CURRENT HEPATOLOGY®

GARY GITNICK

VOLUME 10

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This book is dedicated to those to whom I am most indebted: my wife Cherna; my children, Neil, Kim, Jill, and Tracy; my mother, Ann; and my brother Jerry and his wife, Saranne.

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Preface

The basic and clinical studies of diseases of the liver are surging forward after many years of slow progress. Because the literature has become so extensive, even the most dedicated physician probably cannot read and comprehend all of the studies reported in a given year. *Current Hepatology* provides the reader with an overview of the world's literature in each of the major areas of liver disease. It reviews both clinical and basic material, but does not intend to provide a comprehensive analysis. Rather, it strives to identify those areas of research which seem most significant and to concentrate on reviews of those limited areas. Each author selected to contribute to this book has experience in a specific field within the larger subspecialty of hepatology. Each was asked to read all of the literature in his or her respective field and to prepare a chapter describing major advances, new information, and changes in trends and concepts. Each chapter is not merely a series of abstracts, but rather a description of the relationship among studies in different laboratories and an assessment of important trends. It offers an opinion regarding the direction of the past year's research and expectations for the future. The editor has undertaken to eliminate redundancies of information in most instances; however, some overlap of information was retained in order to demonstrate important differences in views.

When the same experts review their fields annually, they sometimes tend to promote their own personal interests and prejudices. To avoid this fault and to provide a balanced view over the years, new authors are periodically invited to review various aspects of liver disease. To further reduce the possibility of chapters reflecting individual prejudices or omitting important studies, reviews have been conducted by a second expert in the same field as the chapter author. It is hoped that this second level of peer review will provide the reader with a balanced and

complete view of the status of the research in hepatology during the past year. This was an exciting year and I hope this book will instill this excitement in the reader, even in those areas of liver disease in which he or she does not have a specific interest. Read and enjoy.

Gary Gitnick, M.D.

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CHAPTER 1

Hepatitis: Facts and Fables

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Once upon a time, there was a great lord of gastroenterological literature, Sir Yrag of Ticking, who commanded his subjects to write chapters every year until all things in their field were known. One of his vassals was assigned Hepatitis, which annually brought more questions than answers.[1–10] Undaunted, he will again embark on this never-ending quest through a maze of medical journals. Who knows what fables of yesterday will remind us of truths today? What truths of today will become the fables of tomorrow?

ACUTE HEPATITIS

Etiology

The Pied Piper of Hamlin attracted rats; hepatitis investigators attract animal models of the hepatitis B virus (HBV). This year we re-meet the Indian palm tree squirrel virus,[11] first described several years ago in Pennsylvania.[8]

Eeny, meeny, miny, mo, how many viruses will we get to know? It has been suggested that one non-A, non-B (NANB) agent is a retrovirus.[10] The parenterally transmitted agent described by He et al. is too large to be so.[12] Reverse transcriptase, an enzyme associated with the presence of retroviruses, was not found in the sera of patients with NANB posttransfusion hepatitis (PTH).[13]

A spumavirus, isolated from NANB-infected material, did not cause liver disease in two "NANB-susceptible" chimpanzees.[14] It was concluded that the spumavirus was not causally related to NANB hepatitis. However, the animals were not inoculated with known NANB virus to prove their susceptibility.

Another putative NANB virus, the GB hepatitis agent, was given to eight tamarins, including two immune to both hepatitis A and an immunoglobulin (Ig)-borne NANB agent; they could be infected by serum and by liver, but not fecal, extracts.[15] The authors concluded that the GB agent was different from hepatitis A and the Ig-borne NANB virus, and that it was not fecally excreted. However, during this time, one hepatitis A cross infection occurred from another animal housed in the laboratory. If viral cross-contamination was possible, NANB infection could have arisen from sources other than the experimental material.

Jack and Jill went up the hill. Jack suffered a skull fracture as a result. Jill drank the water and got enterically transmitted NANB hepatitis.

Bradley et al. isolated viral particles from outbreaks of enteric NANB hepatitis in Russia, Somalia, and Mexico.[16] These agents demonstrated similar physicochemical and immunological properties, suggesting that the same agent, or at least a close serologic relative, causes the disease worldwide. The mean diameter of these particles was 32 nm. When this group observed that the diameter ranged from 27 to 37 nm, they speculated that the larger forms undergo proteolytic degradation during their travels through the gastrointestinal tract.[17]

In a response to this consideration, Arankalle and Banerjee presented serologic evidence to implicate the smaller (27-nm) particle as the actual agent.[18] However, if the proteolytic degradation does not destroy all of the immunoactive sites, a noninfectious component of the virus could still react in an antigen-antibody system. (Compare the empty coat particles of hepatitis B surface antigen [HBsAg].)

The presence of one hepatitis viral infection may suppress the replication of other viral agents.[7] This phenomenon was appreciated in a chimpanzee chronic carrier of NANB hepatitis who was superinfected with HAV.[19] The markers of HAV replication (hepatitis A antigen [HAAg] in the liver and stool) were much lower than expected.

Measles has been implicated in hepatitis before.[8] Abnormal liver enzyme test results were seen in up to a third of children and two thirds of adults with this infection.[20] Hyperbilirubinemia was even seen in 15% of the adults. None of these patients had symptoms, however.

Hantavirus, endemic in Asia, can cause fever, coagulation defects, and renal dysfunction. Such a patient had a 20- to 40-fold increase in aminotransferase levels.[21]

Bacterial infections also involve the liver. Patients from India with enteric fever *(Salmonella typhi* or *paratyphi)* were prospectively followed up; over half of them had hepatomegaly and abnormal alanine or aspartate aminotransferase (ALT or AST) levels.[22] Hyperbilirubinemia was present in 17% of these patients; 8% were icteric. This degree of liver disease was not seen in Indian patients with other febrile illnesses.

A number of bacterial infections cause liver disease characterized by rises in the alkaline phosphatase. Those reported this year include tuberculosis,[23] syphilis,[24, 25] Lyme's disease,[26] brucellosis,[27] Yersinia,[28] mycoplasma,[29] and Q fever.[30]

Sawyer et al. analyzed 959 blood samples that had been submitted for hepatitis serologic testing[31]; all were negative for HBsAg and IgM antibody to hepatitis A (anti-HA). Six (0.6%) were positive for Q fever. The authors then recommended Q fever testing for patients with NANB hepatitis! This low rate (0.6%) leads me to make the opposite recommendation. Since Q fever classically demonstrates a cholestatic rather than hepatocellular biochemical picture, it should not be mistaken for hepatitis A or B. Are some physicians routinely ordering hepatitis A and B serologies in the evaluation of patients with abnormal alkaline phosphatases?

Little Red Ridinghood's grandmother was no match for the wolf who came to her door. What about immunocompromised patients challenged with viruses? Two reports described cytomegalovirus (CMV) hepatitis in transplanted livers.[32, 33] Since one of the major differential diagnoses in this situation is transplant rejection (which would require increased immunosuppression), both groups recommended liver biopsy to make the differentiation. Cytomegalovirus hepatitis can be suspected if one finds clusters of white blood cells (microabscesses) in the parenchyma; it is confirmed by demonstrating CMV in the tissue.

Patients with the acquired immunodeficiency syndrome (AIDS) are also at risk for various infections. Herpes simplex virus (HSV) causing fulminant hepatitis was described in one such patient by seven authors.[34] Cytomegalovirus hepatitis also occurs.[35] An infant with AIDS had recurrent jaundice and giant cell hepatitis.[36] The disease was steroid-responsive, although its etiology was never determined.

Finally, a curiosity for Dick Whittington's cat. In one family, both parents and three of seven children developed granulomatous hepatitis.[37] Some of them had granulomas in extrahepatic locations (muscle, pleura, and lymph nodes). The disease responded to steroids clinically, although the alkaline phosphatase levels remained abnormal. The cause remains unknown.

Diagnosis

Virtually all of this section will deal with the serology of viral hepatitis. However, there will be one observation for Hans Christian Andersen's Snow Queen. Last year we noted that storing blood in the freezer resulted in a rapid loss of ALT activity.[10] Now we learn that even refrigeration for only a few days reduces activity.[38]

A real princess can detect a small pea buried under a number of mattresses. IgM antibody to HAAg (anti-HA) may be demonstrated for many months after HAV infection resolves,[4, 7, 8, 10] presumably because the sensitive test detects low titers. Sato found that the IgM antibody lasted over 5 months in some patients.[39]

Rabinowitz et al. modified the IgM-anti-HA test to make it less sensitive, and found the IgM antibody "disappeared" within 4 to 6 weeks.[40] They did not report how many cases of acute hepatitis A might be missed due to the poorer sensitivity.

Can a real princess find a fake pea? One patient with drug-induced autoimmune chronic active hepatitis (CAH) had a false positive IgM-anti-HA test due to circulating rheumatoid factor.[41]

We could not protect Jill from the fate described in the last section, because we have no test for the enteric form of NANB hepatitis yet (but see later). Nasser and Metcalf did describe a test for detecting HAAg in river outlets.[42] Will we eventually test potentially contaminated water directly for the virus? We will have to be sure that a test demonstrates live (rather than dead, due to water treatment) HAV.

Do you salivate when you think about Jack Horner's Christmas pie? Salivary anti-HA correlated with serum antibody in 569 of 572 travelers (more than 99%).[43]

The three bears were surprised to find their porridge gone when they came home from a walk. Investigators are sometimes surprised to find HBsAg missing when it should have been in the serum. This can be seen when superimposed infections suppress HBV replication.[44–46] It was observed when a faulty monoclonal antibody was employed in one assay.[47] A prozone effect was also thought to cause this.[48]

Imagine the bears finding an unexpected visitor in one of their beds—much like my surprise at finding HBV where I did not expect to see it. In New Zealand, 27% of supposedly HBsAg-positive sera were negative when retested.[49] This frequency of false positivity may be high because confirmatory HBsAg testing was not routinely performed during the initial analysis.

Assays employing monoclonal (m-assays) antibody to HBsAg (anti-HBs) have found HBsAg in patients who have no other HBV serological markers.[5, 6, 10] These patients are considered, by the proponents of the assays, to be carriers of HBV variants. Is HBsAg really there, or is this only a false positive test?

In Spain, 75 such patients were identified.[50] Eleven of them, having either chronic hepatitis (CH) or no liver disease at all, were known to have been HBsAg-negative by this m-assay in the past; they became positive without any change in their clinical conditions. Follow-up serum samples were available in 27 of the 75; 22 were HBsAg-negative on repeat testing, and none of these developed any HBV-related antibodies.

European and Taiwanese groups looked for HBsAg, using m-assays.[51, 52] This HBsAg appeared and disappeared in an unpredictable way.[51] Tests for antibody to core antigen (anti-HBc), anti-HBs, and hepatitis B e antigen (HBeAg) and its antibody (anti-HBe) were all negative.[52]

It is unclear what a positive HBsAg m-assay means. In the absence of an independent method to establish the presence of hepatitis B (or at least true HBsAg), it seems reasonable to view these assay results as false positives.

What about patients who are HBsAg-positive by the standard polyclonal antibody assay but are negative for anti-HBc? Is this also a false positive test, an issue

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