CURRENT HEPATOLOGY

VOLUME 4

Edited by

Gary Gitnick, M. D.

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Preface

Each year *Current Hepatology* brings together the thoughts of experts in the study of the liver, and this year's volume is an especially outstanding one. The pages that follow offer a concise and balanced assessment of the most recent significant work in hepatology and form a valuable resource for all physicians interested in the current status of the field of liver diseases.

Contributors were asked to review the literature of the past year and to choose the most significant of hundreds of articles published on liver diseases. Discussions of these articles as well as critical comments make up the core of the information provided by each chapter. Selection of manuscripts according to their relevance and importance naturally led to discretionary inclusions and exclusions, often based on the decisions of the authors. To avoid undue bias in selecting the most significant information for each chapter, a second expert in each of the fields discussed in this volume was invited to review the contributor's work. These peer reviewers offered advice on topics that might have been omitted, inappropriately included, or unjustifiably criticized.

I am indebted to the following reviewers who graciously gave up their time to assess the chapters in this book: Stephen Borowsky, M.D., UCLA School of Medicine; Jules Dienstag, M.D., Harvard Medical School; Jay Hoofnagle, M.D., National Institutes of Health; William King, M.D., UCLA School of Medicine; Willis Maddrey, M.D., Thomas Jefferson University School of Medicine; Jay Marks, M.D., UCLA School of Medicine; Kenneth Ramming, M.D., UCLA School of Medicine; Steven Schenker, M.D., University of Texas Health Sciences Center; and Ronald Tompkins, M.D., UCLA School of Medicine.

All those involved in the development of this volume were moved to produce a comprehensive and critical review of the literature. It is hoped that the reader will gain much from such a review.

Gary Gitnick

Contents

CHAPTER 1

Hepatitis: Acute and Chronic and Arthur Conan

Ronald Koretz

Every year, this being the fifth (1–4), over 1,000 references are reviewed in the preparation of this chapter. These papers are, in turn, scattered throughout some 300 medical journals. Decades before this recent information explosion, however, nineteenth-century medical writers demonstrated a remarkably sophisticated knowledge of hepatitis.

As a case in point, consider an obscure English ophthalmologist of that era, Sir Arthur Conan Doyle. If he knew as much about the eye as he did about the liver, his clinical practice probably would have overwhelmed him. Yet he still had the time to record the adventures of Sherlock Holmes. As we shall see, we have to appreciate the dry wit and subtleties of this British author to realize that hepatitis must have been one of his major concerns. For example, why else would he choose 221 *B* Baker Street as the residence of his famous detective?

Several major topics will receive attention this year. The hepatitis B vaccine is still the most important recent advance, and I will cover some epidemiologic as well as clinical work relating to it. I will also focus on hepatitis B surface antigen (HBsAg) negative hepatitis B, hepatitis virus sterilization, decision making based on cost analysis, the course and prognosis of acute viral hepatitis, screening to prevent posttransfusion hepatitis, the δ agent, and the course and treatment of chronic hepatitis.

Mycroft Holmes, Sherlock's older brother, was first introduced in "The Greek Interpreter." His precise role in the British government was not clarified until a later story, "The Adventure of the Bruce-Partington Plans." Mycroft's job was to receive and organize all information made

available to the government and then to put it in perspective. Having attempted to perform this same duty for the past year in hepatitis, let us proceed. Or, as Sherlock might put it, "Come, readers, the game is afoot!"

ACUTE VIRAL HEPATITIS

Etiology

In "The Sign of Four" an aborigine from the Andaman Islands is encountered. Unfortunately this visitor from the Bay of Bengal was shot before Holmes could fully elucidate the nature of the hepatitis B virus. Since the aborigine was using a blowgun, two historic descriptions in hepatitis were delayed for nearly a century—the viral carrier state and the salivary transmission of the disease.

Herpes simplex hepatitis was again reported in immunosuppressed patients (5–7). Fatal fulminant hepatic failure due to herpesvirus was seen in both a mother and her newborn daughter with no apparent immunologic predisposition (8). Fever, leukopenia, and thrombocytopenia often accompany this liver disease (5,7,8).

In "The Dying Detective" Holmes feigned a rare tropical illness. The unusual tropical viral hepatitides were discussed in *Current Hepatology* 2 years ago (3). In the past year hepatitis has been associated with varicella (9) and rubeola (10); in the latter case, the adult patient demonstrated a cholestatic jaundice. Finally, a case of acute anicteric hepatitis due to *Brucella abortus* was reported (11).

Both the stepfather and suitor of a young lady turn out to be the same person in "A Case of Identity." The hepatologic case of identity is the problem of HBsAg-negative hepatitis B. Vergani and co-workers described 13 leukemic children on chemotherapy who failed to demonstrate any serologic evidence of hepatitis B [HBsAg, antibody to hepatitis B core antigen (anti-HBc) or antibody to HBsAg (anti-HBs)] but had positive tissue immunofluorescence studies; eight of these children developed one or more serologic markers when the immunosuppression was withdrawn (12). A subsequent report described a woman with autoimmune serologic features who had positive hepatitis B tissue immunofluorescence (13). One problem in both of these studies is the reliability of immunofluorescence as a true marker of hepatitis B infection.

A surgical resident with fulminant hepatitis was negative for HBsAg but positive for anti-HBc, anti-HBs, and hepatitis B e antigen (HBeAg) on admission; he was known to have been HBsAg positive 2 days earlier (14). Over the next 12 days the anti-HBc and anti-HBs persisted and antibody to HBeAg (anti-HBe) developed. The authors use this example to argue for the routine testing of all hepatitis B markers in fulminant hepatitis. It remains unclear why this patient developed anti-HBs so rapidly; this single atypical case cannot support such routine screening.

Table 1. Use of IgM-Anti-HBc in Acute Non-A, Non-B Viral Hepatitis

Series (reference)	*Denmark (18)*	*Sweden (19)*	*Walter Reed (20)*
Number of patients	169	168	124
IgM-anti-HBc positive	34	13	29
anti-HBs negative[a]	23(12)	4(3)	13(3)
anti-HBs positive	11	9	16

[a] Numbers in parentheses are those in whom anti-HBs seroconversion was documented on follow-up specimens.

A number of reasons for false-negative HBsAg assays have been noted in past years (3,4). This year, a mechanical error by a printer caused a high count to be recorded as low (15).

In some HBsAg negative cases, the amount of antigen present may not be detectable by the currently available assays. Wands and co-workers reported the use of a monoclonal anti-HBs that may be more sensitive (16) or may detect material similar to, but not identical with, HBsAg (17).

Immunoglobin M (IgM) specific anti-HBc is a new test that has been proposed for the diagnosis of acute hepatitis B. Three recently published series, summarized in Table 1 (18–20), have advocated its use in diagnosing hepatitis B in those patients thought to have acute non-A, non-B viral disease because of negative tests for HBsAg and IgM antibody to hepatitis A (anti-HA). Acute NANB hepatitis was initially diagnosed by these criteria in each of the studies.

IgM-anti-HBc was detected in 8–23% of these cases. In many of these patients concomitant anti-HBs, usually considered to be a convalescent phenomenon, was also present. The IgM-anti-HBc may last for up to 6 years in patients with known acute hepatitis B (19). It is found in patients with established chronic hepatitis B (21). The claim that the test identified acute hepatitis B in 20% of patients otherwise called non-A, non-B (18) must be viewed in the perspective that only 7% of them actually had an independent confirmation, anti-HBs seroconversion, of a recent hepatitis B virus (HBV) infection. The precise role of this test remains undefined; it adds no clinical information if a patient with apparently acute hepatitis has concomitant HBsAg.

Diagnosis

In "A Study in Scarlet" we find Holmes at work in the laboratory developing a better guaiac test. He no doubt spent much time working on other procedures, perhaps including some that would be of applicability to acute hepatitis.

Enzymology has received its share of attention this year. New lysosomal ones, as well as older more familiar friends (amylase, ornithine carbamyl

transferase), were compared to the standard aminotransferase and found to be equivalent (22–25). Therefore, why use them?

"The Adventure of the Speckled Band" sounds like the appearance of an immunodiffusion plate in a laboratory. Such techniques (and others) were used to assess the levels of various immunoglobulins in the different viral forms of acute hepatitis in three studies (26–28). Hepatitis A was associated with increased levels of IgM and IgE, perhaps with IgA, but not with IgG. Hepatitis B had elevations in IgM and IgE; non-A, non-B hepatitis was more likely to show increases in IgG with or without increases in IgM and IgA; IgE was not studied. The overlaps between each category and in healthy people make it unlikely that this test will achieve any clinical use. The increase in total IgM levels in hepatitis B may have a bearing on the results and interpretations of IgM-anti-HBc discussed earlier.

Two papers dealt with the different histologic appearances of acute hepatitis A and B (29,30). Hepatitis A demonstrated substantial portal and periportal necrosis, cholestasis, and relative parenchymal sparing. Hepatitis B was associated with extensive parenchymal damage and less severe portal tract disease. Only one of the studies examined non-A, non-B hepatitis (30); eosinophilic cytoplasmic clumps, prominent sinusoidal cell activation, and steatosis were described. Fatty change was not generally found in either hepatitis A or B.

Specific ultrasound patterns in acute hepatitis were mentioned last year (4). In a prospective study by this same group, the echographic findings of acute disease were seen in five of six patients with acute hepatitis, and in three of 300 patients with "normal" livers (31). It is still unclear what value this technique has in the care of patients.

Epidemiology

Population Statistics

The risk of hepatitis varies widely in different populations throughout the world (1–4). Sir Arthur Conan Doyle appreciated this when he wrote "The Adventure of Wisteria Lodge." He observed that the yellow Mr. Henderson had spent a considerable time in the tropics.

Although the prevalence of hepatitis A and B in the United States is lower than in other less-developed areas of the world (1–4), certain subpopulations are at increased risk of being exposed to, and developing, hepatitis. Clearly, knowledge of such information is important in formulating recommendations with regard to prophylaxis.

These groups have been prospectively followed to evaluate the risk of exposure to hepatitis B; the studies are summarized in Table 2 (32–50). The prospective data of neonates of HBsAg-positive mothers were discussed in depth last year (4); the risk was specifically high in neonates whose mothers had acute third trimester hepatitis or were HBeAg-positive carriers.

Table 2. Prospective Studies of High-Risk Subpopulations to Hepatitis B

Group–Subgroup (Reference)	*Incidence of Exposure*
Health care workers	
Dentists (32)	1.2%/2 years[a]
Dental personnel (33)	>0.3%/2 years
Dental students (34)	5%/2 years
Laboratory staff (35)	7%/2 years
Laboratory staff (36)	14%/9 months
Blood bank staff (37)	2%/3 years
Dialysis staff (38)[b]	12.3%/year
Dialysis staff (39)[b]	9.9%/30 months
Medical/surgical housestaff (40)	10%/year
Medical housestaff (41)	0%/year
Surgical housestaff (41)	5%/year
Physicians (32)	3.9%/year[a]
Nurses (32)	2.7%/year[a]
Health care workers (42)[b]	1%/year
Patients	
Hemodialysis[b] (38)	45%/year
Hemodialysis[b] (43)	85%/year
Renal transplant (44)	8%/year[c]
Hemophiliacs (45)	8%/year
Hemophiliacs (46)	>19%/year
Homosexuals	
Homosexual males[b] (47)	34.5%/2 years
Homosexual males[b] (48)	14%/year
Homosexual males (49)	27.6%/year
Preschool children of carrier mothers (Liberian infants) (50)	46.6%/14 months

[a] Includes other forms of hepatitis beside hepatitis B.

[b] Untreated control group for prospective globulin or vaccine trial.

[c] Total incidence of all hepatitis, most of which was due to non-A, non-B agent.

Health care workers are at a substantial continuous risk for hepatitis B exposure, which is especially high in those just entering the field (34,40). Even if the annual risk is only 1%, the probability of being infected by HBV over a 30-year career is approximately 27%. (See discussion to follow.)

Dialysis patients and hemophiliacs are also at considerable risk of HBV infection. Of note is that, in two of these studies (44,46) the risk of non-A, non-B hepatitis was higher than that of hepatitis B.

Hepatitis B seronegative male homosexuals have an extraordinary annual exposure rate in these studies. However, in the Netherlands the rate of 40% in those less than 30 years old fell to only 4.5% in those over

40 years old. Presumably the older homosexuals who have avoided HBV exposure in their earlier years represent a different population than the younger seronegative ones, and it is likely that this same principle extends to other groups at risk.

Hence, all of the data in Table 2 must be interpreted in the light of the relatively short-term follow-up, and it may not necessarily be possible to extrapolate lifetime risks. Furthermore, observed wide variations in risk (35,36) may be due to different demographic characteristics of the groups in each study.

Familial Spread

In "The Adventure of the Second Stain" a promiscuous Englishman is murdered by his temporarily insane wife. Clearly he developed hepatitis from one of his liaisons, transmitted it to his wife, and was subsequently fatally wounded during her early throes of encephalopathy from fulminant hepatic failure.

Villarejos and co-workers prospectively studied the familial contacts of patients with acute hepatitis A (51). In these Costa Rican households, 70–80% of the susceptible family members were subsequently exposed. The initial antibody response in the potentially susceptible adult population was of the IgG type, implying an anamnestic rather than primary exposure. Thus anti-HA is not demonstrable lifelong, but immunity appears to exist in its absence. Furthermore, population screening for anti-HA may underestimate the actual prevalence of past hepatitis A exposure. Finally, among children it appeared that playing together was a more important method of spread than school contact.

A lower rate of household infection by hepatitis A among adults, about 30%, was seen in Sydney, Australia (52). This may reflect better hygienic conditions in Australia.

This Australian study also prospectively examined household contacts of acute hepatitis B (52). In agreement with past studies (1), only a small percentage of children, 5%, underwent seroconversion; in contrast, approximately 25% of the susceptible adults, usually sexual partners, were infected.

In the more rural communities of Panamanian Indians, nonparenteral, nonsexual routes of infection may be important in the spread of hepatitis B. Peters and colleagues cite some indirect epidemiologic evidence in these people that implicates fecal contamination of water supplies (53). This mechanism is not an important one in the United States.

Preschool children in Taiwan, where hepatitis B is endemic, were prospectively followed as a group (54). The susceptible ones seroconverted at a rate of 5% per year. Exposure correlated with a carrier mother or the number of injections received. The development of the carrier state was associated with exposure in the first year of life.

Neonatal Transmission

In "The Adventure of the Sussex Vampire," a mother is found apparently biting the neck of her infant son. The solution of this case reveals not that she was giving her child hepatitis, but rather that she was attempting to clean a needlestick wound inflicted by an older sibling.

Wong et al. found almost 7% of the pregnant women in their Hong Kong clinic to be carriers, and at least half of them were HBeAg positive; they prospectively studied 97 positive mothers and their neonates (55). At least 67 of the neonates became HBsAg positive in the first year, and there was a strong correlation between HBeAg positivity in the mother and subsequent transmission. The authors estimated that 40% of the transmission was due to some interpartum event, probably the swallowing of maternal blood. Cesarian section was recommended for HBsAg positive mothers.

The role of HBeAg in pregnancy was also studied in Taiwan, where 85% of HBeAg-positive mothers had infected offspring (56). Although the data are incomplete, it could also be estimated that between 4% and 30% of the neonates of anti-HBe-positive mothers developed HBsAg during the follow-up examinations.

The issue of cesarian section is still controversial (2). We are reminded, in an editorial in the *British Medical Journal,* that such a technique does not appear effective (57). In a series of Australian recommendations, cesarian section was not even mentioned (58). This latter review did propose the use of hepatitis B immune globulin, in two doses (birth, 6 weeks), in offspring of mothers with third trimester acute hepatitis B, with the HBeAg-positive carrier state, or when previous children had developed HBV infection.

Sexual Transmission

The problem of hepatitis in homosexuals was obviously appreciated by Conan Doyle. Why else entitle a story "A Scandal in Bohemia"? Allusions to the Turkish baths can be found in "The Disappearance of Lady Francis Carfax" and "The Adventure of the Illustrious Client."

The problem of hepatitis A in the gay community was mentioned last year (4). The importance of this issue is reinforced with two reports this year (59,60).

Reiner and co-workers commented on hepatitis B transmission in male homosexuals (61). They observed asymptomatic rectal mucosal lesions due to trauma from rectal intercourse or manipulation. Presumably the rectal environment then becomes contaminated with HBV; the authors found HBsAg in the feces as well as in the rectal and anal mucosa. The active homosexual partner has oral or urethral contamination during rectal-penile intercourse or analingus. The presence of urethral or gastrointestinal mucosal defects would then allow the virus to complete this "parenteral" transmission.

Hepatitis B transmission among homosexuals has been correlated with anal sexual activity (61,62). However, both the active and passive partners appear to be at risk (62). This proposed mechanism may also explain the risk in the passive partner, in that the "tear" may permit viral entry across the rectal mucosa. In a situation such as homosexual behavior, however, in which the reported activity data are often unreliable and a multiplicity of other phenomena are also occurring, the precise mechanism of spread is likely never to be elucidated completely.

Mechanical Vectors

Hepatitis B positive fluids have been discussed during past years (1–4). It is to be hoped that, based on the previous interpretation of "The Adventure of the Second Stain," the investigators handled the blood-stained carpet carefully.

HBsAg was found in the pleural fluid of a carrier with active tuberculosis, and a needle contaminated with this material may have caused hepatitis B in a physician (63). HBsAg was identified in the vesicle fluid of a patient with acute hepatitis B and concomitant herpes zoster (64). Goodman and co-workers reminded us of the potential problem of HBsAg in peritoneal dialysis fluids (65).

HBsAg has been previously described in the pancreas but not in the bile, raising the issue of a biliary inhibitor (3). Feinman and colleagues recently reported an inability to find HBsAg in the duodenal fluids of HBsAg-positive patients (66). From data derived from separate biliary and pancreatic drainage, they concluded that a pancreatic inhibitor was responsible. The bile was HBsAg positive.

Whatever the fluid source, ocular contamination is dangerous. Bond and co-workers placed HBsAg-positive serum on the cornea of a chimpanzee; the animal developed hepatitis B 9 weeks later (67). Even private eyes get hepatitis.

It was well known that Sherlock Holmes was a frequent user of parenteral cocaine. He would have been very interested in studies evaluating the role of various mechanical devices in spreading (or, in this case, not spreading) hepatitis.

Jet injectors, used for mass inoculations, were used on two HBsAg-positive patients; the injection sites and nozzle were then tested for HBsAg (68). The assays were all negative, supporting the contention that hepatitis B transmission does not occur in this manner. Since there was no overt blood contamination in this study, the data cannot be extrapolated to the situation in which frank bleeding does occur.

Fiberoptic endoscopes were shown not to transmit hepatitis B in Nigeria (69). In Switzerland, 10 HBsAg-negative patients were purposely examined after four HBsAg positive ones, the instrument being cleaned with 10% aldehyde between procedures (70). No hepatitis B transmission was seen,

but, as was previously discussed (4,69), no transmission would have been expected if the aldehyde had not been used.

Arthropod transmission of hepatitis continues to be investigated in Philadelphia. Bedbugs fed HBsAg-positive blood demonstrate HBsAg in their stool for up to 2 weeks after their last meal (71). When bedbugs are fed a radioactive meal (labeled albumin), the marker can be found in a subsequent nonradiolabeled feeder, implying an arthropod-borne transfer (72). If albumin is comparable to virus, hepatitis B could presumably be spread the same way.

Institutional Spread

The issue of hepatitis in institutions was evidently well known by Sir Arthur Conan Doyle; he cited two instances in prison populations alone. In "The Hound of the Baskervilles," the escaped prisoner, Seldin, is described as yellow. In "Gloria Scott," we read of a confined inmate of that prison ship suffering from jaundice.

Outbreaks of hepatitis A in two child day-care centers were attributed to diaper changing (73,74). Two hospital outbreaks were thought to be due to a child and an adult with fecal incontinence and diarrhea during the prodrome (75,76). On the other hand, a group of patients with acute hepatitis due to hepatitis A, B, or non-A, non-B were all hospitalized together (not isolated) and prospectively followed for subsequent evidence of exposure to the other viruses to which they were susceptible (77). In spite of relatively close exposure, no spread of disease could be verified. The authors attributed this to the careful use of syringes, needles, and other such instruments, as well as to the fact that hepatitis A fecal shedding is not significant after the appearance of jaundice. This observation is consistent with previous reports (3).

In "The Adventure of the Blanched Soldier," the unfortunate protagonist develops a disease after inadvertently sleeping in a leper hospital. The association of the HBsAg carrier state with lepromatous leprosy has been reviewed in the past; there are papers supporting (2,3) and refuting (3) its existence. Although not statistically significant because of the small number of patients evaluated, a carrier rate of 40% was seen in lepromatous leprosy compared to 24% in the tuberculoid variant and 10% in the control population in the latest of such studies (78).

"The Adventure of the Veiled Lodger" did not refer to unrecognized hepatitis virus carriers in dialysis units. In fact, hepatitis B carriers are usually recognized, and, with conservative measures alone, the spread of hepatitis B is becoming a nonphenomenon (79,80); nonetheless, when a carrier is not recognized, a miniepidemic may ensue (80).

HBsAg carriers in dialysis units underwent psychological screening in New Jersey (81). The carrier state was a greater barrier to close interpersonal relationships than was the renal disease, although the latter disorder was more confining during work and recreational activities.