet 1984; 1: 753-757.
14. Popovic, M; Sarngadharan, MG; Read, E et al: Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 1984; 224: 497-500.
15. Gallo, RC; Salahuddin, SZ; Popovic, M et al: Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 1984; 224: 500-503.
16. Schupbach, J; Popovic, M; Gilden, RV et al: Serological analysis of a subgroup of human T-lymphotropic retroviruses (HTLV-III) associated with AIDS. Science 1984; 224: 503-505.
17. Sarngadharan, MG; Popovic, M; Bruch, L et al: Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS. Science 1984; 224: 506-508.
18. CDC: Hepatitis B vaccine: Evidence confirming lack of AIDS transmission. Morbidity and Mortality Weekly Report 1984; 33: 685-687.
19. McAleer, WJ, Markus, HZ; Wampler, DE et al: Vaccine against human hepatitis B virus prepared from antigen derived from human hepatoma cells in culture. Proceedings of the Society for Experimental Biology and Medicine 1984; 175: 314-319.
20. McAleer, WJ; Buynak, EB; Maigetter, RZ et al: Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307: 178-180.
21. Scolnick, EM; McLean, AA; West, DJ et al: Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. Journal of the American Medical Association 1984; 251: 2812-2815.
22. Alexander, J; Macnab, G and Saunders, R: Studies in *In Vitro* production of hepatitis B surface antigen by a human hepatoma cell line; in Pollard, M (Ed) Perspectives in Virology, Vol 10, pp. 103-120 (Raven Press, New York 1978).
23. Valenzuela, P; Medina, A; Rutter, WJ et al: Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298: 347-350.
24. Tiollais, P; Dejean, A; Brechot, C et al: Structure of hepatitis B virus DNA; in: Vyas, GN; Dienstag, JL and Hoofnagle, JH (Eds) Viral Hepatitis and Liver Disease, pp. 49-65 (Grune & Stratton, Orlando 1984).
25. Tabor, E and Gerety, RJ: Possible role of immune responses to hepatitis B core antigen in protection against hepatitis B infections. Lancet 1984; 1: 172.
26. Murray, K; Bruce, SA; Hinnen, A et al: Hepatitis B virus antigens made in microbial cells immunise against viral infection. Embo Journal 1984; 3: 645-650.
27. Stephan, W; Prince, AM and Brotman, B: Modulation of hepatitis B infection by intravenous application of an immunoglobulin preparation that contains antibodies to hepatitis B e and core antigens but not to hepatitis B surface antigen: Journal of Virology 1984; 51: 420-424.
28. Neurath, AR; Kent, SBH and Strick, N: Location and chemical synthesis of a pre-S gene coded immunodminant epitope of hepatitis B virus. Science 1984; 224: 393-394.
29. Heermann, KH; Goldmann, U; Schwartz, W et al: Large surface proteins of hepatitis B virus containing the pre-S sequence. Journal of Virology 1984; 52: 396-402.
30. Machida, A; Kishimoto, S; Ohnuma, H et al: A hepatitis B surface antigen polypeptide (P31) with the receptor for polymerized human as well as chimpanzee albumins. Gastroenterology 1983; 85: 268-274.
31. Walgate, R: Hepatitis B. Taiwan plans mass vaccination. Nature 1984; 312: 190.
32. Hilleman, MR: Virus vaccines. Nature 1985; 313: 176.
33. Francis, DP; Hadler, SC; Thompson, SE et al: The prevention of hepatitis B with vaccine. Annals of Internal Medicine 1982; 97: 362-366.
34. Szmuness, W; Stevens, CE; Harley, EJ et al: Hepatitis B vaccine in medical staff of hemodialysis units. Efficacy and subtype cross-protection. New England Journal of Medicine 1982; 307: 1481-1486.

35. Murphy, BL; Maynard, JE and LeBouvier, GL: Viral subtypes and cross-protection in hepatitis B virus infections of chimpanzees. Intervirology 1974; 3: 378-381.
36. Gerety, RJ; Tabor, E; Purcell, RH et al: Summary of an international workshop on hepatitis B vaccines. The Journal of Infectious Diseases 1979; 140: 642-646.
37. Davidson, M and Krugman, S: Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985; 1: 108-109.
38. Jilg, W; Schmidt, M; Zoulek, G et al: Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2: 1174-1175.

IMMUNOGENICITY AND REACTOGENICITY OF NEW HEPATITIS B VACCINES. FB Mollinger, Y Sanchez, C Troisi, GR Dreesman, and JL Melnick, Baylor College of Medicine, Houston, TX.

An HBsAg/adw polypeptide (PP) vaccine and a recombinant DNA vaccine produced in yeast (MSD) are being evaluated. The PP vaccine was prepared from 22-nm HBsAg particles, packaged in a micellar form and alum-adsorbed. The starting material (NIH/40) contained 300 HBsAg RIA equivalent units (RSU) based on a HEPTAVAX-B standard of 100 HBsAg RSU. 3 lots containing 5, 1, and 0.2 HBsAg RSU were compared to 2 intact particle vaccines. Vaccine was administered at 0, 1, and 6 months to 52 weight-matched adults. RESULTS: Local and systemic reactions were insignificant. The anti-HBs seroconversion rate at 4 weeks for the 5 RSU PP vaccine group (90%) was considerably better than that seen with HEPTAVAX-B. By 12 weeks, all vaccine recipients in the 1 and 5 RSU PP vaccine groups had seroconverted versus 50% of the 0.2 RSU group ($p<0.02$) which reached 100% seroconversion by month 7. Throughout followup, geometric mean (GM) anti-HBs levels (mIU/ml) in the 5 RSU PP group were significantly higher than in the other PP vaccine groups. At 1 month the GM anti-HBs level for the 5 RSU PP group was 8.9, whereas the 300 RSU NIH/40 vaccine group had a GM antibody level of 5.2. By 3 months, the respective anti-HBs levels were 202 vs 90, rising to 8910 and 3450 by 7 months. The 1 RSU PP vaccine produced antiHBs responses comparable to the 100 RSU HEPTAVAX-B vaccine. Thus, the polypeptide vaccines, with substantially lower RIA HBsAg reactivity, produced superior anti-HBs responses when compared with 22-nm HBsAg vaccines. These studies confirm our previous findings in chimpanzees that critical antigenic determinants are associated with these polypetides, and they provide a link to future vaccine studies using synthetic HBsAg macromolecules. The rapid anti-HBs response that follows the initial inoculation suggests that such an immunogen may be beneficial in postexposure prophylaxis where the early development of immunity is advantageous. Preliminary data through 6 months also will be presented on the immunogenicity of 3 doses (5, 10, and 20 mcg) of an HBSAg vaccine made by recombinant DNA technology in yeast (MSD).

Mollinger FB, Sanchez Y, Troisi C, Dreesman GR, Melnick JL. Immunogenicity and reactogenicity of new hepatitis B vaccines. Hepatology 1984; 4:1027 (Abstract).

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 153, NO. 1 • JANUARY 1986
 0022-1899/86/5301-0026$01.00

Anti-HBs Responses to Vaccination with a Human Hepatitis B Vaccine Made by Recombinant DNA Technology in Yeast

In the United States, the currently licensed vaccine against hepatitis B virus (HEPTAVAX-B®; Merck Sharp & Dohme, West Point, Pa) consists of hepatitis B surface antigen (HBsAg) that is purified from the plasma of chronically infected humans. Antibodies to the group *a* determinant of this complex antigen effectively neutralize the various subtypes of hepatitis B virus (HBV), as shown in a number of controlled clinical trials [1–3]. Despite overwhelming evidence that documents the efficacy of this vaccine, widespread acceptance by those who are at greatest risk of contracting hepatitis B has been less than expected because of a number of unrelated factors. The plasma-derived vaccine is expensive to prepare. A number of physical and chemical inactivation steps are used in purification, and extensive safety testings are mandated by the Food and Drug Administration in laboratory animals, cell cultures, and chimpanzees before the product can be marketed. In addition, there are of necessity batch-to-batch variations in human source material. These problems would have been surmountable in the marketing of this vaccine were it not for two recent events that made potential vaccine candidates overly cautious about accepting this new product: the increased incidence of Guillain-Barré syndrome that followed administration of the swine influenza vaccine in 1976 and the emergence of AIDS in the homosexual population. The latter problem was particularly relevant because HEPTAVAX-B is a plasma-derived product obtained from HBsAg-positive individuals, some of whom are in high-risk groups for AIDS. This raised the question whether AIDS might be transmitted to recipients of this vaccine. Unfortunately, despite numerous studies [4, 5] that eventually have refuted this hypothesis (on the basis of the susceptibility of retroviruses to inactivation by the physical and chemical steps used in producing the vaccine and by the lack of cases of AIDs or antibody seroconversions to human T lymphotropic virus type III observed among vaccinees at low risk of exposure to this disease), many members of groups at risk of contracting hepatitis B have been reluctant to accept this vaccine.

Because of these problems, alternate sources of vaccine are being developed. Among the first to become available for human trials was a 25,000–30,000 molecular weight HBsAg polypeptide derived by disrupting the intact 22-nm HBsAg particle with a nonionic detergent [6]. Immunogenicity of this product was superior to that of the human HBsAg source from which it was prepared, especially during the initial stages of antibody development. More recently a number of other vaccines that do not depend on human plasma as their source of HBsAg have been produced [7]. These include chemically synthesized peptides from several antigenic domains of the HBV, products of recombinant DNA technology, and live vaccinia virus recombinants containing the HBsAg gene.

In this paper we report one-year follow-up data on the immunogenicity and reactogenicity of a nonglycosylated HBsAg hepatitis B vaccine, subtype adw, made by recombinant DNA technology (Merck). The vaccine, prepared in the yeast *Saccharomyces cerevisiae* (strain 2150-2-3) [8, 9] was administered in three different doses (5, 10, and 20 μg) to an adult at-risk population.

Subjects and Methods

After screening 359 Emergency Medical Service personnel in Houston, 105 adult men (median age, 29 years; range, 22–40), determined by RIA or enzyme immunoassay to be free of any seromarkers of hepatitis B infection (Abbott Laboratories, North Chicago, Ill), were admitted to the study. All had antibody to HBsAg (anti-HBs) sample-to-negative-mean (S/N) ratios ≤1.4, levels of antibody to hepatitis B core antigen (anti-HBc) ≤39% inhibition, and HBsAg S/N ratios ≤1.2. These values are substantially below the cutoff levels endorsed by the manufacturers. In addition, each participant was required to have serum levels of liver enzyme (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) ≤50 IU/liter, as determined by the Beckman System TR enzyme autoanalyzer (Beckman Instruments, Palo Alto, Calif). Participants were in good health at the time of enrollment, had not been previously vaccinated against hepatitis B, and had signed informed consent releases. The study was approved by the Baylor College of Medicine Human Investigations Committee.

The 105 volunteers were weight matched within 4.5 kg [9a] into three groups of 35. Each member of each group received 5, 10, or 20 μg of an alum-adsorbed, DNA recombinant hepatitis B vaccine (lot no. 974/CK-446) containing 20 μg of HBsAg/ml. The vaccine was purified from

Received for publication 21 May 1985, and in revised form 9 July 1985.

This work was supported by a grant from Merck & Company, West Point, Pennsylvania. Computational assistance was provided by the CLINFO Project, funded by grant RR-00350 from the Division of Research Resources of the National Institutes of Health.

We thank Dorothy Heiberg for her expert assistance in following the subjects and performing the analyses; the Emergency Medical Service division of the Houston Fire Department for their constructive suggestions and enthusiastic support of the project; and Esperanza Tafallo and Steven Rao for their excellent technical assistance.

Please address requests for reprints to Dr. F. B. Hollinger, Department of Virology and Epidemiology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030.

yeast extract by physical and chemical methods. Hydrophobic-interaction chromatography followed by gel-exclusion chromatography was the major procedure used to prepare the purified antigen. The removal of yeast components was demonstrated in vitro by immunologic methods and in vivo by anaphylactic testing in guinea pigs.

To deliver the inoculum, we used 0.5-ml syringes for the 5 or 10 μg doses and 1.0-ml syringes for the 20 μg dose. All doses were administered by the same person. The vaccine was thoroughly resuspended before use and inoculated im in the deltoid region with a one-inch, 23-gauge needle at months 0, 1, and 6. Blood samples were obtained at one, two, three, six, eight, and 12 months after the initial inoculation (100% participation). A prevaccination oral temperature was obtained, and participants were asked to take and record their temperature with the same calibrated thermometer 4 hr after inoculation and each morning for the next three days. They were also asked to record any local or systemic symptoms experienced during this time. Responses were received by mail from ~90% of the participants.

All blood samples were processed within 24 hr and assayed for liver enzymes. The unit of measurement for anti-HBs was mIU/ml and was determined by the method of Hollinger et al. [10]. On the basis of the statistical analysis of at least 1,000 normal human sera, a value ≥0.7 mIU/ml on replicate samples was considered evidence of the presence of anti-HBs for determination of seroconversion rates. This cutoff level was ≥5 SD above the mean value for the negative control samples. All samples taken at three and eight months were also tested for anti-HBc and HBsAg to rule out unsuspected infection with HBV that might have occurred during the course of the study.

Statistical calculations included Student's *t* test, McNemar's χ^2 test, analysis of variance, and Duncan's multiple range test [11].

Results

No local or systemic reactions of a serious nature were observed by the volunteers. After the first inoculation, 14% of the vaccinees experienced mild discomfort at the site of injection; this figure was 12% after the second and third inoculations. Temperature elevations ≥1.5 F above an individual's baseline level were recorded in 3.8%, 9.3%, and 3.4% of the participants after each of the three injections, respectively. Only four oral temperatures exceeded 100 F, the highest of which was 101.2 F. Among the systemic reactions recorded after the initial inoculation, headaches (10.5%), diarrhea or abdominal complaints (9.5%), and fatigue (7.6%) were noted most frequently. Rates declined substantially after the second and third injections. Such local and systemic reactions are similar to those observed among recipients of placebos in other studies [10].

None of the participants showed serological evidence of infection with HBV during the study. Ten (9.5%) volunteers had aminotransferase levels >50 IU/liter on one or more occasions over the one-year follow-up period. This rate is similar to that observed in a previous study [10]. Muscle trauma caused by excessive physical activity was felt to be the cause of the enzyme elevations in three of these ten participants; this hypothesis was based on an AST value that was higher than the ALT value and on creatine phosphokinase levels of 47,502, 844, and 533 IU/liter. A fourth volunteer sustained a lacerated liver following an auto accident that occurred two weeks before the blood specimen that showed elevated enzyme levels was taken, and three other men were taking medications that have been reported to cause liver damage. In the other three (2.9%) volunteers, the enzyme levels had returned to normal when their blood was retested one week later. There was nothing in their histories to explain these abnormalities.

Seroconversion rates and geometric mean antibody responses for all participants are shown by dose and time in tables 1 and 2. Seroconversion rates were significantly lower in the 5-μg dose group than in the 10- or 20-μg dose

Table 1. Seroconversion rates of anti-HBs by time and dose.

	Time (months)					
Dose	1*	2	3	6*	8	12
5 (n = 35)	8.6	34.3†	45.7†	62.9†	97.1	88.6‡
10 (n = 35)	28.6	80.0	94.3	94.3	97.1	97.1
20 (n = 35)	28.6	82.9	88.6	94.3	100.0	100.0

NOTE. Results are percentages of subjects who were positive at the noted time. Doses are in μg.

* Vaccine was administered at months 0, 1, and 6.

† $P < .002$, 5 μg compared with 10 or 20 μg.

‡ Four persons who were positive for anti-HBs at eight months became seronegative at 12 months, whereas the one person who had not responded by month 8 seroconverted.

Table 2. Geometric mean levels of anti-HBs (mIU/ml) by time and dose.

	Time (months)					
Dose	1*	2	3	6*	8	12
5 (n = 35)	0.1†	0.5‡	0.7‡	2.0‡	45.7‡	10.0‡
10 (n = 35)	0.3	5.1	6.9	14.0	388.6	76.0§
20 (n = 35)	0.4	7.3	9.4	26.4	519.5	184.6

NOTE. Doses are given in μg.

* Vaccine was administered at months 0, 1, and 6.

† $P < .02$, 5 μg compared with 10 or 20 μg.

‡ $P < .001$, 5 μg compared with 10 or 20 μg.

§ $P = .03$, 10 μg compared with 20 μg.

groups at two, three, and six months after the initial inoculation ($P < .002$). By eight months all but two of the participants had produced specific antibodies. One of these two volunteers, who received 5 μg of vaccine, did develop specific anti-HBs at a low level (1.3 mIU/ml) 12 months following his initial inoculation. Therefore, the total seroconversion rate for the 5-μg group through 12 months was 100%, even though four other vaccinees who were positive at eight months were negative at 12 months; this yielded a point prevalance rate of 88.6% (table 1).

Geometric mean concentrations of anti-HBs were considerably lower in the group receiving 5 μg of yeast-derived HBsAg than in the 10- or 20-μg dose groups after the first month ($P < .001$; table 2). Similar differences were observed when weight-matched group members were compared, most notably at six and eight months. No statistically significant differences were seen between the 10- and 20-μg groups during the first eight months in terms of seroconversion rates or geometric mean levels of antibody. At each bleeding interval, however, geometric mean levels of anti-HBs in the 10-μg group were lower than those seen in the 20-μg vaccinees, and a P value of .03 was obtained at 12 months (table 2).

Discussion

The reasons for the significantly larger differences in immune response seen between the 5-μg group and the other two groups in our study are not readily apparent. Lot-to-lot variation is not a factor since the same lot of vaccine was used to inoculate all three groups. The only known variable is the volume of inoculum administered. Thus, the lower doses of vaccine not only contained less HBsAg, but the total amount of alum administered was also reduced even though the protein-to-alum ratio remained constant among the three doses. Whether a finite amount of alum is essential for an optimal response cannot be ascertained in this study, but levels of alum should not vary significantly between batches of vaccine that use identical doses of vaccine. It is interesting that similar muted responses were not seen in another study that compared 5 μg and 10 μg of yeast-derived HBsAg, although a two-fold difference in the geometric mean levels of antibody was reported [12]. Since the RIA activity of equimolar preparations of purified yeast HBsAg has been reported to vary by as much as 2.5 times [8], this might account for the interstudy differences observed at critical threshold levels.

As expected, a decline in anti-HBs concentration was observed in 96% of the subjects between the eighth and 12th months. To examine the slope of this response more completely, we determined the natural logarithms of the differences in the anti-HBs levels after dividing by the number of months between observations for each subject in the three dose groups. Similar data were obtained for adults participating in previous vaccine studies that used 40 μg of an HBsAg plasma-derived vaccine [10] and 20 or 40 μg of HEPTAVAX-B [9a], and the results were compared by analysis of variance. No significant differences in the rate of decline were found between these four groups when equivalent levels of peak anti-HBs responses were evaluated.

When geometric mean levels of anti-HBs at eight months were compared for two different plasma-derived vaccines, values ranged from 2,980 to 3,322 mIU/ml for 40 μg of vaccine to 1,975 mIU/ml for 20 μg of HBsAg [9a, 10] vs. 46 (5 μg), 389 (10 μg), and 520 (20 μg) mIU/ml for the yeast-derived product. These findings lead us to conclude that the lower antibody levels detected in adults receiving the yeast-derived vaccine may be related to the immunogenicity of the product. It is noteworthy that Dandolos et al. [13] reported similar discrepancies in anti-HBs levels between yeast- and plasma-derived vaccines, in which equivalent doses of antigen could be compared, although immune responses were significantly lower with our lot of recombinant vaccine. Since a butyl agarose method was used to remove contaminating yeast antigens from the final product in both of these studies, it is unlikely that this could account for the reduced immunogenicity found in our study. Two other studies [12, 14] did not permit equivalent time and dose comparisons between the two types of vaccines. Variations between lots, dissimilarities in the lipid content of the antigen produced in the yeast as compared with plasma-derived antigen, reduced antigenicity when compared with human HBsAg, and the fact that the yeast-derived HBsAg is not glycosylated [7, 8] may be factors responsible for the relatively lower anti-HBs response seen with the yeast-derived product. Further field trials in different at-risk groups seem appropriate before a specific adult dose of this vaccine is recommended. Nevertheless, several small trials in humans have shown that the vaccine is safe, and we anticipate that durable levels of protection should be achieved if sufficient immunogen is incorporated in the vaccine.

F. B. Hollinger, C. L. Troisi, P. E. Pepe
Departments of Medicine, and Virology and Epidemiology, Baylor College of Medicine; and the City of Houston Emergency Medical and Trauma Services, Houston, Texas

References

1. Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszke WR, William DC, Sadorsky R, Morrison JM, Kellner A. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. N Engl J Med 1980;303:833–41
2. Francis DP, Hadler SC, Thompson SE, Maynard JE, Ostrow DG, Altman N, Braff EH, O'Malley P, Hawkins D, Judson FN, Penley K, Nylund T, Christie G, Meyers F, Moore JN Jr, Gardner A, Doto IL, Miller JH, Reynolds GH, Mur-

phy BL, Schable CA, Clark BT, Curran JW, Redeker AG. The prevention of hepatitis B with vaccine: report of the Centers for Disease Control multi-center efficacy trial among homosexual men. Ann Intern Med 1982;97:362–6
3. Purcell RH, Gerin JL. Hepatitis B vaccines: a status report. In: Vyas GN, Cohen SN, Schmid R, eds. Viral hepatitis. Philadelphia: The Franklin Institute Press, 1978;491–505
4. Stevens CE, Taylor PE, Rubinstein P, Ting RCY, Bodner AJ, Sarngadharan MG, Gallo RC. Safety of the hepatitis B vaccine. New Engl J Med 1985;312:375–6
5. Poiesz B, Tomar R, Lehr B, Moore J. Hepatitis B vaccine: evidence confirming lack of AIDS transmission. MMWR, 1984;33:685–7
6. Hollinger FB, Sanchez Y, Troisi C, Dreesman GR, Melnick JL. Response to a HBsAG/*adw* polypeptide vaccine in a young adult population [abstract no. 8A.5]. In: Vyas G, Dienstag J, Hoofnagle J, eds. Viral hepatitis and liver disease. Orlando, Fla: Grune and Stratton, 1984:656
7. Purcell RH, Gerin JL. Prospects for second and third generation hepatitis B vaccines. Hepatology 1985;5:159–63
8. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. Nature 1984;307:178–80
9. Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984;251:2812–5
9a. Troisi CL, Heiberg DA, Hollinger RB. Normal immune response to hepatitis B vaccine in patients with Down's syndrome. JAMA, 1986 (in press)
10. Hollinger FB, Adam E, Heiberg D, Melnick JL. Response to hepatitis B vaccine in a young adult population. In: Szmuness W, Alter JH, Maynard JE, eds. Viral hepatitis. Philadelphia: The Franklin Institute Press, 1981;451–66
11. Snedecor G, Cochran W. Statistical methods. Ames, Iowa: Iowa State University Press, 1967
12. Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet 1985;1:108–9
13. Dandolos E, Roumeliotou-Karayannis A, Richardson SC, Papaevangelou G. Safety and immunogenicity of a recombinant hepatitis B vaccine. J Med Virol 1985;17:57–62
14. Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984;2:1174–5

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 153, NO. 1 • JANUARY 1986
 0022-1899/86/5301-0027$01.00

The Epidemiology of *Clostridium difficile* with Use of a Typing Scheme: Nosocomial Acquisition and Cross-Infection Among Immunocompromised Patients

Gastrointestinal disturbance, particularly diarrhea, is one of the commonest side effects of the use of antibiotics. Up to 20%–25% of antibiotic-associated diarrhea occurs in conjunction with a fecal isolate of *Clostridium difficile* [1]. This organism is the major cause of pseudomembranous colitis and antibiotic-associated colitis but is also carried in the gastrointestinal tract of 2%–4% of the normal adult population and can be isolated from the feces of 30%–75% of asymptomatic neonates [2].

Received for publication 23 April 1985, and in revised form 5 August 1985.

This work was supported by the Medical Research Council. Dr. Heard was funded by a George Alwyn Research Bursary. Dr. Holland was funded by Automated Microbiology Systems Ltd.

This study would not have been possible without the help of the Sisters and nursing staff on Annie Zunz, Dalziel, Garrod, and Stanmore wards in collecting the clinical specimens. We thank them and Drs. T. A. Lister, P. F. Wrigley, J. Galton, J. Wass, K. Britten, and E. C. Huskisson and Professors J. Malpas, M. Besser, and J. Dickinson for allowing us to study their patients.

Please address requests for reprints to Dr. S. Tabaqchali, Department of Medical Microbiology, St. Bartholomew's Hospital, West Smithfield, London, EC 1A 7BE.

Clusters of antibiotic-associated colitis have been noted [3], and early animal studies suggested that environmental contamination and cross-infection might be important in the etiology of outbreaks of antibiotic-associated diarrhea [4]. However, convincing evidence for the cross-infective potential of *C. difficile*, as well as its demonstration as a predominantly nosocomial infection, has been prevented due to lack of a reliable typing scheme for this organism [5].

Various typing schemes have been suggested [6–10]. Among these, Tabaqchali et al. [8] reported a well-defined scheme for typing this organism on the basis of the incorporation of [^{35}S]methionine into bacterial proteins and have described to date nine distinct groups within the *C. difficile* species (A–E, W–Z), as demonstrated by the radiolabeled protein profile obtained by using SDS-PAGE followed by autoradiography. We have applied this technique to isolates obtained from a prospective six-month study of immunocompromised and general medical patients in an attempt to assess the carriage and acquisition of *C. difficile* among hospital patients. The effect of isolation and containment procedures on the spread of *C. difficile* was also studied.

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

W. JILG B. LORBEER
M. SCHMIDT B. WILSKE
G. ZOULEK F. DEINHARDT

Max von Pettenkofer-Institut, D-8000 München 2, West Germany

Summary Recombinant hepatitis B vaccine prepared from antigen expressed in yeast was given to 30 healthy young volunteers. Seroconversion rates and anti-HBs levels were compared with those in a control group matched for age and sex who had received plasma-derived hepatitis B vaccine. 4 weeks after the third immunisation results were similar in the two groups. In the recombinant vaccine group the immune response developed more slowly during the early phase and seroconversion rates and mean anti-HBs levels were slightly lower in males; this probably reflects use of a lower dose of recombinant vaccine (10 μg compared with 20 μg of the plasma vaccine). Side-effects were slight and antibody titres against *Candida albicans* were not increased in recipients of the recombinant vaccine.

Introduction

CURRENT hepatitis B vaccines are effective and safe.[1] However, because they are prepared from plasma of human hepatitis B virus carriers, supply is restricted by the amount of plasma available and by the cost of purifying the hepatitis B surface antigen (HBsAg) to render it free from hepatitis B virus and other possible infectious agents. Thus, to meet the worldwide need for hepatitis B vaccine, new means of preparation are required. Lately, vectors carrying the DNA sequence for HBsAg were prepared[2] and the antigen was expressed in the yeast *Saccharomyces cerevisiae*.[3] Yeast cells assemble the HBsAg polypeptides into particles similar to the 22 nm particles found in human plasma; yeast HBsAg, however, unlike human HBsAg is not glycosylated. A vaccine developed from yeast HBsAg stimulated antibody production in mice, grivet monkeys, and chimpanzees; and when vaccinated chimpanzees were challenged with human hepatitis B virus of different subtypes, they were completely protected.[4] We now report the immunisation of 30 healthy young volunteers with the first hepatitis B vaccine produced by recombinant DNA technology.

Subjects, Materials, and Methods

Subjects

30 healthy medical students and laboratory workers were studied (17 female, 13 male; mean age 25±3 yr, range 21–34). Subjects in the control group had been immunised with plasma-derived vaccine in an earlier study;[5] they were matched by age and sex to the study group (table I). Before vaccination, all subjects were negative for HBsAg, anti-HBs, and antibodies against hepatitis B core antigen (anti-HBc), and their aminotransferase levels were normal (alanine and aspartate aminotransferases ≤17 and ≤19 IU/l, respectively).

TABLE I—SEX AND AGE DISTRIBUTION OF THE TWO VACCINATION GROUPS*

	Total		Female		Male	
	No	Age (yr)	No	Age (yr)	No	Age (yr)
Recombinant vaccine	30	24·9±3·1 (21–34)	17	24·6±3·5 (21–34)	13	25·3±2·6 (23–32)
Plasma-derived vaccine	41	25·0±2·7 (21–32)	23	24·7±3·0 (21–32)	18	25·4±2·3 (23–32)

*Means and standard deviations (range).

Vaccines

The recombinant hepatitis B vaccine was prepared by Merck Sharp & Dohme research laboratories (lot 934/C-J 625). It consists of purified HBsAg, subtype *adw*, produced in recombinant *S cerevisiae* and absorbed on aluminium hydroxide. 1 ml of vaccine contained 10 μg of HBsAg. Plasma vaccine was also subtype *adw* (lot 773/801-2/C-F 732-2 Merck Sharp & Dohme). Subjects in the study group received 10 μg of recombinant vaccine intramuscularly at 0, 1, and 6 months; subjects in the control group received 20 μg of plasma-derived vaccine at the same intervals. (Since the recombinant vaccine was treated with formalin only, and not with pepsin and urea, it was initially thought to be more immunogenic than the plasma vaccine.) Blood samples were taken on the day of the first vaccination and then monthly. Subjects were asked to keep daily records of body temperature and side-effects for 5 days after each injection.

Serology

HBsAg, anti-HBs, and anti-HBc were tested by radioimmunoassay with commercially available kits ('AUSRIA II', 'AUSAB', 'CORAB', Abbott Laboratories). Anti-HBs concentrations in IU/l were calculated by the method of Hollinger et al,[6] the first WHO reference preparation 1977 being used in a dilution of 1:400.[7] Because *S cerevisiae* and *C albicans* have common antigenic determinants,[8] antibodies against *C albicans* were determined by passive haemagglutination in 26 subjects on day 0 and 4 weeks after the second and third injections of recombinant vaccine. Sera were examined for antibodies against the determinant *a* of HBsAg as previously described.[9]

Results

Seroconversion rates and mean anti-HBs levels during the course of immunisation are shown in table II. The immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels. These differences became non-significant after the booster dose at month 6 when 29 out of 30 subjects (97%) were anti-HBs positive (control, 41 out of 41) with a geometric mean anti-HBs level of 2135 IU/l (control, 4299 IU/l). All anti-HBs-positive individuals in the recombinant vaccine group had anti-HBs values above 10 IU/l; 2 (6·7%) were low responders (anti-HBs below 100 IU/l), 3 (10%) were intermediate responders (anti-HBs 101–1000 IU/l), and 22 (73·3%) were normal to high responders (anti-HBs greater than 1000 IU/l). Similar values

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2:1174-5.

TABLE II—IMMUNE RESPONSES AFTER VACCINATION

Month	Seroconversion (%)		Anti-HBs (IU/l)*		p†
	Recombinant vaccine (n = 30)	Plasma-derived vaccine (n = 41)	Recombinant vaccine	Plasma-derived vaccine	
1	8 (27)	18 (44)	0	15	<0·05
2	21 (70)	39 (95)	38	53	<0·05
3	28 (93)	39 (95)	29	164	<0·05
4	28 (93)	39 (95)	63	228	<0·05
5	28 (93)	39 (95)	79	273	<0·05
6	28 (93)	39 (95)	68	263	<0·05
7	29 (97)	41 (100)	2135	4299	>0·05

*Anti-HBs is given as the geometric mean in responders only.
†Wilcoxon's rank-sum test.

TABLE III—IMMUNE RESPONSES IN MALES AND FEMALES (AFTER THREE INOCULATIONS)

—	Recombinant vaccine	Plasma-derived vaccine	p*
Males:			
Seroconversion (%)†	12/13 (92)	18/18 (100)	
Anti-HBs (IU/l)‡	911	3895	<0·05
Females:			
Seroconversion (%)†	17/17 (100)	23/23 (100)	
Anti-HBs (IU/l)‡	3282	4640	>0·05

*Wilcoxon's rank-sum test.
†Numbers of anti-HBs-positive subjects divided by the total number.
‡Geometric mean.

were obtained in the control group. Although the immune responses to the two vaccines were similar after the full course of immunisation, responses of male and female subjects differed. In both groups all the women seroconverted and the geometric mean anti-HBs levels did not differ significantly (3282 IU/l vs 4640 IU/l). However, in males receiving recombinant vaccine the seroconversion rate was 92% vs 100%, and the geometric mean anti-HBs was 911 vs 3894 IU/l (table III).

Preliminary tests indicate that recombinant vaccine, like the plasma-derived vaccine, induces antibodies against both the *a* and the *d* components of HBs antigen. After month 3, about 38% of the total anti-HBs was directed against determinant *a*.

No important side-effects were observed after immunisation with the recombinant vaccine. Minor local symptoms such as transient pain, itching, burning, and slight swelling at the injection site were reported after 24 of the 90 injections. On no occasion did body temperature rise above 37·9°C.

Of 26 subjects tested, all had antibodies against *C albicans* on day 0 (titres from 1:80 to 1:320) and titres did not increase after immunisation.

Discussion

Three doses of 10 μg recombinant hepatitis B vaccine gave seroconversion rates and geometric mean anti-HBs levels similar to those induced by three doses of 20 μg plasma-derived vaccine. The results were also comparable with those obtained in large trials of conventional vaccines.[10,11]

The immune response to the recombinant vaccine, however, was less strong during the early phase (1–6 months) in all subjects, and in males mean anti-HBs values were lower in the recombinant group even after the complete course of immunisation. These results are comparable with findings in subjects immunised with a smaller dose (5 μg) of conventional vaccine (Jilg W, Zachoval R, Schmidt M, Deinhardt F, unpublished), and may reflect the use of smaller amounts of antigen. Antigen content of both recombinant vaccine and plasma-derived vaccine is determined as HBsAg protein. The vaccines are produced and treated differently, however,[6,12] therefore similar protein content does not necessarily mean similar immunogenicity. The yeast and plasma derived HBsAg differed in reactivity in radioimmunoassay tests; the reactivity of the HBsAg produced in yeast was only 20–50% of the reactivity of plasma-derived HBsAg.[4] Thus, weight-for-weight the immunogenicity of the recombinant vaccine seems to be less than that of the plasma-derived vaccine. Another explanation for the lower immune response may be that 10 μg of recombinant vaccine was given per single dose compared with 20 μg of plasma-derived vaccine. A higher dose (20 or 40 μg) of the recombinant vaccine would probably give the same results as the plasma-derived vaccine.

Despite the slightly lower immunity achieved with the recombinant vaccine, protection will probably be as good as with the conventional vaccine, in that all 29 subjects with detectable anti-HBs had values above the protection level of 10 IU/l.[13] In 73%, anti-HBs levels after the third vaccination were more than 1000 IU/l; this has been shown to guarantee persistence of anti-HBs above the protective limit for at least 3 years.[14] In addition, all subjects who seroconverted had antibodies against the common determinant *a* of HBsAg, indicating cross-protection against infections with other subtypes of HBsAg. Side-effects after the recombinant vaccine were negligible and did not differ from those observed after plasma-derived vaccine. The absence of a rise in antibodies against *C albicans* indicates that no cross-reacting yeast antigens were present in the vaccine.

We thank Mrs Liane Sakreida for expert technical assistance.

Correspondence should be addressed to W. J., Max v. Pettenkofer-Institut, Pettenkoferstr. 9 a, 8000 Munchen 2, West Germany.

REFERENCES

1. Deinhardt F. Control of hepatitis A and B with vaccines. *Ann Clin Res* 1982; 14: 236–44.
2. Valenzuela P, Gray P, Quiroga M, Zaldivar J, Goodman HM, Rutter WJ. Nucleotide sequence of the gene coding for the major protein of hepatitis B surface antigen. *Nature* 1979; 280: 815–19.
3. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298: 347–50.
4. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984; 307: 178–80.
5. Zachoval R, Jilg W, Lorbeer B, Schmidt M, Deinhardt F. Passive-active immunisation against hepatitis B. *J Infect Dis* 1984; 150: 112–17.
6. Hollinger FB, Adam E, Hesberg D, Melnick JL. Response to hepatitis B vaccine in a young adult population. In: Szmuness W, Alter HJ, Maynard JE, eds. Viral hepatitis: 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 451–66.
7. World Health Organization. *WHO Tech Rep Ser* no 638; 1979: 29.
8. Tsuchiya T, Fukazawa Y, Kawahara S. Serologic classification of the genus *Candida*. In: Tokyo Research Committee of Candidiasis. Studies of candidiasis in Japan. Tokyo: Edomasan Ministry of Japan, 1961: 34–36.
9. Jilg W, Delbrueck C, Deinhardt F, Rezvantseva-Karoyanova AJ, Papaevangelou GJ, Mushahwar IK, Overby LR. Hepatitis B surface antigen (HBsAg) subtype — specific antibodies in persons vaccinated against hepatitis B. *J Med Virol* 1984; 13: 171–78.
10. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial on the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981; 1: 377–85.
11. Cremer J, Jungeyr P, Courouce AM, et al. Randomised placebo-controlled trial of hepatitis B surface antigen vaccine in French homosexual/bisexual males. I. Medical staff. *Lancet* 1981; ii: 455–58.
12. Hilleman MR, Buynak EB, McAleer WJ, McLean AA. Human hepatitis B vaccine. In: Krugman S, Sherlock S, eds. Proceedings of the European Symposium on Hepatitis B. Rahway: Merck Sharp & Dohme International, 1981: 120–30.
13. Goudeau A, Courouger P, Barin F, et al. Prevention of hepatitis B by active and passive immunization. In: Szmuness W, Alter HJ, Maynard JE, eds. Viral hepatitis 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 509–25.
14. Jilg W, Schmidt M, Zachoval R, Deinhardt F. Persistenz von Antikörpern gegen Hepatitis B-Oberflächenantigen nach Impfung gegen Hepatitis B. *Dtsch Med Wochenschr* (in press).

Jilg, W., Zoulek, G., Lorbeer, B., Wilske, B. and Deinhardt, F.
CLINICAL COMPARISON OF A RECOMBINANT AND A PLASMA-DERIVED HEPATITIS B VACCINE
Paper presented at the 24th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., Oct. 8-10, 1984, Program Abstract No. 292.

Hepatitis B vaccine, yeast recombinant (Merck), hepatitis B vaccine, plasma derived: Thirty healthy young adults were vaccinated IM at 0, 1, and 6 mo with 10 mcGm HBsAg in aluminum hydroxide adjuvants. A comparable group was vaccinated with 20 mcGm HBsAG derived from plasma. Seroconversions following both vaccines were 30-40% after the 1st vaccination and greater than 90% after the 2nd. Antibody titers for both vaccines were comparable. The percentage of antibodies directed against the common antigenic a component of all hepatitis B virus subtypes was greater than 35%. Side effects were minor or absent. Immune reactions to yeast antigens were not reported in any of the subjects.

Reprinted from Nature, Vol. 307, No. 5947, pp. 178-180, 12 January 1984

Human hepatitis B vaccine from recombinant yeast

William J. McAleer, Eugene B. Buynak, Robert Z. Maigetter, D. Eugene Wampler, William J. Miller & Maurice R. Hilleman*

Division of Virus and Cell Biology Research, Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486, USA

The worldwide importance of human hepatitis B virus infection and the toll it takes in chronic liver disease, cirrhosis and hepatocirclnoma, make it imperative that a vaccine be developed for worldwide application[1]. Human hepatitis B vaccines[2-5] are presently prepared using hepatitis B surface antigen (HBsAg) that is purified from the plasma of human carriers of hepatitis B virus infection. The preparation of hepatitis B vaccine from a human source is restricted by the available supply of infected human plasma and by the need to apply stringent processes that purify the antigen and render it free of infectious hepatitis B virus and other possible living agents that might be present in the plasma. Joint efforts between our laboratories and those of Drs W. Rutter and B. Hall led to the preparation of vectors carrying the DNA sequence[7,8] for HBsAg and antigen expression in the yeast *Saccharomyces cerevisiae*[9]. Here we describe the development of hepatitis B vaccine of yeast cell origin. HBsAg of subtype adw was produced in recombinant yeast cell culture, and the purified antigen in alum formulation stimulated production of antibody in mice, grivet monkeys and chimpanzees. Vaccinated chimpanzees were totally protected when challenged intravenously with either homologous or heterologous subtype adr and ayw virus of human serum source. This is the first example of a vaccine produced from recombinant cells which is effective against a human viral infection.

Several alternative approaches to a hepatitis B vaccine are being developed. HBsAg has been expressed by several transformed mammalian cell lines, such as the human hepatoma line, PLC/PRF/5 (refs 10, 11), simian virus 40-infected monkey kidney cells[12] and mouse L cells[13]. These sources are of some concern, however, because the cell lines may be neoplastic. Although HBsAg has been cloned in bacteria[7,14], expression was very weak. Other laboratories[15-19] have described the synthesis of oligopeptides that carry antigenic determinants of HBsAg but their potency in animals is low and much work will need to be done to potentiate antigenicity. Smith and collaborators[20] have described the construction of a recombinant vaccinia virus which expresses HBsAg and have proposed its use as a live attenuated vaccine; its antigenic potency has been demonstrated but whether such a vaccine would be safe and effective in man is still unknown.

Valenzuela *et al.*[9] originally reported that yeast cells are able not only to express the HBsAg gene but also to assemble the polypeptides into particles that have much the same appearance as particles isolated from human plasma and which are immunogenic in mice. Since then, other laboratories[21,22] have shown that HBsAg produced in yeast is antigenic in rabbits and guinea pigs. With such progress, recombinant yeast has become an attractive alternative to human plasma as a source of antigen for hepatitis B vaccine.

For vaccine preparation, the HBsAg used was of subtype adw and was produced in fermentation cultures of *S. cerevisiae* carrying an expression vector using yeast alcohol dehydrogenase I as a promoter. The yeast strain used in these studies was obtained from G. Ammerer (University of Washington) and is similar to the strain described by Valenzuela *et al.*[9] in which the production of HBsAg in yeast was first reported.

* To whom reprint requests should be addressed.

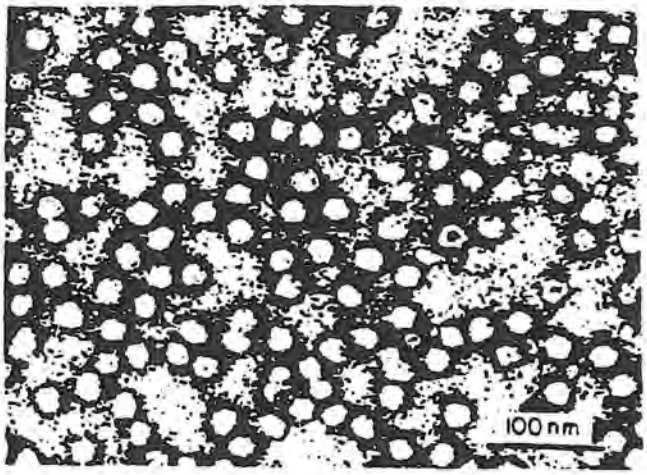


Fig. 1 Electron micrograph of HBsAg particles from recombinant yeast. Cells were grown in a 335-l fermentation vessel, collected by centrifugation, resuspended in an equal volume of 0.01 M sodium phosphate *p*H 7.5, containing 0.01% Triton X-100, and disrupted by rapid stirring with glass beads in a Dyno-Mill (Impandex; see ref. 23). The resulting extract was clarified by centrifugation for 90 min at 10,000*g*. The clarified yeast extract was applied to a column of Sepharose 4B to which had been attached goat antibody to human HBsAg. The column was developed at a flow rate of 2 column vol per h. Extraneous protein was washed away with 5 column vol of buffer A and the HBsAg was eluted with 3 M NH_4SCN. Fractions containing HBsAg were pooled and thiocyanate was removed by dialysis against 0.01 M sodium phosphate *p*H 6.8, containing 0.15 M NaCl. Dialysed antigen was diluted to 40 μg ml^{-1} and visualized by negative staining with 2% phosphotungstic acid.

Cells were collected by centrifugation and broken by homogenization with glass beads[23]. HBsAg particles were purified from the clarified extract by immune affinity chromatography using goat antibody to human HBsAg. Electron microscopy (Fig. 1) revealed a homogeneous array of particles free of extraneous morphological entities. The UV absorption pattern was the same as for the plasma antigen, with an $E^{1\%}$ of 45. SDS-polyacrylamide gel electrophoresis (Fig. 2) in reducing conditions revealed a major band at molecular

Table 1 Antigenic potency in mice of HBsAg purified from yeast and from human plasma

Vaccine source	Antigen dose per injection (μg protein)	Anti-HbsAg response after vaccination No. positive/total	GMT
Human plasma	10	9/10	563
(lot 799-2)	2.5	10/10	2,235
	0.625	4/9	32
	0.156	0/10	4
ED_{50}	0.639		
Yeast	40	10/10	5,432
(lot 81-4)	10	10/10	3,400
	2.5	8/10	673
	0.625	8/10	967
ED_{50}	<0.625		

Groups of 10 5-week-old ICR/Ha mice propagated in our laboratories were given a single 1-ml injection intraperitoneally of serial fourfold dilutions of yeast or human plasma vaccine in alum diluent. The mice were bled individually and tested for serum antibody level 4 weeks later. Human plasma vaccine, lot 799-2, was prepared in these laboratories[2-5]. Yeast-derived vaccine, lot 81-4, was purified as described in Fig. 1 legend and adsorbed to alum. GMT, geometric mean titre, expressed in AUSAB units; ED_{50}, dose required to seroconvert 50% of the mice.

weight 23,000 (23K) corresponding to the non-glycosylated polypeptide which is the major polypeptide of the viral envelope. In this respect it differs from the plasma antigen which has, in addition to the 23K polypeptide, a glycosylated derivative which migrates at 27K. The yeast and plasma antigens differ also in their reactivity in the radioimmunoassay (RIA) (AUSRIA II, Abbott). RIA reactivity of purified yeast-derived HBsAg varied from preparation to preparation in the range 20–50% of the reference human antigen.

Because of this reduced radioimmune reactivity, and because the yeast antigen is not glycosylated, it was important to determine whether the antigen was immunogenic. To test both antigenicity and immunogenicity in animals, purified antigen was formulated into a vaccine by adsorbing on alum adjuvant to contain 40 μg HBsAg protein and 0.5 mg aluminium (hydroxide) per 1 ml dose.

Studies in mice (Table 1) showed the yeast-derived antigen to be at least as antigenic as the antigen purified from human plasma. Grivet monkeys also developed antibody following vaccination with the yeast-derived antigen (Table 2). A single injection of the vaccine at all dose levels resulted in seroconversion of all the animals in both vaccine groups. These results were important as they showed that high antibody titres were maintained for at least a year.

Protective efficacy was tested for by using susceptible chimpanzees. The four chimpanzees that received the recombinant vaccine developed antibody in substantial titre following vaccination (Table 3). Following challenge with infectious human plasma, all four vaccinated animals were protected. By contrast, all four unvaccinated animals developed hepatitis B virus infection with positive antigenaemia, antibody to hepatitis B core antigen (anti-HBcAg), elevation of serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT), and liver histopathology. It is important to note that the animals were protected against both subtype adr and ayw challenge even though the vaccine is of the adw subtype.

Yeast fermentation technology is well established and we have shown that HBsAg can be isolated from yeast extracts in a highly purified form by a single application of immune affinity chromatography. Vaccine made from this antigen is equally as potent as human plasma-derived vaccine in stimulating antibodies in mice, and is protective in challenge experiments in chimpanzees. Antibodies raised by yeast-derived vaccine persisted for at least a year in monkeys, showing no important deviation from that of the plasma vaccine.

Human HBsAg is composed of a sequence of 226 amino acids of which the a antigen determinant is dominant. Small differences in amino acid sequence may occur at several positions in the polypeptide chain and are responsible for the subtype specificities[24]. In previous studies, chimpanzees that were cross-challenged with heterologous subtypes of hepatitis B virus after recovery from infection or vaccination with human plasma-derived antigens, were solidly protected due to the common group specificity of the dominant a antigen that is present in all HBsAg subtypes[25]. A protective efficacy trial in man of subtype ad vaccine of human plasma origin has shown strong protection against the homologous subtype[26,27] and, most recently, against the heterologous subtype ay[28] in studies carried out on the staffs of renal dialysis centres where subtype ay hepatitis is most common. The positive cross-protection afforded against heterologous subtype ayw virus challenge in chimpanzee immunized with type adw vaccine of yeast origin, indicates that the a antigen remains dominant in the recombinant-produced antigen obtained from human plasma.

Fig. 2 SDS-polyacrylamide gel electrophoresis of cell culture and yeast-derived HBsAg. All samples were reduced, denatured and electrophoresed as described by Laemmli[30]. After electrophoresis, polypeptides were visualized with Coomassie brilliant blue (lanes 1–3) or with the silver stain procedure described by Morrissey[31] (lane 4). Lane 1, molecular weight standards (3 μg each): phosphorylase *b* (94K), bovine serum albumin (68K), ovalbumin (43K), carbonic anhydrase (30K), soybean trypsin inhibitor (21K) and lysozyme (14.3K). Lane 2, 30 μg of HBsAg from the human hepatoma cell line PLC/PRF/5 (ref. 10), also purified from yeast as described in Fig. 1 legend. Lane 3, 30 μg of HBsAg purified from yeast as described in Fig. 1. Lane 4, 10 μg of clarified yeast extract as described in Fig. 1 legend.

Table 2 Antigenic potency in grivet monkeys of HBsAg purified from yeast and from human plasma

Vaccine source	Antigen dose per injection (μg protein)	Anti-HBsAg response after initial vaccine dose (geometric mean titre) Week 4	Week 8	Week 12	Week 52
Human plasma (lot 86016)	10	36	213	170	127
	2.5	343	6,227	17,348	9,924
	0.625	53	4,642	3,164	5,688
	0.156	15	128	83	358
Yeast (lot 81-4)	40	88	1,078	7,103	11,554
	10	184	877	8,489	4,984
	2.5	225	1,168	6,361	10,868
	0.625	109	925	518	313

A group of four initially seronegative grivet monkeys (*Cercopithecus aethiops*), weighing 3–5 kg, were each given two 1-ml intramuscular (i.m.) doses of yeast or human plasma vaccine 4 weeks apart. Dilutions of antigen were made in alum placebo of the same composition as the vaccine. Animals were bled at biweekly intervals for 1 yr and tested for antibody to HBsAg by using a commercial RIA kit (AUSAB, Abbott). Protein was measured by the method of Lowry[29]. Human plasma lot 86016 was prepared in these laboratories[3–6].

Table 3 Protective efficacy in chimpanzees of HBsAg purified from yeast and from human plasma

Injection	Chimp no.	Before challenge: Anti-HBsAg titre (at 12 weeks)	Before challenge: Antigen subtype	After challenge (week of onset or weeks of duration): HBsAg Onset	HBsAg Duration	Anti-HBcAg Onset	Anti-HBcAg Duration	SGOT elevation Onset	SGOT elevation Duration	SGPT elevation Onset	SGPT elevation Duration	Liver pathology onset
Yeast vaccine (lot 81-4)	110	1,830	adr	–	–	–	–	–	–	–	–	–
	138	540	adr	–	–	–	–	–	–	–	–	–
	103	18,300	ayw	–	–	–	–	–	–	–	–	–
	120	7,200	ayw	–	–	–	–	–	–	–	–	–
Unvaccinated controls	111	<8	adr	10	10	15	9	17	3	17	6	20
	128	<8	adr	8	11	12	12	17	3	16	5	20
	127	<8	ayw	6	14	12	12	13	3	13	7	16
	130	<8	ayw	6	18	10	14	22	1	14	10	24

Eight chimpanzees, each weighing 40–60 kg, were selected for study based on negative findings in tests for HBsAg, anti-HBsAg, anti-HBcAg, elevation in transaminase, liver histopathology and tuberculin reaction. The animals were separated into two groups, four test animals and four controls. Each of the four test animals was given three 40-μg doses of yeast-derived HBsAg vaccine in 1 ml volume i.m. at 4-week intervals. All eight animals were then challenged by intravenous injection of 1,000 chimpanzee infectious doses of subtype adr or ayw virus in 1 ml of human hepatitis B plasma. Antigen and antibody titres were measured by commercial (Abbott) RIA kits (AUSRIA, AUSAB and CORAB for HBsAg, anti-HBsAg and anti-HBcAg, respectively). SGOT and SGPT assays were performed by the Sigma-Frankel (no. 505) and by the UV absorption (Boehringer-Mannheim) procedures, respectively. SGOT titres >40 and SGPT titres >30 were considered elevated. The subtype adr and ayw human plasmas used for challenge were obtained from Drs R. Gerety and E. Tabor of the Office of Biologics, US Food and Drug Administration; they were of measured viral infectiousness for chimpanzees and were subtyped serologically. The animals were bled at weekly intervals during the 36-week period of observation, covering 12 weeks before virus challenge and 24 weeks after. Liver biopsies were taken at 4-week intervals using a Menghini 16T needle. The tissues were fixed in 10% buffered formalin solution and the haematoxylin/eosin-stained sections were prepared by Dr A. Phelps of these laboratories under blind code number. The tests were carried out in animals that were held in isolation in the facilities of Dr William E. Greer at the Gulf South Research Institute, New Iberia, Louisiana. –, All remained negative.

We thank Dr C. E. Carty and F. X. Kovach for assistance in fermentation, B. J. Harder, N. Grason and J. Bailey for assistance in antigen purification, Dr B. Wolanski and R. Ziegler for electron microscopy, and H. E. Darmofal, J. T. Deviney, K. I. Guckert, R. R. Roehm and L. W. Stanton for assistance in the animal tests.

Received 11 July; accepted 16 November 1983.

1. Deinhardt, F. & Gust, I. D. *Bull. Wld Hlth Org.* **60**, 661–691 (1982).
2. Hilleman, M. R. *et al. Viral Hepatitis* (eds Vyas, G. N., Cohen, S. N. & Schmid, R.) 525–537 (The Franklin Institute Press, Philadelphia, 1978).
3. Hilleman, M. R. *et al.* in *Viral Hepatitis 1981 int. Symp.* (eds Szmuness, W., Alter, H. & Maynard, J.) 385–397 (The Franklin Institute Press, Philadelphia, 1982).
4. Buynak, E. B. *et al. J. Am. med. Ass.* **235**, 2832–2834 (1976).
5. Adamowicz, P. *et al.* in *INSERM Symp.* No. 18 (eds Maupas, P. & Guesry, P.) 37–49 (Elsevier, Amsterdam, 1981).
6. Coutinho, R. A. *et al. Br. med. J.* **286**, 1305–1308 (1983).
7. Valenzuela, P. *et al. Nature* **288**, 815–819 (1979).
8. Edman, J. C., Hallewell, R. A., Valenzuela, P., Goodman, H. M. & Rutter, W. J. *Nature* **291**, 503–506 (1981).
9. Valenzuela, P., Medina, A., Rutter, W. J., Ammerer, G. & Hall, B. D. *Nature* **298**, 347–350 (1982).
10. Alexander, J. J., Bey, E. M., Geddes, E. W. & Lecatsas, G. *S. Afr. med. J.* **50**, 2124–2128 (1976).
11. Barin, F., Maupas, P., Courtaget, P., Goudeau, A. & Chiron, J. P. in *INSERM Symp.* No. 18 (eds Maupas, P. & Guesry, P.) 263–266 (Elsevier, Amsterdam, 1981).
12. Moriarty, A. M., Hoyer, B. H., Shih, J. W-K., Gerin, J. L. & Hamer, D. H. *Proc. natn. Acad. Sci. U.S.A.* **78**, 2606–2610 (1981).
13. Dubois, M. F., Pourcel, C., Rousset, S., Chany, C. & Tiollais, P. *Proc. natn. Acad. Sci. U.S.A.* **77**, 4549–4553 (1980).
14. Burrell, J. C., Mackay, P., Greenway, P. J., Hofschneider, P. H. & Murray, K. *Nature* **279**, 43–47 (1979).
15. Lerner, R. A. *et al. Proc. natn. Acad. Sci. U.S.A.* **78**, 3403–3407 (1981).
16. Dressman, G. R. *et al. Nature* **295**, 158–160 (1982).
17. Blattnager, F. R. *et al. Proc. natn. Acad. Sci. U.S.A.* **79**, 4600–4604 (1982).
18. Prince, A. M., Ikram, H. & Hopp, T. P. *Proc. natn. Acad. Sci. U.S.A.* **79**, 579–582 (1982).
19. Gerin, J. L. *et al. Proc. natn. Acad. Sci. U.S.A.* **80**, 2365–2369 (1983).
20. Smith, G. L., Mackett, M. & Moss, B. *Nature* **302**, 490–495 (1983).
21. Miyanohara, A. *et al. Proc. natn. Acad. Sci. U.S.A.* **80**, 1–5 (1983).
22. Hitzeman, R. A. *et al. Nucleic Acids Res.* **11**, 2745–2763 (1983).
23. Desers, D., Muller, U. & Hamberger, H. *Analyt. Biochem.* **70**, 263–267 (1976).
24. Ono, Y. *et al. Nucleic Acids Res.* **11**, 1747–1757 (1983).
25. Gerety, R. J., Tabor, E., Purcell, R. H. & Tyeryar, F. J. *J. infect. Dis.* **140**, 642–648 (1979).
26. Szmuness, W., Stevens, C. E., Zang, E. A., Harley, E. J. & Kellner, A. *Hepatology* **1**, 377–385 (1981).
27. Francis, D. P. *et al. Ann. intern. Med.* **97**, 362–366 (1982).
28. Szmuness, W. *et al. New Engl. J. Med.* **307**, 1481–1486 (1982).
29. Lowry, O. H., Rosebrough, N. J., Farr, A. L. & Randall, R. J. *biol. Chem.* **193**, 265–275 (1951).
30. Laemmli, U. K. *Nature* **227**, 680–685 (1970).
31. Morrissey, J. H. *Analyt. Biochem.* **117**, 307–310 (1981).

McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR.
Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178-80.

Erste Erfahrungen mit rekombinanter Hepatitis B-Vaccine bei Patienten unter chronischer Haemodialyse-Behandlung

R. Müller[1], J. Bommer[2], H. Braas[3], F. Deinhardt[4], A. Feuerhake[1], W. Jilg[4], G. Küttler[1], B. Weinel[3], Abteilung für Gastroenterologie und Hepatologie, Medizinische Hochschule Hannover[1]; Sektion Nephrologie, Medizinische Klinik Universität Heidelberg[2]; Medizinische Klinik II, Städt. Krankenanstalten Ludwigshafen[3]; Max von Pettenkofer Institut der Ludwig-Maximilian-Universität München[4].

Die Immunogenität natürlicher, aus Humanplasma gewonnener Hepatitis B-Vaccine hat sich bei endogen oder exogen immunsupprimierten Patienten beträchtlich schwächer erwiesen als bei gesunden Personen. Es erschien daher interessant zu prüfen, ob nach Impfung mit einer gentechnologisch gewonnenen HB-Vaccine bei chronischen Haemodialyse-Patienten höhere Seronkonversionsraten für anti-HB_s erzielt werden können als mit natürlichem HB-Impfstoff. 51 HBV empfängliche Patienten unter chronischer Haemodialyse-Behandlung erhielten 3 Impfungen mit je 40 ug Hb,Ag Protein, das in einem DNS-rekombiniertem Stamm der Hefe Saccharomyces cerovisiae hergestellt wurde (Hepatitis B-Vaccine [recombinant] MSD, Westpoint USA, Lot 934/C-J625). Die zweite und dritte Impfung erfolgten einen bzw. 6 Monate nach der ersten Impfung. Einen Monat nach der 2. Impfung hatten 20 von 48 (42%) der Patienten anti-HB_s gebildet. Der mittlere Antikörper-Gehalt betrug 24,7 IU/ml. Bei 21 Patienten ist das Impfprogramm abgeschlossen, 13 von ihnen wiesen im 7. Monat nach Impfbeginn eine Serokonversion nach anti-HB_s auf. Der mittlere anti-HB_s-Gehalt war auf 151 IU/ml angestiegen. Danach lassen sich bei Dialyse-Patienten mit rekombinat hergestellter HB-Vaccine ähnliche Serokonversionsraten erzielen wie mit HB-Impfstoff, der aus Humanplasma gewonnen wurde.

Muller R, Bommer J, Brass H, Deinhardt A, Jilg W, Kuttler G, et al. Erste erfahrungen mit rekombinanter hepatitis B-vaccine bei patienten unter chronischer haemodialyse-behandlung. Gastroenterol 1985; 23:297.

IMMUNOGENICITY OF RECOMBINANT HEPATITIS B VACCINE

SIR,—Jilg et al[1] have compared the immunogenicity of recombinant[2] and plasma derived hepatitis B vaccines. We report for comparison the results of a similar trial of the recombinant vaccine in a younger age group. 55 male armed forces recruits, aged 17–19, all of whom were susceptible to hepatitis B virus were given

IMMUNE RESPONSES AFTER RECOMBINANT (n = 55) OR PLASMA (n = 50) HEPATITIS B VACCINATION

Month	Seroconversion		GMT anti-HBs (IU/l)	
	Recombinant	Plasma	Recombinant	Plasma
1	37 (67%)	32 (64%)	11	4
3	54 (100%)*	49 (98%)	198	278
4	54 (100%)*	49 (98%)	189	493
7	53 (100%)†	50 (100%)	2749	9227

*1 lost to follow-up. †2 lost.

10 µg of recombinant vaccine (lot 979/C-K 564, Merck Sharp and Dohme) intramuscularly at 0, 1, and 6 months. The results can be compared with those in another group of recruits of the same age who had been given 10 µg of the same manufacturer's plasma-derived vaccine at 0, 1, and 6 months in an earlier study.[3]

Seroconversion rates and geometric mean antibody titres (GMT) of anti-HBs (see table) were substantially higher than those reported by Jilg et al.[1] The final GMT was 2749 IU/l (95% confidence interval: 1676–4506) compared with 911 IU/l for 12 males reported by Jilg et al.[1] After the booster dose, all vaccinees had an anti-HBs titre above the protection level of 10 IU/l; 43 (81%) had titres above 1000 IU/l. The stronger immune response in our study than in Jilg's may be explained by the fact that our vaccinees were younger (17–19 vs 21–34). We observed only minor side-effects in 26% of participants; this is as reported by Jilg et al.[1]

The seroconversion rates were the same as those obtained in our earlier trial of a 10 µg dose of the plasma-derived vaccine.[3] In contrast to Jilg et al[1] GMT antibody levels in our recombinant group in the first 3 months were similar ($p>0 \cdot 05$) to those induced by the plasma-derived vaccine, although levels after the booster dose were significantly lower ($p<0 \cdot 001$) in the recombinant group (Mann-Whitney tests, separately at each time).

Our results accord with those of Jilg et al in confirming the safety and immunogenicity of the Merck Sharp and Dohme recombinant vaccine. The minor differences in immune responses show the need for further trials in population groups under consideration for vaccination, before a dose and vaccination scheme are decided on. In assessing the efficacy of this vaccine, information on the quality of the anti-HBs induced should complement the anti-HBs levels achieved.[4]

G. PAPAEVANGELOU
E. DANDOLOS
A. ROUMELIOTOU-KARAYANNIS
S. C. RICHARDSON

National Centre for Viral Hepatitis,
Athens School of Hygiene,
Athens 11521, Greece

1. Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. *Lancet* 1984; ii: 1174–75.
2. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984; 307: 178–80.
3. Papaevangelou G, Roumeliotou A, Vissoulis C, Stathopoulou P, Kolaitis N, Krugman S. Safety and immunogenicity of a further reduced dose (10 µg) of the hepatitis B vaccine. *Develop Biol Standard* 1983; 54: 209–12.
4. Brown SE, Zuckerman AJ, Howard CR, Steward MW. Affinity of antibody responses in man to hepatitis B vaccine determined with synthetic peptides. *Lancet* 1984; ii: 184–87.

Papaevangelou G, Dandolos E, Roumelia tou-Karayannis A, Richardson SC. Immunogenicity of recombinant hepatitis B vaccine. Lancet 1985; 1:455-6.

Edward M. Scolnick, Arlene A. McLean,
David J. West, Jules L. Dienstag,
Eloise Watkins, Friedrich Deinhardt and Wolfgang Jilg

23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

VIRAL HEPATITIS and LIVER DISEASE
ISBN 0-8089-1678-5

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination			
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

Reprinted from the Journal of the American Medical Association
June 1, 1984, Volume 251

Original Contributions

Clinical Evaluation in Healthy Adults of a Hepatitis B Vaccine Made by Recombinant DNA

Edward M. Scolnick, MD; Arlene A. McLean, PhD; David J. West, PhD; William J. McAleer, PhD; William J. Miller, MS; Eugene B. Buynak, PhD

• **A vaccine formulated from hepatitis B surface antigen (HBsAg) produced by a recombinant strain of the yeast *Saccharomyces cerevisiae* was administered to two groups of human volunteers composed of 37 healthy, low-risk adults. Each subject received a 10-μg dose of HBsAg at 0, 1, and 6 months. By one month, 27% to 40% of the vaccinees had antibody to HBsAg, and by three months 80% to 100% were antibody positive. Large boosts in titer followed the third dose at six months. The antibody formed is predominantly specific for the *a* determinant of HBsAg. There have been no serious reactions attributable to the vaccine. The most frequent complaint has been transient soreness at the injection site. As far as we know, this is the first reported use in man of a vaccine prepared by recombinant DNA technology.**

(*JAMA* 1984;251:2812-2815)

WORLDWIDE, human hepatitis B infection constitutes a major public health problem. In addition to the disability associated with acute clinical disease, chronic liver disease, cirrhosis, and primary hepatocellular carcinoma are now recognized sequelae of unresolved hepatitis B infection. Indeed, in some areas of Asia and sub-Saharan Africa, primary hepatocellular carcinoma ostensibly attributable to hepatitis B infection ranks as a leading cause of cancer deaths among males.[1]

See also p 2765.

The reservoir of hepatitis B virus resides mainly in a population of chronic carriers now estimated to number more than 200 million.[2] Infection is transmitted to susceptible persons through contact with the blood, semen, or saliva of chronic carriers or persons suffering acute infection. In low-incidence countries, such as the United States, the risk of hepatitis B infection is still high among certain groups of health care personnel, patients receiving dialysis treatments or blood products made from large pools, children born to Alaskan Eskimos or to Indochinese or Haitian refugees, residents of institutions for the mentally handicapped, prisoners, users of illicit injectable drugs, and persons who are sexually very promiscuous.[3] In high-incidence areas such as Southeast Asia, transmission from mother to child in the perinatal period is the major mode of infection supplemented by horizontal transmission between other family contacts.[3]

From the Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, Pa.

Reprint requests to Merck Institute for Therapeutic Research, Merck Sharp & Dohme Research Laboratories, West Point, PA 19486 (Dr Scolnick).

Since there is no effective treatment for hepatitis B infection, prevention is essential. A safe, effective human hepatitis B vaccine is now available. However, it utilizes hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of hepatitis B virus infection. Consequently, the supply of vaccine is potentially limited by available sources of suitable plasma. In addition, extensive processing and safety testing have been necessary to ensure production of a vaccine antigen that is pure and free of any extraneous living agent that might have been present in the starting plasma. Even though multiple inactivation treatments used in the antigen purification process have been shown to inactivate representatives of all major groups of animal viruses,[4] concern over the theoretical possibility of a living organism such as the etiologic agent of acquired immune deficiency syndrome being present in plasma and surviving the purification and inactivation procedures has slowed acceptance of hepatitis B vaccine.

A promising alternative to infected human plasma as a source of HBsAg for vaccine is the use of recombinant DNA technology to effect synthesis of the surface antigen by a culture of microorganisms. The hepatitis B virus gene coding for HBsAg has been cloned both in *Escherichia coli* and in yeast[5-7]; however, expression of the gene in yeast has been much better than in *E coli*. Furthermore, HBsAg

produced by recombinant yeast cells has been shown to aggregate into particles closely resembling those isolated from human plasma, and this material was shown to include antibodies in mice and guinea pigs.[9]

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for HBsAg has been formulated into a vaccine through adsorption on alum adjuvant. Electron microscopy reveals that the purified HBsAg used for this vaccine exists as aggregate particles 20 to 22 nm in diameter, a morphology also characteristic of free surface antigen in infected plasma and of the purified antigen now used in plasma-derived hepatitis B vaccine. In contrast to HBsAg from human plasma, the antigen produced by recombinant yeast is not glycosylated. Under reducing conditions, sodium dodecyl sulfate electrophoresis of the antigen purified from yeast reveals a single band of molecular weight 23,000, which corresponds to the nonglycosylated polypeptide that is the major component of the hepatitis B virus envelope. The vaccine formulated using this material has now been shown to be immunogenic for mice and for monkeys with a potency equal to or superior to that of vaccine made from plasma-derived antigen. In addition, chimpanzees immunized with this yeast recombinant hepatitis B vaccine (HBsAg subtype *adw*) were fully protected when challenged with virus of either type *adr* or *ayw*, while unimmunized animals all showed evidence of infection when challenged.[8]

In this article we describe results of the first human immunogenicity-safety trial of the yeast recombinant hepatitis B vaccine. To the best of our knowledge, this is the first time that a vaccine prepared by recombinant DNA technology has been used in man.

MATERIALS AND METHODS

Population

Participants in this study were healthy, nonpregnant adult employees of Merck and Co, Inc. Subjects had to be negative for hepatitis B serological markers and have a normal level of alanine aminotransferase and must not have received any other hepatitis B vaccine. Written consent was obtained after providing each participant with information on the source of the investigational yeast recombinant hepatitis B vaccine, animal test results obtained with the vaccine, vaccination and bleeding schedules, and the potential risks and benefits of participation in the study.

Vaccine

Hepatitis B surface antigen for the vaccine was produced in fermentation cultures of a recombinant strain of the yeast *S cerevisiae* containing a plasmid carrying the gene for the *adw* subtype of HBsAg, as described previously.[1,10]

Two methods were employed for the purification of HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends on selection of water-immiscible molecules followed by separation by molecular size. Details of the expression of HBsAg in yeast and the purification of the surface antigen will be published elsewhere. Purified HBsAg was treated with formaldehyde to stabilize the material and to kill any extraneous living agents that might be present. The antigen was then formulated into a vaccine through adsorption on alum adjuvant to give 10 μg of HBsAg and 0.5 mg of aluminum (hydroxide) per 1-mL dose. The final formulation also contained 1:20,000 thimerosal as a preservative. Vaccine was maintained at 2 to 8 °C until used.

Procedures

A blood sample was obtained from each subject approximately two weeks prior to the first vaccination and was tested for HBsAg, antibody to HBsAg (anti-HBs), antibody to core antigen (anti-HBc), alanine aminotransferase (ALT), and yeast antibody. Subjects found eligible on the basis of these assays were scheduled to receive a 1.0-mL (10-μg HBsAg) intramuscular injection of the yeast recombinant vaccine at 0, 1, and 6 months. Postvaccination blood samples for the determination of hepatitis B serological markers, ALT, and yeast antibody were scheduled monthly for seven months and at 9, 12, and 24 months following the first injection.

Vaccinees were asked to take their temperature daily for five days after each injection of vaccine and to report any local or systemic reactions that might occur during this period.

Assays

Standard radioimmunoassay test kits were used for the determination of HBsAg, anti-HBs, and anti-HBc. Titers of anti-HBs were expressed in international milliunits per milliliter using the formulation described by Hollinger et al.[11] A serum sample was considered positive for anti-HBs if the ratio of the sample counts per minute to the negative control serum counts per minute was 2.1 or greater.

Estimates of the proportion of anti-HBs in postvaccination sera specific for the *a* or *d* determinants of HBsAg were based on an assay described by Hoofnagle et al.[12] Briefly, aliquots of each serum sample are incubated with a subtype *ad* HBsAg-positive serum, with a subtype *ay* HBsAg-positive serum, and with normal human serum for two hours at room temperature, and then each mixture is carried through a standard radioimmunoassay to measure residual anti-HBs. Based on the percent of neutralization with the two HBsAg subtype sera when compared with the unneutralized normal human serum, an estimate can be made of the relative amounts of anti-*a* and anti-*d* antibodies present. Since the vaccine is a monovalent-type *adw* preparation, sera will contain either anti-*d* antibodies, anti-*a* antibodies, or a combination of both types, and the amount of neutralization with the HBsAg-*ay* serum is therefore a direct assay for the amount of anti-*a* present. Subtracting the amount of neutralization with the HBsAg-*ay* serum from that found for the HBsAg-*ad* serum then gives an estimate of the amount of anti-*d* present.

A radioimmunoassay was developed to detect yeast antibodies in the sera of vaccine recipients. For this assay, an extract of the parent strain of *S cerevisiae* lacking the plasmid containing the gene for HBsAg was prepared by disrupting a 50% suspension of the cells in a homogenizer and then clarified by centrifugation at 9,000 g followed by passage through a 0.45-mμm membrane filter. The clarified, filtered extract was diluted to a final protein concentration of 80 μg/mL with 0.1 M carbonate buffer and pH 9.6 and adsorbed to ¼-in polystyrene beads overnight at 4 °C. Washed, dried beads were maintained at −20 °C. Two hundred-microliter volumes of sera diluted 1:100, 1:1,000, and 1:10,000 in phosphate-buffered saline containing 0.5% bovine serum albumin and 0.5% Tween 20 were incubated with coated beads for three hours at 37 °C. Following three washes with water, the beads were incubated with 200 μL of iodine 125 protein A (specific activity, 100,000 cpm) for 1.5 hours at 37 °C. The protein A binds and labels any antiyeast antibody on the bead that is of the IgG class. After three additional water washes, the beads were counted and titers of yeast antibody were determined by interpolation from a standard curve derived using dilutions of a hyperimmune guinea pig serum having an antibody titer to parent yeast extract of 1 million.

The serum samples of vaccinees were also measured for changes in preexisting specific yeast antibodies or the appearance of new yeast antibodies using a sodium dodecyl sulfate polyacrylamide gel electrophoresis (reducing), Western blot technique. In this procedure, parent yeast extract is separated on a 12.5% polyacrylamide gel. After transfer to a nitrocellulose sheet, polypeptides from the gel are detected by incubation with a 1:50 dilution of the vaccinee's serum, followed by incubation with ^{125}I protein A and exposure to x-ray film (T. Mason, PhD, oral communication, 1982).

RESULTS

The vaccine has been well tolerated. None of the 37 subjects studied to date has experienced a serious adverse effect attributable to vaccine. There has been no evidence of hepatitis B infection among vaccinees, ie, no elevation of ALT values and no antigenemia. Mild soreness at the injection site generally lasting one to two days was reported by 73% to 80% of vaccinees who received vaccine purified by immune affinity chromatography (lot 934) but by a substantially smaller proportion—20% to 24%—of subjects who received vaccine prepared by hydrophobic interaction chromatography (lot 972) (Table 1). Infrequent systemic complaints occurring within a five-day period following vaccination have included elevated temperature (38.3 to 38.8 °C [101 to 102 °F], oral), fatigue, headache, gastrointestinal disturbance, symptoms of upper respiratory tract infection, and nosebleed.

Table 2 summarizes our observations to date on the human immunogenicity of yeast recombinant hepatitis B vaccine. Fifteen persons (ten men, five women; age range, 23 to 53 years; median age, 33 years) have received all three doses of lot 934 vaccine prepared by the immune affinity chromatography method. Forty percent had a detectable titer of anti-HBs within one month of receiving the first dose. By two months, the proportion of seroconverters rose to 93%, and at three months, all recipients of this vaccine were antibody positive. The geometric mean titer following primary immunization reached a plateau at four months, then increased more than 25-fold following the booster dose at six months.

Table 1.—Proportion (%) of Vaccinees With Clinical Complaints During a Five-Day Period Following Injection of Yeast Recombinant Hepatitis B Vaccine

Nature of Complaint	Vaccine Lot No.	Dose 1	Dose 2	Dose 3
Soreness at injection site	934	12/15 (80)	11/15 (73)	11/15 (73)
	972	5/21 (24)	3/15 (20)	
Systemic* complaints	934	5/15 (33)	3/15 (20)	1/15 (7)
	972	1/21 (5)	2/15 (13)	

*Includes persons with one or more episodes of the following: temperature, 38.3 to 38.8 °C (101 to 102 °F) (two), fatigue (three), gastrointestinal disturbance (four), headache (five), symptoms of upper respiratory tract infection (three), and nosebleed (one).

Table 2.—Seroconversion Frequencies and Geometric Mean Titers (GMTs)* for Anti-HBs Among Initially Seronegative Healthy Adults Receiving 10-μg Doses of Yeast Recombinant Hepatitis B Vaccine†

Vaccine Lot No. (Method of Preparation)	No. of Subjects Vaccinated	Time, mo	Seroconversion Proportion (%)	GMT All Vaccinees‡	GMT Responders Only
934 (Immune affinity chromatography)	15	1	6/15 (40)	1.6	6.0
		2	14/15 (93)	31.7	44.2
		3	15/15 (100)	55.5	55.5
		4	15/15 (100)	78.2	78.2
		5	14/14 (100)	77.2	77.2
		6	15/15 (100)	67.9	67.9
		7	12/12 (100)	1,905.1	1,905.1
972 (Hydrophobic interaction chromatography)	22	1	4/15 (27)	1.4	39.6
		2	8/12 (67)	17.8	108.7
		3	4/5 (80)	56.5	218.5

*In international milliunits per milliliter.
†At 0, 1, and 6 months.
‡All serum samples with titers of less than 0.6 ImU/mL were assigned a value of 0.3 ImU/mL for calculating GMTs.

Table 3.—Percentages of Anti-HBs Specific for *a* and *d* Determinants of HBsAg in Postvaccination Sera*

Vaccine Lot No.	Time, mo	No. of Samples	% Anti-*a* Range	% Anti-*a* Mean	% Anti-*d* Range	% Anti-*d* Mean
934	1	1		47		53
	2	7	87-96	93	2-10	6
	3	10	63-96	86	2-37	13
	4	13	65-96	89	2-35	11
	5	12	80-97	92	2-20	8
	6	8	92-97	94	2-8	5
	7	12	89-100	98	0-11	2
972	1	2	56-81	74	8-44	26
	2	6	87-100	94	0-13	6

*Assay done only on serum samples having an anti-HBs titer of 25 ImU/mL or greater.

Twenty-two subjects have received vaccine from lot 972 made from HBsAg purified by the hydrophobic intraction chromatography method. These vaccinees have not been followed up for as long as the lot 934 recipients, and none has yet received a third dose. Preliminary serological results are shown in Table 2 for 15 of these volunteers (12 men, three women; age range, 24 to 63 years; median age, 40 years). The percentage of seroconverters was 27% at one month, 67% at two months, and 80% at three months. Geometric mean titers within the first three months of follow-up were similar to those observed among recipients of lot 934 vaccine.

Postvaccination serum samples with anti-HBs titers of 25 ImU/mL or greater were assayed to determine the percentage of antibody specific for the *a* and *d* determinants of HBsAg. Table 3 shows the results of these assays. Antibody specific for the *a* determinant predominates. In the interval from two to seven

months following the first dose of vaccine, anti-*a* antibody accounted for approximately 90% of the total anti-HBs.

Earlier studies (unpublished) showed that the yeast recombinant hepatitis B vaccine induced a predominantly anti-*a* form of anti-HBs in African green monkeys and that these antibodies have persisted through two years of follow-up.

Analysis of serum samples from participants in this study has revealed no significant postvaccination increases in yeast antibody titers as measured by radioimmunoassay. By Western blot analysis, each human serum sample shows a unique "fingerprint" spectrum of antibodies to yeast components. There may be only a few or as many as 20 different bands present. Analysis of monthly postvaccination serum samples from participants in this study has shown no change in the yeast antibody pattern for any person as compared with his prevaccination pattern. There has been no appearance of new antibodies in postvaccination sera and no significant increases in the intensity of existing antibody bands.

CONCLUSIONS

The results of this study indicate that an alum-adsorbed hepatitis B vaccine formulated using HBsAg of subtype *adw* synthesized by recombinant yeast cells is safe and immunogenic for man. Seroconversion rates and titers of anti-HBs obtained with the yeast recombinant vaccine in this study are comparable with those observed in earlier studies of healthy adults using vaccine derived from human plasma.[13-17]

Previous studies with hepatitis B vaccine of human plasma origin showed that protection from infection is associated with vaccine-induced anti-HBs.[18-20] Furthermore, one of these trials demonstrated that antibody formed in response to vaccine of HBsAg subtype *ad* provided cross-protection against infection caused by heterologous virus of subtype *ay*.[20] Since the antibody formed by recipients of the yeast recombinant hepatitis B vaccine is predominantly anti-*a*, this vaccine should be protective against all hepatitis B virus subtypes. The efficacy of the yeast vaccine against both homologous *ad* and heterologous *ay* virus challenge in chimpanzees has been demonstrated.[8]

Studies are under way to assess antibody persistence and to determine optimal doses of the yeast recombinant hepatitis B vaccine for both healthy and immunocompromised adults and children.

References

1. Francis DP: Selective primary health care: Strategies for control of disease in the developing world: III. Hepatitis B virus and its related diseases. *Rev Infect Dis* 1983;5:322-329.
2. Gust I: Comparison of the epidemiology of hepatitis A and B, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 129-143.
3. Immunization Practices Advisory Committee: Inactivated hepatitis B virus vaccine. *Ann Intern Med* 1982;97:379-383.
4. Hilleman MR, McAleer WJ, Buynak EB, et al: Quality and safety of human hepatitis B vaccine. *Dev Biol Stand* 1983;54:3-12.
5. Burrell CJ, Mackay P, Greenaway PJ, et al: Expression in *Escherichia coli* of hepatitis B virus DNA sequences cloned in plasmid pBR322. *Nature* 1979;279:43-47.
6. Valenzuela P, Gray P, Quiroga M, et al: Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen. *Nature* 1979;280:815-819.
7. Valenzuela P, Medina A, Rutter WJ, et al: Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982;298:347-350.
8. Hitzeman RA, Chen CY, Hagie FE, et al: Expression of hepatitis B virus surface antigen in yeast. *Nucleic Acids Res* 1983;11:2745-2763.
9. Miyanohara A, Toh-e A, Nozaki C, et al: Expression of hepatitis B surface antigen gene in yeast. *Proc Natl Acad Sci USA* 1983;80:1-5.
10. McAleer WJ, Buynak EB, Maigetter RZ, et al: Human hepatitis B vaccine from recombinant yeast. *Nature* 1984;307:178-180.
11. Hollinger FB, Adam E, Heiberg D, et al: Response to hepatitis B vaccine in a young adult population, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 451-466.
12. Hoffnagle JH, Gerety RJ, Smallwood LA, et al: Subtyping of hepatitis B surface antigen and antibody by radioimmunoassay. *Gastroenterology* 1977;72:290-296.
13. Deinhardt F, Zachoval R, Frosner H, et al: Passive-active immunization against hepatitis B, in Krugman S, Sherlock S (eds): *Proceedings of the European Symposium on Hepatitis*. New York, KPR Infor/Media Corporation, 1981, pp 140-150.
14. Szmuness W, Stevens CE, Harley EJ, et al: The immune response of healthy adults to a reduced dose of hepatitis B vaccine. *J Med Virol* 1981;8:123-129.
15. Krugman S, Holley HP Jr, Davidson M, et al: Immunogenic effect of inactivated hepatitis B vaccine: Comparison of 20 microgram and 40 microgram doses. *J Med Virol* 1981;8:119-121.
16. Hilleman MR, Buynak EB, McAleer WJ, et al: Hepatitis A and hepatitis B vaccines, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 385-397.
17. Desmyter J, Colsert J, Verstraete M, et al: Hepatitis B vaccination of hemophiliacs. *Scand J Infect Dis* 1983;38(suppl):42-45.
18. Szmuness W, Stevens EC, Zang EA, et al: A controlled trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981;1:377-385.
19. Francis DP, Hadler SC, Thompson SE, et al: The prevention of hepatitis B with vaccine: Report of the Centers for Disease Control multicenter efficacy trial among homosexual men. *Ann Intern Med* 1982;97:362-366.
20. Szmuness W, Stevens CE, Harley EJ, et al: Hepatitis B vaccine in medical staff of hemodialysis units: Efficacy and subtype cross-protection. *N Engl J Med* 1982;307:1481-1486.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

Printed and Published in the United States of America

OVERVIEW OF CLINICAL STUDIES WITH HEPATITIS B VACCINE (RECOMBINANT)

Barbara A. Zajac, M.D., Ph.D.
Merck Sharp & Dohme Research Laboratories
David J. West, Ph.D., M.P.H.
William J. McAleer, Ph.D.
Edward M. Scolnick, M.D.

Clinical studies with the Merck recombinant yeast hepatitis B. vaccine were initiated in July 1983. Over 3000 individuals have received at least one dose of vaccine. Vaccination was carried out at 0, 1 and 6 months and doses ranged from 1.25 mcg to 40 mcg. Seroconversion rates, for various populations, are expressed as the percentage of individuals who, at 7-8 months (1-2 months after the third dose of vaccine) had an anti-HBs titer >10 mIU/ml. Geometric mean titers (GMT) are expressed as mIU/ml for responders.

	2.5 mcg Dose		5 mcg Dose		10 mcg Dose	
Population (Age)	Rate(%)	GMT	Rate(%)	GMT	Rate(%)	GMT
Adults (20-69)	97	321	90	335	96	975
Teenagers (16-19)	94	1132	100	2553	100	3059
Children (1-11)	100	4137	100	16000	Not	Tested

The vaccine has been shown to be safe in all populations immunized. The most frequent clinical complaints during a 5-day period following 2179 injections, were soreness, pain and tenderness at the injection site (9%, 4% and 3%, respectively), and fatigue/weakness (5%) or headache (4%).

The recombinant yeast HBsAg is of the ad subtype. In vaccine recipients antibody specific for the a determinant predominates. By 8 months post the first dose of vaccine, the mean percentage of anti-a in all sera tested was 97%.

Sera from 138 vaccine recipients tested for antibodies to yeast antigens showed high antibody titers in both pre and post-vaccination samples. There was no correlation between increased yeast antibody titer and frequency or severity of clinical reactions. The recombinant yeast hepatitis B vaccine has been shown to be safe and immunogenic in all populations studied.

Zajac BA, West DJ, McAleer WJ, Scolnick EM. Overview of clinical studies with hepatitis B vaccine (recombinant). Presented at the fifth biennial scientific meeting, Asian Pacific Association for the Study of the Liver, Symposium on recent advances in the prevention of hepatitis B infection, January 1986, Singapore.