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712363

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 NIH, that they plan to file on behalf of the Government on both the above dockets.

We would appreciate your advising your inventors of the proposed 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

D. S. Zachry, Chief
Oak Ridge Patent Group

MCP:DSZ:dys

CC: Dean E. Carlson, PAT-HQ

10/10/78 – filed by DHEW per Farris
SN 786,202

4,140,761 2/20/79

REPOSITORY Oak Ridge Operations Records Holding
COLLECTION Documents 1944-94
BOX No. B-87-13 Bldg. 2714-H
FOLDER S-47,864 (CNID 3524) Mod. of Hepatitis B Virus Infection

1079078

PATENT INFORMATION WORKSHEET

Section 1

"S" No.	OP.	Pat. No.	Appl.No.	Yr.	Mo.	Day
47864						

Inventor's Last Name	First Name	M.I.
Gerin	John	L.

Source

UCND

Section 2 (Will be completed at Headquarters)

Section 3

Keywords ØR + UCND + C910000 + *INFECTIO

*INTERFERON

Invention Title

PREPARATION OF HEPATITIS B VACCINE

Brief Description of Invention

Carriers of hepatitis B surface antigens are injected with exogenous interferon over an extended period to reduce infection

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

1079079

November 5, 1976

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

Dear Mr. Latker:

ERDA INVENTION DOCKET S-47,864 - GERIN ET AL.

The enclosed Invention Disclosure S-47,864 was received from Union Carbide Corporation under ERDA Contract W-7405-Eng-26. The invention was made at the Rockville Research Laboratory, which is funded by NIAID and is operated for ERDA by Union Carbide. Two of the indicated probable inventors are NIH employees and one is an employee of Stanford University.

We would appreciate your consideration of this invention and advice whether or not DHEW wishes to seek patent protection for the Government.

Your assistance in this matter will be appreciated.

Sincerely,

D. S. Zachry, Chief
Oak Ridge Patent Group

MCP:DSZ/dlm

Enclosure:
Disclosure S-47,864

CC: D. E. Carlson w/encl. and ERDA Form 711

Ferris - HEW will file 2/28/77

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OAK RIDGE NATIONAL LABORATORY
OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION

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OAK RIDGE, TENNESSEE 37831

United States Energy Research and Development
Administration, Oak Ridge Operations
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Oak Ridge, Tennessee 37830

Attention: Mr. D. S. Zachry, Chief
Oak Ridge Patent Group

Gentlemen:

H7,864

Subject: Disclosure - CNID No. 3524

Enclosed are two copies of the subject disclosure entitled "Modification of Hepatitis B Virus Infection in Chronic Carriers of Hepatitis B Surface Antigen", Inventors: John L. Gerin, Hilton B. Levy, Thomas C. Merigan, Robert H. Purcell, and William S. Robinson.

This development was published in Clinical Research, Vol. 1, No. 3, April 1976.

Sincerely,

H F McDuffie

H. F. McDuffie, Director
Information Division

HFM:ha

Enclosures

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

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OAK RIDGE NATIONAL LABORATORY
OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION

POST OFFICE BOX X
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United States Energy Research and Development
Administration, Oak Ridge Operations
Post Office Box E
Oak Ridge, Tennessee 37830

Attention: Mr. D. S. Zachry, Chief
Oak Ridge Patent Group

Gentlemen:

Subject: Disclosure - CNID No. 3524

Enclosed are two copies of the subject disclosure entitled "Modification of Hepatitis B Virus Infection in Chronic Carriers of Hepatitis B Surface Antigen", Inventors: John L. Gerin, Hilton B. Levy, Thomas C. Merigan, Robert H. Purcell, and William S. Robinson.

This development was published in Clinical Research, Vol. 1, No. 3, April 1976.

Sincerely,

H. F. McDuffie

H. F. McDuffie, Director
Information Division

HFM:ha

Enclosures

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

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DISCLOSURE

FROM

UNION CARBIDE CORPORATION, NUCLEAR DIVISION

ERDA CASE NO.: S- 47,864 CNID NO. 3524

INVENTORS: John L. Gerin, Hilton B. Levy,[1] Thomas C. Merigan,[2] Robert H. Purcell,[1] and William S. Robinson[2]

SUBJECT: MODIFICATION OF HEPATITIS B VIRUS INFECTION IN CHRONIC CARRIERS OF HEPATITIS B SURFACE ANTIGEN

ABSTRACT: A method of potential value for treating chronic hepatitis B viral infections in humans, chimpanzees and possibly other primate species susceptible to the virus is described. The method basically comprises the injection of exogenous interferon or certain interferon inducers, for example, a polyriboinosinic-polyribocytidylic acid-poly-l-lysine carboxymethyl cellulose complex, over an extended period to cause a reduction in the various markers of hepatitis B infection. Studies have shown serum Dane particle-associated DNA polymerase, e antigen, hepatitis B surface antigen, intrahepatic hepatitis B surface and core antigens to diminish during treatment.

DESCRIPTION: Background of the Invention

The invention relates generally to the use of exogenous interferon or interferon inducers to modify viral infections and more specifically to the use of these substances as a method of modifying hepatitis B infections.

Recent epidemiological studies indicate as many as 150,000,000 to 200,000,000 people are infected with hepatitis B virus (HBV) at any

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[1]Employees of The National Institutes of Health, Bethesda, Maryland.
[2]Employees of Stanford University, Stanford, California.

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one time. Most chronic HBV infections persist for many years,[1,2] and can transmit infection by blood transfusion and by nontransfusion-associated routes.[3-8] Due to the large number of chronic carriers worldwide and the common occurrence of neonatal transmission from mothers who are chronic carriers,[7,8] elimination of this virus by vaccination is unlikely in the foreseeable future. Unfortunately, current methods of treatment are based upon the use of steroids and antimetabolites that suppress the immune response of the patient rather than affect the course of chronic HBV infection.[9-12]

A need therefore exists to provide a method treating chronic hepatitis viral infections in a manner which actually modifies the virus. The subject development as described hereinbelow was specifically designed to meet this need.

Summary of the Invention

It is an object of the subject development to provide a method of modifying HBV in chronically infected subjects.

In accordance with this and other objectives of the invention, the subject development is a method of modifying HBV in infected subjects by substantially increasing interferon levels in the subject for an extended period of time. This can be accomplished by a prolonged injection schedule with either exogenous interferon or an interferon inducer such as polyriboinosinic-polyribocytidylic acid-poly-l-lysine carboxymethyl cellulose complex (PICLC).

Brief Description of the Figures

Figs. 1a and 1b illustrate the effect of treatment with PICLC on

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markers of chronic hepatitis B virus infection in chimpanzees 814 and 821, the beginning and end of the treatment periods are indicated by arrows on the abscissa;

Fig. 2 illustrates the effect of three separate courses (A, B, and C-H) of human leukocyte interferon on Dane particle-associated DNA polymerase, HB_sAg and HB_cAg in patient 1;

Fig. 3 illustrates the effect of two separate courses (A and B) of human leukocyte interferon on Dane particle-associated DNA polymerase, HB_sAg and HB_cAg in patient 2; and

Fig. 4 illustrates the effect of one course (A) of human leukocyte interferon on Dane particle-associated DNA polymerase, HB_sAg and HB_cAg in patient 3.

Detailed Description of the Preferred Embodiment

Interferon, a naturally occurring glycoprotein with a wide spectrum of *in vitro* and *in vivo* antiviral effects, has been evaluated as a treatment for several human viral infections.[13] In general, the use of interferon or interferon inducers has had limited success in modifying or terminating chronic infections caused by other viruses. However, an absence of detectable interferon in serial serum samples from patients with type B hepatitis has been detected[14] and it has been postulated that decreased production of interferon may be responsible for the chronicity of the disease.[15]

In view of the above, it has been further postulated by the subject inventors that it may be possible to modulate HBV by artificially increasing the level of interferon in chronically infected patients

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undetectable levels within two days of initiation of treatment in chimp 821 and remained undetectable until cessation of treatment, at which time it returned to pretreatment levels. DNAP in the serum of chimp 814 also rapidly fell to undetectable levels but returned to pretreatment levels a week before treatment was terminated. The titer of e antigen fell only two-fold in this latter animal, but fell four- to eight-fold in chimp 821. The titers of HB_sAg, anti-HB_s, and anti-HB_c in the serum and the quantity of HB_sAg and HB_cAg in the liver remained essentially unchanged in both animals during the experiment, as did the histologic findings. Alanine aminotransferase activity became slightly elevated during PICLC treatment in both animals. All laboratory values that were altered by PICLC returned to pretreatment levels following cessation of treatment.

Proof that the inhibitory effect on DNAP was not due to a direct effect of PICLC *in vivo* or *in vitro* was obtained by testing for DNAP activity in the presence of concentrations of PICLC up to 100 μg/ml. PICLC had no inhibiting effect on DNAP activity at these concentrations, which markedly exceeded the maximum anticipated serum levels. Furthermore, PICLC could not be detected in any of the serum or plasma samples when tested by a sensitive *in vitro* assay employing non-human cells. Thus PICLC did not appear to be directly responsible for the results observed, but rather they were probably the result of

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the induction of interferon by this compound.

After it had been determined that increasing interferon levels in chimpanzees with chronic hepatitis was not unduly hazardous, parallel studies on the long-term effects of exogenous interferon on humans and of PICLC on chimpanzees were initiated. These studies are described in examples II and III.

Example II

Chronic carrier chimpanzees 814 and 821 and normal control chimpanzees 16 and 105 were employed in the study of the effects of prolonged PICLC administration on chronic HBV infection and on normal physiology. After two weeks of baseline studies, chimpanzees 814, 821, and 105 were administered 3 mg/kg body-weight PICLC, and chimpanzee 16 was administered carboxymethyl cellulose (CMC) to stabilize the PICLC complex. PICLC was administered once daily for two six-day periods, separated by one non-treatment day, and every other day thereafter for a total of seven weeks. Serum samples were drawn 8 hours after administration of PICLC or CMC for measurement of interferon levels, and plasma samples were obtained immediately prior to PICLC administration at daily to weekly intervals. Biopsies were obtained weekly.

Chimp 814 developed moderate levels of serum interferon within eight hours of administration of PICLC and maintained a responsiveness to PICLC throughout the study (Fig. 1a).

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Within a week after the initiation of PICLC treatment, serum DNAP fell to baseline levels and remained there throughout the treatment but returned to pre-treatment levels within a week of cessation of PICLC infusion. Coincident with the fall of DNAP activity, serum HB_cAg increased markedly, reaching a peak almost six times greater than baseline values at the time that DNAP levels reached their lowest point.

A pool of plasma concentrates from the period of peak HB_cAg activity was banded in a cesium chloride gradient. After treatment of the fractions with detergent, HB_cAg was detected in those fractions which corresponded to the density region of Dane particles (1.21-1.23 g/cm^3) and not in the region of free core particles (>1.28 g/cm^3). Therefore, the HB_cAg appeared to be associated with Dane particles deficient in DNAP activity. Thus, the administration of PICLC and the resultant induction of endogenous interferon caused the synthesis and/or release of presumably defective hepatitis B virions. As can be seen in Fig. 1a, the titer of both the $\underline{e}_1$ and $\underline{e}_2$ components of $\underline{e}$ antigen paralleled the course of DNAP activity during the treatment period. Within three weeks of initiation of PICLC therapy, serum HB_sAg began to decline in titer and subsequently fell to levels only approximately one-fourth of the pretreatment level.

Following cessation of treatment, serum HB_sAg returned to pre-treatment levels. Intrahepatic HB_cAg transiently fell

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to barely detectable levels midway through the treatment period but had returned to pre-treatment levels before cessation of treatment. The effect of PICLC treatment on intrahepatic HB_sAg was more marked: HB_sAg fell to barely detectable levels in the liver in parallel with the fall in serum HB_sAg titer and remained barely detectable until serum HB_sAg increased in titer following discontinuance of treatment. It was of interest that the decline in intrahepatic HB_cAg was characterized by a decrease in the number of fluorescing nuclei without a concomitant decrease in the intensity of fluorescence in individual nuclei, whereas loss of intrahepatic HB_sAg was characterized by a marked decrease in the intensity of cytoplasmic fluorescence of almost all effected cells. The mild type B hepatitis observed during the first experiment had resolved by the time the second experiment began; only non-specific histologic changes were observed during this second infusion of PICLC.

Similar results were obtained with chimp 821 (Fig. 1b). The induction of endogenous interferon was less marked in this animal: serum interferon titers averaged one-third those of chimp 814. Nevertheless, serum DNAP fell to low levels and remained there throughout the treatment period, indicating a striking sensitivity of the hepatitis B virus to low levels of interferon.

The interferon response of chimpanzee 105 was essentially

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identical with that of chimp 814; interferon was not detected in any of the serum specimens from chimp 16, who received only CMC. Histologic findings in chimp 16 were unremarkable, but chimp 105 developed a reactive hepatitis characterized by activation of Kupffer cells and deposition of fat in hepatocytes. These changes were suggestive of hepatoxicity.

Example III

The human subjects for the third example were chosen from twenty-five HB_sAg positive patients with biopsy documented chronic active hepatitis (CAH). Three subjects (Pt. 1, age 21, Pt. 2, age 32, Pt. 3, age 30 years) had elevated levels of serum particle - associated DNA polymerase. In addition, one subject (Pt. 4, age 40) without detectable DNA polymerase was given interferon.

Parenteral interferon given in a dosage range between 17×10^4 U/kg/day and 6.0×10^3 U/kg/day was associated with an immediate and reproducible fall in DNA polymerase levels. In patient 1 (Fig. 2), three successive courses of interferon were all associated with a 10-fold or greater decrease in polymerase levels. In patient 2 (Fig. 3), interferon dosage was gradually increased until at a dose level of 6.0×10^3 U/kg/day, a significant fall in the polymerase level occurred. In patient 3 (Fig. 4), an intermediate dose of 1.2×10^4 U/kg/day also led to a prompt fall in polymerase activity. Comparison of the reduction in polymerase level produced in patient 3 to that observed in patient 1 (courses A and B)

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suggests that the higher dosages produced a more complete effect. Patient 4 (no figure), who had no detectable polymerase prior to interferon therapy, remained polymerase negative throughout a one month treatment with the drug being given at a dosage of 7.5×10^3 U/kg/day. Human leukocyte interferon was added to polymerase-containing sera in vitro at concentrations of 2000 and 100 units/ml. No effect on polymerase activity was observed when such a mixture was incubated at 37°C for 2 hours and room temperature overnight.

Interferon, when given for 10 days or less at a dosage range between 17×10^4 U/kg/day (patient 1, Fig. 2), and 1.2×10^4 U/kg/day (patient 3, Fig. 4), was associated with only a transient fall in polymerase. When therapy was stopped, polymerase values promptly rose toward pretreatment levels. More prolonged therapy (Figs. 2 and 3) at dosages of 6.0×10^3 U/kg/day or greater appeared to suppress polymerase activity more permanently. Patients 1 and 2 have continued to have depressed or negative polymerase values for three weeks and one month, respectively, following the termination of therapy.

Other Dane particle markers including HB_cAg and Dane particle-associated DNA, appear to be similarly affected. In patient 1 (Fig. 2), HB_cAg fell only slightly and transiently during courses A and B, but become undetectable

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during more prolonged treatment (courses C and H). In patient 2 (Fig. 3), a concurrent fall of HB_cAg and polymerase was observed. Again in these two subjects following prolonged interferon therapy, HB_cAg remained down. Patient 3 (Fig. 4), who was treated for 8 days, showed only a transient fall in HB_cAg. Patient 4 had no detectable HB_cAg throughout the study. Interferon affected Dane particle-associated DNA in the same fashion as DNA polymerase activity (patients 1, 2, and 3, Table III).

The effect of interferon therapy on HB_sAg, a viral protein not exclusively associated with Dane particles, appeared to be more variable. In no case did it appear that short term interferon (patients 1 and 3, Figs. 2 and 4), had a measurable effect on HB_sAg levels. Of the three patients treated for a month or longer (patients 1, 2, and 3, Figs. 2 and 3), only patient 1 had a significant change in HB_sAg level. In this patient who received the highest doses of interferon, HB_sAg fell 16-fold from CF titer of 1/128 to 1/8. Patient 2 (Fig. 3) showed no change in HB_sAg and patient 4 (not shown) had a constant titer of 1/32 throughout the study.

Neither short-term or long-term therapy with PICLC or interferon terminated chronic HBV infection in the subjects studied, and all indicators of HBV infection returned to pretreatment levels shortly after discontinuance of treatment. Failure to cure these

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subjects may have been the result of failure to maintain constant serum levels of interferon. However, continuous or frequent administration of interferon or interferon inducer to chronically infected subjects may result in more permanent changes.

RELATED ART: A patent has been applied for by HEW covering the use of PICLC as an interferon inducer. Hilton B. Levy, one of the inventors of the subject development, is listed as an inventor in the PICLC application.

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3. Levin ML, Maddrey WC, Wands JR, et al.: Hepatitis B transmission by dentists. J. Am Med Assoc 228:1139-1140, 1974

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6. Szmuness W, Much IM, Prince AM, et al.: On the role of sexual behavior in the spread of hepatitis B infection. Ann Int Med 83:489-495, 1975

7. Stevens CE, Beasley RP, Tsui J, et al.: Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med 292:771-774, 1975

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of positive and negative transmission of hepatitis B virus to their infants. N Engl J Med 294:746-749, 1976

9. Copenhagen Study Group for Liver Diseases. Lancet i:119, 1969

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1 1. Soloway RD, Summerskill WHJ, Baggenstoss AH, Geall MG, Gitnick GL, Elveback LR, Schoenfield LJ: Gastroenterology 63:820, 1972

12. Murray-Lyon IM, Stern RB, Williams R: Lancet i:735, 1973

13. Merigan TC, Jordan GW, Fried RP: Clinical utilization of exogenous human interferon, Antiviral Mechanisms. Perspectives in Virology IX:249-264, 1975

14. Hill DA, Walsh JH, Purcell RH: Proc Soc Exper Biol Med 136:853, 1971

15. Tolentino P, Dianzani F, Zucca M, Giacchino RJ: Infect Dis 132:459, 1975

The subject invention and the experiments cited in the examples herein are more completely described in the following papers:

16. Purcell RH, Gerin JL, London WT, Wagner J, McAuliffe VT, Popper H, Palmer AE, Lvousky E, Kaplan PM, Wong DC, and Levy HB: Lancet (in press)

17. Greenberg HB, Pollard RB, Lutwick LI, Gregory PB, Robinson WS, Merigan TC: N Engl J Med 295:517, 1976

18. Levy HB, Baer G, Baron S, Buckler CE, Gibbs CJ, Iadarola MJ, London WT, Rice J: J Infect Dis 132:434, 1975

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[redacted]

PROBABLE VALUE: Both endogenous and exogenous interferon appear to be equally effective in modifying chronic HBV infection. Each has advantages and disadvantages. Exogenous interferon is relatively easy to administer and nonimmunogenic but is associated with toxic manifestations. Also, it is very difficult to prepare exogenous interferon in large quantities and it is exceedingly expensive at present. Endogenous interferon must be induced by other substances, and PICLC is the most promising inducer at present. This substance is relatively inexpensive but is also associated with toxic manifestations; in addition, it is potentially immunoreactive and more difficult to administer. More extensive studies of these two potential chemotherapeutic agents are currently in progress to determine which, if either, will be useful for more widespread treatment of chronic HBV infection in man.

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

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PERTINENT FACTS:

Information obtained from: J. L. Gerin (orally) and References 16 and 17 cited herein

Verbal reference number: 4748 (ORNL)

Contract involved: W-7405-eng-26

Inventors' home addresses: (JLG) 8910 Melwood Rd., Bethesda, Md. 20034

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(TCM) 148 Goya Rd., Portola Valley, Calif. 94025

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(WSR) 1991 Bryant St., Palo Alto, Calif. 94301

Date of origin of idea: January 2, 1975 Recorded in: letter

Date of first sketch or drawing: Recorded in:

Date of first written description: January 2, 1975 Recorded in: letter

Date of first model or test unit: Recorded in:

Date of first test of invention: Recorded in:

Date of First Disclosure to Others:

(a) Name: Dr. George Galasso Date: Jan. 2, 1975 Recorded in: letter

(b) Name: Date: Recorded in:

Date of First Written or Oral Disclosure to Public: April 1976

Where Disclosed: Clinical Research, Vol. 1, No. 3, p. 452 a

PREPARED BY: K. H. Pierce DATE: Nov. 3, 1976

APPROVED BY: W. E. Ward DATE: Nov 3, 1976

UCN-9903 (8 1-72) 1079097

Table I

Serum Interferon Levels Following a Single Intravaneous Infusion of PICLC (3 mgm/Kg) in Chimpanzees

Interval (hrs.) after Infusion	Interferon Titer in Indicated Chimp (units/ml)	
	#14 (normal)	#800 (HB_sAG Carrier)
Pre	<10	<10
2	<10	40
4	<10	40
8	20	160
12	160	20
24	<10	<10
36	<10	<10
48	<10	<10

Table II

Effect of 14-Day Treatment with PICLC on Indicators of Chronic Hepatitis B Virus Infection in Chimpanzees

Indicator	Response in Indicated Chimp	
	#814	#821
Serum		
DNA polymerase	diminished	markedly diminished
e antigen	slightly diminished	markedly diminished
HB_sAg	unchanged	unchanged
alanine amino transferase	slightly elevated	slightly elevated
Liver		
HB_sAg	unchanged	unchanged
HB_cAg	unchanged	unchanged

Table III

Effect of Interferon on Hepatic and Hematologic Function with Serum Interferon Levels

		SERUM ASPARTATE AMINOTRANSAMINASE*	WHITE BLOOD CELL COUNT	PEAK SERUM INTERFERON LEVEL
PATIENT 1	Prior to interferon	47 - 70 (50)**	8,100 - 9,400 (8,500)***	<10
	COURSE A	41 - 69 (51)	3,400 - 4,000 (3,900)	1,250
	B	41 - 47 (43)	3,600 - 4,800 (4,400)	---
	C	130 - 294 (218)	5,000 - 5,500 (5,200)	210
	D	119 - 165 (139)	4,900 - 5,600 (5,200)	89
	E	75 - 159 (102)	5,300 - 7,700 (6,400)	50
	F	52 - 74 (63)	6,000 - 7,100 (6,600)	23
	G	35 - 52 (44)	7,200 - 8,100 (7.600)	16
	H	31 - 35 (33)	8,100	---
PATIENT 2	Prior to interferon	293 - 1790 (896)**	10,300 - 14,300 (12,700)***	<10
	COURSE A	117 - 239 (218)	10,300 - 13,300 (11,800)	10
	B	251	9,800	23
	C	463 - 576 (50)	8,600 - 10,400 (9,200)	50
PT. 3	Prior to interferon	51 - 59 (55)	4,300 - 5,800 (5,100)	<10
	COURSE A	87 - 93 (90)	3,200 - 3,700 (3,500)	47
PATIENT 4	Prior to interferon	25 - 43 (44)**	4,900 - 7,200 (6,100)***	<10
	COURSE A	33 - 46 (4)	4,100 - 5,100 (4,800)	45

* Normal value <15

** Range and ( ) mean of 4 or more determinations over previous 2 months

*** Range and ( ) mean of 2 or more determinations over previous 1-2 months

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CHIMP 814

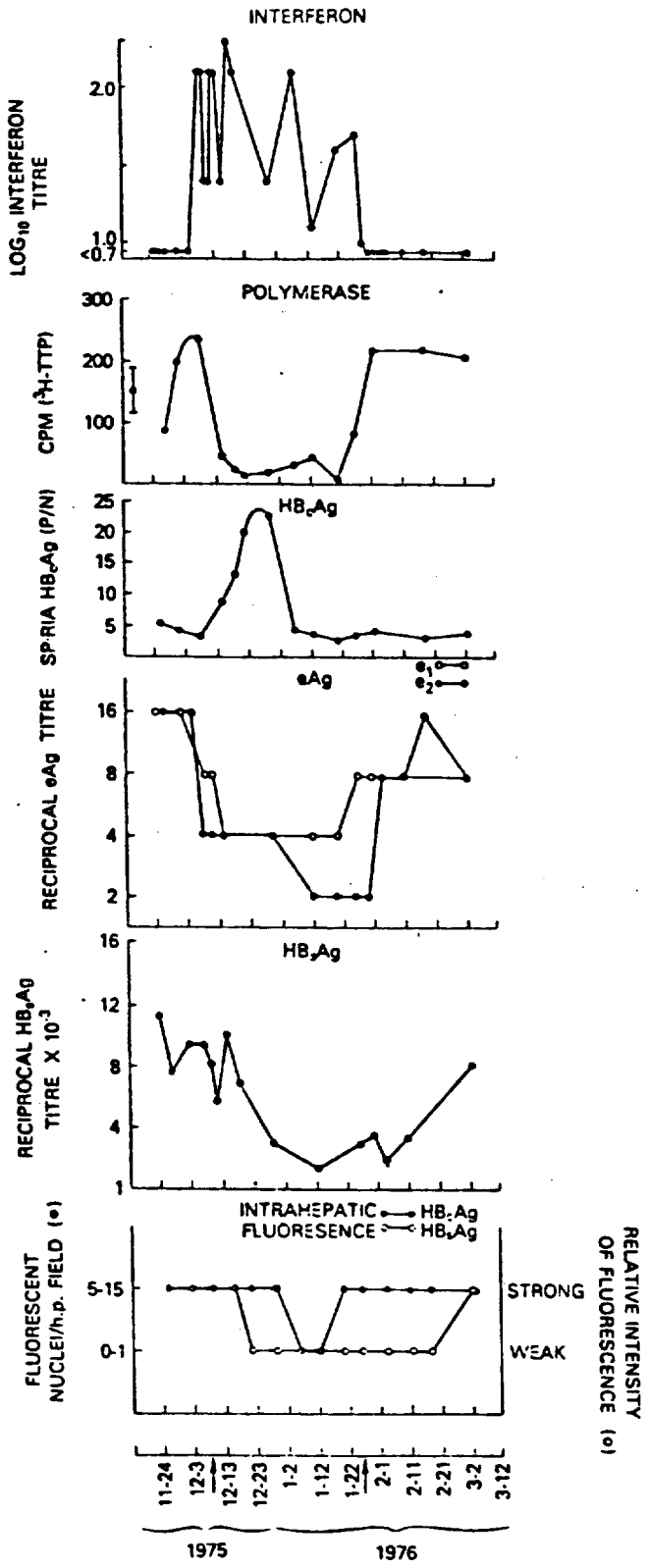

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FIG. 1a

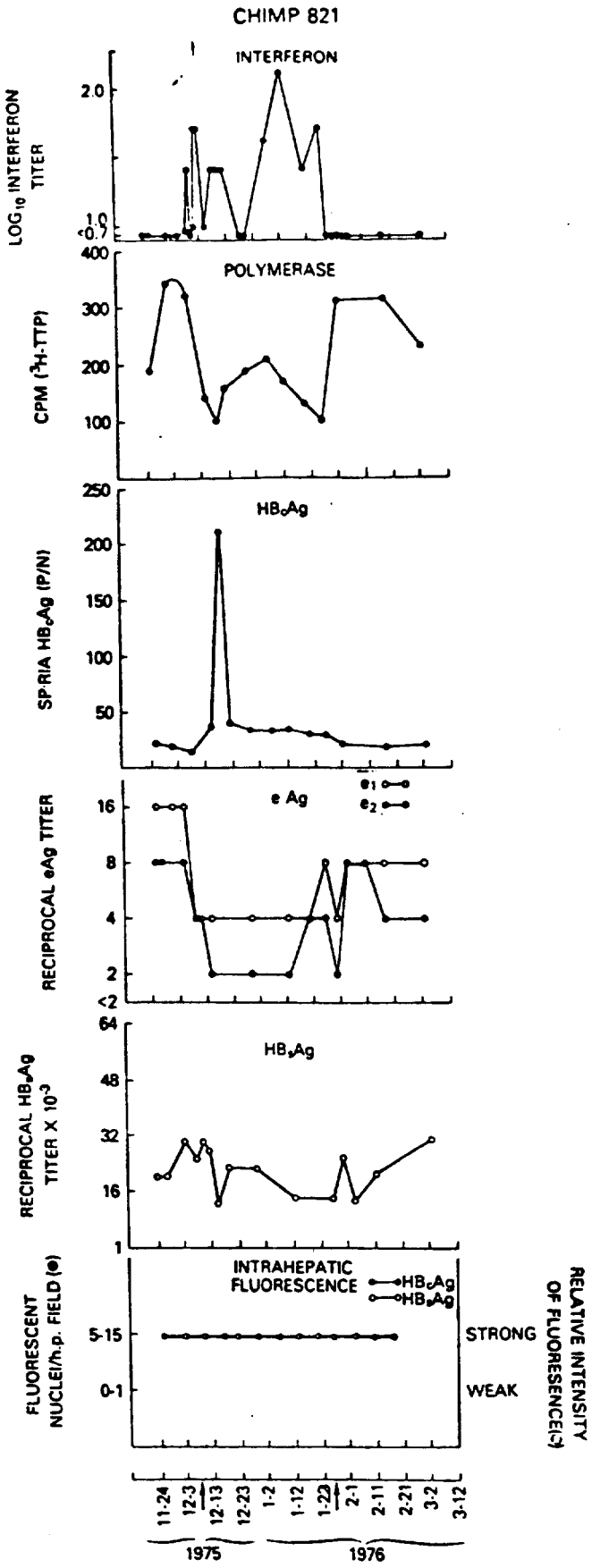

FIG. 1b

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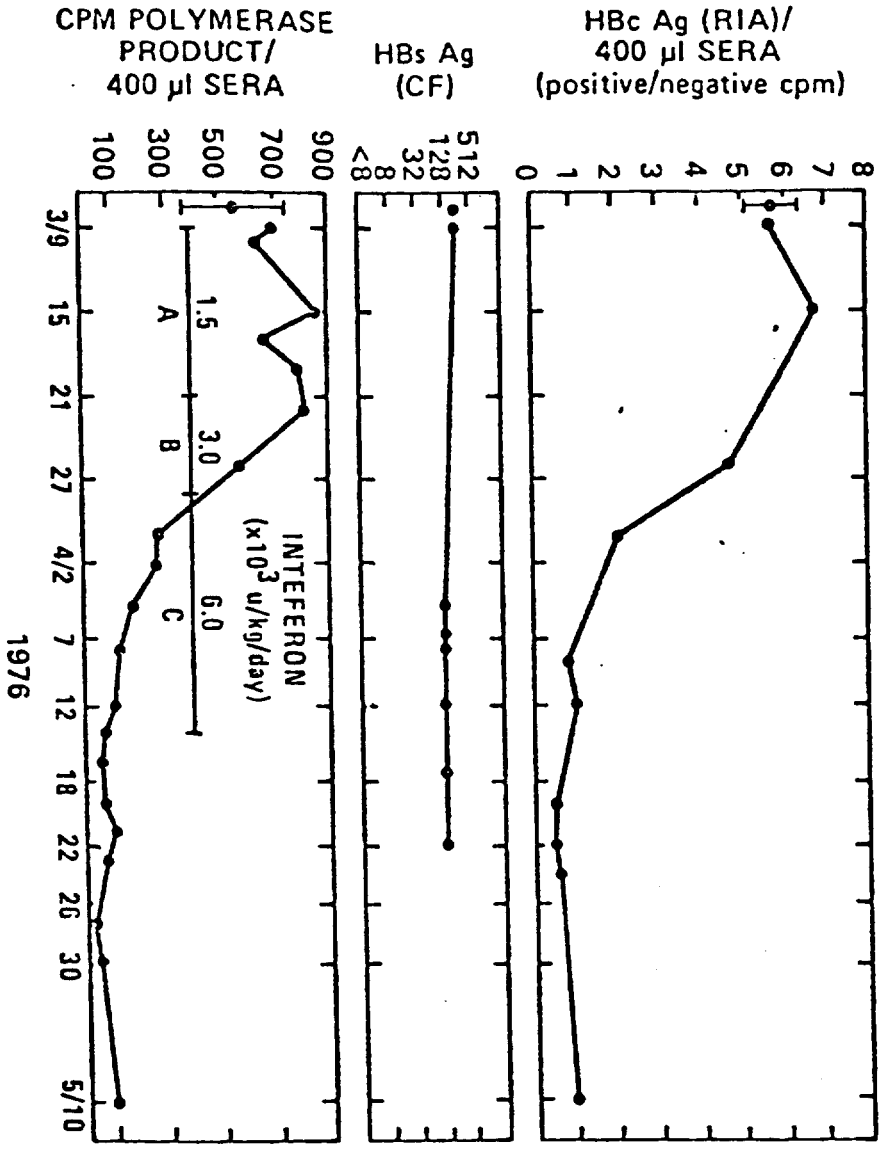

FIG. 3

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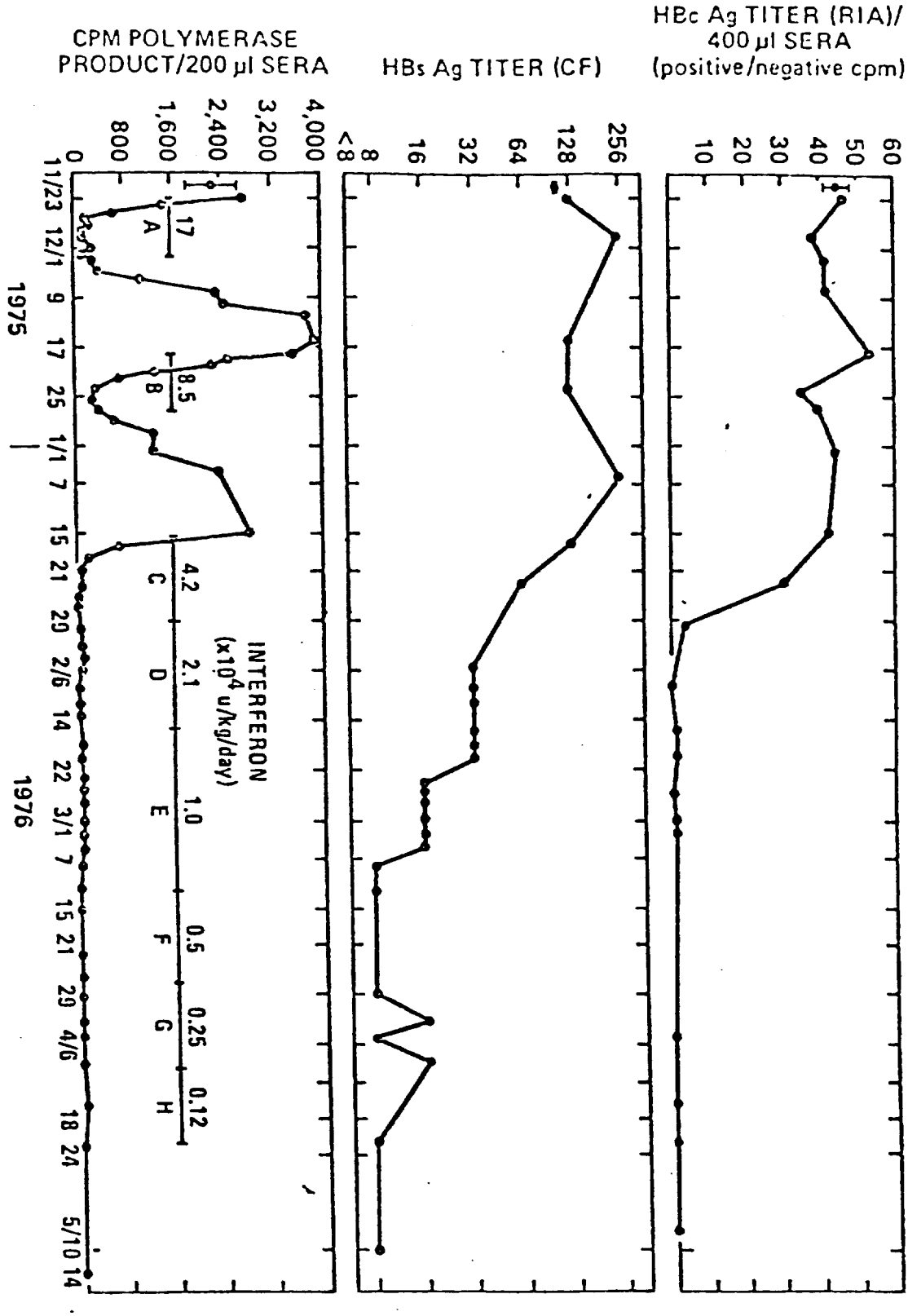

FIG. 2

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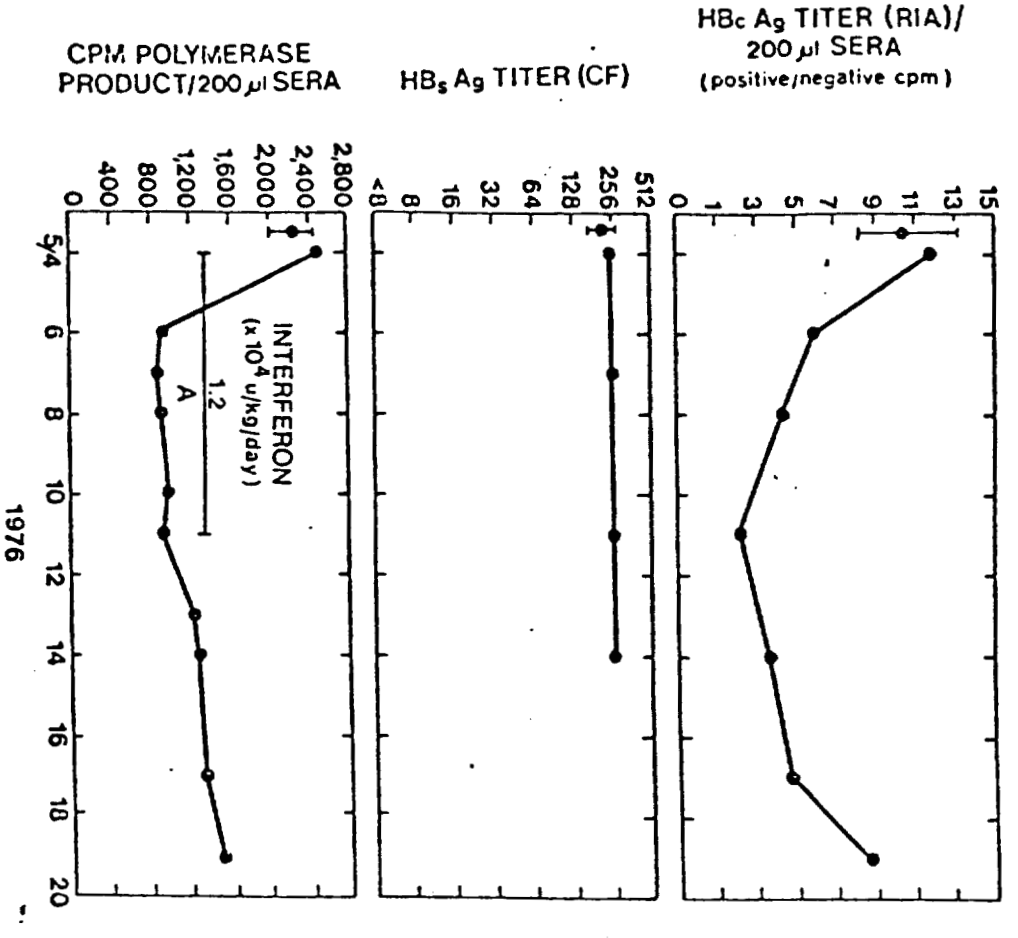

FIG. 4

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