

## Viral Hepatitis: Problems of Incidence and Control in Military Personnel<sup>1</sup>

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(A) Hepatitis B virus (HBV) is now the major cause of infectious viral hepatitis in U.S. military personnel and probably also in the civilian population over 15 years of age. (B) The incidence of icteric, viral hepatitis is much higher in U.S. military personnel than in comparable age groups in the civilian population. The 17- to 20-year-old enlisted men show the highest rates. (C) In parts of the world (e.g., U.S.A., Germany) where most of the inapparent infection is caused by the *adw* subtype of HBV, most of the acute clinical disease is caused by the *ayw* subtype. In the U.S.A. and Germany, 95% or more of HB<sub>s</sub>Ag isolates from U.S. military personnel with acute hepatitis is *ayw*. (D) It may be many years before one can expect to have sufficient data for a decision as to the possible availability of an effective HBV vaccine. Accordingly, a decision is urgently needed regarding either the immediate use of the best practically available hepatitis immune gamma globulin, that can be prepared by modern techniques, for the prevention of hepatitis in U.S. military personnel or postponement of such use until an adequate and properly controlled trial can be carried out in active duty military personnel in an area of high incidence.

Recent advances in our knowledge of viral hepatitis have rendered invalid the continuing custom of equating so-called "infectious hepatitis" with "hepatitis A" and of limiting the diagnosis of "hepatitis B" to those viral hepatitis patients in whose serum the surface antigen (HB<sub>s</sub>Ag) of hepatitis B virus (HBV) has been demonstrated during the first 10 days after onset of jaundice. While common source food- and water-borne outbreaks have been shown to be invariably caused by hepatitis A virus (HAV), such outbreaks account for only a small portion of icteric, viral hepatitis reported in recent years in the U.S.A. or in U.S. military personnel at home and abroad. Recent studies of an outbreak at Fort Hood, Texas by Major Gilbert R. Irwin at the Walter Reed Army Institute of Research (WRAIR) showed that while highly specific tests for HB<sub>s</sub>Ag in the serum were positive in only 35% of 394 military patients with viral hepatitis during the first 7-14 days after onset of jaundice, supplementary tests for antibody vs the core antigen (HB<sub>c</sub>) and vs HB<sub>s</sub>Ag indicated that about 90% of all cases were hepatitis B, i.e., caused by HBV (personal communication). Similar studies by Robert Purcell at the National Institute of Allergy and Infectious Diseases on sera obtained more than 20 years ago from U.S. military personnel with infectious hepatitis in Korea yielded comparable results (personal communication). Thus, the data that have been reported at this symposium on the incidence of hepatitis A and of hepatitis B in military personnel as well as similar reports by the Center for Disease Control (CDC, HEW) for the civilian population must be regarded as inaccurate and misleading in the absence of the tests for the HBV antibodies just mentioned and for the recently reported highly specific HAV antibodies that cannot as yet be carried out on a routine basis. What is urgently needed in civilian and military populations are well-planned, collaborative clinical

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and laboratory studies to determine how much of total icteric, viral hepatitis in persons of different ages and socioeconomic status are caused by HAV and HBV in different geographic areas.

The next question I wish to address is whether icteric, viral hepatitis is currently really much more frequent in military personnel than in civilians of comparable age and sex, or whether differences in reporting of this disease in the military and civilian populations prevent meaningful conclusions. In the military, there are records of patients with the icteric disease who are sick enough to seek help in military medical installations, and the main problem is that data based on admissions diagnosis may show smaller or larger numbers of cases than the more reliable discharge records, and using the date of discharge rather than of admission may result in different annual totals. With few exceptions, the differences are not too great. On the other hand, a recently reported study (1) on the greater New Haven civilian population during 1973-74 showed great variations in the completeness of reporting of viral hepatitis from 16.7% by private physicians, 28.1% by hospitals, and 55.6% by other health facilities. In this study it was also estimated that the annual incidence rates for this geographic region were about 100/100,000 for urban residents and 23/100,000 for suburban residents; certainly a marked difference from the 2007/100,000 in active duty USAREUR personnel in 1973, if one does not take into consideration the much higher proportion of viral hepatitis in young males in the U.S.A. in recent years.

The data in Fig. 1, reported by M. B. Gregg (2) of CDC, and personal communications, 1971, 1973, and 1974, show the continuing increase in prevalence of viral hepatitis in young civilian male adults in the U.S.A. from 1966 to 1974. If one assumes that because of underreporting the 1971-1974 peak rates of 55 to 62/100,000 of the 20- to 24-year age groups (Fig. 1) represent only about 25% of the total incidence, an estimated rate of 200/100,000 is still significantly lower than the rates of 475, 524, and 588/100,000 reported for the U.S. Army in the USA (CONUS) for 1971, 1972,

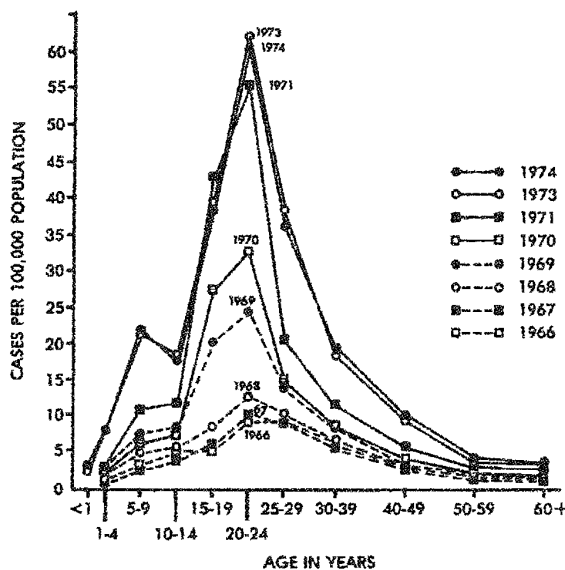


FIG. 1. Viral hepatitis; U.S. distribution of male civilian cases by age.

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TABLE 1  
Incidence of Icteric, Viral Hepatitis: Reported Cases/100,000/Year, U.S. Army Active Duty Personnel vs Indigenous Civilian Population (All Ages) in U.S.A. and West Germany

Group	1971	1972	1973
Civilians (all ages) in U.S.A.	34	31	28
U.S. Army			
Total ZI (CONUS)	475	524	588
Total outside ZI	535	469	1366
Ryukyus	1108	767	607
Korea	922	869	620
Vietnam	955	996	65
Total European Command	100 (445) <sup>a</sup>	409 (737)	1742 (2077)
Civilian population (all ages) of West Germany	15	16	19

<sup>a</sup> Numbers in parentheses, USAREUR Preventive Medicine rates based on discharge clinical records on cover sheets with date of discharge determining the month of record.

and 1973 (see Table 1; except when otherwise noted the data in this table are derived from the reports in "Health of the Army" that were supplied to me by Major Dennis R. Swanson, M.C., SGO, U.S. Army, and may represent admissions diagnosis). It is noteworthy that in 1974 the rate in active duty U.S. Army CONUS personnel based on discharge diagnosis was only 293/100,000, or just half of the 1973 rate, while that in Europe was 1236/100,000 (data provided by Major Robert Chloupeck, M.C., Preventive Medicine, SGO).

The recent increasing incidence of viral hepatitis in active duty USAREUR personnel (predominantly Germany) since 1971 is real, although the exact numbers are difficult to evaluate. The most extensive and thorough compilation of data is contained in a document entitled "Hepatitis Epidemic Among U.S. Army Military Personnel, 1971-1974, USAREUR" of June 21, 1974 by Maj. Gilbert R. Lavoie, M.C. (Chief, Communicable Disease and Epidemiology Branch, HQ, U.S.A. Medical Command, Europe), Cpt. Leonard Garret, Jr., MSC (Environmental Health Engineering, 10th Medical Laboratory), and Cpt. Fred McClain, MSC (Chief, USAREUR Central Medical Records Agency). Despite some differences in total numbers resulting from reporting the diagnosis on admission vs that on discharge (in the first 4 months of 1974 it was 1151 on admission vs 1092 on discharge) and despite underreporting prior to 1971, the total number of cases for the 3 years prior to 1971 was only about 640. During the 4 years of 1971-1974, the total number of cases was about 8600, with a peak of 3975 for 1973 based on discharge diagnosis with the date of admission determining the month of record (Preventive Medicine, HQ, USAMEDCOMEUR). Although the 1973 attack rate of over 2000/100,000/annum (Table 1) dropped to 1236/100,000/annum in 1974, it was again up to 1360/100,000/annum during the first 3 months of 1975 (see Fig. 2).

There is no question that there is much more viral hepatitis among active duty U.S. Army personnel stationed in Europe than among personnel stationed in the U.S.A., and much more than among civilians in the U.S.A. and German civilians in Germany (see Table 1), no matter how big a proper correction factor for underreporting of civilian cases may be. It is of interest, however, to note that the usual seasonal incidence, as well as the unusual peak incidence in 1973 in U.S. Army personnel (Fig. 2), corresponds exactly to that in the German civilian population of

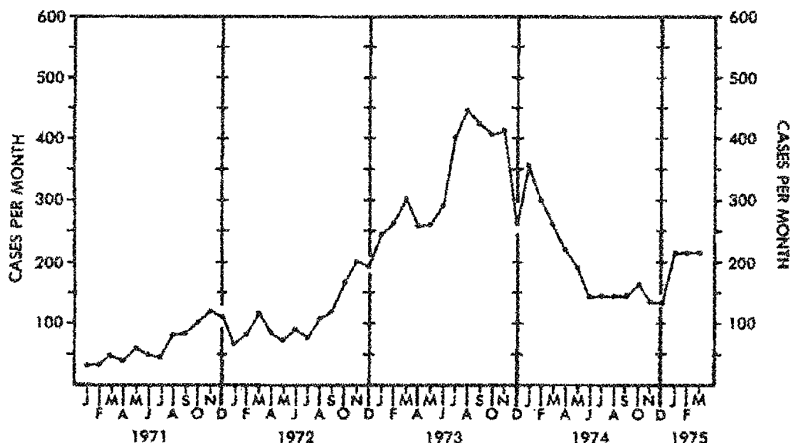


FIG. 2. Hepatitis in active Army, USAREUR. From report of Major Gilbert R. Lavoie, M. C. *et al.*

West Germany (Fig. 3). It is also noteworthy that during the unusual seasonal peak of the 1973 epidemic in August and September, the age-specific attack rate among U.S. enlisted personnel was highest in the 17 to 20 age group, regardless of grade (Fig. 4). During these peak months in 1973 when the attack rates were as high as 6930/100,000/annum among the 17- to 20-year-olds in the enlisted grades 1-4, they were 680 in the 25- to 27-year-old enlisted men of the same grade, 690 in the 2nd lieutenants, and only 5/100,000/annum among the 221,000 U.S. nonmilitary dependents aged 15 and over in Germany at that time (data from report of Lavoie *et al.* cited above). These statistics clearly point to the fact that there is something special about the life style of the active duty U.S. Army personnel in Germany, and especially that of the 17- to 20-year-old enlisted men, that accounts for the high incidence of hepatitis among them.

RIA tests for HB<sub>1</sub>Ag in the serum from USAREUR patients obtained in Sep-

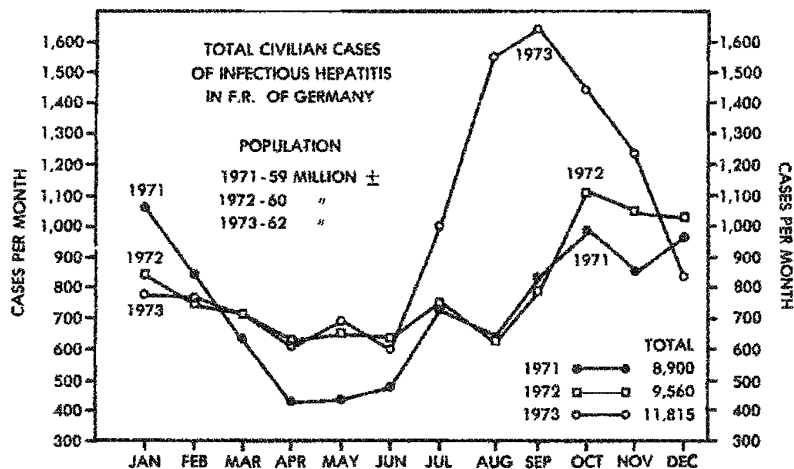


FIG. 3. Total civilian cases of infectious hepatitis in West Germany. From report of Major Gilbert R. Lavoie, M. C. *et al.*

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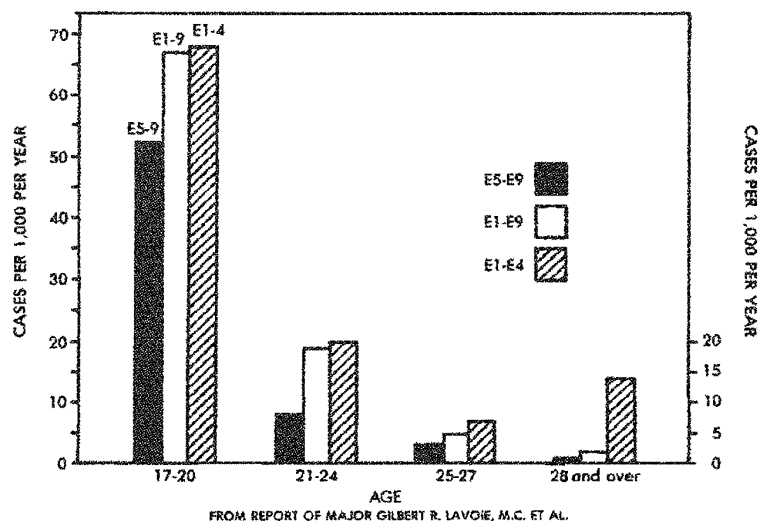


FIG. 4. Age-specific rates of enlisted personnel with hepatitis in USAREUR, July and August, 1973. From report of Major Gilbert R. Lavoie, M. C. *et al.*

tember and December, 1973 and April, 1974 regularly yielded positive results in 70% (personal communication from WRAIR), and it is therefore highly probable that supplementary antibody tests vs HB<sub>s</sub> Ag and HB<sub>e</sub> Ag would have shown that this epidemic was caused by hepatitis B virus. The increasing number of drug addicts and "dirty needle" transmission have been generally blamed for the marked increase in viral hepatitis among U.S. military personnel in Germany and elsewhere, but I find it difficult to accept this explanation as *the main factor* for a number of reasons. I cannot see how it can account for the seasonal incidence, especially the unusual summer peak in the 1973 epidemic (Fig. 2). In November, 1973 a new hepatitis coding system adopted by the Army included information on both tests for HB<sub>s</sub> Ag and history of drug abuse within 8 months prior to onset. According to Maj. Dennis R. Swanson, M.C. (Preventive Medicine, SGO) who examined the worldwide hepatitis records for January-July, 1974, 50% of HB<sub>s</sub> Ag positive hepatitis cases were recorded as having no recent history of drug use, but he believed that there was still a great reluctance to place a drug diagnosis into the discharge summary (letter of 20 September, 1974). It is noteworthy that among civilian hepatitis patients, aged 15 and over, tests for HB<sub>s</sub> Ag have been positive with equal frequency among those who denied or admitted parenteral drug use (Table 2).

It seems to me necessary to recall that the preponderance of hepatitis B virus as a major cause of viral hepatitis in U.S. military personnel antedates the so-called "drug culture," based on the unpublished studies of Purcell on sera from patients in Korea in the early 1950's, mentioned earlier. Moreover, as was already pointed out by Dr. Lewellys Barker in this symposium, sexual intercourse must be considered as an important potential mode of transmission among a number of other pathways that do not involve "needle sticks." *Promiscuous* sexual intercourse has been a way of Army life, especially for young soldiers, for a very long time.

Tests for HB<sub>s</sub> Ag antigenemia by older methods, not including radioimmunoassay, on 175 U.S. military patients in 1970 in Vietnam showed 41% positive despite the fact

TABLE 2  
HB<sub>s</sub> Ag in Acute, Icteric Viral Hepatitis in Los Angeles, California (U.S.A.)  
in Relation to Parenteral Drug Use<sup>b</sup>

Parenteral drug use	HB Ag <sup>a</sup> in patients of indicated age (years)					
	15-24		25 and older		Total	
	Number tested	Percentage HB <sub>s</sub> Ag	Number tested	Percentage HB <sub>s</sub> Ag	Number tested	Percentage HB <sub>s</sub> Ag
Denied	148	52	115	41	263	47
Admitted	145	51	62	55	207	52

<sup>a</sup>HB<sub>s</sub> Ag measured by counterelectrophoresis; much less sensitive than current methods.

<sup>b</sup>From data of James Mosley *et al.*, 1971.

that many of the sera were obtained several weeks after onset. Serum obtained within 7 days after onset yielded 52% positive tests by the less sensitive older methods (3). If the correction factor that Maj. Gilbert Irwin of WRAIR found to be indicated as a result of the tests for HB<sub>s</sub> Ag and HB<sub>e</sub> antibodies in the 1973 Fort Hood, Texas outbreak is also applicable elsewhere, then all or most of the viral hepatitis in the U.S. military in Vietnam was also caused by HBV. Only 15 of the 175 military hepatitis patients in Vietnam had a history of illicit drug use.

In view of these findings one may question how much, if any of icteric, viral hepatitis in U.S. military personnel is caused by HAV (except for the occasional common source food- or water-borne outbreaks), and how much, if any, by the hypothetical hepatitis C virus (except some few cases post-transfusion). While the answer can come only from urgently needed well-planned studies in which the best available specific laboratory tests for HAV and HBV infection (and HCV? when and if available) will be used, the preliminary data now on hand strongly suggest (but do not establish) that HBV is currently the predominant viral cause of hepatitis in U.S. military personnel throughout the world.

One cannot think rationally about various potential methods of prevention of hepatitis B without consideration of our present knowledge of HB<sub>s</sub> Ag subtypes, and whether HB<sub>s</sub> Ag is the only surface antigen by which the HBV particle can attach itself to susceptible cells. Besides the common group antigen "a," HB<sub>s</sub> Ag has additional antigenic determinants of "d" or "y," and of "w" and "r" that are the phenotypic expressions of different HBV genotypes. The four known combinations of *adw*, *ayw*, *adr*, and *ayr* breed true on serial passages in humans and chimpanzees. Individual infections are as a rule caused by a single subtype; i.e., the HB<sub>s</sub> Ag recovered from any one patient or healthy carrier is usually *adw*, *ayw*, *adr*; *ayr* is very rare. The resulting HB<sub>s</sub> Ag antibodies correspond to the infecting subtypes and can be more readily used to determine the prevalence of infection (not disease) caused by the different subtypes in different population groups.

In the U.S.A. the HB<sub>s</sub> Ag recovered from *healthy, volunteer* blood donors is *adw* in 85% and *ayw* in 15%. The HB<sub>s</sub> Ag antibody in *healthy persons without a history of hepatitis* exhibits about the same proportion. A similar predominance of the subtype *adw* has been found in other parts of North America, in South America, in northern and western Europe, in South Africa, East Africa, Indonesia, the Philippines, Taiwan, and Hong Kong. A predominance of about 80 to 85% *ayw* vs 15-20% of *adw* has been found in Romania, Italy, Greece, Yugoslavia, Israel, Egypt, Iran, Pakistan, India, and West Africa. The borderline between *adw* and *ayw* in Africa is between Kenya and North Uganda. The subtype *adr* is predominant in Oceania, Thailand

(83% *adr* vs 17% *adw*), Burma, The People's Republic of China, Korea, and the Kyushu and Honshu islands of Japan. The borderline between *adw* and *adr* predominance in Japan is between Kyushu and Okinawa. Some of the more recent data on the geographic distribution of HB<sub>s</sub> Ag subtypes given here are from the discussion by Dr. Kusuya Nishioka (4).

In the U.S.A. and northwestern Europe, parenteral drug addicts with hepatitis and their non-drug-using intimate contacts with hepatitis yield HB<sub>s</sub> Ag that is *ayw* in 80 to 100% of the isolates, although *ayw* is present in only 15% of healthy carriers in these regions. The *ayw* subtype is also disproportionately prevalent in sporadic acute icteric, viral hepatitis unrelated to drug use in these regions ranging from 40–50% in civilian adults in the U.S.A., France, and Denmark to 88% in Canada and 94% in active duty military personnel in the U.S.A. In the recent outbreaks in U.S. military in Germany, *ayw* was identified in 98% of the HB<sub>s</sub> Ag isolates, although it is present in only 20% of healthy civilian German carriers. In Southeast Asia (Thailand, Cambodia, Vietnam) where *ayw* was not detected in the native population (either patients with hepatitis or healthy carriers) and where 92% of the HB<sub>s</sub> Ag isolates from Thai patients with hepatitis was *adr*, the HB<sub>s</sub> Ag recovered from U.S. military personnel with hepatitis in Vietnam was *ayw* in 52%, *adr* in 20%, *adw* in 5% and *ad* (*r* and *w* determinants not specified) in 23% (5). On the other hand, 33 subtyped HB<sub>s</sub> Ag isolates from U.S. military hepatitis patients in Korea (1967–1969) yielded 85% *ad* and 15% *ay* (6). HB<sub>s</sub> Ag recovered from 10 fatal cases of acute icteric viral hepatitis in civilians in the U.S.A. were reported as exclusively *ay* (7). Thus, while both *ad* and *ay* subtypes of HBV can produce acute icteric hepatitis, the data cited above suggest the existence of pathogenic variants, with a higher frequency of virulent strains among those with the *ay* determinants. The situation may perhaps be comparable to the three types of poliovirus, all of which can produce paralytic disease in man; but over the years 90% of paralytic disease is caused by the type 1 virus.

Recent work on the *e* antigen of HBV (8) indicates that one cannot exclude the possibility that it is another HBV surface antigen, distinct from the HB<sub>s</sub> Ag spherical particle, and that antibody vs the *e* antigen may also play a protective role.

As regards prevention of viral hepatitis in U.S. military personnel, it seems to me that the immediate question is whether or not hepatitis immune gamma globulin, prepared by current techniques involving elimination of HB<sub>s</sub> Ag-containing blood, with known antibody content against various HBV antigens and against HAV should be used in a manner comparable to that employed in the 1967–1969 field trial in Korea (9), i.e., 5 ml repeated at 5- to 7-month intervals during the period of service, or whether it should not be used until another trial, controlled for incidence of HAV and HBV hepatitis by modern techniques, is carried out in an area of especially high incidence.

According to information I received from Major John M. McLean, MSC, Epidemiologist (Office of The Surgeon General, Department of the Army) gamma globulin is now being used prophylactically in U.S. Army personnel in Korea *once* a year in the autumn. It was previously used during the period of 1964–1969 and reintroduced in 1973 (with a recommendation that 5-ml doses be administered once every 6 months) when the hepatitis incidence more than doubled in 1970–72 after discontinuation of gamma globulin. It is noteworthy that while the hepatitis attack rate in U.S. military personnel was 1236 and about 1360/100,000 in 1974 and 1975, respectively, in Europe, it was only 280 and 290/100,000 in Korea during the same period. The continuing statements that gamma globulin can protect against HAV but not against HBV *disease* are based on tests carried out in 1958–1960 (10) when it was not

yet known that a large proportion of sporadic "infectious hepatitis" was caused by HBV, and also because of the ineffectiveness of conventional preparations against posttransfusion or post-"needle-stick" hepatitis. Maj. Gilbert Irwin has reviewed in this symposium several trials in which "standard" gamma globulin may have had an effect on naturally transmitted HBV infection not involving "needle sticks."

In my judgment, the assumption that most HBV hepatitis in U.S. military personnel is now transmitted by "needle sticks" is not supported by the available data, but on the basis of the amount of parenteral drug use still occurring in Armed Forces personnel a portion of the hepatitis is unquestionably so transmitted, and this would have to be taken into consideration in any policy decision. Since gamma globulin may only convert clinically *apparent*, icteric hepatitis into clinically *inapparent* infections, and since chronic hepatitis is more frequently associated with inapparent HBV infections, it is necessary to obtain some estimate of the risk of chronic hepatitis following inapparent HBV infection in reaching a decision on extensive use of gamma globulin for prevention of icteric HBV disease.

A decision on the use or study of gamma globulin in U.S. Army personnel in Europe cannot be postponed on the assumption that an effective HBV vaccine is "around the corner." The data obtained thus far with purified HB<sub>s</sub> Ag vaccine (devoid of *e* antigen) are very preliminary on very small numbers of chimpanzees. They as yet tell us nothing about duration of immunity, about the role of subtypes in cross-immunity when only HB<sub>s</sub> Ag is used, and about the hazards, if any, of repeated inoculations of such antigens if multiple boosters should be required. Trials on even the smallest numbers of human beings should, in my judgment, be postponed until the answers to these and other questions become available from more extensive studies on larger numbers of chimpanzees; all of which cannot be accomplished within a few years.

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