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Hepatitis A: Old and New

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INTRODUCTION

"Viruses"

Before the precise recognition of what we now define as viruses, bacteria, fungi, and protozoa, all infectious agents were referred to as viruses, from the Latin for poison. The work of scientists such as Pasteur, Lister, and Koch in the 1800s led to the isolation of pure cultures of bacteria and the demonstration of their causal role in infectious diseases. By the turn of the century, experimental evidence was accumulating that culture-sterile, filtered preparations could transmit infection (151, 185). For example, Walter Reed published his observations on the transmission of yellow fever by inoculation of human volunteers with filtered serum isolated from patients with clinical disease in 1902. He commented "Yellow fever, like the foot and mouth disease of cattle, is caused by a micro-organism so minute in size that it might be designated as ultra-microscopic" (206). Transmission of foot-and-mouth disease observed in cattle followed earlier reports that tobacco mosaic disease could be transmitted with a filtered inoculum (151, 185). In contrast, the viral etiology of epidemic jaundice was not widely accepted by physicians until the mid-20th century. Indeed, an editorial in the *Journal of the American Medical Association* used the term "catarrhal jaundice" as late as 1943 (15). The basic science of viruses and the clinical science of their associated diseases have made enormous progress this century. The Nobel laureate Peter Medawar succinctly put it when he said that "No virus is *known* to do good; it has been well said that a virus is 'a piece of bad news wrapped up in protein' " (169).

Historical Epidemic Jaundice

According to Cockayne, catarrhal jaundice was recognized in ancient Greece and Rome (46). The ancient Chinese were also apparently aware of its existence. Cockayne accepts the first reference to epidemic jaundice as that occurring in Minorca in 1745, recorded by Cleghorn in *Epidemic Diseases of Minorca 1744 to 1749*, and he reports numerous other instances in the 1700s and 1800s. Clearly, by the time of his review in 1912, there was ample evidence of its occurrence.

Infectious Agent of Epidemic Jaundice

McDonald is credited (115, 272) as the first person to implicate a virus as the etiologic agent of what we now call hepatitis A (166). However, in his report of acute yellow atrophy of the liver being "produced when some special virus acts on a previously damaged liver," he may have used the term in the sense of any infectious agent, not the filterable agent of Reed and other investigators. Similarly, Cockayne in his treatise on the relationship between epidemic and catarrhal (sporadic) jaundice writes "due to virus remaining active" and "a virulent condition" (46). Cockayne considered that many of the features of epidemic and sporadic cases of jaundice were like those of mumps, another disease of uncertain etiology at that time; he concluded that both epidemic and sporadic jaundice was caused by a specific organism of unknown nature.

Viral Etiology of Epidemic Hepatitis

In 1931, Findlay, Dunlop, and Brown presented a paper entitled "Observations on Epidemic Catarrhal Jaundice" at the Royal Society of Tropical Medicine and Hygiene (81). After reviewing the history of epidemic jaundice, current knowledge, and a contemporary outbreak in Surrey, they concluded that it was likely due to an "ultra-microscopic virus which is pathogenic only to man," similar to varicella, herpes zoster, rubella, and dengue. Deliberate experimental transmission to human volunteers was first reported from Germany in 1942 (255) and the Middle East in 1943 (42), more than 25 years before successful transmission in an animal model (116). H. C. Brown, one of the authors of the 1931 paper ascribing the etiology of epidemic jaundice to a virus, developed an illness with the characteristics of a sporadic case of epidemic jaundice. He became ill <5 weeks after handling sera from the epidemic jaundice outbreak in Yorkshire described by Pickles (196). The timing of Brown's symptoms was consistent with what we now know is the incubation period of hepatitis A and perhaps the first documentation of viremic serum transmitting epidemic hepatitis (81).

Virologic Classification

All viruses are classified by their virion properties (morphology, physicochemical and physical properties, genome, proteins, lipids, carbohydrates, genome organization, and replication), antigenic properties, and biologic properties (Table 1). The viral genome is either RNA or DNA and double stranded or single stranded. In addition, the viral particle may be enveloped (host-derived lipid envelope) or nonenveloped. Each of the five major hepatitis viruses (Table 1)—hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), delta hepatitis virus (HDV), and hepatitis E virus (HEV)—belongs to a separate family (the taxonomy of viruses includes family, genus, and species).

TABLE 1. The major hepatitis viruses

Virus	Classification	Genome	Envelope	Spread
HAV	*Picornaviridae*, genus *Hepatovirus*	RNA	Nonenveloped	Fecal-oral
HBV	*Hepadnaviridae*	DNA	Lipid enveloped	Parenteral
HCV	*Flaviviridae*, genus *Hepacivirus*	RNA	Lipid enveloped	Parenteral
HDV	Unclassified	RNA	Lipid enveloped (from HBV)	Parenteral
HEV	*Caliciviridae*, genus proposed	RNA	Nonenveloped	Fecal-oral

HEPATITIS A VIRUS

The *Picornaviridae* are small, nonenveloped, single-stranded RNA viruses. Human pathogens include species in the genera *Rhinovirus* (human rhinoviruses) and *Enterovirus* (poliovirus, coxsackieviruses, echoviruses, and human enteroviruses). Although HAV shares some major characteristics with other genera of the picornavirus family, it is sufficiently different that it is classified as the only species in the genus *Hepatovirus*. There are naturally occurring strains that infect nonhuman primates (three genotypes) as well as four genotypes that comprise the human-infectious viruses (148). The strains belonging to each genotype have ≥85% nucleotide identity. Most human strains belong to either genotype I or III. The prototypic laboratory strains HM175, originally isolated in Melbourne, Australia, and CR326, from Costa Rica, are closely related genotype I strains (148). HAV, unlike other members of the *Picornaviridae* family, is stable at pH 1 and resistant to heat (56°C for 30 min) and shows no cross-hybridization with enteroviruses, rhinoviruses, or other picornaviruses. Details of these characteristics are amply referenced in standard texts (115).

Genome Organization

The organization of the HAV genome is similar to that of the other picornaviruses (115). The positive-sense (i.e., translatable), single-stranded RNA is 7.5 kb in length and consists of a 5′ noncoding region (NCR) of 734 to 740 nucleotides, a coding region of 2,225 to 2,227 nucleotides, and a 3′ noncoding region of 40 to 80 nucleotides (115). The secondary structure of the 5′ NCR is important in translation initiation. The *Picornaviridae* RNA genomes lack the cap assembly found at the 5′ end of mRNA species that normally guides the ribosomal complex to the translation start site. An internal ribosome entry site formed by the 5′ NCR functions to initiate translation in the picornaviruses, including HAV. The 5′ NCR of HCV, another single-stranded, positive-sense, uncapped RNA genome, also includes an internal ribosome entry site.

Proteins

Although HAV was first successfully adapted to cell culture 20 years ago (201), its protein constituents have not been completely defined (115). Infected cells contain only low titers of virus, and consequently protein chemistry has been limited. The P1 region encodes the three major proteins of the viral capsid, VP1, VP2, and VP3. A fourth viral capsid protein (VP4), essential for virion formation (199), is not detected in mature viral particles. Each of the capsid proteins is cleaved from the precursor polyprotein by the viral protease 3C, encoded in the P3 region. The native conformation of the capsid proteins VP1 and VP3 forms a single, dominant, serologic epitope on the viral capsid and elicits a neutralizing antibody response. Nonstructural proteins encoded in the P2 and P3 regions are predicted to function in RNA synthesis and virion formation. VPg (virion protein, genome linked), also encoded in the P3 region, is covalently linked to the 5′ genome terminus and involved in initiation of RNA synthesis.

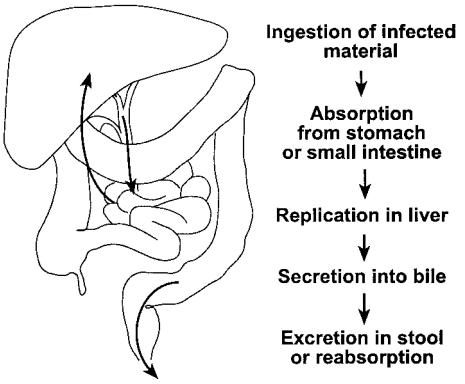

FIG. 1. Possible "enterohepatic" cycling of HAV.

Life Cycle

Available data as to the exact fate of virions immediately after oral intake are sketchy (see Fig. 1). In experimental infection of owl monkeys with human HAV, viral antigen was detectable by immunofluorescence in the stomach, small intestine, and large intestine not only after the initial oral inoculation but also later in the course of the disease (20). The ability to detect viral antigens in intestinal crypt cells using immunofluorescence suggests that viral replication can occur in the intestine (20). Virions presumably reach the liver in the portal blood (or after systemic circulation) and are taken up by hepatocytes. An attachment receptor for HAV in nonliver primate cells has been characterized (21, 77, 131); however, the relationship of this mucin-like class I integral membrane glycoprotein to hepatocyte uptake of virus is not clear. Once HAV has replicated in the liver and been released into bile (see below), the enterohepatic cycle of gastrointestinal uptake and transfer to the liver could continue until neutralizing or other antibodies interrupted the cycle.

Replication

Current evidence indicates that HAV replication is probably exclusive to hepatocytes and gastrointestinal epithelial cells in vivo, although cell culture infection and replication in nonhepatocyte cell lines are well documented (115). Virus-encoded proteins replicate the RNA genome via a negative-strand intermediate and are themselves synthesized from the genomic positive strand. Intact virions contain the RNA genome, the covalently linked VPg protein, and a capsid of the coat proteins VP1, VP2, and VP3 with icosahedral symmetry. Virus particles appear in bile and blood, presumably being released across the apical hepatocyte membrane into the biliary canaliculus and across the basolateral membrane into the bloodstream. The mechanism of viral release and secretion is unknown but clearly is not dependent on cell destruction, since high viral titers are present in stool before there is any evidence of hepatocyte necrosis (51, 139, 245).

Detection

HAV was first visualized after aggregation of fecal material with serum containing specific homologous antibodies (78). The fecal material was collected from Joliet prison volunteers

(34) inoculated with the MS-1 strain of hepatitis virus characterized by Krugman and colleagues (138). The technique of immune electron microscopy of stool was then used to assay for specific anti-HAV antibodies in convalescent-phase sera after episodes of naturally occurring hepatitis and to investigate the transmission of virus (67, 70). HAV can now be detected by a variety of immunologic and molecular techniques, including radioimmunoassay (RIA), DNA-RNA hybridization (245), and reverse transcriptase PCR (RT-PCR) amplification. RT-PCR amplification was used to identify specific viral strains implicated in parenteral transmission of virus (7, 159).

TRANSMISSION

Physicians in the early 1900s recognized that hepatitis A was spread by person-to-person contact (46), food, and possibly water (262). Cockayne extensively reviewed previous literature, generally selecting statements and observations that we now know to be correct. For example, he reports "One man already infected travelled to Flintshire and there passed on the disease to three others." Whereas person-to-person contact was evident, an alimentary mode of spread was not generally accepted. Although most physicians considered that a respiratory-type droplet infection was more likely (33, 54, 81, 84, 92, 154), gastrointestinal transmission was predicted by some authors in Europe (2) and the United States (181).

Oral Transmission

Experimental transmission of infective hepatitis by feeding duodenal juice was first reported by Voegt (255; cited in reference 82). Of note, although published in Germany (in *Muenchener medizinische Wochenschrift* [*Munich Medical Weekly*]) in 1942, the findings were referenced by British investigators in 1943 (82) and Americans in 1944 (104) despite World War II. An underground network apparently procured scientific publications through neutral countries (H. Mayo, personal communication), permitting efficient dissemination of knowledge.

In the United States, Havens and colleagues successfully transmitted jaundice by feeding either serum or a filtrate of stool extract to 12 conscientious objectors who volunteered for studies at Yale University (104). The incubation period was 20 to 30 days in the four persons who became icteric, consistent with transmission of hepatitis A. Stool samples obtained during convalescence were not infectious, whereas hepatitis was transmitted with stool samples collected 5 days after the onset of symptoms (105). In parallel studies, three of five volunteers became jaundiced after intracutaneous inoculation of serum. The incubation period was longer, suggesting hepatitis B (104). In later publications from this group, a distinction between infectious hepatitis (short incubation) and serum jaundice (long incubation) was made (189, 190). Infectious hepatitis (hepatitis A) was transmitted to four of five volunteers by ingestion of preicteric sera and to two of three volunteers after ingestion of stool (190). Hepatitis was apparent less than 40 days after exposure in all volunteers. In contrast, serum jaundice (hepatitis B) was transmitted to 10 of 23 volunteers inoculated with serum but not to three volunteers ingesting serum (190). All in this group developed hepatitis more than 50 days after exposure.

Parenteral Transmission

Voegt injected preicteric serum and produced jaundice in studies performed at the same time as those investigating oral transmission (255; cited in reference 190). Working with British troops in Palestine in 1941 to 1942 and unaware of Voegt's findings (as judged by the references cited and the geographic separation), Cameron injected whole blood or serum from jaundiced patients into seven volunteers (42). One recipient developed jaundice a month after injection, consistent with the incubation period of hepatitis A (10 to 50 days). The serum for this recipient was collected 2 days after the onset of jaundice in the donor. Jaundice eventually developed in five volunteers after various periods of time on active duty. Cameron abandoned further human experiments when he became aware of case fatalities (not from his own series).

Havens and colleagues at Yale also transmitted infectious hepatitis (hepatitis A) by parenteral means to 6 of 11 recipients. Using preicteric serum obtained from volunteers who developed short-incubation hepatitis following ingestion of infected material (190), they observed a short incubation period similar to that noted after ingestion of infected material. Serum obtained 11 days before and 31 days after the onset of symptoms did not transmit hepatitis to any of six volunteers (three in each group), whereas serum collected 4 days after the onset was infectious in three of six recipients (105). Three volunteers were infected sequentially with hepatitis B and then hepatitis A, demonstrating a lack of cross-reactive immunity. The authors interpreted their findings conservatively, as not indicating a fundamental difference between the two diseases, since the clinical features were indistinguishable with the exception of the incubation phase (190).

Infectious Hepatitis versus Serum Jaundice

By the late 1940s, the differentiation between infectious hepatitis and serum jaundice was distinct enough, and the nomenclature was confusing enough, that MacCallum proposed using the terms hepatitis A and hepatitis B in 1947 (16). Whether the differences were explained by two distinct viruses or different strains of the same organism remained uncertain. The term catarrhal jaundice was finally abandoned following the general acceptance that a virus(es) was the etiologic agent(s), because the transmission experiments used filtered material (106, 189).

Willowbrook State School MS-1 and MS-2

Definitive evidence of two different types of hepatitis virus was provided by a series of experiments carried out at the Willowbrook State School on Staten Island. The goal of the original studies was to control hepatitis, which was endemic in this residential school for the mentally disabled. The early work demonstrated the period of infectivity of serum and fecal material (139, 140, 257) and also the usefulness of measurements of serum glutamic oxaloacetic transaminase (SGOT) in the diagnosis of anicteric and asymptomatic infections (139).

Second attacks of hepatitis were observed in some residents (138). To investigate this observation more thoroughly, pools of serum obtained during the two separate episodes in one resident (Mir) were inoculated into newly admitted residents kept in isolation. One pool, designated MS-1 (Mir serum-1),

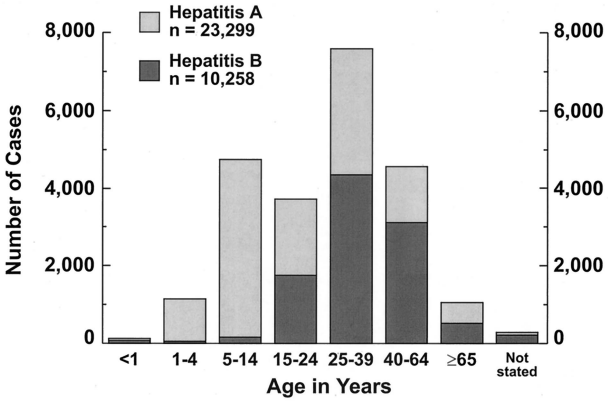

FIG. 2. Age group distribution of reported cases of HAV and HBV infection in 1998. (CDC data.)

caused hepatitis in seven of eight children after a relatively short incubation (hepatitis A), whereas the second pool, MS-2, resulted in long-incubation hepatitis (hepatitis B) in seven of nine children (138). The MS-1 pool was used in the first successful transmission of hepatitis A to animals (marmosets) (116) and to transmit hepatitis to volunteers (in Joliet prison) whose clinical samples were the sources of material for the first detection of virus particles (78). Marmoset livers became the source of infectious material not only for the development of serologic assays but also for cell culture experiments.

MODERN-ERA TRANSMISSION

Hepatitis A is the most common cause of acute hepatitis in the United States, as reported to the Centers for Disease Control and Prevention (CDC) and shown for 1998 in Fig. 2 and 3 (10). The numbers of hepatitis A cases reported in 1996 and 1997 were substantially higher (31,032 and 30,021, respectively); there are no data for 1999 at this time. The latest data from the Viral Hepatitis Surveillance Program (1993) indicate that contact with a person infected with hepatitis A is the most common identifiable source of infection (22%), with day care centers the possible source in 17%, international travel in 6%, homosexual activity in 5%, injection drug use in 2%, and a food- or waterborne outbreak suspected in 2% (www.cdc.gov/nciod/diseases/hepatitis/h96surve.htm). The largest percentage of infected persons, however, have no identifiable source (47%).

Personal Contact

Besides accounting for 22% of attributed sources (website cited above), personal contact with an unidentified source shedding HAV is likely to explain many or all of the cases with no identifiable risk factor. In Salt Lake County, Utah, 98 of 390 (25%) household contacts of 167 persons without identified risk factors demonstrated serologic evidence of recent hepatitis A infection (C. Staes, T. Schlenker, I. Risk, L. Bogdanow, K. Cannon, R. Winn, H. Harris, C. Shapiro, A. Pavia, and B. Bell, Clin. Infect. Dis. **25:**411, 1997, abstract). The highest rate of retrospectively diagnosed recent hepatitis A was in children who were <7 years of age (38 of 81 [47%] household contacts in this age group). Young children are often asymptomatic when infected with hepatitis A (99, 226) and, with their less scrupulous hygiene, may serve as a source of infection.

The virus is hardy, surviving on human hands and inanimate objects (fomites) (163). Studies indicate that viral particles are excreted fecally during clinical illness (223) and that fecal excretion can be prolonged, as determined by detection of viral nucleic acids (by RT-PCR amplification) for 3 to 11 months (126, 269). In a neonatal intensive care unit outbreak of nosocomial hepatitis A, there was prolonged excretion of virus by neonates, as evidenced by detection of viral protein and nucleic acid for 4 to 5 months after initial identification of infection (213). Furthermore, in a large-scale field trial of the efficacy of a formalin-inactivated hepatitis A vaccine, HAV RNA was detected in stool collected 61 to 90 days after onset of illness in 16 of 19 cases of infection in the control group (125). The infectivity of fecal material was not demonstrated in any of these cases. However, taken together, these observations reinforce the need for rigorous personal hygiene in the prevention of transmission. The prolonged excretion of infectious virus plus the hardiness of the virus may well explain the continued occurrence of sporadic cases of hepatitis A in developed countries as well as the endemicity in underdeveloped countries.

Food-Borne Hepatitis A

One of the earliest documented outbreaks of hepatitis A associated with consumption of contaminated material was the demonstration of a rising titer of specific antibody in members of a family who contracted acute hepatitis after eating mussels (68). The largest known modern epidemic of hepatitis A was also from consumption of contaminated seafood. In Shanghai, China, 292,301 cases of acute hepatitis were attributed to eating raw clams (100). Oysters (49, 64) and cockles (183) have also been implicated. HAV may survive for extended periods of time in seawater. Viral nucleic acids were detectable 232 days after being seeded in artificial seawater, whereas they were only detectable for 35 days in cell culture (18). Consequently, the filtering of seawater by bivalves, with the potential for retaining infectious HAV particles resulting from fecal contamination, can lead to the transmission of infection to those who consume the seafood without adequate cooking. Spread of hepatitis A has been reported in the United States and Europe following consumption of contaminated lettuce

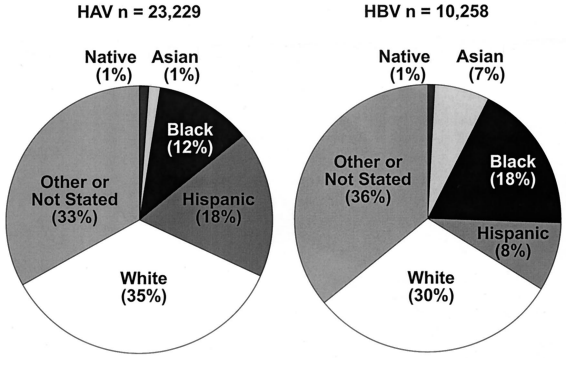

FIG. 3. Race and ethnic distribution of reported cases of HAV and HBV infection in 1998. (CDC data.) Native, American Indian or Alaskan native; Asian, Asian or Pacific islander.

(212), ice slush beverages (27), frozen strawberries (11, 121, 179), and salad food items (155, 192). The global movement of food items that cannot be heated for viral inactivation may be a major cause of outbreaks in developed countries in the future. The recent multistate outbreak of hepatitis A (121) following the illegal use of non-U.S. produce in school lunches (109) illustrates the problem.

Waterborne Outbreaks

In the United States, waterborne transmission of hepatitis A accounts for only a fraction of cases. In one small outbreak, HAV contaminated well water (32). A swimming pool with potential sewage contamination was implicated as the common source in another (157). Hepatitis A is considered an occupational hazard for sewage workers in some countries (65) but not in Israel or the United States (150, 247). HAV was detected in the final effluent from wastewater treatment plants in the Mediterranean (71), demonstrating a potential source for seafood contamination. Waterborne transmission is less important in the spread of hepatitis A than person-to-person contact. In contrast, hepatitis E, particularly in epidemic form, appears to be transmitted by waterborne outbreaks.

Nosocomial Hepatitis A

Transmission of hepatitis A from hospitalized patients with unsuspected disease to staff is well recognized (93). For example, an adult patient with diarrhea after an elective cholecystectomy (94), premature infants (135) with prolonged viral excretion (213), burn patients incubating HAV in hospital (72), and a patient who was immunodeficient and negative for HAV antibodies (41) have all been sources of nosocomial infection. One example of nosocomial spread emphasizes the natural life cycle of the virus. A patient with an overdose and trauma from a motor vehicle accident had a T-tube draining bile during the incubation phase of hepatitis A. The bile was the only apparent source of infection in five cases of nosocomial hepatitis A (101). Vertical transmission is rare (74, 146) but was the apparent source of hepatitis A in a nursery outbreak (258).

Parenteral Hepatitis A Transmission

Once considered rare outside experimental studies (218), parenteral transmission of hepatitis A complicating transfusion of blood and blood products has now been reported many times. Blood from a single donor who became ill 1 week after donation transmitted disease to 11 recipient neonates and thence secondarily to an additional 44 persons (180). Transmission associated with platelet and plasma donation processing (170) and anticancer immunotherapy reagents (259) has also been documented. More recently, identical HAV sequences were detected in clotting factor concentrates and hemophiliac recipients in Italy (159). The solvent-detergent method of viral inactivation was considered inadequate for nonenveloped viruses such as HAV. In late 1995, a similar outbreak occurred in the United States (7). Vapor heating of clotting factor concentrates is experimentally effective in eradicating infective HAV (25).

The other group at risk for HAV infection by parenteral transmission is the injection drug-using population (4, 97). Hepatitis A can also be potentially spread within this group by contamination from rectally carried drugs (237) as well as by unsanitary living conditions, crowding, and lack of the necessary personal hygiene to prevent infection. Approximately 40 to 50% of injection drug users in northern Europe are anti-HAV positive (136), and in Scandinavia and France the seropositive rate is significantly higher than in a matched control population (117, 216, 256, 261). At Johns Hopkins Hospital, seropositive rates were more than twice as high in injection drug users (66%) as in homosexual men (27%) and correlated with poverty (254). Targeting this group for vaccination to prevent HAV infection may decrease their infection rates in the future.

Homosexual Transmission

Although early seroprevalence studies of hepatitis A did not demonstrate increased positivity in homosexual men (238), two prospective studies of seroconversion clearly document a high rate of ongoing infection (50, 53). More recently, hepatitis A outbreaks among homosexual men were reported in the United States and abroad (5, 110, 236). Higher seroprevalence rates of hepatitis A infection are associated with oral-anal contact regardless of sexual orientation (23), not with homosexuality per se (254).

PATHOLOGY

Before the late 1930s, pathologic examination of the liver required either an open-liver biopsy at the time of surgery or death of the patient and an autopsy. Consequently, little information was available regarding the pathologic changes in uncomplicated infectious hepatitis. The findings in acute yellow atrophy were well documented (166), and the relationship between acute yellow atrophy and nonfatal hepatitis was increasingly recognized (46, 80, 88), although the heterogeneity of etiologic factors contributing to cases of acute yellow atrophy was probably underappreciated.

Percutaneous Liver Biopsy

Iversen and Roholm revolutionized liver biopsies by developing a percutaneous technique that is remarkably similar to that in use today—a transthoracic approach with a suction needle (128). In their paper describing the histopathology of acute hepatitis, "sporadic acute benign jaundice of the catarrhal type," they reported on the findings in 38 aspiration biopsy specimens (128). Their descriptions are as apt today as they were 60 years ago. They observed hepatocellular necrosis with ballooning and eosinophilic degeneration, an inflammatory infiltrate of mostly mononuclear cells, and a variable amount of collagen. In follow-up biopsies on 12 patients 25 to 35 days later, there was less inflammation and the connective tissue was unchanged. One patient was biopsied 16 h before succumbing to fulminant hepatitis. The biopsy showed findings similar to those following a benign course but of greater severity, with destruction of the parenchyma and an inflammatory infiltrate.

The technique of percutaneous liver biopsy was rapidly adopted by others. A British study from 1943 reported findings in 14 patients with epidemic hepatitis (mostly HAV), 7 with

serum jaundice (HBV), and 35 with jaundice in relation to arsenotherapy (mostly HBV) (66). No histopathological differences were perceived between the various supposed etiologies. The researchers observed necrosis that was most marked pericentrally and inflammation that was maximal in the portal areas. The extent of involvement was increased with more severe disease. Similar findings were observed in large series reported over the ensuing 30 years (127, 158, 195, 225). All agreed that the cardinal features of acute hepatitis were the presence of hepatocellular degeneration, characterized as either ballooning or acidophilic (apoptotic) change, together with various degrees of portal and lobular inflammation and hepatocyte regeneration.

Modern-Era Liver Biopsy

Although the number of biopsy samples examined was extensive, the older studies of the pathology of acute hepatitis lacked the ability to compare hepatitis A with hepatitis B and hepatitis C in well-documented serologically defined cases. This distinction is of only modest importance since the overwhelming bulk of the findings, like the clinical manifestations, are qualitatively identical (141, 184, 242). As part of the Copenhagen Hepatitis Acuta Programme that monitored over 100,000 patients, liver biopsies were performed routinely until 1980. With the advent of serodiagnosis for acute hepatitis A as a research tool in the late 1970s, a comparison study was undertaken (141). The parenchymal changes (focal necrosis, ballooning, and acidophilic degeneration) were less marked in the biopsy specimens from 86 patients with hepatitis A than in specimens from 78 patients with hepatitis B, whereas the degree of portal inflammation was similar. Follow-up liver biopsy samples (two to four per patient) were obtained for 36 patients at intervals of 1 to 24 months after the acute illness. The biopsy samples were classified as normal (17 of 54 biopsies) and nonspecific reactive changes (24 of 54); continuing acute hepatitis was observed for 1 to 5 months after initial presentation for 13 (141). Fibrin ring granulomas, more often associated with diseases such as Q fever, were described in acute hepatitis A biopsy samples by some investigators (197, 268).

HAV Detection

The technique of in situ hybridization was recently used to localize HAV sequences in human liver biopsies (241). Viral RNA was detected in hepatocytes, sinusoidal cells, and inflammatory cells. Replicative intermediates were not detected. Using a macrophage-specific marker, the investigators confirmed the presence of viral nucleic acids in the cytoplasm of phagocytic cells. Clearance of virus by uptake of antigen-antibody complexes between virions and anti-HAV into these cells seems a plausible explanation for this observation, rather than phagocytosis of virus directly.

IMMUNOLOGY

The immunology of hepatitis A is important for two reasons. First, specific diagnostic tests for the confirmation of HAV as the etiologic agent are dependent on the production of antibody by the humoral immune response (see below). The humoral immune response also leads to the development of circulating immune complexes (160, 248) with associated symptoms and signs in some patients (122, 123). Second, clearance of viral infection and the disease manifestations associated with this process is almost certainly produced by the cellular immune response.

Humoral Immune Response

Immunoglobulin M (IgM), IgG, and IgA antibodies directed against conformational epitopes on the HAV particle are induced and can usually be detected by the onset of clinical illness (228). In addition, total IgM levels are often elevated in acute hepatitis A infection (28 of 33 cases [85%]) but not in acute hepatitis B infection (3 of 24 cases [13%]) (175). The hepatitis A-specific IgM response is limited to the initial infection except in rare instances and thus becomes a useful marker of acute disease. IgA is also produced for a limited period of time. Its role in immunity is uncertain. Theoretically, if antibodies such as secretory IgA were transported into the intestinal tract, then enterohepatic circulation of viral particles could be interrupted by neutralizing the virus. In experimental and naturally acquired hepatitis A, however, neutralizing antibodies are uncommonly found in fecal extracts (229). In contrast, another picornavirus, the poliovirus, elicits effective intestinal and salivary neutralizing antibody (229). The IgG response to HAV is delayed compared with IgM and IgA responses but is long-lived and accounts for resistance to reinfection. In an isolated Amerindian tribe, anti-HAV antibody was present in everyone over the age of 50 years but in no one younger (31). This observation suggests that the tribe members had not been exposed to HAV for 50 years and that anti-HAV IgG persisted for that length of time without need for additional exposure. Loss of detectable antibody following immunosuppression for organ transplantation may occur (19). Whether this represents risk for repeat infection has not been documented.

The antibodies are usually directed against surface proteins. The capsid proteins VP1 and VP3 and the precursor protein VP0 may be recognized (256). Almost all patients expressed both IgG and IgM antibodies to VP1. The IgG response to VP3 was detectable for years after disease resolution (256). Antibodies to nonstructural proteins are also induced. Although they are less abundant and lack neutralizing activity, they are produced in most individuals early in the infection (210). Detection of antibodies recognizing P2 permits differentiation between infection (antibody present) and vaccination (no antibody) as sources of antigenic determinants (210).

Cellular Immune Response

The pathologic changes described above were initially considered to be secondary to viral infection alone. However, large quantities of infectious virus are produced in the liver and excreted in stool before the onset of any recognizable hepatic disease (51, 139, 245). Furthermore, HAV is not directly cytopathic in cell culture but rather is associated with persistent infection without cell injury (115, 201). Taken together, these observations led to the recognition of immune-mediated injury as the most plausible explanation for hepatic inflammation. Consistent with this hypothesis is the observation that cytotoxic

lymphocytes isolated from patients with acute hepatitis A infection lyse autologous, HAV-infected target cells (83, 249). Other cytotoxic cells, such as natural killer cells, may also be involved (83, 142). Their role may be limited, since they lack antigen specificity. Overall, therefore, hepatitis A and hepatitis B are similar not only in their clinical manifestations but also in the mechanism underlying their production, that of cytotoxic T-cell recognition and destruction of virus-infected cells.

SEROLOGY

The specific detection of hepatitis A infection was first accomplished in 1973 using immune electron microscopy of fecal extracts to visualize virus-like particles (78). Antibody in convalescent-phase serum samples from persons with experimentally or naturally acquired infection aggregated the virus and permitted its visualization by electron microscopy. When serum collected before infection or early in the disease was used, few or no virus particles were identified. This research technique was successfully used to investigate the period of infectivity but could not be employed for routine diagnosis of large numbers of clinical samples. The next step was the development of complement fixation (200) and immune adherence (172) tests for detection of serum antibody to HAV antigens in 1974. This required a source of HAV antigen, supplied by liver extracts from marmosets infected with a Costa Rican strain of HAV, CR326.

Despite being cumbersome, the immune adherence test quickly provided a wealth of important data about hepatitis A infection. With the original description of the test came demonstration of simultaneous infection with both HAV and HBV; evidence that HAV antibodies were acquired early in life in areas of high prevalence; association of low socioeconomic status with seropositivity in areas of low incidence; persistence of antibody for at least 7 years; an antigenically related or identical virus infection in chimpanzees, grivets, and rhesus monkeys not experimentally infected; and detection of various quantities of antibody in lots of immune serum globulin (172).

Both the complement fixation test and the immune adherence test were used to examine seroconversion following experimental infection with the MS-1 strain of hepatitis (137). The complement fixation test was not as specific or as sensitive as the immune adherence test. Using the immune adherence test, seroconversion was demonstrated in 20 of 20 infected persons. Antibody was detectable soon after the onset of clinical hepatitis but was present within the first week in only 45%; in 20% detectable seroconversion was delayed for at least 2 weeks after disease onset. Nevertheless, a test that could be used for diagnosis of acute hepatitis A infection was now available. Hemagglutination assays for HBV surface antigen and antibody to HBV core and surface proteins were developed in 1970. Consequently, by 1975, acute viral hepatitis could be ascribed to either HAV or HBV, permitting the recognition of viral non-A, non-B hepatitis (hepatitis C and hepatitis E).

In 1975, solid-phase RIAs developed for the detection of HAV antigen were modified to measure antibody (203). A comparison between immune adherence, immune electron microscopy, and RIA demonstrated that each test was able to detect seroconversion following inoculation with MS-1 virus (69). Antigen partially purified from stool was equivalent to marmoset liver-derived viral antigen in these assays. RIAs were also modified to use minimal quantities of viral antigen and to assay anti-HAV IgM antibody (38).

A competitive binding assay (HAVAB; Abbott Laboratories, North Chicago, Ill.) was developed by 1978 to improve sensitivity (37). In this assay, antibody in patient serum competes with radiolabeled antibody for HAV. The assay was also adapted to measure anti-HAV IgM, which was detected in acute-phase sera but not in convalescent-phase sera (37). However, the absorption of IgG from samples to measure IgM reactivity was difficult to perform, and the resultant assay lacked reliable specificity. In 1980, an alternative technique was developed (HAVAB-M; Abbott Laboratories) in which IgM antibody was directly selected and anti-HAV activity was then measured (63). With these improvements, anti-HAV IgM antibody was detected at the time of onset of symptoms in most patients. IgM titers decreased in the weeks after onset and then became undetectable. This assay could thus be used to diagnose acute hepatitis A at the time of clinical symptoms.

Diagnostic Accuracy

The sensitivity, specificity, and positive predictive value of quantitating IgM-specific anti-HAV was determined in a cluster of cases that occurred in 1979 using normal blood donors as the control population (234). The sensitivity of IgM anti-HAV measurement for acute hepatitis was 100%, the specificity was 99%, and the positive predictive value was 88%. Since its introduction and widespread use, diagnostic difficulties have been uncommon. Occasionally, the test is negative at the time of clinical presentation, but repeat testing 1 to 2 weeks later usually demonstrates positivity (112). One possible explanation for this observation is that dilution of serum before assay, in order to prevent false-negative results, could result in loss of reactivity in sera with low titers. In two episodes of mild acute infection in vaccinees, the appearance of IgM anti-HAV positivity was delayed until convalescence (125), an observation that has not been explained. False-positive Epstein-Barr virus serologies (79) are less of a diagnostic problem than is prolonged positivity in the absence of hepatitis (130, 220).

The length of time that the IgM anti-HAV test remains positive varies (130). In 37 patients followed until the disappearance of antibody, the majority, 32 of 37 (86%), were IgM anti-HAV negative by 7 months after onset, defined as jaundice in all but two anicteric cases, for which the onset of symptoms was used. Twenty-six of 37 (70%) were negative for IgM anti-HAV by 4 months. All cases demonstrated a decrease in titer (positive test value closer to the negative cut-off) before becoming negative in the assay. In contrast, IgM anti-HAV positivity was prolonged beyond 7 months in five individuals whose last positive test was recorded between 9 and 12 months after onset. Eventually, they each had negative IgM anti-HAV test results. In most patients (47 of 50), the biochemical evidence of hepatitis had resolved either prior to or by the time of disappearance of IgM anti-HAV. Of the remaining three patients, two eventually normalized biochemical hepatitis and the third was lost to follow-up. In a second study, two of six patients were IgM anti-HAV positive (low titer) 30 to 32 months after the onset of hepatitis A (220). A diagnostic dilemma may arise if a patient has unrecognized chronic hepatitis before

contracting HAV. The persistence of IgM anti-HAV positivity for more than 12 months together with an unrelated and unidentified cause of hepatitis could potentially lead to an incorrect diagnosis of chronic hepatitis A.

Future Assays

In vaccine trials, the detection of antibody often requires a more sensitive assay because vaccine-induced antibody titers are generally lower than those induced by natural infection. Noninvasive tests, i.e., not requiring blood samples, are also useful for screening large populations. The development of a highly sensitive assay that is specific for IgG anti-HAV and can measure antibody in saliva after vaccination is promising (182). The assay was validated using paired saliva samples from travelers undergoing vaccination. In practice, antibody titers are not measured routinely after vaccination since the response rate to the vaccine and its effectiveness are so high (see below), and a highly sensitive assay therefore has little utility. In contrast, a cheap and robust assay for screening prior to vaccination would be extremely useful in many clinical scenarios (see below). Most assays have used HAV produced in tissue culture as a source of antigen. In the future, recombinant HAV antigen may provide a less costly alternative (143).

CLINICAL DISEASE

The clinical features of viral hepatitis, once symptoms commence, are similar regardless of the specific hepatotrophic alphabet virus involved. Extrahepatic manifestations and complications may differ quantitatively, but qualitatively they also are common. There are unique aspects of clinical hepatitis A, however, because of the different patient populations in which the disease is observed. Thus, hepatitis A can be sporadic, endemic, or epidemic.

Sporadic Hepatitis A

Cockayne was the first observer to recognize that the sporadic form of the disease (at that time referred to as catarrhal jaundice) was identical to the epidemic form of the disease (46). He cites Rolleston (211) as thinking that the febrile cases of sporadic jaundice were the same as the epidemic cases, although few in number. In contrast, Cockayne pointed out that the geographic range, age, seasonal incidence, symptoms, physical signs, variable prevalence ("a peculiarity of all infectious diseases"), occurrence of prolonged jaundice, and relapses were comparable in the sporadic and epidemic cases. He concluded that "Sporadic and epidemic catarrhal jaundice are found somewhat in the same way as sporadic and epidemic poliomyelitis, except that jaundice is more common in the sporadic form and met with more often and over a wider area in the epidemic form."

Endemic Hepatitis A

The endemic form of the disease is more difficult to recognize because of the high incidence of asymptomatic and anicteric cases when the disease is acquired in early childhood. Passive transmission of maternal antibody protects the neonate, but protection wanes during infancy, and young children are ideal fecal-oral transmitters of infection. In the developing world, where sanitation is limited or absent, infection remains almost universal. In Egyptian children 1 to 3 years old, the seroprevalence rate was 100% (58), remaining at this level until age 67. Similarly, 2- to 4-year-old Nicaraguan children have a seroprevalence rate of 73% (194), and in Pune, India, virtually 100% of children are infected by late childhood (17). Immigrants and travelers from areas of low disease rates are therefore at high risk of infection when residing in countries where infection is endemic.

Cameron, who reported on epidemic hepatitis among British troops in Palestine during World War II, recognized the existence of endemic infection in the region (42). He wrote that "a large number of [indigent] children acquire the disease in a mild form and are immune for life, thus reducing the incidence in the adult native population. With each new immigration of settlers [from Germany, for example], a new nonimmune child population is added, and this accounts for epidemics. . . . The arrival of British troops represents another immigration."

The immunity of Indian and Maori troops to epidemic hepatitis during World War II and the relative incidence (10:1) in white and nonwhite American troops (266) can be explained by differences in childhood exposure rates. Similarly, the observation that officers in the British Army and flying personnel in the Royal Air Force had a fourfold-higher rate of infection than ordinary ranks and ground staff (266), a difference not seen in U.S. forces, is also understandable by differences in childhood exposure rates secondary to socioeconomic disparities.

Epidemic Hepatitis A

Long before the advent of serologic testing for hepatitis A and before the development of quantitative tests of hepatocellular necrosis, large series of epidemic jaundice cases were carefully observed and the manifestations were reported. Epidemics of jaundice from HAV (infectious hepatitis) usually commenced early in the fall and peaked in winter, waning then until the next yearly cycle started. This seasonal pattern is unexplained. The clinical picture was and is remarkably similar in all epidemics, with little change despite major differences in age and geography. The cases manifesting specific symptoms and signs in three series are shown in Tables 2 and 3. The cases in these epidemics varied in age as well as place of infection. Of 194 cases reported in Detroit between November 1937 and March 1938, only 27 involved persons more than 14 years old (173). In the military epidemics of World War II, the cases reflected the ages of the troops, with the majority ranging from 19 to 40 years old (102, 113).

Epidemic Hepatitis and War

Epidemics of jaundice are common in military medical history. Blumer reported that the first known epidemic in the United States was in conjunction with the War of 1812 (33). In "The Medical and Surgical History of the War of the Rebellion" (the Civil War), Smart recorded 71,691 cases of jaundice in Federal troops (224). Details in the individual histories are consistent with infectious hepatitis (hepatitis A). The peak incidence occurred in the fall and winter of 1863, also sugges-

tive of the seasonal occurrence of hepatitis A. Cockayne quoted different statistics: 22,569 cases of epidemic jaundice with 161 deaths among 2,218,599 Federal troops during the war between the North and the South (10% infection rate, 0.7% case fatality rate) (46). I have not found an original source for these latter statistics, but based on my assessment of Cockayne (from his published analysis of jaundice, which included 142 references), I consider that they are likely to be more accurate.

In World War I, British, French, and other Allied forces reported epidemics of jaundice starting in 1915 and continuing intermittently (14, 161, 262). The Mesopotamian epidemic is curious in that Indian and British troops were equally affected, and Willcox reported that there was little evidence of person-to-person contact (263). One possible explanation is that hepatitis E accounted for some or all of the cases. Hepatitis A is endemic in India, whereas hepatitis E is more often associated with large epidemics. Furthermore, in hepatitis E, there is less person-to-person spread. Purcell likewise suggests that at least some of the epidemics of hepatitis in Europe in past centuries may have been due to hepatitis E infection in that they predominantly affected young adults and fulminant hepatitis occurred in pregnant women (202). In two recent studies, there was cooccurrence of HAV and HEV as causes of acute hepatitis. Interestingly, in both reports, the hepatitis E cases occurred in the indigent or native population (Nepalese in one instance, Djibouti natives in the other), whereas hepatitis A was found in nonnatives (tourists in Nepal, French troops in Djibouti) (44, 52). The United States escaped most of the epidemics in World War I by late entry into the conflict. Paul and Gardner consider this one of the reasons for U.S. military unpreparedness for the impact of hepatitis epidemics on troops during World War II, since plans for dealing with infectious disease were developed based on experience in the previous war (188).

Campaign jaundice was of major military importance in World War II. Epidemics occurred in British troops in Palestine in 1940 to 1941 (42) and in Allied forces in North Africa in 1942 to 1943 (102, 113, 188, 266); every theater of military operations was affected by the end of hostilities (188). The large numbers of active servicemen involved are illustrated in the El Alamein campaign. At the peak of the epidemic in November 1942, the number of men hospitalized with jaundice (1,861 for the month) was only exceeded by those hospitalized with battle casualties (3,602). Overall, there were ~200,000 recognized cases of hepatitis in the U.S. Army alone (188), with a total in the millions likely in the combined Allied forces. In Germany, the situation was identical or even worse, with 190,000 cases in September 1941, 5 to 6 million cases in their armed forces over a 3-year period, and more than 10 million estimated military and civilian cases during the war (98).

The scientific thinking about hepatitis was further complicated in this era by the recognition of sporadic and epidemic forms of a long-incubation hepatitis (see above). Appreciating the military importance of the disease, the U.S. Army sponsored research that investigated experimental transmission of hepatitis, characterized the features of short-incubation and long-incubation disease, and examined prevention strategies (188). The success of the latter initiative is reported below, and some of the transmission and clinical studies are specifically referenced herein.

TABLE 2. Findings in epidemic jaundice in the 1930s and 1940s[a]

Symptom	% with symptom		
	Detroit civilians (n = 194)	Mediterranean military (n = 200)	New York military (n = 200)
Anorexia	93	82	92
Nausea, vomiting	84	75	79
Malaise	—[b]	82	69
Fever	61	53	42
Headache	57	35	27
Abdominal pain	50	—	57

[a] Data are from references 102, 113, and 173.
[b] —, not reported.

Common Clinical Features

After an incubation phase of 15 to 50 days (mean, 30 days), most infected persons developed nonspecific constitutional symptoms followed by gastrointestinal symptoms (Table 2). This preicteric or prodromal period averaged 5 to 7 days but varied in length from 1 day to more than 2 weeks (102, 113, 173). In approximately 15% of cases, however, there was no obvious prodrome before the appearance of jaundice. The findings resemble other viral prodromes and are indistinguishable from them. Less common manifestations than those tabulated included chills, myalgias and arthralgias, cough and upper respiratory symptoms, constipation, diarrhea, pruritus, and urticaria. The nonspecificity of symptoms is such that the diagnosis of an anicteric case of infectious hepatitis cannot be made with certainty unless modern testing is used. This is illustrated in a retrospective analysis of an outbreak of hepatitis affecting the Holy Cross football team in 1969. The epidemic was considered on clinical grounds to have involved almost all members of the team. However, when anti-HAV antibody was measured in stored sera, the attack rate was only 33% (85). Only the icteric cases were truly infected; all the supposedly anicteric cases were not. The Holy Cross outbreak is unusual in this regard. In other outbreaks of hepatitis A among adults, the percentage with jaundice varies between 40 and 70% (144, 214). One potential explanation for the finding of jaundice in 100% of true hepatitis A cases in the Holy Cross outbreak is that there are strain-related differences in disease severity; there is no supportive evidence for this explanation. Alternatively, another systemic infection may have occurred simultaneously with the hepatitis A. This explanation could account for not only the gastrointestinal symptoms in the non-HAV cases but also the increase in jaundiced cases if the additional infection were associated with an increase in bilirubin load (hemolysis) or another mechanism of interference with bilirubin transport or excretion.

The onset of the icteric phase is heralded by dark urine (conjugated bilirubinuria) before jaundice becomes apparent. The nonspecific and gastrointestinal symptoms often subside but may persist. The duration of jaundice is quite variable. In the Detroit series, the mean length was 7 days, with a range of 4 to >22 days (173). In contrast, the modal length reported by Havens was 20 to 29 days (102). Actual quantitation of biliru-

TABLE 3. Physical examination findings in epidemic jaundice during World War II[a]

Sign	% with symptom	
	Mediterranean (n = 200)	New York (n = 200)
Hepatomegaly	59	51
Hepatic tenderness	54	38
Splenomegaly	11	14
Bradycardia	9	25

[a] Data are from references 102 and 113.

bin (in milligrams per deciliter rather than the earlier "icterus index") was not performed routinely until the 1950s, and consequently precise levels from the older epidemics are sparse. The maximum bilirubin in 60 patients from Havens' series was 10.8 mg/dl (102). In the series from the Rockefeller Institute Hospital in New York (113), the average was 6.7 mg/dl. Since all patients in these case series were icteric, they form a more homogeneous group than later series, in which infections could be identified by biochemical, serologic, or virologic means. Abnormal physical examination findings apart from jaundice occurred in approximately half the patients or fewer (Table 3).

Disease duration, not unexpectedly, varied with the duration of jaundice. In Detroit, the mean length was 15 days. This relatively short duration may reflect their younger age. In Havens' cases, hospitalization length averaged 30 days, ranging from 7 to 87 days. Patients recovered uneventfully; relapse and other complications were uncommon in most series. Three relapses among 200 patients were observed by Havens (102) although Hoagland and Shank reported retention of sulfobromophthalein, an organic anion transported like bilirubin, in 18.5% of cases after initial normalization (113), indicating a decrease in hepatic function during relapse. The military burden, however, was quite considerable because of the large numbers of men involved and the length of time before return to full duty.

Anicteric and Asymptomatic Hepatitis

The accurate diagnosis of anicteric hepatitis and recognition of the existence of asymptomatic hepatitis required the development of an objective measurement of hepatic injury as indirect evidence of acute hepatitis. In 1955, Wróblewski and LaDue reported their work on the release of GOT with liver injury (267). They measured SGOT activity in 10 patients with jaundice from parenterally transmitted hepatitis and in 5 patients with jaundice without any recognized parenteral risk factors. SGOT levels were elevated in all patients and returned to normal with recovery from the acute illness. Using measurement of SGOT, Krugman and colleagues demonstrated the existence of asymptomatic infection with HAV following ingestion of infectious material (140). Serum collected at the time of modest elevation of SGOT transmitted infection to additional recipients, demonstrating a temporal relationship between the elevated SGOT levels and infectivity. In addition, measurement of SGOT levels permitted the unequivocal detection of anicteric cases of both hepatitis A and hepatitis B (138).

Careful analysis of a food-borne outbreak of hepatitis A at a naval facility in San Diego demonstrated that 14% of patients were asymptomatic and that 30% were not jaundiced (214). This study used aminotransferase levels in case finding and also confirmed etiology by demonstrating rising titers of anti-HAV antibodies. Common symptoms and signs in this outbreak occurred less frequently than in the epidemics from the late 1930s and early 1940s but were qualitatively similar, with few exceptions (Tables 4 and 5). Arthralgias were noted in 10% and a rash in 14%, symptoms that are more often associated with acute hepatitis B. A recent review of 59 patients hospitalized in Pasadena, Calif., for sporadic hepatitis A between 1985 and 1994 reveals virtually identical findings (Table

TABLE 4. Findings in epidemic and sporadic hepatitis A[a]

Symptom	% with symptom		
	Epidemic cases		Sporadic cases, 1985–1994 (hospitalized)
	1930s–1940s[b] (hospitalized)	San Diego 1974 (all)	
Anorexia	89	71	75
Nausea, vomiting	79	61	—[c]
Malaise	76	76	80
Fever	52	18	58
Headache	40	19	22
Abdominal pain	54	26	41

[a] Data are from references 70, 102, 113, 173, and 246.
[b] Mean data for icteric cases from Table 2.
[c] Not stated except as between 41 and 75%.

TABLE 5. Physical examination findings in epidemic and sporadic hepatitis A[a]

Sign	% with symptom		
	Epidemic cases		Sporadic cases, 1985–1994 (hospitalized)
	1930s–1940s[b] (hospitalized)	San Diego 1974 (all)	
Hepatomegaly	55	14	78
Hepatic tenderness	46	39	Not stated
Splenomegaly	13	3	7
Bradycardia	17	—[c]	—

[a] Data are from references 70, 102, 113, 173, and 246.
[b] Mean data for icteric cases from Table 3.
[c] —, not reported.

TABLE 6. Laboratory investigations among hospitalized patients with sporadic hepatitis A[a]

Test	Pasadena, 1985–1994	Dallas, 1997–1998
Bilirubin (mg/dl)	7	13.3[b] (4.9–46.4)
Alkaline phosphatase (U/liter)	319	335 (117–1,104)
AST (mIU/liter)	1,754	3,664 (428–10,420)
ALT (mIU/liter)	1,952	3,628 (1,029–9,220)
Albumin (g/dl)	—[c]	2.6 (1.5–3.1)
Globulin (g/dl)	—	4.0 (3.2–5.6)
Prothrombin time(s)	—	15.1 (11.7–26.4)

[a] Data are mean peaks (ranges). Data are from reference 246 and unpublished sources.
[b] Mean peak of 10 mg/dl, excluding data for a patient with hemolysis and hepatitis A (bilirubin, 46.4 mg/dl).
[c] —, not reported.

6) (246). Arthralgias (19%) and rash (7%) were also observed in this cohort. Findings on physical examination were qualitatively similar for both epidemic and sporadic hepatitis A to those reported in earlier outbreaks.

The ratio of anicteric to icteric cases (1:3.5) in the San Diego epidemic likely reflects the ages of the individuals. In young children, the fraction of inapparent infections can be much higher. In an outbreak of hepatitis A in a religious community, where all diagnosed patients were under 20 years old, a limited household serosurvey detected IgM anti-HAV in 15 individuals, only 2 of whom developed jaundice, a ratio of 7.5:1 (191). Clinically obvious disease, however, can occur even in infancy. In a series of six infants aged 2 weeks to 8 months reported by Linder et al., bilirubin levels were 5 to 12 mg/dl and the alkaline phosphatase was strikingly elevated (mean, 5.9-fold; range, 1.2 to 12.1-fold) (153). This may represent a cholestatic form of hepatitis A in infancy.

The attack rate in members of households exposed to infection is consistent with asymptomatic disease in young children (84). Thus, Ford observed that the rate of clinically apparent disease was much lower in children under 5 years of age (2 of 73 [3%] compared with 20 of 72 [28%] for 5- to 10-year-old children and 18 of 66 [27%] for 10- to 15-year-old children) despite apparently identical risks of infection. The low attack rate in adults (8 of 438 [2%]) almost certainly reflects immunity rather than inapparent infection (84). In 1937, Hugh Barber correctly predicted the natural history of hepatitis A infections based on his own observations and a review of the literature. He wrote, "If infective hepatic jaundice is due to a virus, which sets up acute hepatitis; if it is highly infectious in children, but well resisted by them; if most adults have acquired immunity, but those who become infected have a liver less capable of regeneration than the child, the natural history of epidemic and sporadic cases may be explained" (24).

Laboratory Investigations of Acute Hepatitis A

As with the clinical symptoms and signs, there are no pathognomonic findings in the laboratory investigations that distinguish HAV from other hepatotrophic viruses. The maximum elevation of alanine aminotransferase and aspartate aminotransferase can be substantially higher than that observed in acute hepatitis B, but there is a wide range. In general the degree of aminotransferase elevation roughly correlates with the severity of the acute hepatitis A in that asymptomatic cases have lower aminotransferase levels. The overall severity of the infection, however, is demonstrated by the bilirubin level as well as the prothrombin time. Most cases of hepatitis A have a bilirubin of $\leq$10 mg/dl in the absence of hemolysis, an indication that hepatitis A is usually not severe.

Relapsing, Prolonged, and Cholestatic Hepatitis A

Relapses in the course of hepatitis A occur in some patients (45, 46, 91, 102, 129, 240, 246). For example, Cockayne wrote that "Relapse may occur after it has completely disappeared . . ." (46). However, the cases that he documents are difficult to distinguish from second infections with a different etiologic agent without the availability of specific diagnostic tests. Similar criticisms can be applied to most reports of relapse prior to the isolation of HAV and development of specific assays for the virus. Demonstration of HAV in stool during relapse (223) provides the best evidence of causality. The techniques of immune electron microscopy, RIA, and molecular hybridization were used, indicating that both protein and nucleic acid components of the virus were present and thus suggesting continued infectivity.

The rate of hepatitis A relapse varies: 3 of 200 (1.5%) in Havens' case series, 17 of 256 (6.6%) in Argentina, and 7 of 59 (11.9%) patients hospitalized in Pasadena, Calif., in the 10 years between 1985 and 1994 (102, 223, 246). The severity of symptoms and biochemical abnormalities during the second phase are essentially the same as observed during the initial illness except for a tendency to greater cholestasis (91, 240). A relapse necessarily lengthens the course, and the overall duration of disease is similar to those with a prolonged (but not biphasic) illness (240).

In some individuals, the course of hepatitis A is unusually prolonged. Havens observed jaundice for up to 120 days (17 weeks) in his series, for example (102). Complete follow-up of almost all the cases in the San Diego naval outbreak revealed a prolonged course (abnormal aminotransferase levels after 14 weeks) in 11 of 130 cases (8.5%). Liver biopsies performed at that time demonstrated portal inflammation with piecemeal necrosis, periportal fibrosis, and lobular hepatitis. All biochemical abnormalities eventually resolved by 5 months. Since prolonged excretion of virus (i.e., viral nucleic acid detected by RT-PCR) may occur in patients with persistent elevation of alanine aminotransferase (269), any patient with either relapse or a prolonged course should be regarded as potentially infectious. Fatigue may persist after resolution of biochemical abnormalities in some patients. When patients were questioned up to 30 months postinfection, fatigue was more frequent in those hospitalized for hepatitis A or B than in those hospitalized with other infections (28). Most patients, however, recover completely in 6 months or less (246).

The occurrence of "cholangiolytic" or cholestatic variants of acute hepatitis A was described in 1984 (95) after the advent of specific diagnostic testing that permitted identification of the etiologic agent. Previous accounts of this variant (reviewed in reference 95) did not have the benefit of such tests. Severe pruritus, diarrhea, weight loss, and malabsorption may accompany the cholestasis. Although resolution occurred in all patients, symptomatic relief was obtained with corticosteroids in some patients without untoward sequelae (95). However, the report of persistent aminotransferase elevation and viral excretion with progressive hepatic fibrosis in one patient treated with corticosteroids (166) is cautionary when considering treating what is otherwise a relatively benign variant.

Fulminant Hepatitis A

Like hepatitis B, delta hepatitis, and hepatitis E, hepatitis A can cause acute hepatic failure. Fulminant hepatitis A was diagnosed in 20 of 295 patients in a recent retrospective study of acute hepatic failure in the United States, less frequent than acetaminophen toxicity (60 of 295) and hepatitis B (30 of 295) (217). The fatality rate for hepatitis A is generally low, quoted as $<$1.5% of all hospitalized icteric cases (115). Between 1983 and 1987, 381 deaths due to hepatitis A were reported to the CDC (147). With $\sim$30,000 reported cases yearly, this gives an

estimated fatality rate of 1.3%, likely a maximum rate because of relative underreporting of nonfatal disease. Fulminant disease occurs more frequently in adults than children (264) but can occur in childhood (62). The spontaneous recovery rate for patients with fulminant acute hepatitis A in the recent retrospective U.S. study, which included all age groups, was 35%, whereas it was 39% in a French pediatric population (62). Other patients may survive following liver transplantation (62, 217). Occasionally, hepatitis A infection recurs following transplantation (75, 86).

In the largest recent epidemic, in Shanghai, where 292,301 cases were reported between January and March 1988, there were 32 deaths (100), a minuscule fatality rate of 0.01%. In contrast, five deaths were associated with a large urban epidemic in Tennessee in 1994 and 1995. Of 256 patients hospitalized in Tennessee for severe disease, 3 developed classic fulminant hepatic failure, of whom 2 died. One patient with underlying chronic liver disease also died. Two cases of prolonged illness were classified as autoimmune hepatitis on the basis of positive antinuclear antibody (titer, >1:640) and liver biopsy samples consistent with that diagnosis. These patients also died. Factors that contributed to mortality in those with severe disease included age of >40 years (deaths of 3 of 53 hospitalized patients who were older than 40 years) and other comorbid conditions (e.g., chronic hepatitis C).

Chronic Liver Disease and Acute Hepatitis A

The risk of fulminant hepatitis is increased in patients with underlying chronic liver disease who develop acute viral hepatitis, regardless of etiology (133), and patients without prior exposure should be vaccinated (13). However, the report from Italy of an unexpectedly high rate of fulminant hepatitis A in patients with underlying chronic hepatitis C (7 of 17 [41%]) but not chronic hepatitis B (0 of 10) (253) has not been confirmed by other investigators (22, 108).

The classic teaching for many years has been that hepatitis A infection does not cause chronic liver disease and that there is no chronic carrier state. With the advent of highly sensitive assays for HAV detection, it has become clear that in rare patients, viral nucleic acids can be detected in stool for many weeks after the onset of infection, even when hepatic enzymes have returned to normal (269). Does this represent chronic infection or one end of the normal spectrum? One patient had HAV RNA in stool (by RT-PCR) 11 months after onset of illness, at which time he also had persistent aminotransferase elevation and detectable anti-HAV of the IgM class (126). A liver biopsy at that time showed portal inflammation and interface hepatitis. The patient developed esophageal varices at 25 months, and aminotransferase elevations and IgM anti-HAV were still present after 31 months. Although reported as chronic hepatitis A, it may represent two separate diseases, prolonged hepatitis A and a second, unidentified cause of chronic liver disease.

Similarly, a case report of chronic hepatitis A with persistent IgM class anti-HAV antibody and progressive liver disease (165) may represent observations that are true but unrelated. In the absence of chronic liver disease, low-level IgM anti-HAV can be detected up to 32 months after acute infection (220). Furthermore, the titer of IgM anti-HAV is normally such that early in the course of infection samples are diluted 1:4,000 before assaying to avoid a false-negative prozone effect. IgM class antibodies may therefore be detectable, albeit at a lower level, for many months as the titer gradually declines. Thus, it would seem that persistence of detectable IgM class anti-HAV antibody does not prove persistent infection.

Chronic liver disease can appear to follow acute hepatitis A but lack a direct etiologic relationship (120, 204, 252). The triggering of autoimmune hepatitis by HAV infection in two subjects was reported in 1991 in a prospective study of relatives of patients with autoimmune chronic active hepatitis (252). With the overwhelming advantage of a prospective evaluation and the observation of autoimmune hepatitis occurring in two study subjects, these data are difficult to refute. Similarly, when aminotransferase levels are normal before HAV infection and the illness is characterized as steroid-responsive liver disease that recurs on steroid withdrawal (204), the assumption that HAV infection is triggering or unmasking autoimmune hepatitis seems reasonable. However, when the diagnosis of autoimmune hepatitis is made in persons with concurrent HAV infection, it is quite problematic, since viral hepatitis is associated with antinuclear antibody positivity and the features on liver biopsy are sufficiently similar to preclude absolute diagnoses.

Extrahepatic Manifestations

A variety of extrahepatic manifestations can be observed in patients with acute hepatitis A. In order of frequency, as seen in 256 patients hospitalized in Tennessee in 1994 to 1995, these include hemolysis (10 patients), acalculous cholecystitis (10 patients), acute renal failure (3 patients), and pleural or pericardial effusion, acute reactive arthritis, and pancreatitis (1 patient each) (264). Neurologic manifestations, although not reported in this particular series, may also be seen.

Hemolysis is precipitated by viral hepatitis, including hepatitis A, in patients with glucose-6-phosphate dehydrogenase deficiency (119, 219). In addition, red cell survival in the absence of an underlying red cell abnormality can be shortened by acute infectious hepatitis (presumptive hepatitis A) (132). Hemolysis may be autoimmune in nature, associated with antibodies to triosephosphate isomerase (208, 209), and can be severe (156, 244). Other hematologic abnormalities include aplastic anemia (73), autoimmune thrombocytopenic purpura (47), and pure red cell aplasia (221).

Acute cholecystitis and acute pancreatitis may complicate hepatitis A. The exact pathogenesis of acute cholecystitis is uncertain. In one patient, HAV antigen was detected in bile duct epithelium and the gallbladder wall, suggesting a direct effect of viral infection rather than a secondary phenomenon (176). Most cases of acute pancreatitis complicating viral hepatitis occur in fulminant hepatitis (reviewed in reference 61). Occasionally, however, pancreatitis may be encountered in nonfulminant disease (61, 264).

Occasionally, patients with HAV infection manifest symptoms consistent with circulating immune complex formation. These include cutaneous vasculitis, arthritis, and cryoglobulinemia (57, 122, 123). Either IgM or IgG anti-HAV is detected in the cryoglobulins (122, 123). The symptoms resolve spontaneously with resolution of the hepatitis A.

Interstitial nephritis (90), renal failure with proteinuria and hypocomplementemia suggesting immune complex disease (43), immune complex mesangial proliferative glomerulonephritis (164, 271), and acute tubular necrosis (76, 152) occur in the absence of fulminant hepatitis. The lack of severe liver disease precludes a missed diagnosis of hepatorenal syndrome. The exact mechanism(s) involved has not been defined. Immune complex formation may be an important etiologic factor.

Mononeuritis (193), mononeuritis multiplex (215), Guillain-Barré syndrome (239), postviral encephalitis (60, 243), and transverse myelitis (39) have been described in patients with acute hepatitis A. The etiology of these findings is uncertain; they may be caused by vasculitis.

MANAGEMENT

No specific management is necessary for most patients with uncomplicated HAV infection. Common sense prescribes appropriate rest (when necessary) and diet (avoiding foods that may cause digestive discomfort, such as fatty food). In the past, however, strict bed rest until complete resolution of all symptoms was common. Hoagland and Shank analyzed the relationship between the length of time from onset of symptoms until hospitalization and the average duration of illness (113). They found that when hospitalization was delayed for 30 or more days, the illness lasted an average of 81 days. In contrast, when the patient was hospitalized within the first 14 days, the illness lasted for an average of 46 days. Their conclusions were that prompt hospitalization and freedom from activity were important. An alternative explanation is that a slower, more subfulminant course was associated with a longer period until complete resolution and that the degree of bed rest (or need for hospitalization) was unproven. In 1969, a randomized study that compared "early and vigorous exercise" with traditional rest was published (207). No difference in the duration of illness was observed with the institution of a deliberate exercise program. Early, however, was defined as when symptoms (anorexia and malaise) and signs (liver tenderness) were graded as slight or 2+ (on a 1+ to 4+ scale). Nevertheless, this study led to the abandonment of strict bed rest in the management of acute hepatitis.

In hepatitis complicated by fulminant hepatic failure, management is determined by the complications that develop and the availability of transplantation. Similarly, extrahepatic manifestations such as renal failure and pancreatitis are managed in a routine manner. The expectation for all patients is for complete recovery without sequelae, which occurs in the vast majority.

PREVENTION AND RISK OF INFECTION

Gamma Globulin (Passive Immunoprophylaxis)

Almost 25 years before the successful transmission of hepatitis A to animals and nearly 30 years before visualization of the virus and development of assays for detection, prevention of clinical hepatitis A was achieved (233) as the result of a series of events. First, the recognition that human serum could attenuate or prevent clinical measles in susceptible individuals was reported in 1937 (167). Convalescent-phase serum (enriched in specific antibody) was superior to pooled adult serum, and placental extract (containing passively transferred maternal antibody only) was ineffective. Second, methods were developed in the early 1940s to separate serum into component fractions (48). An average 25-fold concentration in antibody was achieved in fraction III, containing the immune globulins. Large-scale plasma fractionation programs were then undertaken by the Red Cross during World War II to provide plasma expanders. Gamma globulin was another product of the separation procedure. Finally, the demonstration of the effectiveness of the gamma globulin fraction in attenuation and prevention of measles in susceptible individuals exposed by household contact was made in 1944 (187, 232).

During the summer of 1944, an outbreak of hepatitis occurred at a children's camp near Philadelphia (177). Joseph Stokes, Jr., a pediatrician on the faculty of the University of Pennsylvania School of Medicine, who knew that gamma globulin prevented or attenuated measles in susceptible, exposed individuals (232), was consulted regarding the epidemic. With knowledge of the effectiveness of gamma globulin in measles epidemics, Stokes took the next step, using gamma globulin to prevent the further transmission of epidemic hepatitis (hepatitis A) (233).

In the children's camp, icteric hepatitis developed in 125 of 278 (45%) putatively exposed individuals who did not receive gamma globulin and in 3 of 53 (6%) randomly selected individuals who were given gamma globulin (0.15 ml/lb of body weight). At this dose, they used all the available gamma globulin, hence the difference in numbers in the two groups (233). Confirmation of similar efficacy quickly followed in both military (89) and civilian (103) populations. Immune serum (gamma) globulin (ISG) was protective for up to 9 months, and doses as small as 0.01 ml/lb were effective (231, 257).

More recently, immune globulin was used to arrest an ongoing outbreak of hepatitis A in a religious community in 1989 (191). Preliminary data indicated that persons under age 20 were uniformly susceptible, whereas the majority of older individuals were predicted to be immune (16 of 18 [89%] tested were anti-HAV positive and IgM anti-HAV negative). After administration of gamma globulin (0.02 ml/kg) to 2,287 individuals (total cost for vaccine and syringes, $3,620), there were only seven further cases of hepatitis A diagnosed between 2 weeks and 7 months after injection. The effectiveness of gamma globulin was calculated at 89% (191). Low levels of neutralizing antibody can be detected in recipients after ISG administration, although commercial tests for antibody are negative (265).

The current question is whether ISG preparations will continue to provide protection. The decrease in anti-HAV seropositivity in the general population may result in failure of protection from standard doses. The report of clinical hepatitis A in two recipients of standard doses of ISG in the United Kingdom is of great concern (26). In one individual who developed acute hepatitis A, transmission of infection was calculated to have occurred 2 months after the individual received 2.5 ml of ISG. In a second individual in whom fatal hepatitis A developed, symptoms commenced 10.5 weeks after inoculation. The titers of anti-HAV in the immune globulin preparations were 103 and 120 IU/ml (26), lower than those previously reported for similar preparations. The minimum protective level in recipients of ISG is unknown (265), but estimates of 10

mIU/ml are used. Simple mathematics indicate that 2.5 ml would administer 300 IU (120 IU/ml) initially. If the volume of distribution was 3 liters, then the level immediately after injection would be 100 mIU/ml. In one study, anti-HAV titers were measured 5 days after injection of ISG and again at 1, 2, 5, and 6 months (270). The half-life for the first interval (day 5 to 1 month) was 35 days, and for the remaining two intervals it was 21 days. Using these half-lives, an initial level of 100 mIU/ml would reach 6.25 mIU/ml in 98 days (14 weeks). With a larger volume of distribution, such as 4 liters, then the level falls below 10 mIU/ml before 11 weeks. These calculations are consistent with failure of protection for more than 2 to 2.5 months, as observed (26).

Since there may be a continued need for ISG unless universal vaccination is carried out, one solution may be to prepare ISG from donors with a history of jaundice, as suggested by Hopkins (118). He demonstrated a 10-fold-higher titer of anti-HAV activity in immunoglobulin preparations from HBV surface antigen-negative donors with a history of jaundice (118). Persons with a history of jaundice are usually dissuaded from donating blood because of the risk of transmitting disease. Despite sensitive assays for antigens and antibodies to detect evidence of various hepatitis viruses, there will be a small risk of transmission unless an assay for viral nucleic acids is introduced. Inevitably, some donated blood will be obtained during the "window" period, when the blood may be negative for antigen and antibody and yet contain virus.

Vaccination (Active Immunoprophylaxis)

The advent of an efficacious vaccine to prevent hepatitis A solves some (but not all) of the problems, from waning titers of anti-HAV antibody to increasing numbers of susceptible persons in the population. In 1991, a preliminary study of a vaccine manufactured at the Biologics Research Department, Walter Reed Army Institute of Research (appropriate, since Reed was the first person to transmit a viral disease, yellow fever, in human experiments), was published (222). The authors demonstrated acquisition of neutralizing anti-HAV antibody in recipients of a formalin-inactivated viral vaccine preparation. A live attenuated HAV vaccine was also capable of eliciting neutralizing antibody (171). Unlike those administered the inactivated vaccine, recipients developed IgM anti-HAV positivity without clinical hepatitis or evidence of significant liver dysfunction, although 40% reported gastrointestinal side effects.

By 1992, the clinical efficacy of the formalin-inactivated hepatitis A vaccines HAVRIX (Smith-Kline Beecham) (3) and VAQTA (Merck, Sharpe and Dohme) was apparent (260). Both use laboratory-attenuated strains of hepatitis A (HM175 for HAVRIX and CR326F for VAQTA) for production of a formalin-inactivated vaccine. A large-scale, double-blind, randomized, controlled field trial in elementary school children in Thailand demonstrated the efficacy of HAVRIX (124, 125). Of 40 cases of clinical hepatitis A that occurred among 40,119 children in the year following a single dose of vaccine, only 2 occurred in vaccinated individuals (125). The adverse reactions reported for the vaccine were minimal, and seroconversion after two doses was 99.8% in healthy individuals (3).

In a double-blind, placebo-controlled trial, the VAQTA vaccine was administered to 519 seronegative children aged 2 to 16 years living in a religious community in New York State, where hepatitis A was highly endemic. From day 21 after a single-dose injection, there were no cases of hepatitis A in the vaccine group, whereas 34 cases occurred in the placebo group. The seven cases in the vaccine group that occurred before day 21 were almost certainly due to transmission before vaccination. Similarly, hepatitis A outbreaks in two villages in Slovakia (198) and in rural communities in Alaska (168) were controlled with vaccination programs. Combined passive-active immunoprophylaxis is also effective (3, 96, 270), although the titers achieved are generally lower than with vaccine only (96, 270).

The Food and Drug Administration (FDA) licensed HAVRIX in February 1995 for administration to children who were $\geq$2 years old and adults. The CDC recommendations included use for travelers to areas other than western Europe, Scandinavia, Canada, Japan, Australia, and New Zealand (6). They indicated that screening for existing antibody should be considered for potential recipients aged >40 years and those who had resided in areas of high endemicity (see below). VAQTA has also been licensed in the United States by the FDA. In addition to travelers, the American College of Physicians recommends that other high-risk groups be vaccinated (87). These include homosexual men, injection drug users, persons with chronic liver disease, and workers with an occupational risk of infection. When HBV vaccination is also recommended, combined HAV and HBV vaccination can be undertaken (1, 3). The Advisory Committee on Immunization Practices issued guidelines for hepatitis A prevention in late 1996 (9). They recommended routine vaccination of travelers to countries with high or intermediate endemicity of infection and of children who were >2 years of age and living in U.S. communities that have high rates of hepatitis A infection (700 to 1,000 cases per 100,000 population annually). Other populations at increased risk of HAV infection or at increased risk of adverse outcomes, i.e., the high-risk groups identified by the American College of Physicians, were also recommended for vaccination.

Trials of efficacy, safety, and reactogenicity are carried out in healthy persons. However, if those with chronic liver disease are to be vaccinated, it is important to determine the response to vaccination in this group. The anti-HAV titer achieved in those with chronic liver disease was lower in two separate studies (134, 145), although most patients (94% in reference 134) did achieve detectable antibody levels. Similarly, titers were lower in homosexual men with human immunodeficiency virus (HIV) infection than in those without HIV infection (111, 178), and overall, seroconversion rates were somewhat lower (88% in reference 178) compared with 100% in non-HIV-infected individuals. The vaccines were well tolerated in all studies. Vaccine-induced antibody is predicted to be long-lived and persist for >20 years (250).

The most recent recommendations for prevention of hepatitis A from the Advisory Committee on Immunization Practice (13) broaden the target groups for vaccination. Routine vaccination is now recommended for children in states, counties, and communities with rates of hepatitis A infection that are twice the 1987 to 1997 national average of 10 cases per 100,000 population (Table 7) (13). In order of incidence, the states are Arizona (48 cases per 100,000 population), Alaska (45 cases), Oregon (40 cases), New Mexico (40 cases), Utah

TABLE 7. Reported cases of acute hepatitis A in the United States[a]

Site	No. of cases/100,000 population		Total cases	
	1985–1994	1987–1997	1996	1997
Total U.S.			31,032	30,021
California	21.9	20	6,653	6,422
Texas	15.0	16	3,460	4,511
Arizona	48.1	48	1,767	2,330
Oklahoma	12.5	24	2,586	1,445
Michigan	NS	NS	506	1,372
New York	3.6	NS	1,047	1,302
Missouri	14.4	19	1,414	1,151
Washington	5.6	30	1,001	1,015
Utah	27.2	33	1,073	550

[a] CDC data (10, 13; www.cdc.gov/nciod/diseases/hepatitis/h96surve.htm). NS, not stated.

(33 cases), Washington (30 cases), Oklahoma (24 cases), South Dakota (24 cases), Idaho (21 cases), Nevada (21 cases), and California (20 cases). In addition, states, counties, and communities with rates exceeding the national average should consider routine childhood vaccination. These states include Missouri (19 cases per 100,000 population), Texas (16 cases), Colorado (16 cases), Arkansas (14 cases), Montana (11 cases), and Wyoming (11 cases). The recommendations for protection of travelers, men who have sex with men, users of illegal drugs, persons who are at occupational risk for infection, persons who have clotting factor disorders, and persons with chronic liver disease were unchanged.

Screening Prior to Vaccination

Considerable differences exist in recommendations for serologic screening before vaccination (40, 230, 251). The aim is to reduce the cost of vaccination by eliminating those with previous natural infection. The economics are determined by the rate of seropositivity, the cost of screening, and the cost of vaccination. If two doses of vaccine are administered, then cost neutrality occurs when the fractional rate of seropositivity is equal to the screening cost divided by the vaccination cost. For example, anti-HAV seropositivity was 33% (or 1 in 3) in the National Health and Nutrition Examination Survey III (NHANES III), and therefore, the costs of screening before vaccination and of vaccinating all persons are identical if the screening cost (total anti-HAV testing) is one third the vaccination cost, e.g., $20 for screening tests and $60 for two vaccinations. If screening is cheaper, e.g., $10, or vaccination is more expensive, e.g., $80, then screening first generates cost savings on a population basis. Similarly, if the seropositive rate is higher in a given population, screening will be cost beneficial. Alternatively, if vaccination is cheaper, e.g., $40, then it is economically better to vaccinate without screening.

There are some disadvantages to screening before vaccination of high-risk groups other than the potential cost and the need to obtain samples for testing. Because the test results are not available immediately, screened persons must return for vaccinations. Consequently, there is a possible loss of vaccinees who do not follow up after screening. Another difficulty in deciding between screening first and universal vaccination is the lack of valid seroprevalence data for many populations. We have analyzed seropositivity in the Parkland Memorial Hospital Liver Clinic population with chronic HCV infection (J. A. Cuthbert, G. Vinson, J. S. Reisch, and M. Q. Ansari, submitted for publication). There were ethnic differences in seroprevalence. In Hispanics, 42 of 47 (89%) were anti-HAV positive, whereas 51 of 74 (69%) African-Americans and 49 of 102 (48%) non-Hispanic Caucasians were anti-HAV positive. There was no difference with age of <50 years in any ethnic group. The estimated screening cost is $17.50, and the vaccine cost (without supplies or labor charges) is currently $16.17 per dose (government contract rate). For the Dallas County Hospital District, screening will be cost-beneficial in Hispanics and African-Americans, but vaccination without screening appears to be rational for non-Hispanic Caucasians. Similarly, in Ireland, universal vaccination without screening is considered the best strategy if the seroprevalence rate is <45% (205).

Why Prevent Hepatitis A?

Different populations have different goals. Governments want to save money, armies want to have healthy troops, and travelers want to enjoy their vacations. For prospective travelers, an estimate of the risk of hepatitis A infection can be obtained by examining seroprevalence data. The rates are lowest in Scandinavia. Thus, the anti-HAV positive rate was 2% in Swedes born after 1950 (35). In heterogeneous populations, particularly those with immigrants, the overall prevalence of anti-HAV is predictably higher and differs with birthplace. For example, 45% of U.K.-born Londoners are anti-HAV positive but 70% of those born in a foreign country are positive (30). Intermediate rates of seropositivity are found in the Mediterranean. In Spain, the effect of socioeconomic level is shown by the 63% anti-HAV positive rate among gypsy children aged 1 to 14 years, compared with 46% for children in an orphanage and 23% for nongypsy families (174). In Italy, seropositive rates are higher in the southern part of the country, e.g., 27% anti-HAV positivity in persons aged 3 to 19 years, compared with 5% in northern Italy (235). Among U.S. military personnel, deployment in the Carribean was associated with an increased seroprevalence rate (107). Consistent with endemicity in the Carribean, 73% of children 2 to 4 years of age in Nicaragua were seropositive (194). At the far end of the spectrum, 97% of elementary school children in Sierra Leone were anti-HAV positive (114), as were 100% of Australian aboriginals 11 to 15 years of age living at the "top end" of the Northern Territory (36); 100% of Egyptian village children aged 1 to 3 years were seropositive (58); and 100% of Indian children in Pune were anti-HAV positive by late childhood (17). From these data, it is apparent that there is a considerable risk of hepatitis A infection with travel to Africa, the Indian subcontinent, and the Carribean, lower risk in the Mediterranean area, and negligible risk in Scandinavia.

From the economic perspective, hepatitis A is a costly burden to society that could be mitigated by universal childhood vaccination. The cost of HAV infection was recently calculated to be $332 million to $580 million annually in the United States (29). A food-borne outbreak of hepatitis A in Denver, for example, was calculated to cost $689,314 for disease control, including $450,397 for 16,293 ISG injections (56). The medical

costs for hepatitis A cases requiring hospitalization are estimated to be $1,070 to $2,460 each (56, 149). One economic analysis indicated that either universal vaccination or screening and vaccination of 2-year-old children should be considered cost-effective in developed countries (59). In another analysis, neither universal vaccination nor screening and vaccination of adults who were >50 years old were cost-effective (183). These data support the most recent recommendation of universal vaccination of children in U.S. areas of high endemicity as a method of disease control.

CONCLUDING REMARKS

Hepatitis A is common worldwide. Although it remains endemic in developing countries, there are falling seroprevalence rates in residents of developed countries. In young children, acute HAV infection is often asymptomatic. In contrast, older children and adults demonstrate a range of clinical manifestations from mild, anicteric infection to fulminant hepatic failure, with substantial morbidity and economic consequences. Passive immunoprophylaxis, using pooled ISG, prevents or attenuates disease in exposed individuals but does not provide long-term protection. Vaccination (active immunoprophylaxis) with predicted long-term protection against and future eradication of this disease is now possible.

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