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712364

(R)

March 2, 1977

Union Carbide Corporation  
Law Department  
ATTN: Mr. G. Wilson Horde  
P. O. Box Y  
Oak Ridge, Tennessee

S-47,108 (CNID 3407) AND S-47,864 (CNID 3524)

Gentlemen:

We have been advised by Mr. Tom Farris, Patent Attorney for  
HH, that they plan to file on behalf of the Government on  
both the above docket.

We would appreciate your advising your inventors of the pro-  
posed action. We will send you copies of the filed applications  
for your records when we receive them.

Sincerely,

BEST COPY AVAILABLE

ORIGINAL SIGNED BY  
D. S. ZACHRY

MCP:DSZ:dys

D. S. Zachry, Chief  
Oak Ridge Patent Group

CC: Dean E. Carlson, PAT-HQ

*10/10/78 Farris wants updated dict. from inventors  
In clinical testing on humans - awaiting results.*

*3/28 Farris - closed.*

REPOSITORY Oak Ridge Operations  
Records Holding Area  
COLLECTION Documents 1944-94  
BOX No. B-87-13 Bldg. 2714-H  
S-47,108 (CNID 3407) Preparation  
FOLDER of Hepatitis B

1079105

March 22, 1976

Union Carbide Corporation  
Law Department  
ATTN: Mr. G. Wilson Horde  
Post Office Box Y  
Oak Ridge, Tennessee

AEC CASE S-47,108 (CNID 3407)

Gentlemen:

The Atomic Energy Commission has determined, on the basis of information furnished by your office in the subject Invention Disclosure, that it ~~(will)~~ (will not) ~~is holding abeyance its decision to~~ file a patent application on the disclosed invention at this time.

Unless you have been authorized to release information describing this invention by a signed Invention Memo form, please withhold release of such information on cases held in abeyance or those on which AEC will file pending filing of the patent application.

A Record of Invention should be furnished for inventions where AEC will file or release of the invention is requested.

Sincerely,

D. S. Zachry, Chief  
Oak Ridge Patent Group

MCP:DSZ

*P.S. Not patentable over 3,636,191. See attached  
Search report.*

1079106



UNITED STATES  
ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION  
WASHINGTON, D.C. 20545

March 19, 1976

D. S. Zachry, Chief  
Oak Ridge Patent Group

S-47,108

We have received the copy of the letter from HEW indicating that Agency will not file a patent application on the subject case. In view of this determination, we are closing this docket.

Dean E. Carlson, Chief  
Prosecution Branch, Patents



1079107

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
OFFICE OF THE SECRETARY

TO : Dr. Robert H. Purcell, NIH/NIAID/LID  
Dr. John Gerin, MAN Program  
Oak Ridge National Laboratory

DATE: March 15, 1976

FROM : Patent Counsel, HEW/GS/GCB

SUBJECT: Employee Invention - "Preparation of Hepatitis B Vaccine" -  
Case No. E-173-75 - Determination of Rights

Reference is made to your report of the subject invention which you developed during your employment with the National Institutes of Health and the Oak Ridge National Laboratory.

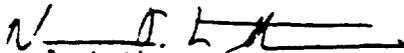
The material submitted has been reviewed by qualified personnel of this Department as to the novelty and utility of your discovery. This evaluation indicates that your invention, although novel and useful, does not differ from similar inventions in the prior art to the degree necessary to justify the expense of preparing a patent application. Accordingly, it has been concluded that the best interests of the public will be served by dedication of the invention to the public through publication and/or public use.

In view of the circumstances surrounding the development of the invention and consistent with paragraph 1(a) of Executive Order 10096, as amended, it is the determination of the Department of Health, Education, and Welfare that (1) insofar as the invention may be patentable, the equitable ownership of all domestic and foreign rights shall be in the United States Government, (2) no patent application will be filed by this Department, and (3) your invention will be dedicated to the public by publication and/or public use.

No question appearing with respect to its consistency with applicable law or regulations, or with Department policy, the foregoing determination of ownership constitutes the decision of the Department of Health, Education, and Welfare.

As noted in section 7.8 of the DHEW patent regulations, this determination is subject to the right of appeal to the Commissioner of Patents within thirty days after receipt.

Thank you for bringing your invention to the attention of the Department.

  
Norman J. Latker

Enclosures: E.O. 10096  
E.O. 10930  
DHEW Patent Regulations

cc: Dr. Robert M. Chanock - NIH/NIAID/LID  
Dr. D. S. Zachry - ERDA

1079108



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
OFFICE OF THE SECRETARY  
WASHINGTON, D.C. 20201

March 8, 1976

OFFICE OF THE  
GENERAL COUNSEL

D. S. Zachry, Esquire  
Chief, Oak Ridge Patent Group  
United States Energy Research and  
Development Administration  
P. O. Box E  
Oak Ridge, Tennessee 37830

Re: PURCELL/GERIN, "Hepatitis B Subunit Vaccine."  
Case No. E-173-75.

Dear Mr. Zachry:

This is in reply to your letter of January 19, 1976 requesting that we let you know our decision with regard to patenting the subject invention.

We had a patentability search done by one of our contract patent attorneys, Mr. Marvin R. Stern. A copy of Mr. Stern's report is enclosed herewith. We concur with Mr. Stern's conclusion that the subject invention is not patentable over the Blumberg patent and will make a Determination to dedicate this invention to the public by publication in a scientific journal.

As a matter of interest, the Blumberg patent is assigned to DHEW and has recently been licensed on a royalty-bearing non-exclusive basis to Merck and Company.

Your assistance in this matter is greatly appreciated.

Sincerely yours,

Norman J. Latker  
Patent Counsel

Enclosure *ok*

cc: Dr. Robert H. Purcell  
Dr. John L. Gerin

*copy sent to DEC 3/11/76*

1079109

JOHN CLARKE HOLMAN  
MARVIN R. STERN  
HERBERT I. CANTOR  
DENNIS O. KRAFT

JEROME M. TEPLITZ\*  
STUART J. FRIEDMAN\*  
J. WEBSTER PAXTON\*  
J. REED BATTEN, JR.\*  
ROBERT T. LYON\*  
SAMUEL MEERKREBS\*

LAW OFFICES

*Holman & Stern*

2401 Fifteenth Street, N.W.  
Washington, D. C. 20009

March 2, 1976

PATENT AND TRADE MARK COUNSELLORS

TELEX RCA "248555" IDEA UR  
TELEPHONE (202) 463-2234  
TELEGRAPH "HOLPAT"  
\*MO. AND ILL. BARS  
\*PATENT AGENT  
\*OF COUNSEL

OUR REF.  
YOUR REF.

*Patent Counselors*

MAR 3 1976

Thomas G. Ferris  
Patent Attorney  
National Institutes of Health  
Westwood Bldg., Room 5A-03  
Bethesda, Maryland 20014

RE: PURCELL/GERIN, "Hepatitis B Subunit Vaccine"  
Case No. E-173-75

Dear Mr. Ferris:

Pursuant to your authorization, we have now completed our patentability evaluation in regard to the subject invention disclosure.

The disclosure relates to the preparation of a Hepatitis B Vaccine prepared from the Hepatitis B Surface Antigen, formally known as the Australia Antigen. The Hepatitis B Surface Antigen is obtained from the plasma of a human chronic carrier of the Antigen by subjecting the plasma to a three-step purification procedure to remove or inactivate infectious Hepatitis B Virus. The first step involves removal of infectious Dane particles by centrifugation. The second step involves purification of the remaining, small, non-infectious particles by differential density centrifugation in a solution of cesium chloride. The third step involves inactivation of the purified vaccine with formalin.

After discussing this matter with the inventors and reviewing the prior art, including the Blumberg, et al Patent 3636191, forwarded with the original invention disclosure, as well as several prior publications furnished us by the inventors, it is our opinion that the present invention disclosure does not contain any patentable subject matter. The Blumberg, et al Patent discloses a vaccine against viral hepatitis, including Hepatitis B,

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Thomas G. Ferris, Esquire  
Page - 2 -  
March 2, 1976

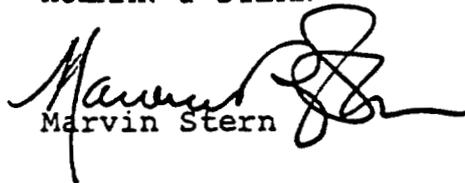
prepared from Australia Antigen obtained by purification of plasma of a human chronic carrier of the Antigen. The purification procedure described by Blumberg, et al includes a first-step of centrifugation in an ultra-centrifuge, a subsequent step of differential density centrifugation in a solution of cesium chloride, and a final step of attenuation or alteration of the vaccine by treatment with formaldehyde solution. The specific cesium chloride centrifugation step described in the invention disclosure is disclosed in the Gerin, et al publications appearing in Journal of Virology, Volume 7, Number 5, May 1971, pages 569-576; and "Progress in Transfusion and Transplantation, 1972", pages 167-190.

From our discussion on this matter with the inventors, it is our understanding that the techniques they employed in preparing their vaccine are fairly well described in the above-discussed prior art, and that the only thing possibly new is their description of safety and efficacy tests in chimpanzees employing such vaccine. Assuming this to be the case, this would not constitute patentable subject matter in view of Blumberg, et al's teaching of the use of the purified Australia Antigen as a vaccine against Hepatitis B, regardless of whether or not Blumberg, et al actually clinically tested such vaccine.

In view of the above, we are closing out our files on this matter.

Very truly yours,

HOLMAN & STERN

  
Marvin Stern

MS:gj

*Kindly please send debit note  
for payment. F 3/4/76*

1079111

PATENT INFORMATION WORKSHEET

Section 1

"S" No.	Op.	Pat. No.	Appl. No.	Yr.	Mo.	Day
47108						
Inventor's Last Name			First Name		I.I.	
Gerin			John		L.	
Source						
UCND						

Section 2 (Will be completed at Headquarters)

Section 3

Keywords

\* Vaccine \* + centrifugation \* + separation

Invention Title

Preparation of Hepatitis B Vaccine

Brief Description of Invention

Preparing vaccine from plasma of carriers of HBAg from by isopycnic banding, zonal centrifugation and rate zonal sedimentation

Check Priority	Page No.	Total No. Pages
P1 P2 P3 (P0)		

January 19, 1976

Mr. Norman J. Latker  
Patent Counsel  
Department of Health, Education & Welfare  
National Institute of Health  
Room 5A03  
Bethesda, Maryland 20014

ERDA DISCLOSURE S-47,108

Dear Mr. Latker:

Enclosed is a disclosure reported to us by Union Carbide under our contract W-7405-Eng-26 and ERDA-NIH Interagency Agreement 40-194-69.

We understand from Mr. Ferris that you have had a search made and may be ready to decide whether or not you wish to file a patent application on this vaccine preparation process. Please let us know your decision, and call upon us or Mr. Carlson at ERDA Headquarters for any assistance we can provide.

Sincerely,

ORIGINAL SIGNED BY  
D. S. ZACHRY

D. S. Zachry, Chief  
Oak Ridge Patent Group

MCP:DSZ:dys

Enclosure:  
Disclosure S-47,108

CC: D. E. Carlson, PAT, HQ w/encl.

1079113

OAK RIDGE NATIONAL LABORATORY

OPERATED BY  
UNION CARBIDE CORPORATION  
NUCLEAR DIVISION



POST OFFICE BOX X  
OAK RIDGE, TENNESSEE 37831

January 15, 1976

United States Energy Research and Development  
Administration, Oak Ridge Operations  
Attention: Mr. D. S. Zachry, Chief  
Oak Ridge Patent Group  
Post Office Box E  
Oak Ridge, Tennessee 37830

Gentlemen:

Subject: Disclosure - CNID No. 3407

5-47, 108

Enclosed are two copies of the subject disclosure entitled  
"Preparation of Hepatitis B Vaccine," Inventors:  
John L. Gerin and Robert H. Purcell.

This work was performed under ERDA-NIH Interagency Agreement  
40-194-69.

This development was given oral presentation January 7, 1975,  
at the Hepatitis B Vaccine Workshop, Bureau of Biologics,  
Bethesda, Maryland.

Sincerely,

A handwritten signature in cursive script that reads "H F McDuffie".

H. F. McDuffie, Director  
Information Division

HFM:ha

Enclosures 2

cc: H. Postma  
J. B. Storer  
K. H. Pierce - RC

1079114

OAK RIDGE NATIONAL LABORATORY

OPERATED BY  
UNION CARBIDE CORPORATION  
NUCLEAR DIVISION



POST OFFICE BOX X  
OAK RIDGE, TENNESSEE 37831

January 15, 1976

United States Energy Research and Development  
Administration, Oak Ridge Operations  
Attention: Mr. D. S. Zachry, Chief ✓  
Oak Ridge Patent Group  
Post Office Box E  
Oak Ridge, Tennessee 37830

Gentlemen:

Subject: Disclosure - CNID No. 3407

Enclosed are two copies of the subject disclosure entitled  
"Preparation of Hepatitis B Vaccine," Inventors:  
John L. Gerin and Robert H. Purcell.

This work was performed under ERDA-NIH Interagency Agreement  
40-194-69.

This development was given oral presentation January 7, 1975,  
at the Hepatitis B Vaccine Workshop, Bureau of Biologics,  
Bethesda, Maryland.

Sincerely,

Original signed by

H. F. McDuffie

H. F. McDuffie, Director  
Information Division

HFM:ha

Enclosures

cc: H. Postma  
J. B. Storer  
K. H. Pierce - RC

1079115

[REDACTED]

DISCLOSURE

FROM

UNION CARBIDE CORPORATION, NUCLEAR DIVISION

ERDA CASE NO.: S- 47,103

CNID NO.: 3407

INVENTORS: John L. Gerin and Robert H. Purcell

SUBJECT: PREPARATION OF HEPATITIS B VACCINE

ABSTRACT: A method of preparing a hepatitis B vaccine from preparations of blood samples supplied by chronic HB<sub>s</sub>Ag carriers is described. The method very basically comprises the following steps:

- 1) removal of infectious Dane particles from the preparation;
- 2) purification of the 22nm non-infectious form in cesium chloride; and 3) inactivation of the purified vaccine with formalin, a licensed inactivant that has been used successfully for a number of other inactivated virus vaccines.

DESCRIPTION:

Background of the Invention:

Seroepidemiologic studies of hepatitis B virus (HBV) infection indicate that infection with this virus is more prevalent than the frequency of clinical illness discloses. Furthermore, non-percutaneous (or obscure percutaneous) transmission appears to occur more frequently than previously suspected, reaching endemic levels in certain populations such as patients undergoing hemodialysis, residents of institutions and members of developing cultures. There appears to be a need to protect these individuals and others coming in contact with them from hepatitis, type B. Although some protection is afforded by the identification of carriers of hepatitis B antigens and the institution of protective

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~~CONFIDENTIAL~~

measures, a more effective means of control utilizing immunoprophylaxis appears warranted. The feasibility of one method of immunoprophylaxis, vaccination, has been studied by Krugman et al<sup>1</sup> and Soulier et al<sup>2</sup> who attempted to immunize human volunteers with heated human serum that contained hepatitis B antigens. Krugman achieved partial protection against hepatitis B virus infection in children immunized with antigen-positive serum that had been diluted in water and heated to boiling for one minute, but recipients of the Soulier vaccine, which had been subjected to heat of 60°C for 10 hours, had serologic evidence of hepatitis B virus infection, indicating incomplete inactivation of the virus in the vaccine preparation.

A major objective of the subject development was to isolate the 22nm spherical form of HB<sub>s</sub>Ag from serum containing hepatitis B antigens in order to prove that this antigen could be an effective vaccine.

Another objective of the subject development was to provide a method of vaccine preparation so that a more complete inactivation of the virus is accomplished.

Summary of the Invention:

The invention is a method of preparing a hepatitis B vaccine from the plasma of chronic carriers of HB<sub>s</sub>Ag having antigens of the 22nm spherical form of HB<sub>s</sub>Ag, where the method comprises:

- (a) isopycnicly banding the antigen in cesium chloride;
- (b) separating the antigen from the bulk of plasma

~~CONFIDENTIAL~~

- components using batch-type zonal rotor methods;
- (c) rebanding the separated antigen in cesium chloride; and
  - (d) allowing the rebanded antigen to further separate from other components of the plasma by rate zonal sedimentation.

Brief Description of the Figures:

Fig. 1 illustrates the distribution of antigen in a gradient using a batch-type zonal rotor.

Fig. 2 illustrates the distribution of antigen after it has been rebanded in cesium chloride.

Fig. 3 illustrates the separation of antigen after rate-zonal sedimentation.

Detailed Description of the Preferred Embodiment:

The hepatitis B antigen has a buoyant density of 1.20-1.21 in CsCl. This physical property is used to advantage in the separation of the antigen from the bulk of the host serum components. Fig. 1 illustrates the desirable feature of the buoyancy by illustrating the distribution of antigen of such a gradient using the batch-type zonal rotor. There are three basic advantages of preparing the vaccine by this method: 1) this procedure concentrates the antigen and purifies it from the bulk of serum components; 2) this procedure also helps to separate the free antigen from circulating immune complexes, a heavy subpopulation of Dane particles, and free cores, if present; and 3) the banding agent used in this procedure, cesium chloride, tends to inactivate the

[REDACTED]

infectivity of the hepatitis B virus.

Referring now to Fig. 2, the antigen is rebanded in cesium chloride in which the antigen is floated away from higher density but slower sedimenting serum proteins at the right of the figure. By this stage the antigen has been in cesium chloride for greater than 48 hours. Throughout this time, the infectivity of the hepatitis B virus is decreasing due to the effect of the cesium chloride on the lipoproteins in the serum.

The third and final purification step is rate-zonal sedimentation. This is illustrated in graph of Fig. 3. This procedure has two desirable features for vaccine purification: 1) it separates the antigen from the remaining host serum proteins; and 2) it separates the various antigenic forms of 1.2 density.

In order to maintain the vaccine in its desired state, a half percent human albumin is added as a stabilizer in the gradient in order to stabilize the antigenicity of the purified particles.

Another embodiment of the method of preparing a hepatitis B vaccine comprises the following steps:

- (a) isopycnic banding the antigen in cesium chloride;
- (b) isopycnic banding the antigen in cesium chloride a second time to more completely purify the antigen;
- (c) performing a rate-zonal separation of the isopycnic banded antigen from the other components of the plasma;
- (d) rebanding the separated antigen in cesium chloride;

- [REDACTED]
- (e) dialysing the rebanded antigen against phosphate buffered saline having a ph of 7.4;
  - (f) stabilizing the dialysation product with human serum albumin;
  - (g) adding formalin to the stabilized product until a final concentration of 1:2000 is obtained; and
  - (h) incubating the resulting concentration at approximately 37°C to react the formalin with the stabilized product.

RELATED ART:

The following two papers were used as major sources of information for this disclosure:

Robert H. Purcell and John L. Gerin: "Hepatitis B Subunit Vaccine: A Preliminary Report of Safety and Efficiency Tests in Chimpanzees": American Journal of Medical Science 270(2): 395-399 (1975). J. L. Gerin: Hepatitis B Vaccine Workshop, Food and Drug Administration: Bureau of Biologics (Jan. 7, 1975).

The closest known related prior art is U.S. Patent No. 3,636,191 issued January 18, 1972 to B. S. Blunberg and I. Millman for a "Vaccine Against Viral Hepatitis and Process."

References cited in this disclosure are as follows:

1. Krugman, S., Giles, J. P.: Viral hepatitis, type B (MS-2 Strain). N. Engl. J. Med. 288: 755-760, 1973.
2. Soulier, J. P., Blatix, C., Courouce, A.M. et al.: Prevention of virus B hepatitis (SH hepatitis). Am. J. Dis. Child. 123: 429-434, 1972.

PROBABLE VALUE: The vaccine may have important applications among hospital personnel, patients undergoing hemodialysis and members of developing cultures as previously discussed.

RECOMMENDATION: The filing of a patent application may be warranted.

~~CONFIDENTIAL~~  
~~SECRET~~

**PERTINENT  
FACTS:**

Information obtained from: John L. Gerin

Verbal reference number: 4559 (ORNL), ERDA-NIH Interagency Agreement 40-194-69

Contract involved: W-7405-ENG-26

Inventors' home addresses: John L. Gerin                      Robert H. Purcell

~~\_\_\_\_\_~~                      ~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~                      ~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~                      ~~\_\_\_\_\_~~

Date of origin of idea: August 23, 1971                      Recorded in: Notebook Records

Date of first sketch or drawing: None                      Recorded in: \_\_\_\_\_

Date of first written description: August 23, 1971                      Recorded in: Notebook Records

Date of first model or test unit: None                      Recorded in: \_\_\_\_\_

Date of first test of invention: March 1, 1974                      Recorded in: Contract Report

Date of First Disclosure to Others:

(a) Name: Saul Krugman                      Date: Oct. 22, 1971                      Recorded in: Report from J.L.G. and R.H.P. to S.K.

(b) Name: Robert Byrne                      Date: Jan. 25, 1972                      Recorded in: Memo

Date of First Written or Oral Disclosure to Public: January 7, 1975

Where Disclosed: Hepatitis B Vaccine Workshop; Bureau of Biologics;

Bethesda, Maryland

PREPARED BY: Kay H. Pierce                      DATE: Jan. 12, 1976

APPROVED BY: D. E. Wood                      DATE: Jan 12, 1976

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1079122

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ORNL-DWG 73-6433

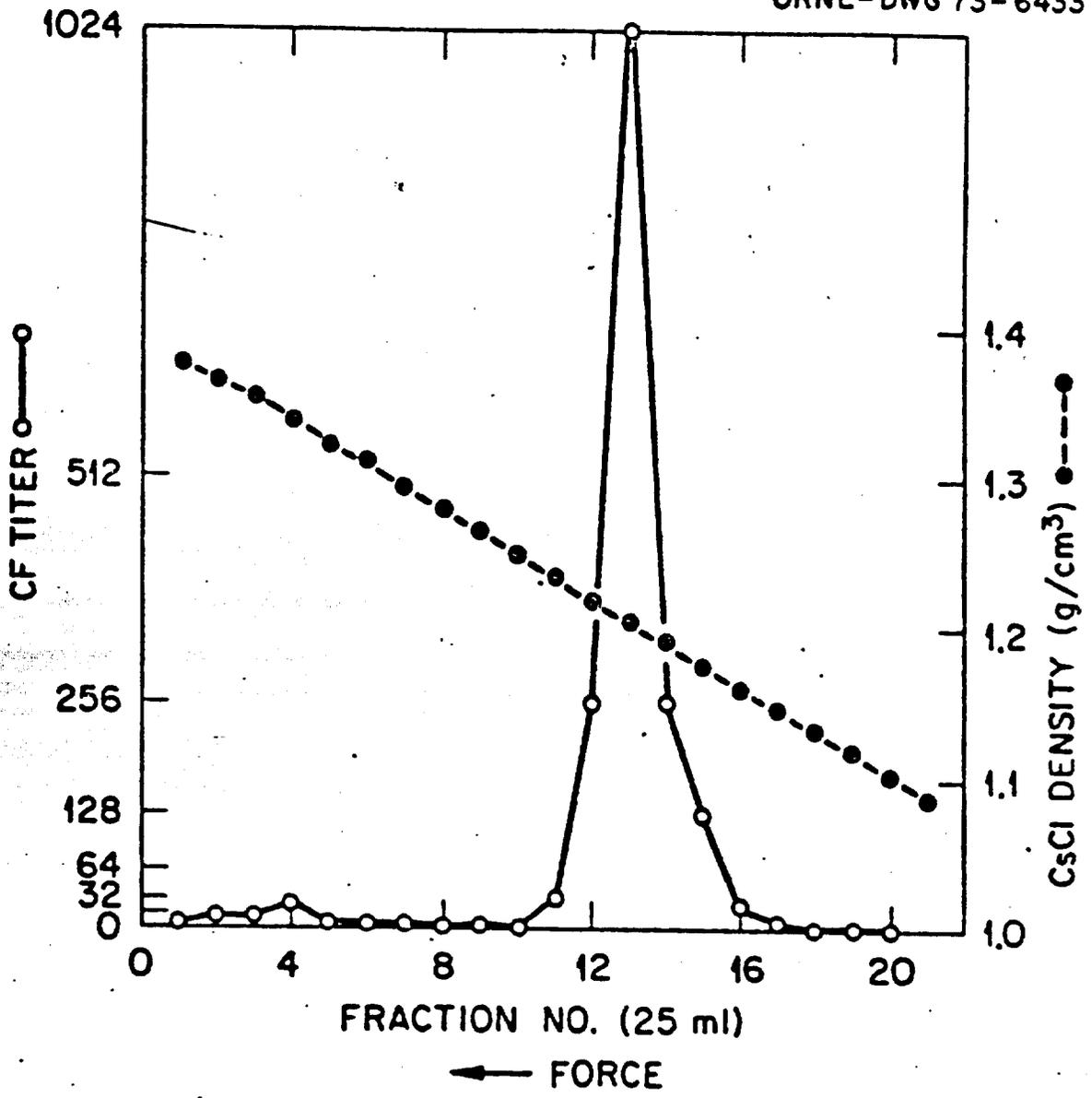


Figure 1

1079123

[REDACTED]

[REDACTED]

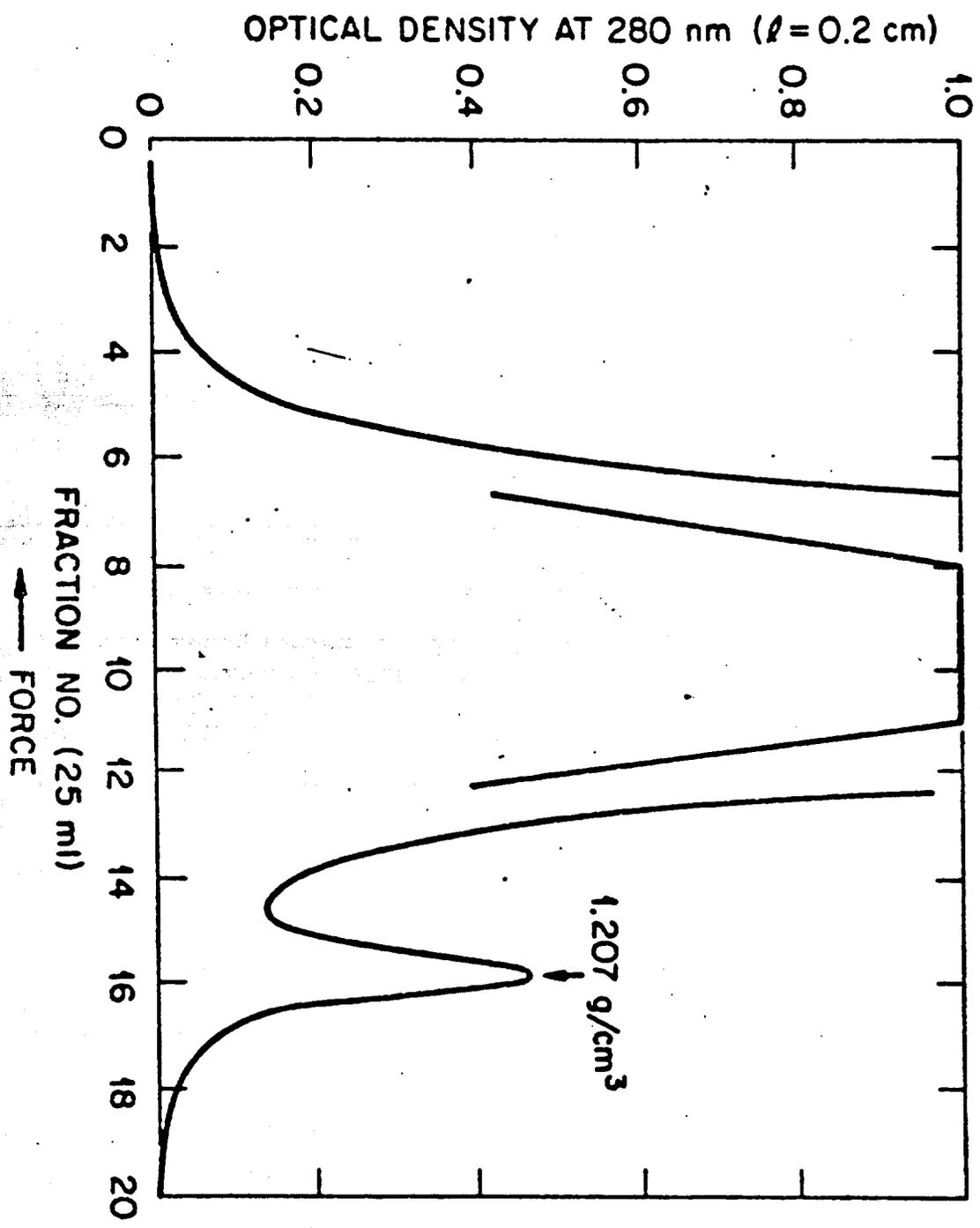
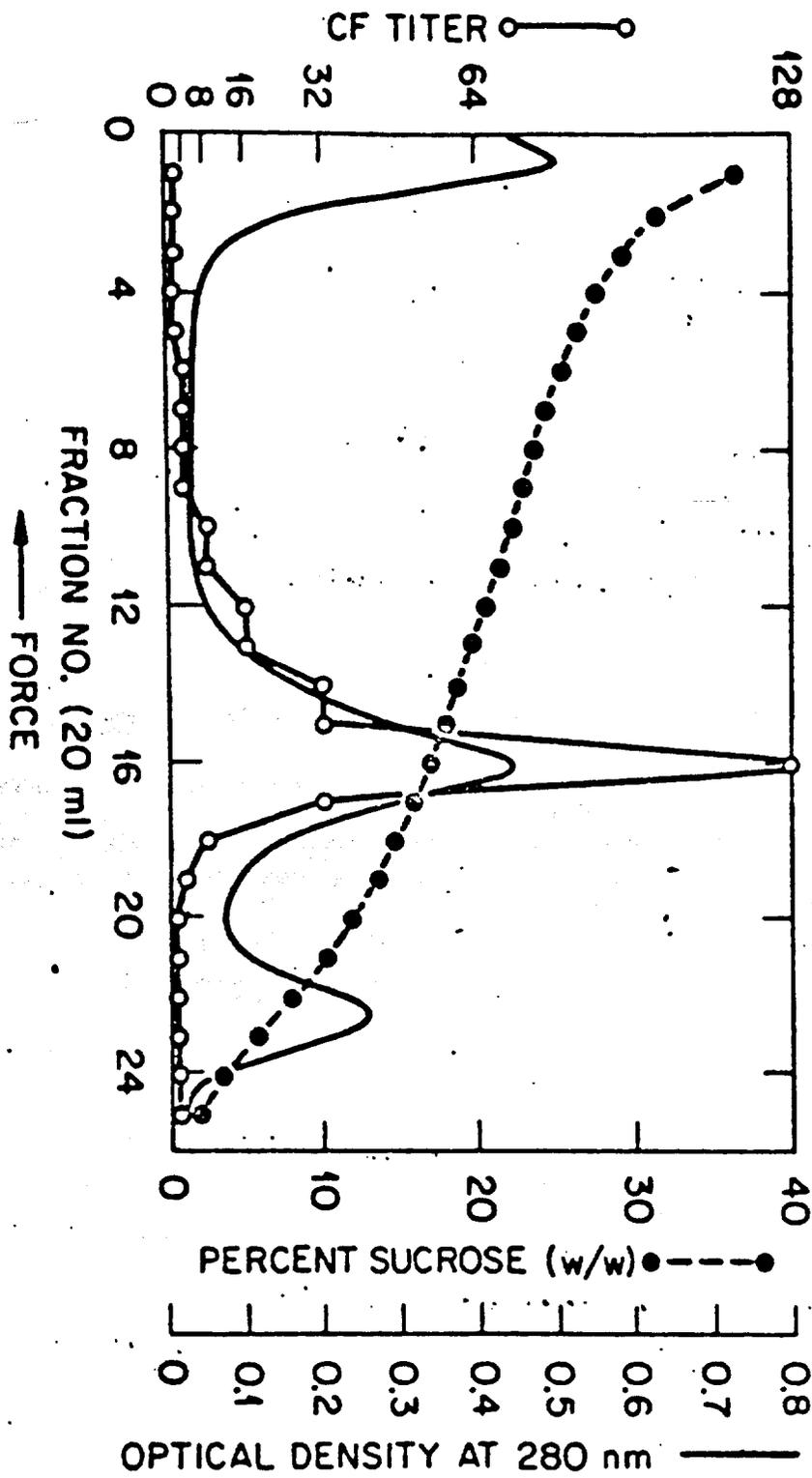


Figure 2

1079124

[REDACTED]



ORNL-DWG 73-6435

Figure 3

1079125

INVENTION RECORD DATA

Contractor UCCND-ORNL S- 47,108  
ERDA-NIH Interagency Agmt. 40-194-69  
Contract W-7405-Eng-26

Title "Preparation of Hepatitis B Vaccine"

Inventors John L. Gerin and Robert H. Purcell

Disclosure Received 1-16-76 Contractor's I.D. CNID 3407

Assigned for Evaluation to DZ on 1-16

Forwarded to AGCP or NIH on \_\_\_\_\_

Authorized for Preparation \_\_\_\_\_ by AGCP.

Placed in Abeyant Status Pending Further Developments on \_\_\_\_\_

Assigned to \_\_\_\_\_ for Preparation on \_\_\_\_\_

STATUS

Date	Remarks	Date	Remarks
3/26/75	publ. inv. notes sent to NIH closed		