CURRENT

HEPATOLOGY

VOLUME 7

Edited by

Gary Gitnick, M.D.

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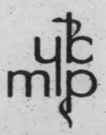

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Preface

The study of liver diseases has experienced greater growth in recent years than at any time in medical history. It is now a medical subspecialty, encompassing many areas of expertise. Its role in internal medicine has become increasingly prominent. This annual review does not attempt to provide an encyclopedic survey of the field of hepatology, but rather focuses on those areas thought by the authors to be most significant.

The authors of the chapters in this text are renowned experts in their fields. They reviewed the most significant articles published during the past year. They were instructed to avoid discussing every article reviewed but rather to provide the reader with a summary of those concepts, ideas, and approaches thought to be of greatest importance. They were asked to provide the reader with the most current and most essential information and to avoid unnecessary descriptions of work thus far unsubstantiated or unlikely to lead to significant new concepts.

A text in which contributors review the work of their own peers may suffer from its authors' prejudices. In order to ensure that each chapter presents a balanced assessment of research performed during the prior year, experts in each area reviewed the final chapters and identified work inappropriately omitted or unnecessarily stressed. I am indebted to the following colleagues who served as reviewers for the chapters in this text: David Van Thiel, M.D.; Gregory Sarna, M.D.; Emmet Keeffe, M.D.; Jules Dienstag, M.D.; Fenton Shaffner, M.D.; John Galambos, M.D.

As with previous volumes, our goal was to present the reader with an easily understood, practical guide to new concepts based on the most important scientific articles published during the previous year. I am indebted to the authors and reviewers for the text that resulted.

Finally, I am deeply indebted to Mrs. Susan Dashe, whose remarkable efficiency and organizational ability resulted in the compilation of these chapters. I am also indebted to my friends at Year Book Medical Publishers, Inc., Nancy Chorpenning and Elizabeth Sugg. Both have worked tirelessly to ensure that these books are well written and that they are indeed current.

GARY GITNICK, M.D.

Contents

CHAPTER 1

Acute Hepatitis Papers: The Sports Section

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The single most identifiable logo for athletics probably is the symbol for the Olympic Games, five intertwined rings. (No, the symbol I had in mind was not the $!) In ancient Greece, the "five year" cycle between the stagings of these events only encompassed four years, as the first year was the year of the previous contests. As these books have one year cycles, I welcome you to the Eighth Current Hepatologiad.[1–7]

This chapter will deal mostly with viral-induced disease. We will highlight the problems presented by low titer antibody to hepatitis B surface antigen (anti-HBs), immunoglobulin-M specific antibody to hepatitis B core antigen (IgM-anti-HBc), the purported danger of mentally retarded hepatitis carriers in the classroom, the risks to and from health care workers, the course of acute hepatitis B, the use of alanine aminotransferase (ALT) screening of blood, and hepatitis B vaccine responsiveness. Let the Games begin!

ETIOLOGICAL CONSIDERATIONS

In 1969, an outbreak of hepatitis on the Holy Cross football team claimed 90 of the 97 team members and coaches. The water-borne epidemic was thought to

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be due to hepatitis A. Friedman and co-workers reinvestigated this event, using stored sera.[8] IgM-specific antibody to hepatitis A (IgM-anti-HA) was only found in those individuals who had developed jaundice. (This observation underscores a recently reconfirmed finding that hepatitis A is more severe in adults than in children, in whom it is usually asymptomatic.)[9] The cause of the hepatitis in the remainder of the cases was not ascertained.

A putative agent implicated in a water-borne epidemic of non-A, non-B (NANB) hepatitis in Nepal may have been isolated.[10] This 27-nm particle caused hepatitis (enzyme abnormalities) in marmosets.

Animal challenge studies have implied that there are at least two blood-borne NANB agents. Now Brotman et al. have described chimpanzees who appeared to resist a Hutchinson strain challenge, but then developed disease when exposed to material containing a 100-fold higher infectivity titer.[11] The authors wondered if second episodes of hepatitis in experimental animals are due not to second agents, but to large doses of the first agent overwhelming the acquired immunity. It should be noted that some animals who "resisted" the initial challenge actually developed ALT elevations, and that cytoplasmic tubules, a histologic characteristic of the original infection, were not seen in all of the rechallenges. In the absence of specific serologic tests, we cannot rule out an unappreciated infection by yet another NANB agent.

Is NANB really B?[6, 7] Hepatitis B virus (HBV) DNA was not found in the sera and livers of chimpanzees with NANB hepatitis.[12]

Cockfighting was introduced by the Romans, who took it to Spain, from where it spread to the New World with Spanish explorers hundreds of years later. The delta agent was also described first in Italy, but is now recognized worldwide. American workers have found antibody to this agent (anti-delta) in standard immune globulin (SIG) from 1944.[13]

Delta hepatitis virus infection is diagnosed by the presence of anti-delta. DeCock and his co-workers described a patient with icteric disease who had anti-delta (including a positive IgM fraction), a high titer positive IgM-anti-HBc, hepatitis B e antigen, and a negative hepatitis B surface antigen (HBsAg).[14] Over the nine days of follow-up, the patient developed a rising titer of anti-HBs. The case was reported as an example of delta infection in the absence of circulating HBsAg.

Jacobson et al. observed Epstein-Barr viral hepatitis in a 38-year-old woman with prominent abdominal pain but without pharyngitis or lymphadenopathy.[15] A review of the literature indicated that "older" patients may present with this "atypical" picture.

"Judo" means "the gentle way" and "karate" refers to an "open hand," terms that belie the end results to the recipients. Similarly, a usually innocuous virus, the adenovirus, caused massive hepatic necrosis in an immunocompromised host.[16]

Finally, *Salmonella typhi* caused icteric hepatitis in six patients in India.[17, 18] Liver biopsy specimens in four demonstrated portal tract lymphocytes, granulomas, and fatty infiltration.

HEPATITIS TESTING

Strategy plays an important role in sports; sometimes it works and sometimes it doesn't. Italian patients with acute NANB hepatitis were found to be positive for autoantibodies in significant numbers.[19] Austrian donors infected with NANB hepatitis at a plasmapheresis center had no such serologic findings.[20] Hepatitis fans—take your pick!

Let us take time out for phenomenology. Patients with acute hepatitis have increased levels of serum and urinary magnesium.[21] Six of 35 patients with acute hepatitis who underwent ultrasound examinations of their right upper quadrants had contracted gall bladders.[22]

The bulk of this section will be devoted to considerations about the serology of viral hepatitis. The persistence of IgM-anti-HA beyond six months, discussed last year,[7] is still being reported. Hatzakis and Hadziyannis found it in 38% of their female, but none of their male patients; asymptomatic patients cleared it faster.[23] IgM-anti-HA was still demonstrable in 78% of 69 Italian patients one year after their hospitalization for acute hepatitis A.[24] Three of 11 Polish patients were still positive (employing a nonstandardized test) after two to three years.[25] The IgM-anti-HA found in one patient 19 months after her illness was thought to be due to a rheumatoid factor–like substance, not true antibody.[26] Chen and Sung speculated that different lots of a commercially available assay may have different sensitivities.[27]

Did Abner Doubleday invent baseball at Cooperstown, New York? History tells us that the game was actually derived from an older English game, rounders. As time goes on, other commonly held beliefs may fall by the wayside. We are beginning to appreciate the problem of "low-titer" anti-HBs; is the test really measuring antibody?

Table 1 summarizes data concerning the incidence of low-titer anti-HBs in various populations, mostly health care workers.[28–35] About 10% of these populations are positive for anti-HBs; approximately one half of them have concomitant anti-HBc. Of those with only anti-HBs, one half to two thirds have low-titer anti-HBs. This test is reproducibly positive at least 50% of the time, but the majority of those with low titer antibody do not demonstrate an anamnestic response when challenged with the hepatitis B vaccine. We already know about people with positive anti-HBs tests who still develop hepatitis B.[7, 36] Animals have been found who have IgM-like material that reacts in the anti-HBs testing system, but which does not seem to be true antibody to hepatitis B.[7, 37] The problem presented by false-positive anti-HBs testing in hepatitis vaccine screening is obvious; 3% of health care workers may be incorrectly identified as being immune.

A serologic test engendering confusion in this reviewer's mind is the IgM-anti-HBc. Partly this has been due to the different assay techniques reported; this year we will mainly focus on only two, a commercially available enzyme immunoassay

TABLE 1.

Anti-HBs Positivity Frequency (%)*

REFERENCE	POPULATION (NO.)	ANTI-HBs	ONLY ANTI-HBs	ONLY LT ANTI-HBs	REPRODUCIBLE LT ANTI-HBs†	ANAMNESTIC RESPONSE‡
28	Mixed (9390)	14	3.7	2.2	55§	0
	HCW (1626)‖	12	3.8	2.5		
29	Commercial blood Donors (637)	17	1.8	0.5¶		
30	Medical/dental students (813)	6	3.8	3.1	70	40
31	HCW (908)	12	4.2	3.5		
32	HCW (2109)	13	6.0	4.0	52	23
33	Anti-HBs positive HCW (192)	(100)	(47)	(30)		
34	HCW (620)	6	4.2	3.2		
35	HCW (825)	11	5.5	4.4		

*Anti-HBs, antibody to hepatitis B surface antigen; LT, low titer (S/N ratio < 10); HCW, health care workers.
†LT anti-HBs still demonstrable when second specimen tested.
‡In LT anti-HBs individuals, S/N ratio greater than 100 two weeks after one-dose vaccine.
§Individuals re-evaluated after variable intervals and variable number of times (55% is average of all data at first follow-up).
‖Included in 9,390 individuals.
¶Defined by IgM characteristics rather than S/N ratio.

(CORZYME-M, Abbott Laboratories) and a radioimmunoassay developed at the Walter Reed Army Hospital (WRAH).

Courouce and co-workers identified subjects positive for HBsAg but negative for anti-HBc; all who were followed for more than 19 days developed anti-HBc.[38] The IgM-anti-HBc (CORZYME-M) was only positive if the anti-HBc was present in high titers. Using the same assay, Chen et al. found that infants who developed hepatitis B in the first 9 months of life never demonstrated IgM-anti-HBc.[39] In these two situations, the IgM-anti-HBc test missed many acute hepatitis B infections.

Fasel-Felley et al. used their own IgM-anti-HBc assay to diagnose hepatitis B in five HBsAg-negative patients.[40] The patients, all seen within six days of the onset of symptoms, had anti-HBc and anti-HBe as the only markers of HBV exposure. (These patients were presumed to be in the serologic "window" when neither HBsAg nor anti-HBs are detected.) All five patients were positive for IgM-anti-HBc, and they all developed anti-HBs within four to eight weeks. Coltorti and colleagues[41] utilized their IgM-anti-HBc assay to study its value in the window phase. They identified two such patients, who were positive for IgM-anti-HBc in the first week of illness.

Although neither group used the commercially available IgM-anti-HBc test, they have presented data concerning its potential use in patients in the serologic window. Since an individual also may be positive only for anti-HBc late in the convalescence of HBV infection (if anti-HBs has disappeared), the IgM-anti-HBc assay could separate these two phases (window and late convalescence). Indeed, the above papers support this idea. However, a closer inspection of the Coltorti data reveal some problems.

This Italian group also followed 45 HBsAg-positive patients. Two months after the onset of illness, 15 of them were in the window phase, but only 40% to 80% of them still demonstrated IgM-anti-HBc. Hence, the IgM antibody may disappear during the window phase!

The other IgM-anti-HBc assay to be discussed is the one developed at the WRAH.[42] Sjogren and Hoofnagle found it to be much more sensitive than CORZYME-M.[43] They found IgM-anti-HBc in 99 of 100 patients with HBeAg positive chronic hepatitis B (CHB), one of ten asymptomatic anti-HBe positive chronic HBsAg carriers (with normal ALT), and ten of ten patients with anti-HBe positive CHB. The HBV-DNA and/or DNA-polymerase (DNAP) was found in 99 of the 100 HBeAg-positive CH patients, none of the asymptomatic carriers, and only intermittently in five of the ten patients with anti-HBe positive CH. When they serially followed 38-HBeAg positive patients with CHB, IgM-anti-HBc persisted when HBeAg and CHB did; 13 underwent a seroconversion, and the IgM-anti-HBc became undetectable in 12 about two years later. As HBV-DNA and DNAP levels paralleled the e status, the authors concluded that IgM-anti-HBc, as detected in their assay, was a marker for active immune response to persistent viral replication.

There is an alternative perspective. In the 120 patients initially analyzed, the IgM-anti-HBc test better correlates with the presence of CH, being present in 109 of 110 patients with, and only one of ten patients without, CH. It was seen in five of ten patients with anti-HBe positive CH who never demonstrated HBV-DNA or DNAP. The IgM-anti-HBc disappeared as disease activity (measured by ALT levels), fell. A correlation was found between the radioimmunoassay ratio ("titer") of the antibody and the aminotransferase level and with the histologic severity of the disease. Even though the test is thought to measure a specific antibody, perhaps its presence merely reflects disease activity. Viral replication and liver damage are not necessarily synonymous.

This group used this IgM-anti-HBc assay to follow patients in a placebo-controlled trial of pulse prednisolone therapy.[44] IgM-anti-HBc titers paralleled the ALT levels closely; while steroids reduce aminotransferase levels, they increase hepatitis B replicative markers.[4] Using the WRAH assay, a Greek group also reported a parallelism between ALT levels and IgM-anti-HBc in one patient with CAHB.[45]

Two groups evaluated the effect of immunosuppression on IgM-anti-HBc detected by CORZYME-M in patients with CHB.[46, 47] In general, the ALT level paralleled the IgM-anti-HBc titer.

In 1870, the All England Croquet Club acquired four acres of land and established a permanent playing field at Wimbledon. When one of the courts was turned over to lawn tennis players, croquet completely disappeared there. Is this the case here? Is a test originally developed as an assay for hepatitis B virus infection going to find more use as a monitor of disease activity?

EPIDEMIOLOGY

Population Studies

In sports, officials are often called on to make difficult decisions with limited data. Sophisticated technology may make their job more precise. Epidemiologic statistics are limited by under-reporting of hepatitis. Public health officials in Kentucky compared "active surveillance" (contacting physicians on a regular basis using the sophisticated technology of the telephone) to "passive surveillance" (letting the physicians contact them).[48] Initially, 216 physicians were allocated to each group. There were 14 cases of hepatitis A identified from the 126 physicians who were actually actively surveyed, compared with five cases reported from the 216 physicians in the other group. Assuming all of the physicians were equally likely to see cases of hepatitis A, one can calculate that passive surveillance only results in 21% of the cases being reported ($5/14 \times 126/216$). The authors estimated that it cost $562 to identify each additional case.

A tuna fish–borne outbreak of hepatitis A was seen in a volleyball team.[49] The inverse correlation between the incubation period and the number of sandwiches consumed suggested that the incubation period of hepatitis A is dose-dependent. The first United States outbreak of fulminant hepatitis B related to delta coinfection was recently reported among parenteral drug abusers.[50]

As athletes become bigger and stronger, the rules of the games may change to accommodate them. Similarly, as the environment changes, the principles of yesterday may be altered. In third world countries, hepatitis A has been a disease of childhood, with virtually the entire population being positive for anti-HA by the age of 20.[2] With the advent of better sanitation and better socioeconomic conditions, hepatitis A exposure in young people is decreasing. Table 2 summarizes data from four recent studies; although high rates of anti-HA positivity were seen in all four areas in the past, the rates are only staying high where the economic and sanitary situation is not improving.[51–54]

Hepatitis B is endemic in the Eskimo population; a recent seroepidemiologic

TABLE 2.
Prevalence of Antibodies to Hepatitis A in Young People*

	POPULATION		
GEOGRAPHICAL AREA	SE STATUS/ SANITATION	AGE, YR	FREQUENCY ANTI-HA, %
Mexico[51]	Poor	5	89
Greece[52]	Good	15–19	16
Finland[53]	Good	20–24	0.3
Shanghai[54]	Good	1–9	10.5

*SE, socioeconomic; anti-HA, antibody to hepatitis A.

survey suggested that a recent decline in HBV infections is occurring.[55] The authors found hepatitis B markers to be uncommon in those less than 20 years of age and that the identified HBsAg carriers all had markers of long-standing hepatitis B infection (negative for IgM-anti-HBc, HBeAg, and DNAP; positive for anti-HBe). Other public health measures occurring in this group of people, such as moving out individuals with tuberculosis (which includes women of child-bearing potential) and immunostimulating individuals who might otherwise become HBsAg carriers, may be responsible for this decline.

Three different groups have looked at the incidence of concomitant delta infections in patients presenting with apparently acute hepatitis B.[56–58] In the United States, 5% of such patients had delta markers, while 14% of Australian cases were so infected; interestingly, no German or Swiss patients could be so identified. The vast majority of the cases of delta infection were observed in drug addicts, prisoners, hemophiliacs, and dialysis patients.[56] Although generally thought not to be a problem in the homosexual population, sporadic cases were reported.[56, 57, 59]

Chiou et al. performed a serologic survey in southern Taiwan.[60] They found that 5% to 10% of the HBsAg-negative population had an abnormal ALT. The authors speculated that a "considerable proportion" of these people may be afflicted with NANB disease.

Fishermen, beware! Italian investigators are relating the water-borne spread of NANB hepatitis to shellfish.[61]

Interpersonal Spread

The horizontal bars are familiar pieces of gymnastic equipment; they are used by athletes from all over the world. Horizontal, rather than vertical, spread of hepatitis B may be the important route of transmission among families all over the world. In Melanesia, homosexual activity with young boys and the chewing and sharing of betel nuts were implicated.[62] In Japan, sibling-to-sibling spread appeared more important than maternal transmission.[63] In Zambia, new hepatitis B infections in children and adults of families without maternal carriers suggested that horizontal routes of infection were important.[64] In a prospective study, Senegalese neonates of HBsAg (and even HBeAg) positive carrier mothers usually failed to show evidence of hepatitis B infection in the first year of life; subsequently, more and more of the children displayed evidence of hepatitis B.[65]

Piazza reflected on an interesting conundrum regarding the familial spread of NANB disease.[66] He asked why we view the intrafamilial spread of these viruses to be unimportant. If the carrier rate of these agents is high, and if the vast majority of people in the United States are not exposed to overt parenteral mechanisms, how did the carriers get infected?

Typically, neonates of HBsAg-positive mothers demonstrate HBsAg in their own blood at about the third month of life, implying that the significant hepatitis