Viral Hepatitis

Edited by
F. Callea, M. Zorzi, and V. J. Desmet

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Dr. FRANCESCO CALLEA

Aggregaat Hoger Onderwijs, Catholic University of Leuven
Histochemistry Unit, 1st Department of Pathology
Spedali Civili of Brescia, 25100 Brescia, Italy

Professor Dr. MARIO ZORZI

Professor of Pathology and Chairman, 1st Department of Pathology
Spedali Civili of Brescia, 25100 Brescia, Italy

Professor Dr. VALEER J. DESMET

Professor of Pathology
Laboratory of Histochemistry and Cytochemistry
Catholic University of Leuven, 3000 Leuven, Belgium

Legend for cover design. Electron microscopic appearance of Delta virus particles isolated from chimpanzee serum. A few 20 nm HBsAg particles are also present. × 175000 (picture by courtesy of Dr. M. G. Canese).

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Preface

The Brescia division of the Italian Association of Blood donors (AVIS-Brescia) celebrated its 50th anniversary in 1985. The idea of organizing a Postgraduate Course on Viral Hepatitis on this occasion developed for obvious reasons. Viral hepatitis is a major concern in blood transfusion and Brescia is located in the region of Lombardy characterized by a high HBsAg carrier rate in its population.

Thus it seemed timely to convene a scientific forum in which the present state of knowledge on viral hepatitis would be summarized. This would allow us to review the tremendous progress achieved over the last 15 years, and also to focus on latest developments which pave the way for future investigation.

The publication of the proceedings of this meeting was considered useful, since it provides a tangible reminder of a comprehensive overview of the broad topic of viral hepatitis, its complications, and its connections with the practice of blood transfusion.

The organizers were fortunate in obtaining the active participation of recognized experts in a variety of hepatological disciplines. Their contributions summarized the more mature areas of knowledge in the field, including clinical aspects, epidemiology and morphology, as well as newer developments in the forefront of hepatitis research, like new diagnostic techniques, oncogenesis, treatment, and vaccination.

Therefore we believe that this book will be useful to the busy practitioner in allowing him to find the newest information which otherwise is hidden in a flood of primary literature, and to the specialist in providing a broader framework in which to project his own research efforts.

We are grateful to the speakers and participants for their valuable contributions and thank them for their ready cooperation.

We should like to thank explicitly the AVIS-Brescia, the Assessorato Sanita' and Igiene of the Lombardia Region and Prof. A. Albertini for advice and support, and Springer-Verlag for editing the proceedings.

The Editors

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The Problem of Posttransfusion Hepatitis

F. DEINHARDT[1]

1 Introduction

The problem of posttransfusion hepatitis has changed considerably since the establishment of AVIS 50 years ago. Viral hepatitis has been characterized clinically: the pathology, immunology and virology have been defined, even though much remains to be learned, and this information will be summarized in various chapters of this book (for review see: Vyas et al. 1984). Perhaps the greatest changes in posttransfusion hepatitis have come about primarily by the ability to diagnose hepatitis B virus carriers and secondarily through vaccination against hepatitis B. More change can be expected as the vaccines of the future (prepared by molecular techniques, hybrid viruses or consisting of small synthetic oligopeptides) come into use.

In this brief introduction, I will discuss (1.) the current epidemiological situation, (2.) some experience with recombinant hepatitis B vaccine in healthy adults and in dialysis patients, and (3.) preventive measures against posttransfusion hepatitis.

However, at the outset, it must be understood that not every case of viral hepatitis occurring at the proper interval after blood transfusion is necessarily posttransfusion hepatitis (PTH) caused by hepatits viruses present in the transfused blood (Aach et al. 1978). As an example, Reinicke (1982) reported several prospective studies of patients undergoing open heart surgery: 30 cases of hepatitis B occurred among 429 patients receiving transfusions (7%) and 13 cases among 151 cases not receiving transfusions or only autologous blood (8.6%). Cases of hepatitis non-A, non-B were not included in these studies. In another study of duodenal ulcer patients treated with truncal vagotomy and pyloroplasty, no hepatitis occurred in 36 patients receiving blood transfusions, and one case of hepatitis non-A, non-B occurred in 49 patients receiving no blood transfusion. These data indicate clearly that despite all precautionary measures, the transmission of hepatitis during ambulatory and/or hospital medical or surgical treatments that do not involve blood transfusions has not been entirely eliminated. It would therefore be incorrect to assume that each case of hepatitis occurring after blood transfusion was caused by the blood transfusion.

1 Max von Pettenkofer Institute for Hygiene and Medical Microbiology, University of Munich, Pettenkoferstr. 9a, 8000 Munich 2, FRG

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2 Viruses Causing Posttransfusion Hepatitis

Several viruses may cause PTH: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis delta virus (HDV), hepatitis non-A, non-B viruses (HNANBV), cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) (Aach 1982, Fiedler 1982, Hollinger 1984, Tabor 1985). The distribution of HB and HNANB in several studies is given in Table 1, and the breakdown of CMV, EBV, HAV and HNANBV in cases of hepatitis not caused by HBV is given in Table 2. As can be seen, 91% of all PTH cases are cases of hepatitis non-B, and the majority of these (96%) are caused by the as yet unidentified HNANB viruses.

Hepatitis A has a very short viremic phase, and infection never leads to a chronic virus carrier state. Transmission through blood transfusion, although theoretically possible if blood were to be transfused from a donor during the last days of the incubation period, is extremely rare and plays no practical role. There are very few documented cases of transmission of hepatitis A through blood transfusion.

In more recent studies, less than 10% of PTH is caused by hepatitis B: Its decline to near disappearance as a cause of PTH is due solely to the ability to identify HBV carriers through the detection of HBsAg in the serum, a screening that today's tests for HBsAg have made so sensitive that almost no HBV carriers remain undetected. Theoretically, transmission is possible if blood is donated during the incubation period when HBsAg is still not detectable but when the blood already contains small amounts of infectious HBV. A few cases of chronic, low grade HBV carriers have been reported who were clinically and biochemically undetectable as carriers but who had both circulating

Table 1. Incidence of posttransfusion hepatitis (PTH): Prospective studies

Authors	No. of Patients	Transfused Units/Pat.	Hepatitis	PTH
Reference				
USA	1513	2.4–4.3	171	15 Hepatitis B
TTVS 1981 (4 Centers)			11.3%	156 Hepatitis Non-A, Non-B
Aach et al. 1981			(4%–18%)	91.2%
USA	283	12.7	36	35 Hepatitis Non-A, Non-B
Alter et al. 1981	(Cardiac surgery)		12.7%	97%
West Germany	305	5.6	23	1 Hepatitis B
Sugg et al. 1982	(Cardiac		7.5%	22 Hepatitis Non-A, Non-B
(Univ. Hospital Tübingen)	surgery)			95.6%
Australia	842	5.1–6.0	18	3 Hepatitis B
Cossart et al. 1982	(Cardiac		2.1%	1 CMV
(2 Centers)	surgery)			14 Hepatitis Non-A, Non-B
				78%
(from Seidl 1982)				

Table 2. Etiologies of hepatitis non-B following transfusion

Reference	No. hepatitis non-B total hepatitis (% non-B)	Hepatitis A No.	CMV No. (%)+	EBV No. (%)+	HNANB No. (%)+
Cossart et al. 1982	15/18 (78)	0	1[a] (7)	0 –	14 (93)
Tremolada et al. 1982	33/34 (90)	0	3[b] (9)	0 –	30 (91)
Tateda et al. 1979	116/126 (92)	0	0[a] –	0 –	116 (100)
Katchaki et al. 1981	15/18 (78)	0	1[a] (7)	1 (7)	13 (87)
Hollinger et al. 1982	137/151 (91)	0	0[a] –	0 –	137 (100)
Alter et al. 1982	57/61 (94)	0	9[c] (16)	0 –	48 (84)
Total	373/408 (91)	0	14 (3.8)	1 (0.3)	358 (96)

+ % of all non-B cases
[a] anti-CMV detection by complement fixation (TTVS, only selected cases; Katchaki also by RIA)
[b] anti-CMV detection non-specified
[c] anti-CMV detection by indirect hemagglutination

virus and antibody in their blood even though tests for HBsAg were negative. Testing for anti-HBc titres might identify such individuals because they usually have very high anti-HBc IgG titres and sometimes also anti-HBc IgM titres; however, these cases occur so seldom that extra testing of all blood donations for anti-HBc would be unjustified. Blood is more highly infectious if it contains not only HBsAg and/or HBV DNA. Additional tests for HBsAg and HBV DNA are not recommended for blood donors because the tests are less sensitive than those for HBsAg, they are more expensive, and HBsAg-positive blood must be considered as potentially infectious even when HBeAg and HBV DNA is undetectable.

Hepatitis delta (for review see: Verme et al. 1983) is caused by a defective virus which can only multiply in the presence of HBV; it is not known whether HDV only needs the envelope of HBV to survive outside cells and to be able to infect cells via the cell receptors for HBV, or if HDV also needs HBV for its intracellular replication. Regardless of the mechanism, HDV can only infect and cause hepatitis if exposure to HBV and HDV occurs simultaneously or if a chronic HBV carrier becomes infected with HDV. In the case of infection of an HBV carrier with HDV, very severe forms of hepatitis result. Both the simultaneous primary infection with HBV and HDV, as well as the infection of an HBV carrier, should be excluded by testing all blood donors for HBsAg as almost all HDV-positive bloods also contain detectable amounts of HBV. Nevertheless, severe and fatal cases of hepatitis occur in those parts of the world where testing for HBsAg is insufficient when already debilitated patients become infected with HBV and HDV simultaneously or when HBV carriers become infected with HDV. There is no vaccine or special immunoglobulin available against HDV, but vaccination against HBV also protects indirectly against HDV. Only individuals already infected with HBV remain at risk because HBV vaccines do not terminate or change an HBV carrier state.

The most frequent cause of PTH is hepatitis non A, non B (HNANB) (Hollinger et al. 1981, Tabor and Gerety 1983). Two forms of HNANB have been distinguished: the

orally and the parenterally transmitted forms of the disease. The orally transmitted disease has many similarities with HA, and, although not shown conclusively, disease is probably caused by a picornavirus (Purcell et al. 1982). The disease spreads by contaminated water and food supplies as well as by other faecal-oral transmissions associated with poor hygiene. Like hepatitis A, it probably has only a short viremic phase, and transmission via transfusion of blood or blood products has not been reported. Parenterally transmitted HNANB tends to become chronic even more frequently (up to 40–60%) than hepatitis B, but it also appears to resolve by itself more frequently after some years. The persistence of a carrier state over many years has been established by transmission from the same donor over prolonged periods of time to various recipients of blood transfusion. Today, this form of hepatitis is the most frequent type of PTH. A specific exclusion of HNANB virus carriers from donor panels remains impossible because the causative agents have not been identified, and no tests have been developed to diagnose a carrier state.

Cytomegalovirus (CMV) is the second most frequent cause of PTH after HBV and is responsible for 0–16% of PTH in various studies (Table 2). These widely different incidences of CMV-PTH may be due partly to inadequate diagnosis in some studies, but they may also be due to differences in the population groups. In general, CMV probably accounts for 5–10% of all PTH. Immunosuppressed patients without antibodies to CMV are particularly at risk of developing serious posttransfusion CMV infections, and these patients should only receive blood from CMV-free donors. Inoculation of larger amounts of immunoglobulins with high antibody titers against CMV (anti-CMV) has been advocated if CMV-free blood is not available for transfusion, or if the immune status of an immunosuppressed recipient is unknown. The results of such prophylaxis with high titered anti-CMV immunoglobulins have varied, and such recommendations are still under debate.

Epstein-Barr virus may also cause PTH, together with a generalised disease similar to the infectious mononucleosis occurring after natural EBV infections. It would be preferable to use EBV-free blood for immunosuppressed patients, but the very high incidence for EBV infections in the general population, and the probable life-long carrier state after a primary EBV infection, make this very difficult to achieve.

3 Vaccination Against Viral Hepatitis

Vaccination against hepatitis A is in the early stages of development: live attenuated, inactivated whole virus, and recombinant or synthetic oligopeptide vaccine preparations are under study. These vaccines will be of general public health importance but will not influence PTH.

The plasma-derived HBsAg hepatitis B vaccine has been shown to be absolutely safe, highly efficacious and free of major side reactions. However, the vaccine is not sufficiently immunogenic in immunosuppressed individuals such as dialysis patients, and the vaccine is expensive. Its source (HBsAg-containing human plasma) is limited and will become increasingly so in future. Attempts have been made, therefore, to prepare HBsAg by molecular techniques: the entire genome of HBV has been cloned, mapped and sequenced, thus making it possible to identify the genome regions coding for

HBsAg. These genome fragments can be cut out of the genome, amplified in plasmids in bacteria, and used to produce HBsAg in an expression system such as yeast cells. Use of mammalian cells as expression systems for the production of HBsAg has also been discussed: the cost and potential contamination of primary cells with other viruses, and the potential neoplastic characteristics of established cell lines carrying oncogenes, make these cells generally unacceptable. Vaccines prepared in such cells may become acceptable once ways of production are developed that exclude all possible harmful nucleic acid or protein contamination. The experience with recombinant hepatitis B vaccines prepared in yeast has been summarized recently (for review see: Vyas et al. 1984) and the results obtained by various groups of investigators were very similar. In our own studies with the recombinant hepatitis B vaccine (prepared in yeast by the Merck Sharp & Dohme Research Laboratories, West Point, PA, USA), seroconversion rates and antibody titres (anti-HBs) were comparable to results previously obtained with plasma-derived vaccines, with the exception that antibody rises occurred somewhat but insignificantly later than after vaccination with plasma-derived vaccine (Jilg et al. 1984, 1985; Jilg and Deinhardt 1986). The vaccine was free of major side reactions, and minor reactions were similar in frequency and severity to the reactions observed after use of plasma-derived vaccine; i.e., short term swelling, itching and reddening of the injection site and a low grade fever, that however, also occurred with a similar frequency in non-vaccinated controls.

Results of vaccination of healthy adults with the recombinant vaccine prepared in yeast cells by the Merck Sharp and Dohme Research Laboratories are given in Figs. 1 and 2 and of dialysis patients in Fig. 3. As can be seen, high seroconversion rates and

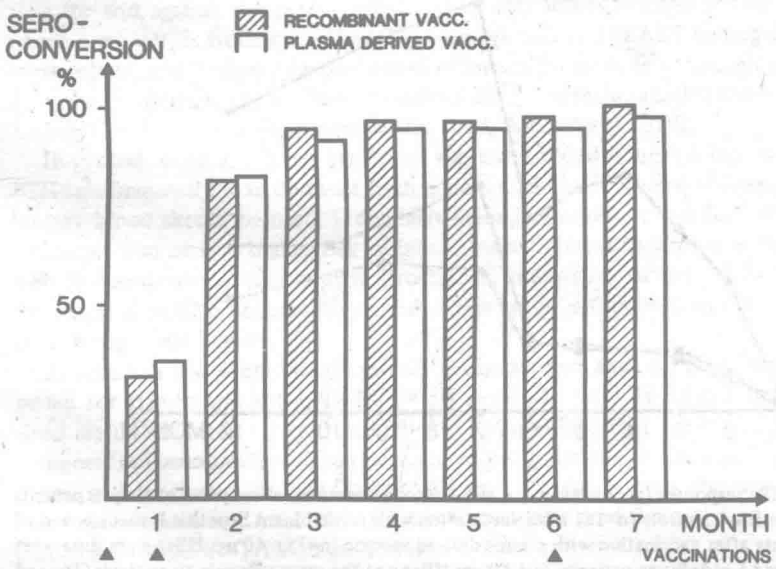

Fig. 1. Seroconversion rates after vaccination with recombinant or plasma-derived hepatitis B vaccine. 10 μgr of HBsAg was given at 0, 1 and 6 months (Jilg and Deinhardt 1986)

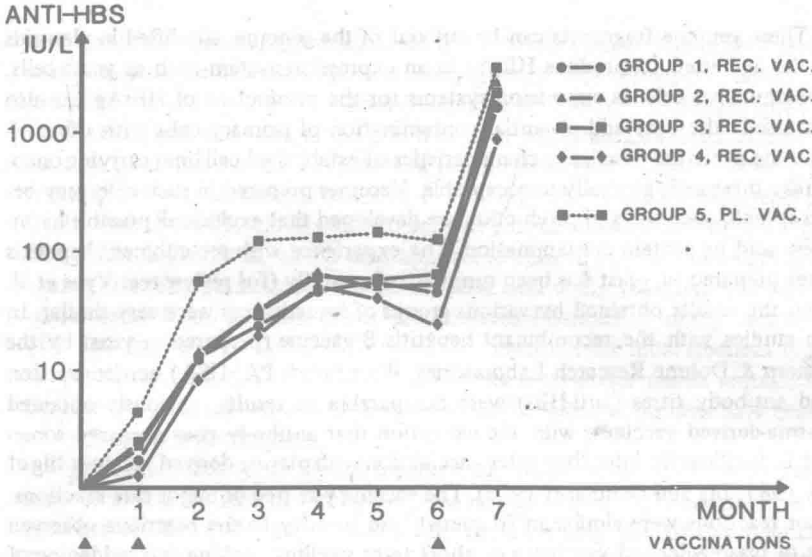

Fig. 2. Comparison of recombinant and plasma-derived hepatitis B vaccine. 10 μgr of HBsAg was given at 0, 1 and 6 months. Groups 1–4 received different lots of recombinant vaccine and group 5 plasma-derived vaccine (Jilg and Deinhardt 1986)

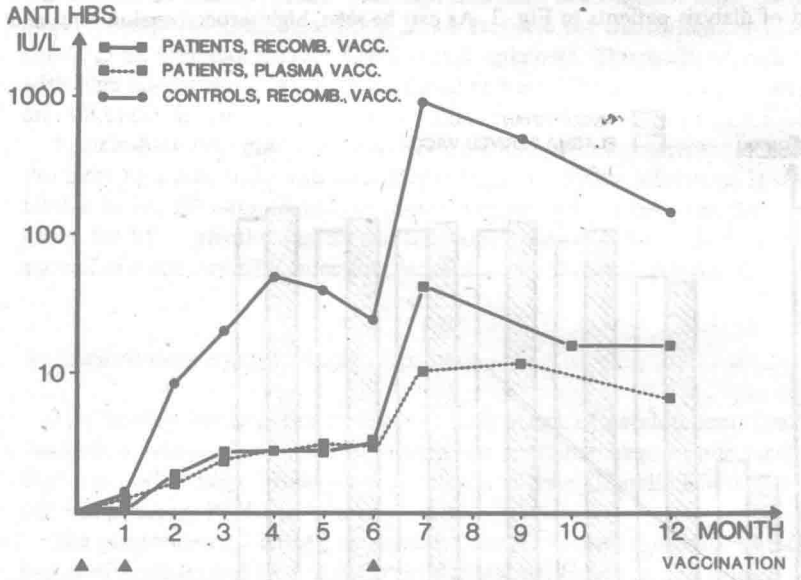

Fig. 3. Anti-HBs responses (geometric mean anti-HBs concentration, all subjects) of dialysis patients (n=49) and healthy controls (n=16) after vaccination with recombinant hepatitis B vaccine, and of dialysis patients after vaccination with plasma-derived vaccine (n=75). 40 μgr HBsAg per dose were given at 0, 1 and 6 months to patients, and 10 μgr HBsAg at the same schedule to controls (Jilg and Deinhardt 1986)

adequate antibody titres were achieved in healthy young adults, but only 60% seroconversion and lower anti-HBs levels in dialysis patients. The response of dialysis patients to the recombinant vaccine was slightly better than to the plasma-derived vaccine, but this difference was statistically insignificant and does not solve the problem of the lack of efficient immunization of all dialysis or other immunosuppressed patients. Preliminary data also indicate that the recombinant vaccine can be used safely and effectively in newborns, with or without simultaneous inoculation of hepatitis B immunoglobulin (HBIG) (Stevens 1986). Vaccination is recommended for all groups at risk of infection with HBV, particularly newborns of HBV carrier mothers, medical and dental personnel, dialysis patients, patients with hemophilia or patients before major operations during which blood transfusions can be foreseen. In the future, if broader vaccination programs can be instituted in high incidence areas for hepatitis B, this disease may be completely eradicated.

No immunoprophylactic measures either in form of specific immunoglobulins or of vaccines are available for HNANB because the causative agents are unknown, and vaccines against CMV and EBV are not yet available or are still in the development.

4 Prevention of Posttransfusion Hepatitis

Exclusion of HBV carriers as blood donors through testing for HBsAg has become routine and needs no further discussion here. In addition to testing for HBsAg, testing serum alanine aminotransferase (ALT) levels of all blood donations has also been recommended as a means of preventing about 1/3 of all PTH, including HNANB (Seidl 1982). Testing for ALT has been discussed frequently on both sides of the Atlantic, and opinions for and against the cost-effectiveness of this test have been argued vehemently (Aach et al. 1978; Hollinger 1984). My own opinion is that ALT testing does provide extra safety, and it should be performed whenever possible. Even though unimportant for preventing hepatitis, all blood donations should be tested also for antibodies against LAV/HTLV III to exclude carriers of this virus, the cause of AIDS.

In general, donations from genuinely voluntary blood donors transmit all forms of PTH less frequently than do those from commercial blood donors: if possible, only voluntary blood should be used. Individuals belonging to risk groups for LAV/HTLV III infections also carry a higher risk of infections with hepatitis viruses: such risk groups include homosexuals, drug addicts, prostitutes, and sexual partners of these groups. In the past, hemophilia patients were another risk group, although their disease prevented them being blood donors.

Transfusion of "warm blood" should be discouraged, and only blood which has been tested for HBsAg and anti-LAV/HTLV III should be used. If "warm blood" transfusions are unavoidable, a donor panel should be assembled that is tested regularly and is composed of individuals who can be assumed not to belong to a risk group. Blood products, such as clotting factors (factor VIII and IX), which carry the risk of transmitting hepatitis and/or LAV/HTLV III should be inactivated (heat of β-propiolactone in combination with UV) (Hollinger 1984).

Last but not least, blood transfusions should be given only when really necessary. Even today, blood transfusions are given unnecessarily, often without weighing possible

benefit against the unavoidable risks. It is probably true that most single unit blood transfusions are unnecessary, and evaluation of their frequency in a particular setting indicates the stringency with which decisions to transfuse are handled.

All of the above measures will reduce the incidence of PTH, but control of this problem will become possible only after the agents of HNANB have been identified and characterized, and after tests have been developed to identify HNANBV carriers. Control of the much smaller numbers of PTH caused by CMV and EBV must wait until effective vaccines for general use against these viruses have been developed and appropriate vaccination programs have been implemented.

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