Current Hepatology

VOLUME 2

EDITED BY

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Preface

The study of the liver, its function, and its diseases is now surging forward after many years of slow progress. Because the literature in this field is so extensive, even the most dedicated physician probably could not read and comprehend all of the studies reported in a given year.

Current Hepatology seeks to provide the reader with an assessment of the world's literature in each of the major areas of liver disease research. Authors were selected who have experience documenting expertise in a specific field within the larger subspecialty of hepatology. Each author was requested to read all of the literature in his or her respective field and prepare a chapter describing major advances, new information, and changes in concepts and trends. Each chapter was to be not merely a series of abstracts, but rather a description of relationships among studies of different laboratories and an assessment of trends in various areas that would provide the reader with an opinion regarding the direction of research during the past year and expectations for the future.

The editor has undertaken to eliminate repetition of information in most instances; however, some overlap was allowed to remain when authors had reasonable and important differences of opinion and views that seemed to add strength to the volume. Also, when experts review their fields annually, they sometimes tend to promote their own personal interests and prejudices. To avoid this fault and provide a balanced view over the years, new authors are periodically invited to review various aspects of liver disease in this annual series. To further reduce the possibility of chapters reflecting individual prejudices or omitting important studies, this year reviews have been conducted by a second expert in the same field as the chapter author, in addition to the editor. It is hoped that this additional level of peer review will provide the reader with a balanced and complete view of the status of research in hepatology during the past year.

The past year was another exciting one. I hope that this book will be able to instill this excitement in the reader, even in those areas of liver disease in which he or she may not have a specific current interest. I am indebted to the chapter authors, the reviewers, and my colleagues who have been extremely supportive in the development of these volumes. Read and enjoy.

Gary L. Gitnick

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Hepatitis: Retrospecti Et Prospecti

Ronald L. Koretz

The Roman god Janus is most noted for his biphysiognomic features. This guardian of portals and patron of beginnings and endings had two faces, so he could look at once both forward and backward. I will now don my Janus mask(s) to perform a similar task for hepatitis. Most of the time the work of the year gone by will be examined, but I will also attempt to project and extrapolate this material so that a prediction of next year's chapter will emerge. (This is only fair; as you are reading the former, I am probably hard at work on the latter.)

By way of preview (what else?), this chapter has been divided into two larger and two smaller sections: Acute Viral Hepatitis, Chronic Hepatitis, Immunology of Hepatitis, and Hepatitis and the Law.

Among other things, the section on acute hepatitis will focus on sexual and health care worker transmission, blood donor screening, newer techniques of liver support in fulminant failure, and vaccine production. Highlights of this year's progress in chronic hepatitis include the development and prognosis of the hepatitis B surface antigen (HBsAg) carrier state, pregnancy and its consequences, the long-term course of treated chronic active hepatitis, and interferon therapy. Immunologic theories concerning the genesis of chronic hepatitis will be discussed.

In addition to all this, some ancient folklore will be interwoven; the careful reader should not myth a thing. With my humblest apologies to you classicists who object to the mixing of Latin and Greek in the title, let us begin.

ACUTE VIRAL HEPATITIS

Etiology

The vast majority of clinically important acute viral hepatitis is caused by hepatitis A, hepatitis B, and the non-A, non-B agents (of which there are probably at least two). Dr. Overby, in Chapter 2, will provide all of the current information on the serodiagnosis of these agents, and I need not repeat that information here. I would only like to stress a few concepts and make a couple of comments on some papers in the recent literature.

Hepatitis B

Hepatitis B core antigen (HBcAg) represents a component of the nucleoprotein center of the hepatitis B virus (HBV). Antibody to core antigen (anti-HBc) is an important serologic tool. However, the presence of anti-HBc does not necessarily imply active HBV replication. In fact, anti-HBc persists for years after the HBV infection has cleared by all other clinical, biochemical, and serologic parameters (1,2). Thus the presence of anti-HBc in the absence of HBsAg or antibody to HBsAg (anti-HBs) does not necessarily indicate active disease. (This serologic combination is uninterpretable.) On the other hand, the demonstration of IgM-specific anti-HBc in the absence of HBsAg and anti-HBs usually appears to indicate active infection (3), a situation comparable to the serodiagnosis of hepatitis A.

HBsAg and anti-HBs have again been found together, and again a subtype difference between the antigen and antibody was present (4). This has clear implications with regard to potential vaccines.

Some puzzling (even distressing) serologic observations deserve brief attention. Hepatitis B e antigen (HBeAg), previously only seen in association with HBsAg, has now been reported as present in four adult Ugandans without the surface antigen (5). Three patients have transiently seroconverted from HBsAg to anti-HBs positivity, then reverted to an HBsAg positive status, during bouts of acute hepatitis (6). Two patients with very high titers of HBsAg have been found to have too much antigen to be neutralized in the standard confirmatory test; in most clinical laboratories, these people would be reported as HBsAg negative (7)!

Where does the HBV live? In the past it has been assumed to be a liver-specific virus. Hoefs et al. have found that, even though pancreatic juice contains inhibitors that block the detection of HBsAg, some HBV-positive individuals have HBsAg in their pancreatic secretions (8). One such person had HBsAg in his pancreatic juice but not in his bile. (Inhibitors are also present in the bile, however, which may explain this finding.) The authors go on to speculate that perhaps the virus replicates in the pancreas, and that it may even be responsible for some pancreatic disease! Although the accompanying editorial (9) appropriately considers this as a "less-than-likely possibility," we will probably see further studies looking for HBV in other tissues. (Markers other than HBsAg will be sought; HBsAg may be demonstrated solely because it is in the vascular spaces of all organs.)

Non-A, Non-B Hepatitis

Sisyphus was sentenced by the gods to an eternity of labor. Each day he rolled a heavy rock up to the top of a hill, and each night it came crashing back down. This year, as in past years, we have reports of possible identification of the non-A, non-B agent(s). These reports include serologic tests for antigens (10,11) and antibodies (12), as well as visualization of viral particles in tissue (11,13–15) or body fluids (15–17). Like Sisyphus, a large number of investigators have expended much time and effort with frustration as their sole reward. We can only hope that one or more of this year's candidates will have found out how to keep the rock at the top of the hill.

Table 1. Characteristics of "Exotic" Hepatic Viruses[a]

Virus	*Nucleic Acid*	*Geographic Location*	*Incidence Jaundice*	*Mortality*	*Other Organs Involved*
Lassa Fever	RNA	Nigeria	0	30–70%	Coagulopathy
Marburg virus	?RNA	Africa	0	20%	Coagulopathy Lungs Kidneys Skin
Ebola virus	N.S.[b]	Africa	5%	50%	Coagulopathy Lungs
Rift Valley Fever	RNA	Africa	N.S.	N.S. (high if jaundice)	Coagulopathy Kidneys Lungs Central nervous system

[a]Information on this table derived from reference 20.

[b]N.S. = not stated.

Other Agents

Occasionally other infectious agents produce hepatitis. Herpes simplex has previously been shown to cause fulminant hepatitis in the immunosuppressed host; it was reported to cause mild hepatitis in an otherwise normal adult (18). However, in this case, the diagnosis was only established by an eightfold rise in complement fixation titers. The patient in question had also been transfused, and he may have had concomitant herpes simplex and non-A, non-B hepatitis viral infections. Cytomegalovirus caused fulminant fatal hepatitis in a 10-month-old girl receiving chemotherapy for a neuroblastoma (19).

An interesting review was written by Zuckerman and Simpson describing "exotic" viral liver diseases (20). These are a series of disorders caused by viral agents endemic to underdeveloped areas of the world. Typically, severe cases of hepatitis with or without other organ involvement occurred in inhabitants of these regions or in persons exposed to animals or patients returning from these places. (These diseases are probably comparable to the yellow fever that occurred when the Panama Canal was built.) It should be noted that, in spite of other evidence of liver failure, jaundice did not regularly occur in most patients. Features of these exotic infections are summarized in Table 1.

Finally, secondary syphilis appeared to be responsible for at least one case of otherwise typical anicteric hepatitis (21).

Epidemiology

General Population Data

The reported frequencies of the viral etiologies for acute hepatitis are presented in Table 2 (22–31). Although hepatitis B appears to comprise roughly 50% of the cases (less if less sensitive techniques are employed), it must be remembered

Table 2. Frequencies of A, B, and Non-A, Non-B Hepatitis

	Source of Patients		*HBsAg*	*% of Cases*		
Reference	*Patient Status*	*Geographical*	*Technique*[a]	*A*	*B*	*Non-A, Non-B*
22	In/out patients	World Survey	Sensitive	—	53	—
23		Aukland	Not stated	—	30	—
24		Iran	Less sensitive	—	38	—
25		West London	Less sensitive	$\leqslant$ 52	20	$\geqslant$ 3
26	Hospitalized	Greece	Sensitive	10	80	10
27		Denmark	Sensitive	58	36	6
28		Milan	Sensitive	31	51	18
29		Somalia	Sensitive	—	33	—
30		Melbourne	Sensitive	—	26	—
31		Israel	Not stated	—	49	—

[a]Sensitive assays include radioimmunoassay and reverse passive hemagglutination. Less sensitive assays include immunodiffusion, complement fixation, and counter-electrophoresis.

that the raw data are derived from a number of selected subpopulations.* In addition, different areas of the world vary greatly in such parameters as living conditions, social behavior, and HBsAg carrier rates. Hepatitis B is less common in children (22,32). Thus it is meaningless (in a clinical sense) to attempt to ascertain precise frequencies; rather it is clear that A, B, and the non-A, non-B agents are all common enough causes of hepatitis to warrant consideration (and serologic confirmation or exclusion) in any given case.

Epidemiologic conclusions based on serologic studies of healthy populations were discussed last year (2). Although several papers have been published since, the general concepts remain the same. Hepatitis A is a disease of childhood in underdeveloped areas, where virtually 100% of the population is affected in the first 2 decades of life (33,34). The prevalence of anti-HA increases with age in other populations (34,35). As socioeconomic and hygienic conditions improve, less hepatitis A exposure occurs (36).

Hepatitis B exposure may result in either viral clearance or the development of the chronic carrier state. The frequency of the carrier state varies widely in different areas of the world as well as in certain subpopulations within these areas (36–38). These subpopulations will be discussed in some of the sections to follow.

Several epidemics of "infectious" hepatitis were studied. Day-care centers in Arizona were thought to be foci of hepatitis A, with the children then passing the illness on to members of their families (39). This is a pattern that has been previously recognized for school children. A food handler incubating hepatitis A may have transmitted the disease in submarine sandwiches sold by a softball team in Pennsylvania (40). Epidemiologists in Ohio have suggested that water-

*The 80% figure in the Greek study (26) probably represents an overestimate of hepatitis B. That study considered anti-HBc alone as a marker for acute hepatitis B. It also assumed that all patients with HBsAg had acute hepatitis rather than being chronic carriers with acute disease due to some other agent. [Greece has a carrier rate of 6–8% (22).]

borne sources are probably only responsible for a small percentage of nonepidemic hepatitis A in the United States because they found no relationship between water supplies and/or treatment procedures and the endemic hepatitis A rates (41). Meanwhile, in India, Khuroo reported a waterborne outbreak of non-A, non-B disease that behaved very similarly to hepatitis A and underwent fecal–oral transmission (42).

Sexual Transmission

Hepatitis (B in particular) has been viewed as a sexually transmitted disease, and the data concerning this concept have been previously reviewed (1,2). Male homosexuals with multiple sex partners, already known to be at risk for acute and chronic hepatitis B (27,43,44), have now been shown to have an increased risk for hepatitis A (45). The risk in female homosexuals is less clear (46). In this same letter (46), Bolan also raised the question whether male heterosexuals with recurrent genital herpes might be protected from hepatitis by interferon formation induced by the herpes virus! There are no data supporting this speculation.

A prospective trial of a hepatitis B vaccine in homosexual men with multiple partners (47) will be discussed later in this chapter. None of the participants had serologic evidence of past or present HBV infection at the beginning of the study. Of epidemiologic note was the observation that subsequent HBV infection was seen in 27% of the placebo recipients within the 18-month follow-up period.

One of the early reports of possible spouse transmission of hepatitis was King Midas. He allegedly merely touched his wife and she turned yellow. This year it is the women's turn. A study in Japan showed that husbands of HBsAg carriers are more likely to demonstrate serologic evidence of HBV infection than mates of HBsAg-negative women (48). Contrary to other studies, the sputa and vaginal secretions in these Japanese women were negative for HBsAg except during menses. Although Greek prostitutes have the same carrier rate as that of the general population (approximately 10%), they have a higher frequency of other hepatitis B markers (49), indicating a greater risk of viral exposure.

Most of the evidence associating hepatitis with sexual intercourse is indirect. The large bulk of it is the statistical association of an increased risk in those subgroups who also have increased sexual activity. Most studies, unlike the one of Inaba et al. (48), have identified HBsAg in the semen, saliva, or vaginal secretions of HBsAg-positive individuals. HBsAg-containing semen or saliva can cause hepatitis when injected parenterally into experimental animals. These data are consistent with the observation that hepatitis is a disease of intimacy, but they do not prove direct genital mucosal entry.

Scott et al. instilled HBsAg-positive semen into the vaginal vault of a gibbon and then simulated intercourse with a gloved finger; the vaginal secretions were subsequently found to be tinged with blood (50). The animal developed hepatitis. Although this may not be a completely valid model of intercourse (since, in vivo, the semen is not rubbed into the vaginal mucosa), this is the strongest line of evidence to date that genital mucosal entry may occur. (It is unknown whether Cupid's arrows carry hepatitis markers.) Interestingly, the same authors administered HBsAg-positive saliva to gibbons by means of a naso-oral aerosol and followed this by vigorous toothbrushing without producing hepatitis.

Neonatal Transmission

Shortly after his birth, Achilles was dipped into the river Styx. His mother Thetis held him by one heel, which was therefore the only portion of his body not made invulnerable. This proved to be his undoing when, during the Trojan War, he was wounded in that heel by a poisoned arrow. The defect acquired in the neonatal period that is of interest in this section is hepatitis B transmission.

In the Western world, among non-Asians, offspring of mothers with acute third-trimester hepatitis B are at the greatest risk of developing HBV infection and even the chronic carrier state; the offspring of HBsAg carrier mothers are not at much risk (2). This general rule is not true in Oriental families, where the children of carrier mothers often develop the carrier state themselves.

Three studies in the past year reinforced these latter concepts. Tong et al. (51) studied the families of Asian and non-Asian patients with HBsAg-positive hepatocellular carcinoma, chronic hepatitis, or the asymptomatic carrier state. Genetic relatives of the Asian patients, whether they were born in the Orient or the United States, were far more likely either to be carriers or to have other serologic evidence of hepatitis B infections than were the blood relatives of the non-Asian patients. Woo et al. (52) studied offspring of carrier mothers in London; eight out of 18 offspring of Chinese mothers developed HBsAg, compared to six out of 92 born to non-Chinese women. Eighteen children of HBsAg-positive Sicilian mothers were prospectively followed by Mollica et al. (53). At least 14 demonstrated evidence of HBV exposure (HBsAg or endogenous anti-HBs), but only three became chronic carriers.

HBeAg positivity is also associated with the transmission of the HBV to neonates. This relationship is not all or none, however, as has been previously noted (1,2). In the study of Woo et al. (52), nine of the 12 offspring of HBeAg-positive mothers developed HBsAg, but so did three of 45 children of anti-HBe–positive mothers.

When considering family studies, it is important to realize that a carrier may not necessarily be exposed at birth. For example, some of the patients of Tong et al. (51) may have acquired the carrier state later in life; perhaps the Oriental background only provides the propensity for HBV tolerance to occur. The age-specific HBsAg-positivity rate in children living in areas where the virus is endemic increases over the first decade of life (54). Although other explanations exist, the simplest one implies continued exposure and infection beyond the neonatal period.

Health Care Workers

Aesculapius was a renowned physician whose feats of healing were legendary. He was never known to have developed hepatitis nor even to have checked his own serology. (Being of Greek background, where the HBsAg carrier rate is high, he may very well have had serologic evidence of hepatitis B exposure.) Since his time, however, hepatitis has come to be recognized as an occupational hazard of health care workers.

Table 3 summarizes some of the older (55–57) as well as more recent (58–63) serologic surveys of various groups of health care providers. Although the HBsAg carrier rate varies widely from study to study (reflecting the country of origin of the paper), there does not seem to be an increased rate among the

Table 3. Hepatitis B Markers in Health Care Workers

	Health Care Workers			*Control Subjects*		
Reference	*Occupation (Number)*	*HBsAg+ (Number, %)*	*Anti-HBs+ (Number, %)*	*Occupation (Number)*	*HBsAg+ (Number, %)*	*Anti-HBs+ (Number, %)*
55	Hospital personnel (1,052)	8(0.8)	171(16)	Nonhospital workers (1,052)	4(0.4)	92(9)
56	Hospital personnel (1,666)	27(1.6)	279(17)	Hospital administrators (149)	3(2.0)	13(9)
	Lab techs (86)	4(4.7)	31(36)	Metal workers (131)	3(2.3)	14(11)
57	Dentists (288)	1(0.3)	42(15)	Blood donors (210)	0	6(2.9)
58	Surgeons (224)	0	51(23)	Blood donors (960)	0	35(3.6)
				Hospitalized patients	"0.7%"	"8.2%"
59	Military health workers (934)	12(1.3)	161(17)	Food service (113)	0	22(19)
				Other military (1,768)	19(1.1)	272(15)
60	Hospital personnel (1,008)	7(0.7)	Not done	Patients (1,106)	10(0.9)	Not done
61	Hospital personnel (473)	23(4.9)	88(19)	General population	"1.5%"	"13%"
62	Medical students (486)	34(7.0)	Not done	General population	"5–10%"	Not reported
63	Dental personnel (495)	0	11(2)	General population (800)	1(0.1)	28(3.5)

health care personnel, with the possible exception of laboratory technicians in Germany (56) and hospital personnel in Prague (61). On the other hand, the frequency of anti-HBs positivity is usually higher in the health workers, possibly indicating a higher intensity of past exposure to the virus. (In one study where this anti-HBs finding was not found (59), the authors noted that the rate of anti-HBs positivity was higher among doctors and dentists, 16%, than among non-hospital officers, 11%.)

Another approach to appreciating the magnitude of this problem is to look at the annual occurrence of hepatitis; the above data only measure hepatitis infection at some time in the past. The annual attack rate of clinically apparent disease in laboratory personnel in Britain in 1977–78 was 29 per 100,000 workers (64). Among hospital employees in Minnesota in 1974–75 this rate was 136/100,000 (65). This latter study showed a dramatic risk for dialysis personnel (approximately 10,000 cases/100,000 workers/year) and laboratory workers (568/100,000). These Minnesota figures are order(s) of magnitude higher than those in the British study; this probably represents the efficiency of subsequently introduced control techniques and education, since the attack rate in British laboratory staff in 1973–74 (identically collected data) was 143/100,000 (66).

Three recent studies have prospectively followed identified health care workers for 1–2 years, with serial serologic evaluations for hepatitis B. The groups followed were military health care personnel (67), hospital laboratory workers (68), and dental students (69). All three studies suffer from incomplete follow-up in a substantial proportion of individuals, infrequent determination of serologic status (usually yearly or less often), and no attempt to look for other causes or cases of hepatitis (except as noted). Of 642 initially HBV-seronegative military personnel, nine (1.4%) seroconverted, and seven others developed apparently non-B clinical hepatitis. In both the negative laboratory workers and dental students the 2-year seroconversion rate was 5%. [By way of comparison, a similar study of New York house staff, reported in last year's review, showed a 10% annual conversion rate (70).] Another interesting observation in two of these prospective studies (68,69) was that low-titer, preexistent anti-HBs disappeared during the follow-up period in at least 80% of the cases.

Hepatitis in dentists has received a fair amount of attention in the past year. Dentists have historically asked about past episodes of, or potential exposures to, hepatitis as part of the intake routine. Unfortunately this may not be a technique for protection for two reasons. First of all, most patients with hepatitis have subclinical disease; this is especially a problem with asymptomatic chronic carriers of HBsAg. Goebel screened 272 dental patients and found four antigen carriers; two of them had no history of liver disease or potential viral exposure (71). Tullman et al. found that an even higher proportion, 18/22 (81%), of HBsAg-positive dental patients had no history of liver diseases (72).

More importantly, however, the vast majority of patients with histories of hepatitis are not carriers of HBsAg and probably do not pose threats to the dentist. In Goebel's study, only five out of 140 (4%) people with histories of potential viral contact had demonstrable HBsAg (71). As will be discussed later, most blood donors with a history of jaundice are not HBsAg positive (probably < 1%); these proples usually have had hepatitis A.

If the history is not useful, can all dental patients be screened for HBsAg?