Hepatitis A: Ancient Disease, Emerging Threat?

A Modern Review with Historical Emphasis

Jennifer A. Cuthbert, M.D.
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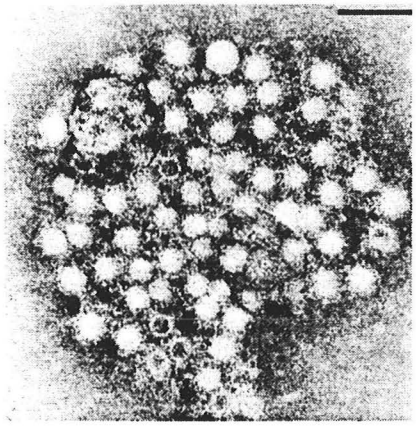
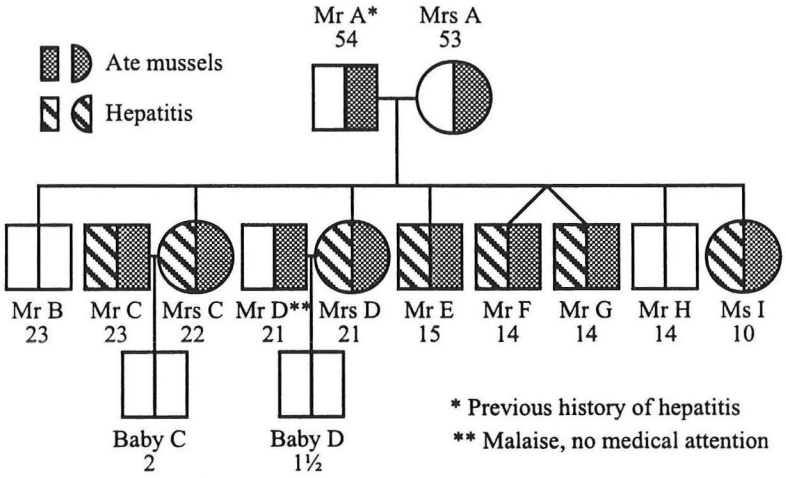


Hepatitis A Virus



Consumption of Mussels and Development
of Acute Hepatitis A

A virus is "..a piece of nucleic acid surrounded by bad news".
(Nobel laureate Peter Medawar, 1983)

Jennifer A. Cuthbert, M.D.
Professor of Internal Medicine
Division of Digestive and Liver Diseases

Clinical interests:
- Acute hepatitis
- Genetic liver diseases
- Ascites

"In the study of disease clinical observation is of the first importance, but it can carry us only a certain distance towards the goal of full knowledge. Clinical observation by the physician must go hand in hand with scientific experiment by the experimental worker if progress is to be sure and rapid. Neither alone can achieve the result. The physician and the scientific worker in the laboratory should be familiar each with the other's work and aspirations, and should ever lead a guiding hand to one another. The medicine of the future will attain that perfect advancement and full knowledge which all desire by the association of the physician and the scientific worker, not only in the laboratory, but also at the bedside."

Sir William Willcox, in the Lettsomian Lectures
"Jaundice with special reference to types occurring during the war"
Br Med J 1919

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INTRODUCTION

Illustrative Case

A 50 year old Caucasian executive requests advice when seeing you for a routine health visit. The patient's spouse would like them to celebrate their 25th wedding anniversary by taking a week-long cruise in either the Mediterranean or the Carribean. Your patient asks you about the "health risks" of such a venture.

What do you say about the risk of hepatitis A infection? Should you use passive or active immunoprophylaxis? Who will pay and how much can they expect to pay?

To answer these questions, one must know not only about the transmission of hepatitis A virus to susceptible individuals and its prevention but also about the features of the virus itself and the clinical disease with which it is associated.

"Viruses"

Before the precise recognition of what we now define as viruses, bacteria, fungi and protozoa, all infectious agents were referred to as "viruses", Latin for poison. The work of such illustrious scientists 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.[1, 2] Walter Reed, in 1902, for example, published his observations on the transmission of yellow fever by inoculation of human volunteers with filtered serum isolated from patients with clinical disease. 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."[3] (The observation, of transmission of foot and mouth disease in cattle, followed earlier reports that tobacco mosaic disease could be transmitted with a filtered inoculum [1, 2]) In contrast, the viral etiology of epidemic jaundice was not widely accepted by physicians until the mid-20th century. Indeed, an editorial in *JAMA* used the arcane terminology "catarrhal jaundice" as late as 1943.[4] 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 a virus "... is a piece of nucleic acid surrounded by bad news"[5] (cited in 2).

Historical Epidemic Jaundice

According to Cockayne, so-called catarrhal jaundice was recognized in ancient Greece and Rome. [6] Many writers consider that *De Internis Affectionibus* was written by Hippocrates and that a fourth kind of jaundice reported therein was catarrhal jaundice. 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* 1744-1749 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(s) of Epidemic Jaundice

McDonald is credited[7, 8] as the first person to implicate a virus as the etiologic agent of what we now call hepatitis A.[9] My own reading of his original description [regarding acute yellow atrophy of the liver - "... produced when some special virus acts on a previously damaged liver"], however, leaves the impression that he used the term in the sense of any infectious agent, not the filterable agent of Reed and other investigators. Similarly, Cockayne in his insightful treatise on the relationship between epidemic and catarrhal (sporadic) jaundice writes "... due to virus remaining active" and "... a virulent condition".[6] He (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 and he concluded that both epidemic and sporadic jaundice were caused by a specific organism of unknown nature.

The diagnostic picture in the early 1900s was further complicated by the occurrence of jaundice in the setting of a plethora of infectious diseases, as outlined by Sir William Willcox, a colonel in the army medical servie, in the Lettsomian Lectures on jaundice in British troops during World War I.[10] He recognized simple obstructive jaundice and "hemo-hepatogenous or toxaemic jaundice". The latter category included malaria, typhoid, paratyphoid, typhus, yellow fever and Weil's disease as well as mushroom poisoning and complications of pneumonia, dysentery and pyemia or sepsis. However, Willcox clearly differentiated epidemic (cartarrhal) jaundice as a separate entity. Blumer, reviewing infectious jaundice in the United States between 1812 and 1923, also concluded that the responsible organism was unknown. [11]

Viral etiology of epidemic hepatitis: In 1931, Findlay, Dunlop and Brown presented a paper entitled "Observations on Epidemic Catarrhal Jaundice" at an ordinary meeting of the Royal Society of Tropical Medicine and Hygiene.[12] 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 in 1942 [13] cited in [14] and 1943 [15] more than 25 years before successful transmission in an animal model. [16] 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 symptomatic <5 weeks after handling sera from the epidemic jaundice outbreak in Yorkshire described by Pickles,[17] consistent with what we now know is the incubation period of hepatitis A, and perhaps the first documentation of viremic serum transmitting epidemic hepatitis.[12]

Virologic Classification

All viruses are classified by their virion properties (morphology, physico-chemical and physical properties, genome, proteins, lipids, carbohydrates, genome organization and replication), antigenic properties and biologic properties. 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 non-enveloped. Each of the 5 major hepatitis viruses, hepatitis A virus (HAV), hepatitis B virus (HBV) hepatitis C virus (HCV), delta hepatitis (HDV) and hepatitis E virus (HEV), belongs to a separate viral family (the taxonomy of viruses includes family, genus and species). Fields *Virology* is an excellent resource for those interested in any aspect of viral disease.

HEPATITIS A VIRUS

The *Picornaviridae* are small, non-enveloped, single-stranded RNA viruses. Human pathogens include species in the genera *Rhinovirus* (human rhinoviruses) and *Enterovirus* (poliovirus, coxsackieviruses, echoviruses and human enteroviruses). Although the hepatitis A virus shares some major characteristics with other genera of the picornavirus family, it is sufficiently different that it is classified as the only species of the genus *Hepatovirus.* There are naturally occurring strains that infect non-human primates (3 genotypes) as well as 4 genotypes that comprise the human infectious viruses.[18] The strains belonging to each genotype share ≥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.[18] The hepatitis A virus, unlike other members of the *Picornaviridae* family, is stable at pH 1, resistant to heat (56°C for 30 mins) and shows no cross-hybridization with enteroviruses, rhinoviruses or other picornaviruses. Details of these characteristics are amply referenced in Fields *Virology*.

Genome Organization [8]

The organization of the hepatitis A virus genome is similar to that of the other picornaviruses (see Figure 1). The positive-sense (i.e. translatable), single-stranded RNA is 7.5 kb in length and consists of a 5′ non-coding region (NCR) of 734-740 nucleotides, a coding region of 2225-2227 nucleotides and a 3′ non-coding region of 40-80 nucleotides. [8] 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 ribosomal entry site (IRES) formed by the 5′ NCR functions to initiate translation in the picornaviruses, including the hepatitis A virus. The 5′ NCR of the hepatitis C virus, another single-stranded, positive-sense, uncapped RNA genome, also includes an IRES.

Viral Proteins [8]

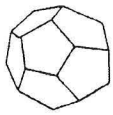
Although hepatitis A virus was first successfully constituents are not completely defined. Infected cells contain only low titers of virus, consequently protein chemistry has been limited. The P1 region encodes the three major proteins of the viral capsid, VP1, VP2 and VP3. A fourth viral capsid protein, found in other adapted to cell culture 20 years ago, [19] its protein picornaviruses (VP4) is predicted to include ≤23 amino acids in HAV

Table I: The Major Hepatitis Viruses — A, B, C, D and E

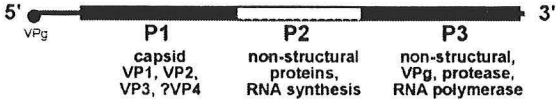
Genome		**Non-enveloped** (fecal-oral)		**Envelope** (parenteral)	
DNA	(double-stranded)			*Hepadnaviridae*	**HBV**
RNA	(single-stranded)	*Picornaviridae* Genus: *Hepatovirus*	**HAV**	*Flaviviridae* Genus: *Hepacivirus*	**HCV**
		Caliciviridae Genus: proposed	**HEV**	Unclassified	**HDV**

Hepatitis A Virus

- Family: *Picornaviridae*
  Genus: *Hepatovirus*
- Virion: 27-32nm
  Icosahedral non-enveloped

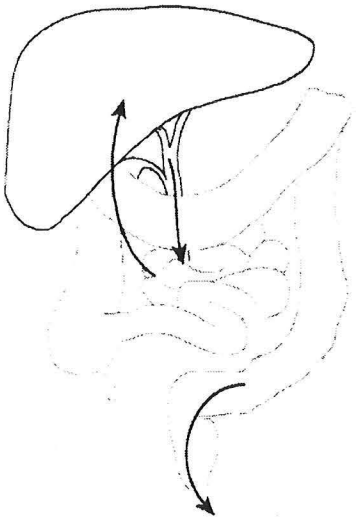


- Genome Characteristics:
  Single-stranded polyadenylated 7.48 kb RNA



and has remained elusive. The capsid proteins are 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. Non-structural proteins encoded in the P2 and P3 regions are predicted to function in RNA synthesis and virion formation. VPg (*V*irion *P*rotein, *g*enome), also encoded in the P3 region, is covalently linked to the 5´ genome terminus and involved in initiation of RNA synthesis.

Possible "Enterohepatic" Cycling of Hepatitis A Virus



Ingestion of infected material
↓
Absorption from stomach or small intestine
↓
Replication in liver
↓
Secretion into bile
↓
Excretion in stool or reabsorption

Viral "Life Cycle"

Available data are sketchy as to the exact fate of virions immediately after oral intake. 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] 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 non-liver primate cells has been characterized, [21, 22, 23] however, the relationship of this mucin-like class I integral membrane glycoprotein to hepatocyte uptake of virus is not clear. Once HAV is replicated in the liver and 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.

Virus Replication [8]

Current evidence indicates that HAV replication is probably exclusive to hepatocytes *in vivo*, although cell culture infection and replication in non-hepatocyte cell lines is well-documented. [8] Viral 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 blood stream The mechanism of viral release/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. [24-26]

Virus Detection

The hepatitis A virus was first visualized after aggregation of fecal material with serum containing specific homologous antibodies. [27] The fecal material was collected from Joliet prison volunteers [28] inoculated with the MS-1 strain of hepatitis virus characterized by Krugman and colleagues. [29] The technique of immune electron microscopy of stool was then used to assay for specific anti-HAV antibodies in convalescent sera after episodes of naturally occurring hepatitis. [27, 30] and to investigate the transmission of virus. [31, 32] HAV can now be detected by a variety of immunologic and molecular techniques including radioimmunoassay and DNA-RNA hybridization [26] as well as the now ubiquitous polymerase chain reaction (PCR) amplification. PCR amplification was used to identify specific viral strains implicated in parenteral transmission of virus. [33, 34]

TRANSMISSION

Physicians in the early 1900s recognized that hepatitis A was spread by person-to-person contact [6] and by food and possibly water [35]. 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." Although person-to-person contact was evident, an alimentary mode of spread was not generally accepted. Most physicians considered that a respiratory-type droplet infection was more likely [11, 12, 36-39] although gastro-intestinal transmission was predicted by some authors in Europe [40] and the U.S. [41]

Hepatitis A versus Hepatitis B: Transmission studies, in the absence of specific disease markers, are difficult to interpret with our current knowledge of hepatitis viruses and the occurrence of hepatitis B (homologous serum jaundice) in both sporadic and epidemic forms as well as hepatitis A. Thus, during the pre-war era and early in World War II, jaundice associated with the injection of human serum (hence the term homologous serum jaundice) was increasingly reported on both sides of the Atlantic. It was recognized as a complication of treatment or prevention of measles with convalescent human serum in 1936 [42] and of yellow fever immunization (the vaccine contained human serum) in 1937. [43-45] The epidemic that occurred after yellow fever vaccination of U.S. troops (28,585 cases and 62 deaths) in 1942 brought widespread recognition of this form of transmission of jaundice. Since both hepatitis A and hepatitis B abounded in many of the military populations under study, the conclusions originally drawn from the results of the early studies may be flawed.

Oral Transmission of Hepatitis A

Experimental transmission of infective hepatitis, by feeding duodenal juice was first reported by Voegt [13] (cited in 14). Of note, although published in Germany (in *Münchener medizinische Wochenschrift*, the Munich Medical Weekly) in 1942, the findings were referenced by British investigators in 1943, [14] and Americans in 1944 [46] despite World War II. An underground network apparently procured scientific publications through neutral countries, [47] thereby permitting efficient dissemination of knowledge.

U.S. studies of oral transmission: Working with conscientious objectors who volunteered for studies at Yale University, Havens and colleagues successfully transmitted jaundice by feeding either serum or a filtrate of stool extract. [46] The incubation period was 20-30 days in 4 persons, consistent with transmission of hepatitis A. Another volunteer developed mild "subicteric" hepatitis after 84 days, an observation that cannot be interpreted without additional data. Stool samples obtained during convalescence were not infectious, whereas hepatitis was transmitted with stool samples collected 5 days after the onset of symptoms. [48] In parallel studies, jaundice was transmitted by intra-cutaneous inoculation of serum. The incubation period was substantially longer, suggesting hepatitis B. In later publications from this group, a distinction between hepatitis A ("infectious hepatitis", short incubation) and hepatitis B ("serum jaundice", long incubation) was made. [49, 50] Infectious hepatitis (hepatitis A) was transmitted by ingestion of pre-icteric sera. In contrast, serum jaundice (hepatitis B) was not transmitted by oral ingestion of serum. [49]

In the summer of 1944, an epidemic of hepatitis occurred at a children's camp. [51] Fecal-oral transmission of infectious hepatitis, with an incubation period of 18-37 days, was demonstrated with stool samples collected during the epidemic. However, the authors' data supporting their conclusion that the epidemic was due to a water-borne agent is suspect since the incubation period following ingestion of water was >60 days and none of the recipients were overtly jaundiced. [51]

Other Non-parenteral Transmission

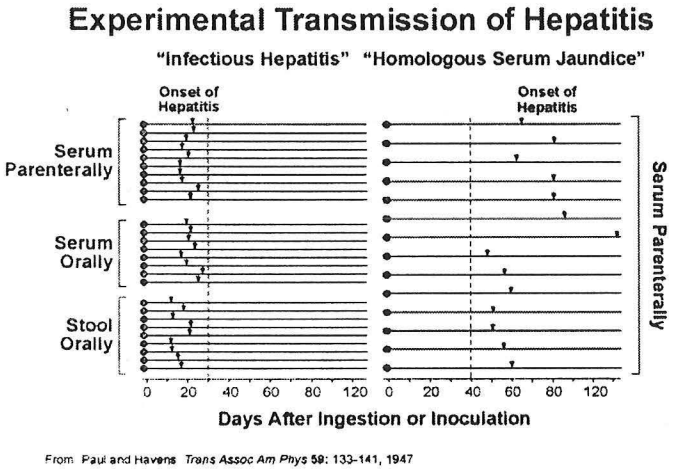
During the 1940s, investigators also reported transmission of jaundice via intra-nasal and/or pharyngeal instillation of fecal material, with an incubation period of 27-31 days. [52] One feasible explanation is that the material was swallowed and thereby gained access. However, the development of "subicteric" hepatitis after 24-28 days in persons exposed to nasopharyngeal washings [52] was not reproduced by other investigators using a similar protocol [51] and is more difficult to reconcile with today's knowledge.

Parenteral Transmission of Hepatitis A

Voegt injected pre-icteric serum into recipients and produced jaundice, in studies performed at the same time as those investigating oral transmission [13] (cited in 14). Working with British troops in Palestine in 1941-1942 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 volunteers. [15] One recipient developed jaundice a month after injection, consistent with the incubation period of hepatitis A (10-50 days). The donor serum for this recipient was collected two days after the onset of jaundice. In the other 5 volunteers from whom information was collected, jaundice was delayed (2-6 months). In retrospect, it is apparent that the longer incubations likely resulted from the experimental transmission of hepatitis B or infection from other sources. Cameron abandoned further human experiments when he became aware of case fatalities (not from his own series). [15]

U.S. studies of parenteral transmission: Havens and colleagues at Yale also transmitted infectious hepatitis

(hepatitis A) by parenteral means. They used pre-icteric serum obtained from volunteers who developed short incubation hepatitis following ingestion of infected material. [49] They observed a similar, short incubation period as that noted after ingestion of infected material. Serum obtained 11 days before and 31 days after the onset of symptoms did not transmit hepatitis, whereas serum collected 4 days after the onset was infectious. [48] Three volunteers were infected sequentially with hepatitis B then hepatitis A, demonstrating a lack of cross-reactive immunity. The authors interpreted their findings conservatively, as not indicating a fundamental difference in the two diseases, since the clinical features were indistinguishable with the exception of the incubation phase. [49]



From Paul and Havens *Trans Assoc Am Phys* 59: 133-141, 1947

Serum Jaundice and Infectious Hepatitis

By the late 1940s, the differentiation between the infectious hepatitis and serum jaundice was distinct enough, and the nomenclature confusing enough, that MacCallum proposed using the terms hepatitis A and hepatitis B in 1947. [53] Whether the differences were explained by two distinct viruses or different strains of the same organism remained uncertain. Despite the remaining uncertainties, however, the term "catarrhal jaundice" was finally abandoned following the general acceptance that a virus or viruses were the etiologic agent(s) because the transmission experiments used filtered material. [50, 54]

Chronic Carriers of Hepatitis

In the early 1950s, prolonged excretion of hepatitis A was suggested by the transmission of icteric hepatitis using fecal material collected 5-6 months after onset of illness in an infant aged 11 months and a 28 month old child. During the illnesses, the infant and child were not icteric and the tests of liver function available at the time were non-specific. [55] Additional studies were carried out using material from donors implicated in transmission of hepatitis B. [55] A donor whose blood was associated with post-transfusion hepatitis was identified. Inoculation of his serum into 4 volunteers resulted in hepatitis and jaundice in one recipient. Clinical symptoms were present in the recipient after 33 days and jaundice evident by 68 days. The donor's history and liver biopsy suggested Laennec's cirrhosis to the investigators and clinicians at the time. In retrospect, I would propose that the blood donor actually had chronic hepatitis C with the development of cirrhosis in conjunction with alcohol excess. The liver biopsy photomicrograph (figure 1)[55] is a "classic" example of what we now recognize as hepatitis C. Taken together with the incubation period in the lone volunteer with jaundice, and the lack of obvious infection in the other 3 subjects, the findings are all consistent with that diagnosis. These observations underscore once again the difficulties facing clinical investigators lacking markers with specificity (and sensitivity). It was in this challenging investigative setting that the studies at the Willowbrook State School on Staten Island were undertaken.

Willowbrook, MS-1 and MS-2

The goal of the original studies was to control hepatitis which was endemic in this residential school for the mentally disabled. Increasing numbers of hepatitis cases were occurring in the school during the early 1950s and the studies of infection after feeding virus were considered preliminary to experiments of immunoprophylaxis (see below for details of prevention studies). Consent was obtained from the parents of the residents and the protocols were approved by the New York State Department of Mental Hygiene and the Armed Forces Epidemiological Board, Office of the Surgeon General. The early studies defined the period of infectivity of serum and fecal material [24, 56, 57] and also demonstrated the usefulness of measurements of serum glutamic oxaloacetic transaminase (SGOT) in the diagnosis of anicteric and asymptomatic infections. [24]

Two type of hepatitis: Second attacks of hepatitis were observed in some residents. [29] 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, caused hepatitis after a relatively short incubation (hepatitis A) whereas the second pool, MS-2, resulted in long incubation hepatitis (hepatitis B). [29] The MS-1 pool was later used in the first successful transmission of hepatitis A to animals (marmosets) [16] and to transmit hepatitis to volunteers (in Joliet prison) whose clinical samples were the sources of material for the first detection of virus particles. [27]

Marmoset livers became the source of infectious material for not only the development of serologic assays but also the cell culture experiments that have led to the production of an effective vaccine. There was apparently little contemporary criticism of the fact that the initial studies were carried out on institutionalized mentally disabled residents, although they were openly criticized by some journals and individuals. [58]

MODERN ERA TRANSMISSION

Hepatitis A has not disappeared since the acquisition of definitive knowledge about its transmission by fecal-oral contamination. It remains by far the commonest cause of acute hepatitis in the U.S., as reported to the Centers for Disease Control. The latest data from the Viral Hepatitis Surveillance Program (1993) indicate that contact with a person infected with hepatitis A is the commonest identifiable source (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%. The largest percentage of infected persons, however, have no identifiable source (47%).

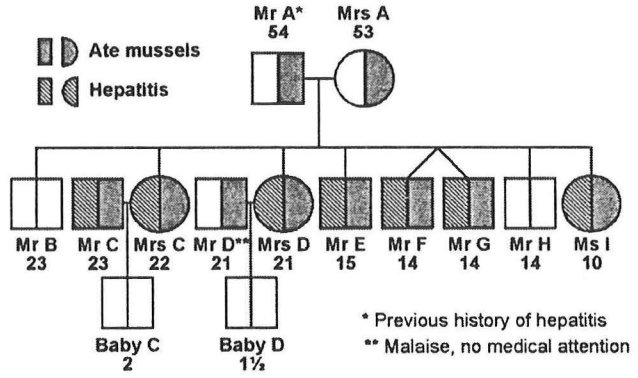
Personal Contact

The virus is hardy, surviving on human hands and inanimate objects (fomites). [59] Studies indicate that there is fecal excretion of viral particles during clinical [60] and that fecal excretion can be prolonged as determined by detection of viral nucleic acids (by PCR amplification) for 3 to 11 months. [61, 62] In a neonatal intensvie 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 4-5 months after initial identification of infection. [63] Furthermore, in a large-scale field trial of the efficacy of a formalin-inactivated hepatitis A vaccine, hepatitis A virus RNA was detected in stool collected 61-90 days after onset of illness in 16 of 19 cases of infection in the control group. [64] The infectivity of fecal material was not demonstrated in any of these cases. Taken together, however, 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. [65] The largest known modern epidemic of hepatitis A was also from consumption of contaminated seafood. In Shanghai, 292,301 cases of acute hepatitis were attributed to eating raw clams. Oysters [66] and cockles [67] have also been implicated. The hepatitis A virus may survive for extended periods of time in seawater. Thus, viral nucleic acids were detectable 232 days after being seeded in artificial seawater whereas they were only detectable for 35 days in cell culture. [68] Consequently, the filtering of seawater by bivalves, with the potential for retaining infectious hepatitis A particles resulting from fecal contamination, can lead to the transmission of infection to those who consume the seafood without adequate cooking to destroy infectivity. Spread of hepatitis A has also been reported in the U.S. and Europe following consumption of contaminated lettuce, [69] ice slush beverages, [70] frozen strawberries [71, 72] and salad food items [73, 74] 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.

Consumption of Mussels and Development of Acute Hepatitis A



Water-borne Outbreaks

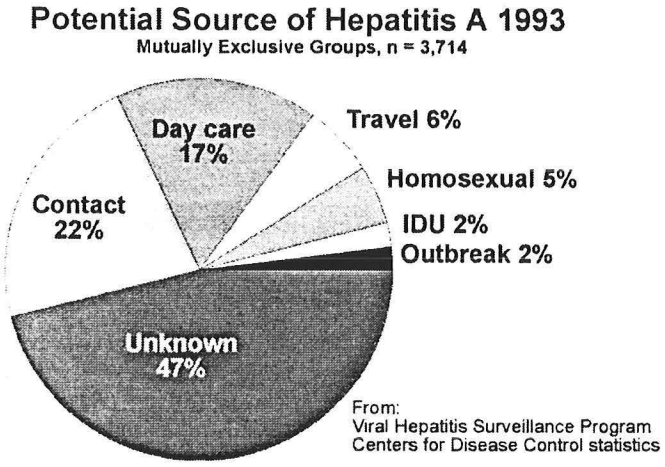
Hepatitis A was recovered from water supplies implicated in the transmission of disease, [75] swimming pools may be a source in outbreaks [76] and for sewage workers hepatitis A may be an occupational hazard. [77] HAV was detected in the final effluent from waste-water treatment plants in the Mediterranean [78] demonstrating the potential source for seafood contamination. Water-borne 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 in water-borne outbreaks.

Nosocomial Hepatitis A

Transmission of hepatitis A from hospitalized patients with unsuspected disease to staff is well recognized. [79] For example, an adult patient with diarrhea after an

elective cholecystectomy [80] premature infants [81] with prolonged viral excretion, [63] burn patients incubating hepatitis A in hospital, [82] and a patient with immunodeficiency (and anti-HAV negativity) [83] 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 5 cases of nosocomial hepatitis A. [84]

Vertical transmission is rare [85, 86] but can be the source of hepatitis A in a nursery outbreak. [87]



Parenteral Hepatitis A Transmission

Once considered rare outside experimental studies, [88] parenteral transmission of hepatitis A has become increasingly important. 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. [89] Transmission associated with platelet and plasma donation processing [90]and in anti-cancer immunotherapy reagents [91] has also been documented. More recently, identical HAV sequences were detected in clotting factor concentrates and hemophiliac recipients in Italy. [33] The solvent-detergent method of viral inactivation was considered inadequate for non-enveloped viruses such as the hepatitis A virus. In late 1995, a similar smaller outbreak occurred in the U.S. [34] Vapor heating of clotting factor concentrates is experimentally effective in eradicating infective hepatitis A. [92]

Injection drug users: The other group at risk of hepatitis A infection by parenteral transmission is the injection drug using population. [93, 94] Hepatitis A can also be potentially spread within this group by contamination from rectally carried drugs [95, 96] by unsanitary living conditions, crowding and lack of the necessary personal hygiene to prevent infection. Approximately 40-50% of injection drug users in northern Europe are anti-HAV positive [97] and in France the seropositive rate is significantly higher than in a control population. [98] At Johns Hopkins, seropositive rates were more than twice as high in injection drug users (66%) than in homosexual men (27%) and correlated with poverty. [99] Targeting this group for vaccination to prevent hepatitis A infection may decrease their infection rates in the future.

Homosexual Transmission

Although early seroprevalence studies of hepatitis A did not demonstrate an increased positivity in homosexual men, [100] a prospective study of seroconversion rates clearly documented a high rate of ongoing infection. [101] More recently, the hazard of hepatitis A acquisition during homosexual encounters was documented. [102-104] This is not universally demonstrated, however. [105]

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 examination. Consequently, little information was available regarding the pathologic changes in uncomplicated infectious hepatitis. The findings in acute yellow atrophy were well documented [9] and the relationship between acute yellow atrophy and non-fatal hepatitis was increasingly recognized, [6, 106, 107] although the heterogeneity of etiologic factors contributing to cases of acute yellow atrophy was probably under-appreciated.

Percutaneous liver biopsy

Iversen and Roholm revolutionized the process by undertaking percutaneous liver biopsies, using a technique that is remarkably similar to that in use today - a transthoracic approach with a suction needle.[108] In their paper describing histopathology of acute hepatitis, "sporadic acute benign jaundice of the catarrhal type", they reported on the findings in 38 aspiration biopsy specimens. [109] There 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 25-35 days later, there was less inflammation and the connective tissue was unchanged. One patient was biopsied 16 hours before succumbing to fulminant hepatitis. The biopsy showed similar findings to those following a benign course but of greater severity, with destruction of the parenchyma and an inflammatory infiltrate.

Early comparison of different hepatitides: The technique of percutaneous liver biopsy was rapidly adopted by others. A British study from 1943 reported their findings in 14 patients with epidemic hepatitis (mostly HAV), 7 with serum jaundice (HBV) and 35 with jaundice in relation to arsenotherapy (mostly HBV). [110] They could not perceive any histopathological differences between the various supposed etiologies. They observed necrosis that was most marked peri-centrally and inflammation that was maximum in the portal areas. The extent of involvement was increased with more severe disease.

Pre-icteric, icteric and post-icteric biopsies

In 1947, Mallory reported experience with peritoneoscopic liver biopsy in 137 volunteers with acute hepatitis. [111] Biopsies were obtained in all stages of the disease and examined histopathologically. He compared 34 biopsies from patients in the pre-icteric phase (obtained during the acute disease but before onset of jaundice) with 20 biopsies selected to illustrate the icteric phase. In 18 cases, his non-icteric group, biopsies were obtained from patients with a similar prodrome but the patients never became jaundiced. However, 5 biopsies demonstrated all the changes observed in biopsies from those cases that became jaundiced and 5 demonstrated one or more of the classical findings, suggesting that these represent anicteric hepatitis. The final 8 biopsies in the group were normal, indicating either very mild disease or an incorrect diagnosis.

Pre-icteric phase biopsies: In the pre-icteric phase, he observed periportal and lobular inflammation, lobular disarray, focal necrosis and regenerative activity. The severity of the lesions was comparable to (or more severe than) the icteric phase biopsies. In patients who never developed frank jaundice (bilirubin <2.5 mg/dl), the findings were similar but less pronounced.

Icteric phase biopsies: Biopsies obtained during the period of jaundice also demonstrated periportal and lobular inflammation togther with lobular disarry. [111] Mallory agreed with the previous investigators regarding a common form of necrosis in the lobule that differed from the autolytic character of fulminant disease. He wrote, "The stippled cytoplasm of the normal cell becomes homogeneous and intensely eosinophilic. The nucleus becomes first pyknotic, then fragmented and finally disappears. The cell separates from its neighbors and from the sinusoidal membrane, loses its polygonal shape and shrinks into a hyaline spherical body somewhat resembling the Councilman body of yellow fever." An excellent description of apoptosis. (William Thomas Councilman [1854-1933] was an American pathologist.) Mallory observed balloon degeneration less frequently than the formation of Councilman bodies. Regenerative activity was prominent in the icteric phase biopsies, with numerous multinucleated giant cells.

Post-icteric phase biopsies: During recovery, biopsies were repeated. [111] The findings were variable. Some showed complete resolution of inflammation and necrosis others minimal abnormalities, in some there was residual inflammation despite a comparable length of time since the onset of symptoms. Biopsies obtained during relapse demonstrated similar findings to the initial biopsies. In patients with a prolonged course, biopsies were often normal or minimally abnormal, however, 15 of 40 demonstrated persistent portal and lobular inflammation and focal necrosis, perhaps reflecting chronic hepatitis (B).

Modern comparison of different hepatitides: Although extensive in the number of biopsies examined, 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. As part of the Copenhagen Hepatitis Acuta, 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. [112] The parenchymal changes (focal necrosis, balooning, acidophilic degeneration) were less marked in the hepatitis A than in hepatitis B whereas the degree of portal inflammation was similar. Non-specific reactive changes were observed in some follow-up biopsies of hepatitis A patients during convalescence. [112] Fibrin ring granulomas, more often associated with diseases such as Q fever, were described in acute hepatitis A biopsies by some investigators. [113, 114]

Hepatitis A virus detection

The technique of *in situ* hybridization was recently used to localize hepatitis A virus sequences in human liver biopsies. [115] 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 seems plausible.

IMMUNOLOGY

The immunology of hepatitis A is important for two reasons. First, specific diagnostic tests for the confirmation of hepatitis A 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 [116, 117] with associated symptoms and signs in some patients. [118, 119] Secondly, clearance of viral infection and the disease manifestations associated with this process are almost certainly produced by the cellular immune response.

Humoral immune response

IgM, IgG and IgA antibodies directed against conformational epitopes on the hepatitis A viral particle are induced and can usually be detected by the onset of clinical illness. [120] 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%). [121] 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 an 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. [122] In contrast, another picornavirus, the poliovirus, elicits effective intestinal and salivary neutralizing antibody. [122] The IgG response is delayed when compared with IgM and IgA responses but is long-lived and accounts for the resistance to reinfection. In an isolated Amerindian tribe, anti-HAV antibody was present in everyone over age 50 years but in no-one younger. [123] This observation suggests that the tribal members were not exposed to hepatitis A virus for 50 years and that IgG anti-HAV persisted for that length of time without need for additional exposure.

The antibodies are usually directed against conformational epitopes on the viral surface. The capsid proteins VP1 and VP3 and the precursor protein VP0 may be recognized. [98] Almost all patients expressed both IgG and IgM antibodies to VP1. The IgG response to VP3 was detectable for years after disease resolution. [98] Antibodies to non-structural proteins may also be induced, however they are less abundant and lack neutralizing activity.

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. [24, 25, 26] Furthermore, hepatitis A is not directly cytopathic in cell culture but rather is associated with persistent infection without cell injury. [8, 19] and references therein. 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, hepatitis A-infected, target cells. [124, 125] Other cytotoxic cells, such as natural killer cells, may also be involved. [126, 125] 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.

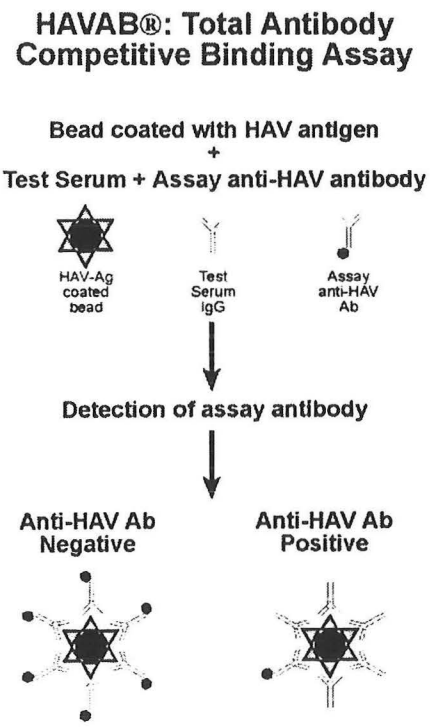
SEROLOGY

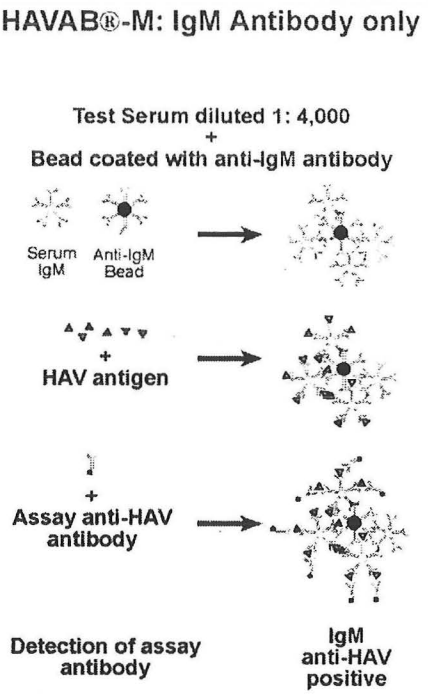
The specific detection of hepatitis A infection was first accomplished using immune electron microscopy of fecal extracts to visualize virus-like particles. [27] Antibody in convalescent serum from persons with experimentally- or naturally-acquired infection aggregated the virus and permitted its visualization 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 was not a method that could be employed for routine diagnosis of large numbers of clinical samples. The next step was the development of complement fixation [127] and immune adherence [128] tests for detection of serum antibody to hepatitis A viral antigens. This required a source hepatitis A virus antigen, supplied by liver extracts from marmosets infected with a Costa Rican strain of hepatitis A, CR326.

Immune adherence assay: 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 hepatitis A and hepatitis B; evidence that hepatitis A 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 varying quantities of antibody in lots of immune serum globulin.[128]

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. [129] The complement fixation test was not as specific nor 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 hepatitis B surface antigen and antibody to hepatitis B core and hepatitis B surface proteins were developed in 1970. Consequently, by 1975, acute viral hepatitis could be ascribed to either HAV or HBV etiology, permitting the recognition of viral non-A, non-B hepatitis (hepatitis C and hepatitis E).

Radioimmunoassays: Solid-phase radioimmunoassays (RIAs), developed for the detection of hepatitis A viral antigen, were modified to measure antibody. [130] In a comparison between immune adherence, immune electron microscopy and radioimmunoassay, each test was able to detect seroconversion following inoculation with MS-1 virus. [131] 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 IgM anti-HAV antibody. [132]





A competitive binding assay (HAVAB®, Abbott Laboratories, N. Chicago, IL) was developed to improve sensitivity. [133] In this assay, antibody in patient serum competes with radiolabeled antibody for HAV. The assay was also adapted to measure IgM anti-HAV which was detected in acute phase sera but not convalescent sera. [133] However, the absorption of IgG from samples, in order to measure IgM reactivity, was difficult to perform and the resultant assay lacked reliable specificity. An alternative technique was developed (HAVAB®-M, Abbott Laboratories, N. Chicago, IL) whereby IgM antibody was directly selected and anti-HAV activity then measured.[134] With these improvements, IgM anti-HAV 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 predictve value of quantitating IgM-specific anti-HAV was determined in a cluster of cases using normal blood donors as the control population. [135] 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, repeat testing 1-2 weeks later usually demonstrates positivity. [136] 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, [64] an observation that has not been explained. False positive Epstein-Barr viral serologies. [137] is less of a diagnostic problem than is prolonged positivity in the absence of hepatitis. [138] [139]

Persistence of IgM anti-HAV: The length of time that the IgM anti-HAV test remains positive is variable. [138] In 37 patients followed until 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 2 anicteris cases where onset of symptoms was used. In 70% (26 of 37), IgM anti-HAV was negative 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 5 individuals whose last positive test was recorded between 9-12 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. In the remaining 3 patients, 2 eventually normalized biochemical hepatitis and the third was lost to follow-up. In a second study, 2 of 6 patients were IgM anti-HAV positive (low titer) 30-32 months after the onset of hepatitis A.[139] A diagnostic dilemma may arise if a patient has unrecognized chronic hepatitis before contracting hepatitis A. 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 since vaccine-induced antibody titers are generally lower than those induced by natural infection. Non-invasive tests, i.e. not requiring blood samples, are also useful in 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. [140] The assay was validated using paired saliva samples in travelers undergoing vaccination. 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. [141]

CLINICAL FEATURES

The clinical features of viral hepatitis, once symptoms commence, are similar regardless of the specific hepatotrophic alphabet virus involved. Extra-hepatic manifestations and complications may differ quantitatively, but qualitatively they also are conserved. 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 endemic, sporadic or epidemic.

Sporadic and Epidemic 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. [6] He cites Rolleston [142] as thinking that the febrile cases of sporadic jaundice were the same as the epidemic cases, although few in number. In contrast, he

Table II: Findings on History Taking in Epidemic Jaundice

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

From: references 147, 148, 149

(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' transmitters of fecal-oral infections. In the developing world, where sanitation is limited or absent, infection remains almost universal. In 1-3 year old Egyptian children, the seroprevalence rate was 100%, [143] remaining at this level until age 67. Similarly, 2-4 year old Nicaraguan children have a seroprevalence rate of 73% [144] and in Pune, India virtually 100% of children are infected by late childhood. [145] Immigrants and travelers from areas of low disease rates are therefore at high risk of infection when residing in countries with endemic infection.

Cameron, who reported on epidemic hepatitis amongst British troops in Palestine during World War II, [15] recognized the existence of endemic infection in the region. "...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 non-immune 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 of 10:1 in white and non-white American troops [146] 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 4 fold higher rate of infection than ordinary ranks and ground staff [146] (a difference not seen in U.S. forces) is also understandable by differences in childhood exposure rates secondary to socioeconomic disparities.

Epidemic (Icteric) Hepatitis

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 reported. Epidemics of jaundice from hepatitis A (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 geographic whereabouts. The percentage of cases manifesting specific symptoms and signs in three series is shown in Tables II and III. 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 13 were less than 15 years old. [147] In contrast, the cases in the military epidemics of World War II reflected the ages of the troops, with the majority ranging in age from 19 to 40 years old. [148, 149]

Pre-icteric phase: After an incubation phase of 15-50 days (mean 30 days), most infected persons developed non-specific constitutional symptoms followed by gastrointestinal symptoms. This pre-icteric or prodromal period averaged 5-7 days but varied in length from 1 day to more than 2 weeks. [147, 148, 149] In approximately 15% of cases, however, there was no obvious prodrome before

Table III: Physical Examination Findings in Epidemic Jaundice

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

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 non-specificity 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%.[150] Only the icteric cases were truly infected, all the supposedly anicteric cases were not.

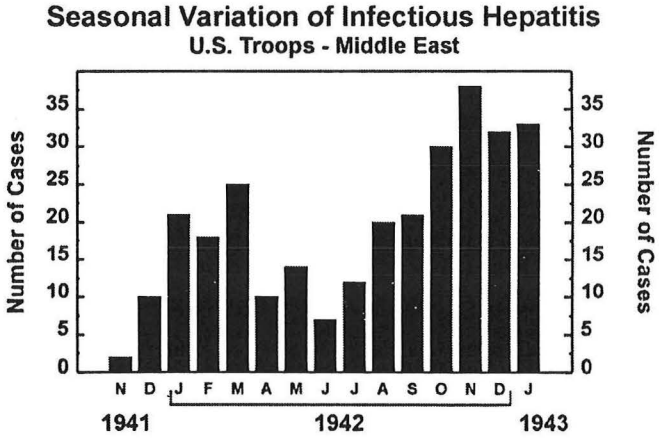
Icteric phase: The onset of the icteric phase is heralded by dark urine (conjugated bilirubin) before jaundice becomes apparent. The nonspecific and gastrointestinal symptoms often subside but may persist. The duration of jaundice is quite variable. In the Detroit series, the mean length was 7 days with a range of 4 days to >22 days. [147] In contrast, the modal length reported by Havens was 20–29 days. [148] Actual quantitation of bilirubin (in mg/dl rather than the earlier 'icterus index') was not performed routinely until the 1950s, consequently precise levels from the older epidemics are sparse. The maximum bilirubin in 60 patients from Havens' series was 10.8 mg/dl. [148] In the series from the Rockefeller Institute Hospital in New York, [149] 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 where patients could be identified by biochemical, serologic or virologic means. Physical examination findings, apart from jaundice, occurred in approximately half the patients or fewer (Table III).

Disease duration, not unexpectedly, varied with the duration of jaundice. In Detroit, the mean length was15 days. This relatively short duration may be a reflection of their younger age. In Havens' cases, hospitalization length averaged 30 days, ranging from 7-87 days. Patients recovered uneventfully, relapse and other complications were uncommon in most series (3 relapses in 200 patients observed by Havens) [148] although Hoagland and Shank reported abnormalities of sulfobromothalein retention in 18.5% of cases after initial normalization. [149] 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.

Epidemic Hepatitis and War

Epidemics of jaundice are common in military medical history. Blumer reported that the first known epidemic in the U.S. was in conjunction with the War of 1812. [11] In "The Medical and Surgical History of the War of the Rebellion", Smart recorded 71,691 cases of jaundice in Federal troops. [151] Details in the individual histories are consistent with infectious hepatitis (hepatitis A). The peak incidence occurred in the fall and winter of 1863, also suggestive of the seasonal occurrence of hepatitis A. Cockayne quoted different statistics, 22,569 cases of epidemic jaundice with 161 deaths in 2,218,599 Federal troops during the war between the North and the South (10% infection rate, 0.7% case fatality rate). [6] 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 accurate.

In World War I, British, French and other Allied forces reported epidemics of jaundice starting in 1915 and continuing intermittently. [35] [152] [153] The Mesopotamian epidemic is curious in that Indian and British troops were equally affected and there was little evidence of person-to-person contact. [154] 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. In two recent studies, there was co-occurrence of hepatitis A and hepatitis E as causes of infection. Interestingly, 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 non-natives (tourists in Nepal, French troops in Djibouti). [155, 156] The U.S. escaped most 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 in the epidemics of World War II. [157]



Epidemic hepatitis in World War II: Campaign jaundice was of major military importance in World War

II. Epidemics occurred in British troops in Palestine in 1940-41 [15] and in Allied forces in North Africa in 1942-43; [146-149, 157] every theater of military operations was affected by the end of hostilities.[157] The large numbers of active servicemen involved is 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 [157] 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, 5-6 million cases in their armed forces over a three year period and more than 10 million estimated military and civilian cases during the war. [158]

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. [157] The success of the latter initiative is reported below and some of the transmission and clinical studies are specifically referenced herein.

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 glutamic oxaloacetic transaminase (GOT) with liver injury. [159] 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 hepatitis A following ingestion of infectious material. [57] Serum collected at the time of modest elevation of SGOT transmitted infection to additional recipients thereby 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. [29]

Careful analysis of a food-borne outbreak of hepatitis A at a naval facility in San Diego demonstrated that 14% of cases were asymptomatic and 30% were not jaundiced. 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 (Table IV). 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, CA for sporadic hepatitis A between 1985 and 1994 reveals virtually identical findings. [160] Arthralgias (19%) and rash (7%) were also observed in this cohort. Findings on physical examination were qualitatively similar in both epidemic and sporadic hepatitis A to those reported in earlier outbreaks.

Table IV: Findings on History Taking in Epidemic and Sporadic Hepatitis A

Symptom	Icteric Epidemic Cases* (hospitalized)	San Diego, CA 1974 (all)	Pasadena, CA 1985-1994 (hospitalized)
Anorexia	89%	71%	75%
Nausea, vomiting	79%	61%	**
Malaise	76%	76%	80%
Fever	52%	18%	58%
Headache	40%	19%	22%
Abdominal pain	54%	26%	41%

Table V: Physical Examination Findings in Epidemic and Sporadic Hepatitis A

Sign	Icteric Epidemic Cases* (hospitalized)	San Diego, CA 1974 (all cases)	Pasadena, CA 1985-1994 (hospitalized)
Hepatomegaly	55%	14%	78%
Hepatic tenderness	46%	39%	not stated
Splenomegaly	13%	3%	7%
Bradycardia	17%	-	-

* Mean data from Table III above

The ratio of anicteric to icteric cases (1:3.5) in the San Diego epidemic likely reflects the age of the susceptible 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 cases 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. [161] Clinically obvious disease, however, can occur even in infancy. In a series of 6 infants aged 2 weeks to 8 months reported by Linder *et al*, bilirubin levels were 5-12 mg/dl and the alkaline phosphatase was strikingly elevated (mean 5.9 fold, range 1.2-12.1 fold). [162] 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. [39] Thus, Ford observed that the rate of clinically apparent disease was much lower in children under 5 years of old (2 of 73 (3%), compared with 20 of 72 (28%) for 5-10 year old and 18 of 66 (27%) for 10-15 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. [39] 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." [163]

Table VI: Laboratory Investigations in Hospitalized Patients with Sporadic Hepatitis A

Test	Pasadena, CA 1985-1994	Dallas, TX 1997-1998 (14 in-patients at PMH)	
	mean peak	mean peak	range
Bilirubin	7 mg/dl	13.3 mg/dl*	4.9 - 46.4
Alkaline phosphatase	319 U/L	335 U/L	117 - 1104
GGT	-	579 IU/L	187 - 1753
AST	1,754 mIU/L	3,664 IU/L	428 - 10,420
ALT	1,952 mIU/L	3,628 IU/L	1,029 - 9,220
Albumin	-	2.6 g/dl	1.5 - 3.1
Globulin	-	4.0 g/dl	3.2 - 5.6
Prothrombin time	-	15.1 secs	11.7 - 26.4

* 10 mg/dl excluding patient with hemolysis and hepatitis A (bilirubin 46.4 mg/dl)

Laboratory Investigations in Acute Hepatitis A

As with the clinical symptoms and signs, there are no pathognomonic findings in the laboratory investigations that distinguish hepatitis A from other hepatotrophic viral hepatitides. The maximum elevation of alanine aminotransferase (ALT ≡ SGPT) and aspartate aminotransferase (AST ≡ SGOT) can be substantially higher than that observed in acute hepatitis B but there is a wide range. In general the height of the aminotransferases 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 ≤10 mg/dl in the absence of hemolysis, an indication that hepatitis A is usually not severe.

Variants – Relapsing, Prolonged and Cholestatic Hepatitis A

Relapses in the course of hepatitis A occur in some patients. [6, 148, 160, 164-167] Cockayne, for example, wrote that "Relapse may occur after it has completely disappeared..." [6] however, without the availability of specific diagnostic tests, the cases that he documents are difficult to distinguish from second infections with a different etiologic agent. Similar criticisms can be applied to most reports of relapse prior to the isolation of the hepatitis A virus and development of specific assays for the virus. However, the demonstration of hepatitis A virus in stool during the relapse [60] provides the best evidence of causality. The techniques of immune electron microscopy, radioimmunoassay and molecular hybridization were used, indicating that both protein and nucleic acid components of the virus were present and thereby suggesting continued infectivity.

Relapsing hepatitis A: The rate of relapse is variable, 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, California in the 10 years between 1985 and 1994. [60, 148, 160] The severity of symptoms and biochemical abnormalities during the second phase is essentially the same as that observed during the initial illness except for a tendency to greater cholestasis. [166, 167] The occurrence of a relapse necessarily lengthens the course and the overall duration of disease is similar to those with a prolonged (but not biphasic) illness. [166]

Prolonged hepatitis A: 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. [148] Complete follow-up of almost all the cases in the San Diego naval outbreak revealed a prolonged course (abnormal aminotransferases 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 PCR) may occur in patients with persistent elevation of alanine aminotransferase,[61] any patient with either relapse or a prolonged course should be regarded as potentially infectious.

Cholestatic hepatitis A: The occurrence of "cholangiolytic" or cholestatic variants of acute hepatitis A was described in 1984 [168] after the advent of specific diagnostic testing that permitted identification of the etiologic agent. Previous accounts of this variant, reviewed in [168], 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. [168] However, the report of persistent aminotransferase elevation and viral excretion with progressive hepatic fibrosis in one patient treated with corticosteroids [169] is cautionary for 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 U.S., less frequent than acetaminophen toxicity (60/295) and hepatitis B (30/295). [170] The fatality rate for hepatitis A is generally low, quoted as <1.5% of all hospitalized icteric cases. [8] Between 1983 and 1987, 381 deaths due to hepatitis A were reported to the CDC. [171] With ~30,000 reported cases yearly, this gives an estimated fatality rate of 1.3%, likely a maximum rate because of relative under-reporting of non-fatal disease. Fulminant disease occurs more frequently in adults than children [172] but can occur in childhood. [173] 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. [173] Other patients may survive following liver transplantation. [170, 173] Occasionally, hepatitis A infection recurs following transplantation. [174, 175]

In the largest recent epidemic, in Shanghai, where 292,301 cases were reported between January and March 1988, there were 32 deaths, [176] a minuscule fatality rate of 0.01%. In contrast, there were 5 deaths 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 patients with prolonged illness were classified as autoimmune hepatitis on the basis of positive anti-nuclear antibody (titer >1:640) and liver biopsies consistent with that diagnosis. They also died. Factors that contributed to mortality in those with severe disease include age (>40 years, deaths in 3 of 53 hospitalized patients older than 40 years) and other co-morbid conditions (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. [177] 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), [178] has not been confirmed by other investigators. [179] [180]

Chronic Hepatitis

The classic teaching for many years has been that hepatitis A infection does not cause chronic liver disease and there is no chronic carrier state. With the advent of highly sensitive assays for hepatitis A virus 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. [61] Does this represent chronic infection or one end of the normal spectrum? One patient had HAV RNA in stool (by PCR) 11 months after onset of illness, at which time he also had persistent aminotransferase elevation and detectable anti-HAV of IgM class. [62] 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, hepatitis A that was prolonged 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 [169] 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. [139] Furthermore, the titer of IgM anti-HAV is normally such that early in the course of infection samples are diluted 1:4000 before assaying, to avoid a false negative prozone effect. IgM class antibodies may be therefore 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.

Autoimmune liver disease and hepatitis A: Chronic liver disease can appear to follow acute hepatitis A but lack a direct etiologic relationship. [181-183] The triggering of autoimmune hepatitis by hepatitis A infection in 2 subjects was reported in 1991 in a prospective study of relatives of patients with autoimmune chronic active hepatitis. [181] With the overwhelming advantage of a prospective evaluation and the observation of autoimmune hepatitis occurring in 2 study subjects, these data are difficult to refute. Similarly, when aminotransferase levels are normal before hepatitis A infection and the illness is characterized as steroid-responsive liver disease that recurs on steroid withdrawal [182] the assumption of hepatitis A infection triggering or unmasking autoimmune hepatitis seems reasonable. However, when the diagnosis of autoimmune hepatitis is made in persons with concurrent hepatitis A infection, it is quite problematic since viral hepatitis is associated with anti-nuclear antibody positivity and the features on liver biopsy are sufficiently similar as to preclude absolute diagnoses.

Extra-hepatic Manifestations

A variety of extra-hepatic manifestations can be observed in patients with acute hepatitis A. In order of frequency as seen in 256 patients hospitalized in Tennessee in 1994-1995,[172] these include hemolysis (10 patients), acalculous cholecystitis (10 patients), acute renal failure (3 patients), pleural or pericardial effusion, acute reactive arthritis and pancreatitis (1 patient each). Neurologic manifestations, although not reported in this particular series, may also be seen.

Hemolysis: Hemolysis is precipitated by viral hepatitis, including hepatitis A, in patients with glucose-6-phosphate dehydrogenase deficiency. [184, 185] In addition, red cell survival in the absence of an underlying red cell abnormality can be shortened by acute infectious hepatitis (presumptive hepatitis A). [186] Hemolysis may be autoimmune in nature, associated with antibodies to triose phosphate isomerase, [187, 188] and can be severe.[189, 190] Other hematologic abnormalities include aplastic anemia, [191] autoimmune thrombocytopenic purpura, [192] and pure red cell aplasia, [193]

Acalculous cholecystitis: The exact pathogenesis of this complication 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. [194]

Immune complex syndromes: Occasionally, patients with hepatitis A infection manifest findings consistent with circulating immune complex formation. These include cutaneous vasculitis, arthritis and cryoglobulinemia. [118, 119, 195] Either IgM or IgG anti-HAV is detected in the cryoglobulins. [118, 119] The findings resolve spontaneously with resolution of the hepatitis A.

Acute renal failure: Interstitial nephritis, [196] renal failure with proteinuria and hypocomplementemia suggesting immune complex disease, [197] immune complex mesangial proliferative glomerulonephritis,[198, 199] and acute tubular necrosis [200, 201] 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 are not defined. Immune complex formation may be an important etiologic factor.

Pancreatitis: Most cases of acute pancreatitis complicating viral hepatitis occur in fulminant hepatitis (for review see reference 202). Occasionally, however, pancreatitis may be encountered in non-fulminant disease. [172, 202]

Neurologic Manifestations: Mononeuritis, [203] mononeuritis multiplex, [204] Guillain-Barré syndrome, [205] post-viral encephalitis, [206, 207] and transverse myelitis, [208] have been described in patients with acute hepatitis A. The etiology of these findings is uncertain, they may be caused by a vasculitis.

MANAGEMENT

There is no specific management necessary for most patients with uncomplicated hepatitis A infection. Common sense prescribes appropriate rest (when necessary) and diet (avoiding foods that may cause digestive discomfort, for example fatty food). In the past, however, strict bed rest until complete resolution of all findings 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. [149] They found that when hospitalization was delayed for 30 or more days, the illness lasted an average of 81 days. In contrast, when hospitalization occurred within the first 14 days, the illness lasted for an average 46 days. Their conclusions were that prompt hospitalization and freedom from activity were important. An alternative explanation would be that a slower, more sub-fulminant course was associated with a longer period until complete resolution and that the degree of bed rest (or necessity for hospitalization) were unproven. In 1969, a randomized study that compared "early and vigorous exercise" with traditional rest was published. [209] No difference in the duration of illness was observed with the institution of a deliberate exercise program. The definition of "early", however, was 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, the management is determined by the complications that develop and the availability of transplantation. Similarly, extra-hepatic manifestations such as renal failure and pancreatitis are managed in a routine manner. The expectation with all patients is for complete recovery without sequelae and this 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 its visualization and the development of assays for detection, prevention of clinical hepatitis A was achieved. [210] This was the result of a series of events. First, the recognition that human serum could attenuate or prevent clinical measles in susceptible individuals. [211] Convalescent serum (enriched in specific antibody) was superior to pooled adult serum and placental extract (containing passively transferred maternal antibody only) was ineffective. Secondly, the development of methods to separate serum into component fractions. [212] 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. [213 214]

History of Initial Use of Gamma Globulin: During the summer of 1944, an outbreak of hepatitis occurred at a children's camp near Philadelphia. [51] 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, [213] was consulted by Charles Brown, M.D. chairman of medicine at Temple University School of Medicine regarding the epidemic. Dr. Brown, who was called by the camp directors regarding the outbreak, knew that Dr. Stokes was director of the Commission on Measles and Mumps of the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in

the Army Preventive Medicine Service, Office of the Surgeon General, U.S. Army. An *ad hoc* committee of the Preventive Medicine Service, known as the Hepatitis Study Group, included Dr. Stokes and Capt. Neefe in Philadelphia (members of the Commission on Measles and Mumps) and Dr. Paul and Maj. Havens in New Haven (members of the Neurotropic Virus Disease Commission). [157] With knowledge of the effectiveness of gamma globulin in measles epidemics, Stokes and Neefe took the next step, using gamma globulin to prevent the transmission of epidemic hepatitis (hepatitis A). [210]

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 (0.15ml/lb body weight). At this dose, they used all the available gamma globulin, hence the difference in numbers in the two groups. [210] Confirmation of similar efficacy quickly followed, in both military [215] and civilian [216] populations. Immune serum (gamma) globulin (ISG) was protective for up to 9 months and doses as small as 0.01ml/lb body weight were effective. [56, 217]

Modern Use of Immune Serum Globulin Prophylaxis:[218] In 1989, immune globulin was used to arrest an ongoing outbreak of hepatitis A in a religious community. [161] Preliminary data indicated that persons under age 20 were uniformly susceptible whereas the vast majority of older individuals were predicted to be immune (16 of 18 (89%) tested were anti-HAV positive, IgM anti-HAV negative). After administration of gamma globulin (0.02ml/kg) to 2,287 individuals (total cost for vaccine and syringes $3,620), there were only 7 further cases of hepatitis A diagnosed between 2 weeks and 7 months after injection. The effectiveness of gamma globulin was calculated at 89%. [161] Low levels of neutralizing antibody can be detected in recipients after immune serum globulin administration, although commercial tests for antibody are negative.[218]

Anti-HAV titers: 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. [219] In one individual who developed acute hepatitis A, transmission of infection was calculated to have occurred 2 months after receiving 2.5 ml ISG. In a second individual in whom fatal hepatitis A developed, symptoms commenced 10½ weeks after inoculation. The titers of anti-HAV in the immune globulin preparations were 103 and 120 IU/ml, [219] lower than those previously reported for similar preparations. The minimum protective level in recipients of ISG is unknown [218] but estimates of 10 mIU/ml are used. Simple mathematics calculate that 2.5 ml would administer 300 IU (120 IU/ml) initially. If the volume of distribution was 3 L, 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. [220] The half-life time for the first interval (day 5 to 1 month) was 35 days and for the remaining 2 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 L, then the level falls below 10 mIU/ml before 11 weeks. These calculations are consistent with failure of protection after > 2-2½ months, as observed. [219]

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. [221] Usually, blood donation is declined from persons with a history of jaundice, however, with the ability to exclude anti-hepatitis B core antibody positive units and anti-hepatitis C virus antibody positive units, such practices may have to be reconsidered. Hopkins demonstrated a 10-fold higher titer of anti-HAV activity in immunoglobulin preparations from HBsAg-negative donors with a history of jaundice. [221]

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 and 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 hepatitis A virus vaccine was also capable of eliciting neutralizing antibody. [223] Unlike the inactivated vaccine, recipients developed IgM anti-HAV positivity without clinical hepatitis or evidence of significant liver dysfunction although 40% reported gastrointestinal side-effects.

Efficacy in preventing hepatitis A: By 1992, the clinical efficacy of formalin-inactivated hepatitis A vaccines, Havrix® (Smith-Kline Beecham) [224] and Vaqta® (Merck, Sharpe and Dohme) was apparent. [225] Both use laboratory-attenuated strains of HM175 hepatitis A for

production of formalin-inactivated vaccine. A large-scale, double-blind, randomized, controlled field trial in elementary school children in Thailand demonstrated efficacy of Havrix®. [64, 226] Of 40 cases of clinical hepatitis A that occurred amongst 40,119 children in the year following a single-dose of vaccine, only two were in vaccinated individuals. [64] The adverse reactions reported for the vaccine were minimal and seroconversion after 2 doses was 99.8% in healthy individuals. [224]

Control of hepatitis A outbreaks by vaccination: In a double-blind, placebo-controlled trial the Vaqta® vaccine was administered to 519 seronegative children aged 2 to 16 years old living in a religious community in New York 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 occurred in the placebo group. The 7 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 [227] and in rural communities in Alaska,.[228] were controlled with vaccination programs.

Combination studies: Combined passive-active immunoprophylaxis is also effective, [220, 224, 229] although titers achieved are generally lower than with vaccine only. [220, 229] In addition, combined hepatitis A and hepatitis B vaccination can be undertaken. [224, 230]

Licensure in U.S.: The Food and Drug Administration licensed Havrix® in February 1995 for administration to children ≥2 years old and adults. The CDC recommendations included use for international travelers to areas other than Western Europe, Scandinavia, Canada, Japan, Australia and New Zealand. They indicated that screening for pre-existing antibody should be considered in potential recipients aged >40 years and those who had resided in areas of high endemicity (see below). Vaqta® has also been licensed in the U.S. by the FDA. In addition to travelers, the American College of Physicians recommends that other high risk groups be vaccinated. [231] These include homosexual men, injection drug users, persons with chronic liver disease and workers with an occupational risk of infection.

Vaccination of persons with chronic disease: 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 2 separate studies, [232, 233] although most patients (94% [233]) did achieve detectable antibody. Similarly, titers were lower in homosexual men with human immunodeficiency virus infection than in those without HIV infection, [234, 235] and overall seroconversion rates were somewhat lower (88% in reference [235] compared with 100% in non-HIV individuals). The vaccines were well tolerated in all studies.

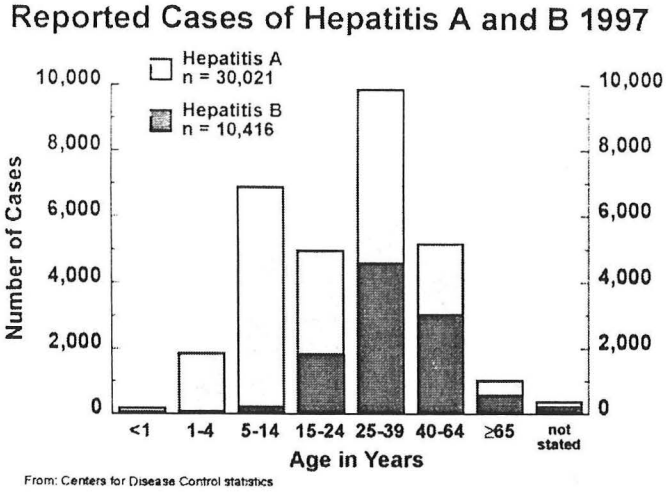
Screening before vaccination: Considerable differences exist in recommendations for serologic screening before vaccination.[236-238] The aim is to reduce the cost of vaccination by eliminating those with previous natural infection. The economics are determined by the rate of seropositivity, the cost 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), therefore, the costs of screening before vaccination and of vaccinating all persons are identical if the screening cost (total anti-HAV testing) is ⅓ 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.

We have analyzed seropositivity in the PMH Liver Clinic population with chronic hepatitis C infection. 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 <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, however, vaccination without screening appears to be rational in non-Hispanic Caucasians.

Why Prevent Hepatitis A - a generally mild disease without chronicity?

Different populations have different goals. Governments want to save money, armies want to have healthy troops and travelers want to enjoy their vacations.

Cost of hepatitis A outbreaks: The cost of hepatitis A infection is calculated as ~$200,000,000 annually in the U.S. The cost of a food-borne outbreak of hepatitis A in



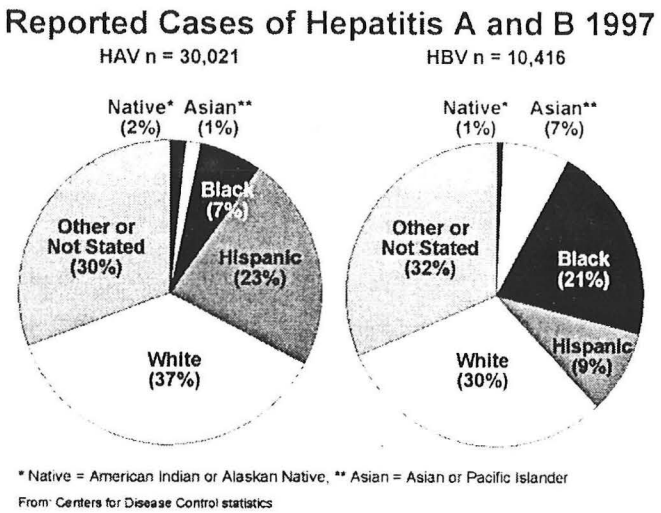


Table VII: Incidence of Reported Cases of Acute Hepatitis A in the U.S.

Site	/100,000 Population 1985-1994	1996	1997
U.S.		31,032	30,021
California	21.9	6,653	6,422
Texas	15.0	3,460	4,511
Arizona	48.1	1,767	2,330
Oklahoma	12.5	2,586	1,445
Michigan	(rank below 15)	506	1,372
New York	3.6	1,047	1,302
Missouri	14.4	1,414	1,151
Washington	5.6	1,001	1,015
Utah	27.2	1,073	550

From: The Centers for Disease Control statistics

Denver, for example, was calculated to be $689,314 for disease control costs, including $450,397 for 16,293 ISG injections. [239] The medical costs for hepatitis A cases requiring hospitalization are estimated to be $1,070 - $2,460. [239] [240] Economic analysis indicates that either universal vaccination or screening/vaccination should be considered in developed countries. [241]

Which travelers (and military personnel) should be vaccinated?: An estimate of 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. [242] In heterogeneous populations, particularly those with immigrants, the overall prevalence of anti-HAV is predictably higher and differs with birthplace, for example 45% anti-HAV positivity in U.K.-born Londoners but 70% in those born in a foreign country. [243] 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 in gypsy children aged 1 to 14 years compared with 46% for children in an orphanage and 23% for non-gypsy families. [244] In Italy, seropositive rates are higher in the southern part of the country, 27% anti-HAV positivity in the 3 to 19 year old age group, compared with 5% in northern Italy. [245] In U.S. military personnel, deployment in the Carribean was associated with an increased seroprevalence rate. [246] Consistent with endemicity in the Carribean, 73% of children 2-4 years of age in Nicaragua

were seropositive. [144] At the far end of the spectrum, 97% of elementary school children in Sierra Leone were anti-HAV positive [247] as were 99% of Australian aboriginals older than 20 years of age living at the "top end" of the Northern Territory, [248] 100% of Egyptian village children aged 1-3 years were seropositive [143] and 100% of Indian children in Pune were anti-HAV positive by late childhood.[145]

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. Even in the U.S. there may be travel risks!

References

1. Levine, AJ: The origins of virology. *In* Virology, (ed Fields, B. N. and Knipe, D. M. et al.), Raven Press, New York; 1-14, 1996.
2. Oldstone, MBA *In* Viruses, plagues, and history, (ed Oldstone, MBA), Oxford University Press, New York; , 1998.
3. Reed, W: Recent researches concerning the etiology, propagation, and prevention of yellow fever by the United States Army Commission. *J Hyg* **2:** 101-119, 1902.
4. (Editorial): Epidemic hepatitis, or catarrhal jaundice. *JAMA* **123:** 636-637, 1943.
5. Medawar, PB and JS Medawar *In* Aristotle to Zoos, (ed Medawar, PB and JS Medawar), Cambridge; , 1983.
6. Cockayne, EA: Catarrhal jaundice, sporadic and epidemic, and its relation to acute yellow atrophy of the liver. *Q J Med* **6:** 1-29, 1912.
7. Zuckerman, AJ: Viral hepatitis and the Australia-SH antigen. *Nature* **223:** 569-572, 1969.
8. Hollinger, FB and J Ticehurst: Hepatitis A virus. *In* Virology, (ed Fields, B. N. and Knipe, D. M. et al.), Raven Press, New York; 735-782, 1996.
9. M'Donald, S: Acute yellow atrophy of the liver. *Edin Med J* **1:** 83-88, 1908.
10. Willcox, WH: Jaundice: With special reference to types occurring during the war. Pathology, diagnosis and treatment. *Br Med J* **1:** 565-569, 605-610, 639-642, 671-675, 706-709, 1919.
11. Blumer, G: Infectious jaundice in the United States. *JAMA* **81:** 353-358, 1923.
12. Findlay, GM, JL Dunlop and HC Brown: Observations on epidemic catarrhal jaundice. *Trans Roy Soc Trop Med Hyg* **25:** 7-24, 1931.
13. Voegt, H: Zur aetiologie der hepatitis epidemica. *Münch Med Wochenschr* **89:** 76-79, 1942.
14. Findlay, GM and NH Martin: Jaundice following yellow-fever immunisation. *Lancet* **i:** 678-680, 1943.
15. Cameron, JDS: Infective hepatitis. *Q J Med* **12:** 139-155, 1943.
16. Holmes, AW, LRH Wolfe and F Deinhardt: Hepatitis in marmosets: Induction of disease with coded specimens from a human volunteer study. *Science* **165:** 816-817, 1969.
17. Pickles, WN: Epidemic catarrhal jaundice. An outbreak in Yorkshire. *Br Med J* **1:** 944-946, 1930.
18. Lemon, SM, RW Jansen and EA Brown: Genetic, antigenic and biological differences between strains of hepatitis A virus. *Vaccine* **10:** S40-4, 1992.
19. Provost, PJ and MR Hilleman: Propagation of human hepatitis A virus in cell culture in vitro. *Proc Soc Exp Biol Med* **160:** 213-221, 1979.
20. Shavrina Asher, LV, LN Binn, TL Mensing, RH Marchwicki, RA Vassell and GD Young: Pathogenesis of hepatitis A in orally inoculated owl monkeys (Aotus trivirgatus). *J Med Virol* **47:** 260-268, 1995.
21. Kaplan, G, A Totsuka, P Thompson, T Akatsuka, Y Moritsugu and SM Feinstone: Identification of a surface glycoprotein on African green monkey kidney cells as a receptor for hepatitis A virus. *EMBO J* **15:** 4282-4296, 1996.
22. Ashida, M and C Hamada: Molecular cloning of the hepatitis A virus receptor from a Simian cell line. *J Gen Virol* **78:** 1565-1569, 1997.
23. Feigelstock, D, P Thompson, P Mattoo and GG Kaplan: Polymorphisms of the hepatitis A virus cellular receptor 1 in African green monkey kidney cells result in antigenic variants that do not react with protective monoclonal antibody 190/4. *J Virol* **72:** 6218-6222, 1998.
24. Krugman, S, R Ward and JP Giles: The natural history of infectious hepatitis. *Am J Med* **32:** 717-728, 1962.
25. Coulpis, AG, SA Locarnini, NI Lehmann and ID Gust: Detection of hepatitis A virus in the feces of patients with naturally acquired infection. *J Infect Dis* **141:** 151-156, 1980.
26. Ticehurst, JR, SM Feinstone, T Chestnut, NC Tassopoulos, H Popper and RH Purcell: Detection of hepatitis A virus by extraction of viral RNA and molecular hybridization. *J Clin Microbiol* **25:** 1822-9, 1987.
27. Feinstone, SM, AZ Kapikian and RH Purcell: Hepatitis A: Detection by immune electron microscopy of a virus-like antigen associated with acute illness. *Science* **182:** 1026-1028, 1973.
28. Boggs, JD, JL Melnick, ME Conrad and BF Felsher: Viral hepatitis. Clinical and tissue culture studies. *JAMA* **214:** 1041-1046, 1970 Nov 9.
29. Krugman, S, JP Giles and J Hammond: Infectious hepatitis. Evidence for two distinctive clinical, epidemiological, and immunological types of infection. *JAMA* **200:** 365-73, 1967.
30. Gravelle, CR, CL Hornbeck, JE Maynard, CA Schable, EH Cook and DW Bradley: Hepatitis A: Report of a common-source outbreak with recovery of a possible etiologic agent. II. Laboratory studies. *J Infect Dis* **131:** 167-181, 1975 Feb.
31. Dienstag, JL, SM Feinstone, AZ Kapikian, RH Purcell, JD Boggs and ME Conrad: Faecal shedding of hepatitis-A antigen. *Lancet* **ii:** 765-767, 1975.
32. Dienstag, JL, JA Routenberg, RH Purcell, RR Hooper and WO Harrison: Foodhandler-associated outbreak of hepatitis type A. An immune electron microscopy study. *Ann Intern Med* **83:** 647-650, 1975.
33. Mannucci, PM, S Gdovin, A Gringeri, M Colombo, A Mele, N Schinaia, N Ciavarella, SU Emerson and RH Purcell: Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. The Italian Collaborative Group. *Ann Intern Med* **120:** 1-7, 1994 Jan 1.
34. Anonymous: Hepatitis A among persons with hemophilia who received clotting factor concentrate--United States, September-December 1995. *MMWR Morb Mortal Wkly Rep* **45:** 29-32, 1996.
35. Willcox, WH: The epidemic jaundice of campaigns. *Br Med J* **1:** 1916.
36. Glover, JA and J Wilson: An extensive epidemic of catarrhal jaundice. *Lancet* **i:** 722-725, 1931.
37. Lisney, AA: Epidemic catarrhal jaundice in school children. *Br Med J* **1:** 703-706, 1937.
38. Cullinan, ER: The epidemiology of jaundice. *Proc Roy Soc Med* **32:** 933-945 (discussion 945-950), 1939.

39. Ford, JC: Infective hepatitis: 300 cases in an outer London borough. *Lancet* **i:** 675-678, 1943.
40. Andersen, TT: The etiology of hepatitis epidemica. *Acta Med Scand* **93:** 209-227, 1937.
41. Norton, JA: Acute infectious jaundice. *JAMA* **113:** 916-917, 1939.
42. Memorandum prepared by medical officers of the Ministry of Health: Homologous serum jaundice. *Lancet* **i:** 83-88, 1943.
43. Findlay, GM and FO MacCallum: Note on acute hepatitis and yellow fever immunization. *Trans Roy Soc Trop Med Hyg* **31:** 297-308, 1937.
44. Findlay, GM and FO MacCallum: Hepatitis and jaundice associated with immunization against certain virus diseases. *Proc Roy Soc Med* **31:** 799-805 (discussion 806), 1938.
45. Findlay, GM, FO MacCallum and F Murgatroyd: Observations bearing on the aetiology of infective hepatitis (so-called epidemic catarrhal jaundice). *Trans Roy Soc Trop Med Hyg* **32:** 575-586, 1939.
46. Havens Jr., WP, R Ward, VA Drill and JR Paul: Experimental production of hepatitis by feeding icterogenic materials. *Proc Soc Exp Biol Med* **57:** 206-208, 1944.
47. Mayo, H: personal communication. 1999.
48. Havens, WP: Period of infectivity of patients with experimentally induced infectious hepatitis. *J Exp Med* **83:** 215-258, 1946.
49. Paul, JR, WP Havens, AB Sabin and CB Philip: Transmission experiments in serum jaundice and infectious hepatitis. *JAMA* **128:** 911-915, 1945.
50. Paul, JR and WP Havens Jr.: Recent advances in the study of infectious hepatitis and serum jaundice. *Trans Assoc Am Phys* **59:** 133-141, 1946.
51. Neefe, JR and J Stokes Jr.: An epidemic of infectious hepatitis apparently due to a water-borne agent. *JAMA* **128:** 1063-1075, 1945.
52. MacCallum, FO and WH Bradley: Transmission of infective hepatitis to human volunteers. *Lancet* **ii:** 228, 1944.
53. Editorial: Homologous serum hepatitis. *Lancet* **ii:** 691-692, 1947.
54. Havens, WP: The etiology of infectious hepatitis. *JAMA* **134:** 653-655, 1947.
55. Stokes Jr., J, E Berk, LL Malamut, ME Drake, JA Barondess, WJ Bashe, IJ Wolman, JD Farquhar, B Bevan, RJ Drummond, Wd Maycock, RB Capps and AM Bennett: The carrier state in viral hepatitis. *JAMA* **154:** 1059-1065, 1954.
56. Ward, R, S Krugman, JP Giles, AM Jacobs and O Bodansky: Infectious hepatitis: Studies of its natural history and prevention of viral hepatitis. *N Engl J Med* **258:** 407-416, 1958.
57. Krugman, S, R Ward, JP Giles, D Bodansky and AM Jacobs: Infectious hepatitis: detection of virus during the incubation period and in clinically inapparent infection. *N Engl J Med* **261:** 729-734, 1959.
58. Goldby, S: Experiments at the Willowbrook State School. *Lancet* **i:** 749, 1971.
59. Mbithi, JN, VS Springthorpe, JR Boulet and SA Sattar: Survival of hepatitis A virus on human hands and its transfer on contact with animate and inanimate surfaces. *J Clin Microbiol* **30:** 757-63, 1992.
60. Sjogren, MH, H Tanno, O Fay, S Sileoni, BD Cohen, DS Burke and RJ Feighny: Hepatitis A virus in stool during clinical relapse. *Ann Intern Med* **106:** 221-6, 1987.
61. Yotsuyanagi, H, K Koike, K Yasuda, K Moriya, Y Shintani, H Fujie, K Kurokawa and S Iino: Prolonged fecal excretion of hepatitis A virus in adult patients with hepatitis A as determined by polymerase chain reaction. *Hepatology* **24:** 10-3, 1996.
62. Inoue, K, M Yoshiba, H Yotsuyanagi, T Otsuka, K Sekiyama and R Fujita: Chronic hepatitis A with persistent viral replication. *J Med Virol* **50:** 322-4, 1996.
63. Rosenblum, LS, ME Villarino, OV Nainan, ME Melish, SC Hadler, PP Pinsky, WR Jarvis, CE Ott and HS Margolis: Hepatitis A outbreak in a neonatal intensive care unit: risk factors for transmission and evidence of prolonged viral excretion among preterm infants. *J Infect Dis* **164:** 476-82, 1991.
64. Innis, BL, R Snitbhan, P Kunasol, T Laorakpongse, W Poopatanakool, CA Kozik, S Suntayakorn, T Suknuntapong, A Safary, DB Tang and JW Boslego: Protection against hepatitis A by an inactivated vaccine. *JAMA* **271:** 1328-34, 1994.
65. Dienstag, JL, ID Gust, CR Lucas, DC Wong and RH Purcell: Mussel-associated viral hepatitis, type A: Serological confirmation. *Lancet* **i:** 561-564, 1976.
66. Desenclos, JC, KC Klontz, MH Wilder, OV Nainan, HS Margolis and RA Gunn: A multistate outbreak of hepatitis A caused by the consumption of raw oysters. *Am J Public Health* **81:** 1268-72, 1991.
67. O'Mahony, MC, CD Gooch, DA Smyth, AJ Thrussell, CLR Bartlett and ND Noah: Epidemic hepatitis A from cockles. *Lancet* **i:** 518-520, 1983.
68. Arnal, C, JM Crance, C Gantzer, L Schwartzbrod, R Deloince and S Billaudel: Persistence of infectious hepatitis A virus and its genome in artificial seawater. *Zentralbl Hyg Umweltmed* **201:** 279-284, 1998.
69. Rosenblum, LS, IR Mirkin, DT Allen, S Safford and SC Hadler: A multifocal outbreak of hepatitis A traced to commercially distributed lettuce. *Am J Public Health* **80:** 1075-9, 1990 Sep.
70. Beller, M: Hepatitis A outbreak in Anchorage, Alaska, traced to ice slush beverages. *West J Med* **156:** 624-7, 1992 Jun.
71. Niu, MT, LB Polish, BH Robertson, BK Khanna, BA Woodruff, CN Shapiro, MA Miller, JD Smith, JK Gedrose, MJ Alter and al et: Multistate outbreak of hepatitis A associated with frozen strawberries. *J Infect Dis* **166:** 518-24, 1992.
72. Anonymous: Hepatitis A associated with consumption of frozen strawberries--Michigan, March 1997. *MMWR Morb Mortal Wkly Rep* **46:** 288, 295, 1997.
73. Lowry, PW, R Levine, DF Stroup, RA Gunn, MH Wilder and C Konigsberg Jr: Hepatitis A outbreak on a floating restaurant in Florida, 1986. *Am J Epidemiol* **129:** 155-64, 1989.
74. Pebody, RG, T Leino, P Ruutu, L Kinnunen, I Davidkin, H Nohynek and P Leinikki: Foodborne outbreaks of hepatitis A in a low endemic country: an emerging problem?. *Epidemiol Infect* **120:** 55-9, 1998.
75. Bloch, AB, SL Stramer, JD Smith, HS Margolis, HA Fields, TW McKinley, CP Gerba, JE Maynard and RK Sikes: Recovery of hepatitis A virus from a water supply responsible for a common source outbreak of hepatitis A. *Am J Public Health* **80:** 428-30, 1990.
76. Mahoney, FJ, TA Farley, KY Kelso, SA Wilson, JM Horan and LM McFarland: An outbreak of hepatitis A associated with swimming in a public pool. *J Infect Dis* **165:** 613-8, 1992.
77. De Serres, G and D Laliberte: Hepatitis A among workers from a waste water treatment plant during a small community outbreak. *Occup Environ Med* **54:** 60-2, 1997 Jan.
78. Divizia, M, V Ruscio, AM Degener and A Pana: Hepatitis A virus detection in wastewater by PCR and hybridization. *New Microbiol* **21:** 161-7, 1998.
79. Goodman, RA: Nosocomial hepatitis A. *Ann Intern Med* **103:** 452-4, 1985.
80. Goodman, RA, CC Carder, JR Allen, WA Orenstein and RJ

Finton: Nosocomial hepatitis A transmission by an adult patient with diarrhea. *Am J Med* **73:** 220-226, 1982.
81. Klein, BS, JA Michaels, MW Rytel, KG Berg and JP Davis: Nosocomial hepatitis A. A multinursery outbreak in Wisconsin. *JAMA* **252:** 2716-2721, 1984.
82. Doebbeling, BN, N Li and RP Wenzel: An outbreak of hepatitis A among health care workers: risk factors for transmission [see comments]. *Am J Public Health* **83:** 1679-84, 1993.
83. Burkholder, BT, VG Coronado, J Brown, JH Hutto, CN Shapiro, B Robertson and BA Woodruff: Nosocomial transmission of hepatitis A in a pediatric hospital traced to an anti-hepatitis A virus-negative patient with immunodeficiency. *Pediatr Infect Dis J* **14:** 261-6, 1995 .
84. Hanna, JN, MR Loewenthal, P Negel and DJ Wenck: An outbreak of hepatitis A in an intensive care unit. *Anaesth Intensive Care* **24:** 440-444, 1996.
85. Leikin, E, A Lysikiewicz, D Garry and N Tejani: Intrauterine transmission of hepatitis A virus. *Obstet Gynecol* **88:** 690-1, 1996.
86. Erkan, T, T Kutlu, F Cullu and GT Tumay: A case of vertical transmission of hepatitis A virus infection. *Acta Paediatr* **87:** 1008-1009, 1998.
87. Watson, JC, DW Fleming, AJ Borella, ES Olcott, RE Conrad and RC Baron: Vertical transmission of hepatitis A resulting in an outbreak in a neonatal intensive care unit. *J Infect Dis* **167:** 567-71, 1993.
88. Sherertz, RJ, BA Russell and PD Reuman: Transmission of hepatitis A by transfusion of blood products. *Arch Intern Med* **144:** 1579-80, 1984.
89. Noble, RC, MA Kane, SA Reeves and I Roeckel: Posttransfusion hepatitis A in a neonatal intensive care unit. *JAMA* **252:** 2711-2715, 1984.
90. Meyers, JD, JC Huff, KK Holmes, ED Thomas and JA Bryan: Parenterally transmitted hepatitis A associated with platelet transfusions. Epidemiologic study of an outbreak in a marrow transplantation center. *Ann Intern Med* **81:** 145-151, 1974.
91. Weisfuse, IB, DJ Graham, M Will, D Parkinson, DR Snydman, M Atkins, RA Karron, S Feinstone, AA Rayner, RI Fisher and al et: An outbreak of hepatitis A among cancer patients treated with interleukin-2 and lymphokine-activated killer cells. *J Infect Dis* **161:** 647-52, 1990.
92. Barrett, PN, H Meyer, I Wachtel, J Eibl and F Dorner: Inactivation of hepatitis A virus in plasma products by vapor heating. *Transfusion* **37:** 215-20, 1997.
93. Anonymous: Hepatitis A among drug abusers. *MMWR Morb Mortal Wkly Rep* **37:** 297-300, 305, 1988.
94. Grinde, B, K Stene-Johansen, B Sharma, T Hoel, M Jensenius and K Skaug: Characterisation of an epidemic of hepatitis A virus involving intravenous drug abusers--infection by needle sharing?. *J Med Virol* **53:** 69-75, 1997.
95. Sundkvist, T, B Johansson and A Widell: Rectum carried drugs may spread hepatitis A among drug addicts. *Scand J Infect Dis* **17:** 1-4, 1985.
96. Ballesteros, J, R Dal-Re, A Gonzalez and J del Romero: Are homosexual males a risk group for hepatitis A infection in intermediate endemicity areas?. *Epidemiol Infect* **117:** 145-8, 1996.
97. Krook, A, J Albert, S Andersson, G Biberfeld, J Blomberg, I Eklund, A Engstrom, I Julander, K Kall, C Martin, P Stendahl, J Struve and A Sonnerborg: Prevalence and risk factors for HTLV-II infection in 913 injecting drug users in Stockholm, 1994. *J Acquir Immune Defic Syndr Hum Retrovirol* **15:** 381-6, 1997.
98. Wang, CH, SY Tschen, U Heinricy, M Weber and B Flehmig: Immune response to hepatitis A virus capsid proteins after infection. *J Clin Microbiol* **34:** 707-13, 1996 .
99. Villano, SA, KE Nelson, D Vlahov, RH Purcell, AJ Saah and DL Thomas: Hepatitis A among homosexual men and injection drug users: more evidence for vaccination. *Clin Infect Dis* **25:** 726-8, 1997 Sep.
100. Szmuness, W, JL Dienstag, RH Purcell, EJ Harley, CE Stevens and DC Wong: Distribution of antibody to hepatitis A antigen in urban adult populations. *N Engl J Med* **295:** 755-759, 1976.
101. Corey, L and KK Holmes: Sexual transmission of hepatitis A in homosexual men: incidence and mechanism. *N Engl J Med* **302:** 435-8, 1980.
102. Anonymous: Hepatitis A among homosexual men--United States, Canada, and Australia. *MMWR Morb Mortal Wkly Rep* **41:** 155, 161-164, 1992 Mar 6.
103. Henning, KJ, E Bell, J Braun and ND Barker: A community-wide outbreak of hepatitis A: risk factors for infection among homosexual and bisexual men. *Am J Med* **99:** 132-6, 1995 .
104. Anonymous: Hepatitis A vaccination of men who have sex with men--Atlanta, Georgia, 1996-1997. *MMWR Morb Mortal Wkly Rep* **47:** 708-11, 1998.
105. Hansen, HL, PL Andersen, L Brandt and O Brolos: Antibodies against hepatitis viruses in merchant seamen. *Scand J Infect Dis* **27:** 191-4, 1995.
106. Findlay, GM and JL Dunlop: A fatal case of acute necrosis of the liver associated with epidemic catarrhal jaundice. *Br Med J* **1:** 652-656, 1932.
107. Gaskell, JF: The changes in the liver in a fatal case of epidemic "catarrhal" jaundice. *J Path Bact* **36:** 257-262, 1933.
108. Iversen, P and K Roholm: On aspiration biopsy of the liver, with remarks on its diagnostic significance. *Acta Med Scand* **102:** 1-16, 1939.
109. Roholm, K and P Iversen: Changes in the liver in acute epidemic hepatitis (catarrhal jaundice) based on 38 aspiration biopsies. *Acta Path Microbiol Scand* **16:** 427-442, 1939.
110. Dible, JH, J McMichael and SPV Sherlock: Pathology of acute hepatitis. Aspiration biopsy studies of epidemic, arsenotherapy and serum jaundice. *Lancet* **ii:** 402-408, 1943.
111. Mallory, TB: The pathology of epidemic hepatitis. *JAMA* **134:** 655-662, 1947.
112. Kryger, P and P Christoffersen: Liver histopathology of the hepatitis A virus infection: a comparison with hepatitis type B and non-A, non-B. *J Clin Pathol* **36:** 650-654, 1983.
113. Ponz, E, JC Garcia-Pagan, M Bruguera, J Bruix and J Rodes: Hepatic fibrin-ring granulomas in a patient with hepatitis A. *Gastroenterology* **100:** 268-70, 1991.
114. Yamamoto, T, M Ishii, H Nagura, Y Miyazaki, M Miura, T Igarashi and T Toyota: Transient hepatic fibrin-ring granulomas in a patient with acute hepatitis A. *Liver* **15:** 276-9, 1995.
115. Taylor, M, RD Goldin, S Ladva, PJ Scheuer and HC Thomas: In situ hybridization studies of hepatitis A viral RNA in patients with acute hepatitis A. *J Hepatol* **20:** 380-7, 1994.
116. Margolis, HS and OV Nainan: Identification of virus components in circulating immune complexes isolated during hepatitis A virus infection. *Hepatology* **11:** 31-7, 1990.
117. Tsai, JF, HS Margolis, JE Jeng, MS Ho, WY Chang, MY Hsieh, ZY Lin and JH Tsai: Increased IgM class circulating immune complexes in acute hepatitis A virus infection. *Clin Immunol Immunopathol* **78:** 291-5, 1996.
118. Inman, RD, M Hodge, ME Johnston, J Wright and J Heathcote: Arthritis, vasculitis, and cryoglobulinemia associated with relapsing hepatitis A virus infection. *Ann Intern Med* **105:** 700-3, 1986.
119. Ilan, Y, M Hillman, R Oren, A Zlotogorski and D Shouval: Vasculitis and cryoglobulinemia associated with persisting

cholestatic hepatitis A virus infection. *Am J Gastroenterol* **85:** 586-7, 1990.
120. Stapleton, JT: Host immune response to hepatitis A virus. *J Infect Dis* **171:** S9-14, 1995.
121. Mosley, JW, KA Visoná and VM Villarejos: Immunoglobulin M level in the diagnosis of type A hepatitis. *Am J Clin Pathol* **75:** 86-87, 1981.
122. Stapleton, JT, DK Lange, JW LeDuc, LN Binn, RW Jansen and SM Lemon: The role of secretory immunity in hepatitis A virus infection. *J Infect Dis* **163:** 7-11, 1991.
123. Black, FL and DL Jacobson: Hepatitis A antibody in an isolated Amerindian tribe fifty years after exposure. *J Med Virol* **19:** 19-21, 1986.
124. Vallbracht, A, P Gabriel, K Maier, F Hartmann, HJ Steinhardt, C Muller, A Wolf, KH Manncke and B Flehmig: Cell-mediated cytotoxicity in hepatitis A virus infection. *Hepatology* **6:** 1308-14, 1986.
125. Fleischer, B, S Fleischer, K Maier, KH Wiedmann, M Sacher, H Thaler and A Vallbracht: Clonal analysis of infiltrating T lymphocytes in liver tissue in viral hepatitis A. *Immunology* **69:** 14-9, 1990.
126. Kurane, I, LN Binn, WH Bancroft and FA Ennis: Human lymphocyte responses to hepatitis A virus-infected cells: interferon production and lysis of infected cells. *J Immunol* **135:** 2140-4, 1985.
127. Provost, JJ, OL Ittensohn, VM Villarejos and MR Hilleman: A specific complement-fixation test for human hepatitis A employing CR 326 virus antigen. Diagnosis and epidemiology. *Proc Soc Exp Biol Med* **148:** 962-968, 1975.
128. Miller, WJ, PJ Provost and WJ*ea* McAleer: Specific immune adherence assay for human hepatitis A antibody. Application to diagnostic and epidemiologic investigations. *Proc Soc Exp Biol Med* **149:** 254-261, 1975.
129. Yoshizawa, H, Y Itoh, S Iwakiri and *et al*: Diagnosis of type A hepatitis by fecal IgA antibody against hepatitis A antigen. *Gastroenterology* **78:** 114-118, 1980.
130. Purcell, RH, DC Wong, Y Moritsugu, JL Dienstag, JA Routenberg and JD Boggs: A microtiter solid phase radioimmunoassay for hepatitis A antigen and antibody. *J Immunol* **116:** 349-356, 1976.
131. Dienstag, JL, S Krugman, DC Wong and RH Purcell: Comparison of serological tests for antibody to hepatitis A antigen, using coded specimens from individuals infected with the MS-1 strain of hepatitis A virus. *Infect Immun* **14:** 1000-3, 1976.
132. Bradley, DW, JE Maynard, SH Hindman, CL Hornbeck, HA Fields, KA McCaustland and EH Cook Jr: Serodiagnosis of viral hepatitis A: detection of acute-phase immunoglobulin M anti-hepatitis A virus by radioimmunoassay. *J Clin Microbiol* **5:** 521-30, 1977.
133. Bradley, DW, HA Fields, KA McCaustland, JE Maynard, RH Decker, R Whittington and LR Overby: Serodiagnosis of viral hepatitis A by a modified competitive binding radioimmunoassay for immunoglobulin M anti-hepatitis A virus. *J Clin Microbiol* **9:** 120-7, 1979.
134. Decker, RH, SM Kosakowski, AS Vanderbilt, CM Ling, R Chairez and LR Overby: Diagnosis of acute hepatitis A by HAVAB-M, a direct radioimmunoassay for IgM anti-HAV. *Am J Clin Pathol* **76:** 140-7, 1981.
135. Storch, GA, C Bodicky, M Parker, LJ Blecka and RD Aach: Use of conventional and IgM-specific radioimmunoassays for anti-hepatitis A antibody in an outbreak of hepatitis A. *Am J Med* **73:** 663-8, 1982.
136. Hirata, R, Y Hoshino, H Sakai, F Marumo and C Sato: Patients with hepatitis A with negative IgM-HA antibody at early stages. *Am J Gastroenterol* **90:** 1168-9, 1995 Jul.
137. Fikar, CR and C McKee: False positivity of IgM antibody to Epstein-Barr viral capsid antigen during acute hepatitis A infection. *Pediatr Infect Dis* **13:** 413-414, 1994 May.
138. Kao, HW, M Ashcavai and AG Redeker: The persistence of hepatitis A IgM antibody after acute clinical hepatitis A. *Hepatology* **4:** 933-6, 1984.
139. Sikuler, E, A Keynan, N Hanuka, G Zagron-Bachir and I Sarov: Persistence of a positive test for IgM antibodies to hepatitis A virus in late convalescent sera. *Isr J Med Sci* **23:** 193-5, 1987.
140. Ochnio, JJ, DW Scheifele, M Ho and LA Mitchell: New, ultrasensitive enzyme immunoassay for detecting vaccine- and disease-induced hepatitis A virus-specific immunoglobulin G in saliva. *J Clin Microbiol* **35:** 98-101, 1997.
141. LaBrecque, FD, DR LaBrecque, D Klinzman, S Perlman, JB Cederna, PL Winokur, JQ Han and JT Stapleton: Recombinant hepatitis A virus antigen: improved production and utility in diagnostic immunoassays. *J Clin Microbiol* **36:** 2014-8, 1998.
142. Rolleston, RD: Diseases of the Liver. *In* Encyclopedia Medica, 1905.
143. Darwich, MA, R Faris, JD Clemens, MR Rao and R Edelman: High seroprevalence of hepatitis A, B, C, and E viruses in residents in an Egyptian village in the Nile Delta: a pilot study. *Am J Trop Med Hyg* **54:** 554-558, 1996.
144. Perez, OM, W Morales, M Paniagua and O Strannegard: Prevalence of antibodies to hepatitis A, B, C, and E viruses in a healthy population in Leon, Nicaragua. *Am J Trop Med Hyg* **55:** 17-21, 1996.
145. Arankalle, VA, SA Tsarev, MS Chadha, DW Alling, SU Emerson, K Banerjee and RH Purcell: Age-specific prevalence of antibodies to hepatitis A and E viruses in Pune, India, 1982 and 1992. *J Infect Dis* **17:** 447-450, 1995 .
146. Witts, LJ: Some problems of infective hepatitis. *Br Med J* **1:** 739-743, 1944.
147. Molner, JG and MF Meyer: Jaundice in Detroit. *Am J Pub Health* **30:** 509, 1940.
148. Havens Jr., WP: Infectious hepatitis in the Middle East: a clinical review of 200 cases seen in a military hospital. *JAMA* **126:** 17-23, 1944.
149. Hoagland, CL and RE Shank: Infectious hepatitis: a review of 200 cases. *JAMA* **130:** 615-621, 1946.
150. Friedman, LS, TF O'Brien, LJ Morse, LW Chang, WE Wacker, DM Ryan and JL Dienstag: Revisiting the Holy Cross football team hepatitis outbreak (1969) by serological analysis. *JAMA* **254:** 774-6, 1985.
151. Smart, C: Medical History, Part III. being the third medical volume. *In* The Medical and Surgical History of the War of the Rebellion, Government Printing Office, Washington, D.C.; **I:** 874-879, 1888.
152. Editorial : Jaundice at Alexandria. *Br Med J* **1:** 320-321, 1916.
153. Martin, CJ: Concerning the pathology and etiology of the infectious jaundice common at the Dardenelles, 1915. *Br Med J* **1:** 1917.
154. Willcox, WH: Jaundice: With special reference to types occurring during the war. Epidemic catarrhal jaundice. *Br Med J* **1:** 671-675, 1919.
155. Clayson, ET, BL Innis, KS Myint, R Snitbhan, DW Vaughan and MP Shrestha: Short report: relative risk of hepatitis A and E among foreigners in Nepal. *Am J Trop Med Hyg* **52:** 506-507, 1995.
156. Coursaget, P, Y Buisson, N Enogat, R Bercion, JM Baudet, P Delmaire, D Prigent and J Desrame: Outbreak of enterically-transmitted hepatitis due to hepatitis A and hepatitis E viruses. *J Hepatol* **28:** 745-50, 1998.
157. Paul, JR and HT Gardner: Viral hepatitis. *In* Preventive medicine in World War II. (ed Hoff, E. C. volume ed Coates

Jr. Col. J. B. ed in chief), Office of the Surgeon General, Department of Army, Washington, D.C.; **V:** Communicable diseases transmitted through contact or by unknown means 411-462, 1960.

158. Gutzeit, K: Die hepatitis epidemica. *Münch Med Wschr* **92:** 1295-1301, 1950.
159. Wróblewski, F and JS LaDue: Serum glutamic oxaloacetic transaminase activity as an index of liver cell injury: a preliminary report. *Ann Intern Med* **43:** 345-360, 1955.
160. Tong, MJ, NS el-Farra and MI Grew: Clinical manifestations of hepatitis A: recent experience in a community teaching hospital. *J Infect Dis* 171 Suppl 1:S15-8, 1995.
161. Pavia, AT, L Nielsen, L Armington, DJ Thurman, E Tierney and CR Nichols: A community-wide outbreak of hepatitis A in a religious community: impact of mass administration of immune globulin. *Am J Epidemiol* **131:** 1085-93, 1990.
162. Linder. C. R., YV Karetnyi, JME Kuint and R Dagan: Symptomatic hepatitis A virus infection during the first year of life. *Pediatr Infect Dis* **14:** 628-629, 1995.
163. Barber, H: Infective hepatic jaundice. *Br Med J* **1:** 67-68, 1937.
164. Jacobson, IM, BJ Nath and JL Dienstag: Relapsing viral hepatitis type A. *J Med Virol* **16:** 163-9, 1985.
165. Cobden, I and OF James: A biphasic illness associated with acute hepatitis A virus infection. *J Hepatol* **2:** 19-23, 1986.
166. Tanno, H, OH Fay, JA Rojman and J Palazzi: Biphasic form of hepatitis A virus infection: a frequent variant in Argentina. *Liver* **8:** 53-57, 1988.
167. Glikson, M, E Galun, R Oren, R Tur-Kaspa and D Shouval: Relapsing hepatitis A. Review of 14 cases and literature survey. *Medicine (Baltimore)* **71:** 14-23, 1992.
168. Gordon, SC, KR Reddy, L Schiff and ER Schiff: Prolonged intrahepatic cholestasis secondary to acute hepatitis A. *Ann Intern Med* **101:** 635-7, 1984.
169. McDonald, GS, MG Courtney, AG Shattock and DG Weir: Prolonged IgM antibodies and histopathological evidence of chronicity in hepatitis A. *Liver* **9:** 223-8, 1989.
170. Schiodt, FV, E Atillasoy, A Obaid Shakil, ER Schiff, C Caldwell, KV Kowdley, R Stribling, JS Crippen, S Flamm, KA Somberg, H Rosen, TM McCashland, JE Hay, WM Lee and the Acute Liver Failure Study Group: Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transplant Surg* **5:** 29-34, 1999 Jan.
171. Lemon, SM: Inactivated hepatitis A vaccines. *JAMA* **271:** 1363-4, 1994.
172. Willner, IR, MD Uhl, SC Howard, EQ Williams, CA Riely and B Waters: Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. *Ann Intern Med* **128:** 111-4, 1998.
173. Debray, D, P Cullufi, D Devictor, M Fabre and O Bernard: Liver failure in children with hepatitis A. *Hepatology* **26:** 1018-22, 1997.
174. Fagan, E, G Yousef, J Brahm, H Garelick, G Mann, A Wolstenholme, B Portmann, T Harrison, JF Mowbray, A Mowat and al et: Persistence of hepatitis A virus in fulminant hepatitis and after liver transplantation. *J Med Virol* **30:** 131-6, 1990.
175. Gane, E, R Sallie, M Saleh, B Portmann and R Williams: Clinical recurrence of hepatitis A following liver transplantation for acute liver failure. *J Med Virol* **45:** 35-9, 1995.
176. Halliday, ML, LY Kang, TK Zhou, MD Hu, QC Pan, TY Fu, YS Huang and SL Hu: An epidemic of hepatitis A attributable to the ingestion of raw clams in Shanghai, China. *J Infect Dis* **164:** 852-9, 1991.
177. Keeffe, EB: Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol* **90:** 201-5, 1995 Feb.
178. Vento, S, T Garofano, C Renzini, F Cainelli, F Casali, G Ghironzi, T Ferraro and E Concia: Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* **338:** 286-90, 1998.01 29.
179. Heibling, B, R Kammerlander and EL Renner: Acute hepatitis A (AHA) in patients with chronic hepatitis C (CHC): No increased case-fatality rate (abstract). *Hepatology* **28:** 276A, 1998.
180. Asselah, T, J Bernuau, M Martinot-Peignoux, F Durand, BN Pham, V Le Breton, JP Benhamou, S Erlinger, D Valla and P Marcellin: Lack of evidence of hepatitis C virus infection in patients with severe acute hepatitis A [abstract]. *Hepatology* **28:** 367A, 1998.
181. Vento, S, T Garofano, G Di Perri, L Dolci, E Concia and D Bassetti: Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type 1 in susceptible individuals. *Lancet* **337:** 1183-7, 1991.
182. Rahaman, SM, P Chira and RS Koff: Idiopathic autoimmune chronic hepatitis triggered by hepatitis A. *Am J Gastroenterol* **89:** 106-8, 1994.
183. Huppertz, HI, U Treichel, AM Gassel, R Jeschke and KH Meyer zum Buschenfelde: Autoimmune hepatitis following hepatitis A virus infection. *J Hepatol* **23:** 204-8, 1995.
184. Huo, TI, JC Wu, CF Chiu and SD Lee: Severe hyperbilirubinemia due to acute hepatitis A superimposed on a chronic hepatitis B carrier with glucose-6-phosphate dehydrogenase deficiency. [Review] [10 refs]. *Am J Gastroenterol* **91:** 158-9, 1996.
185. Siddiqui, T and AH Khan: Hepatitis A and cytomegalovirus infection precipitating acute hemolysis in glucose-6-phosphate dehydrogenase deficiency. *Mil Med* **163:** 434-5, 1998.
186. Katz, R, M Velasco, C Guzman and H Alessandri: Red cell survival estimated by radioactive chromium in hepatobiliary disease. *Gastroenterology* **46:** 399-404, 1964.
187. Ritter, K, A Uy, S Ritter and R Thomssen: Hemolysis and autoantibodies to triosephosphate isomerase in a patient with acute hepatitis A virus infection. *Scand J Infect Dis* **26:** 379-82, 1994.
188. Ritter, S, S Schroder, A Uy and K Ritter: Haemolysis in hepatitis A virus infections coinciding with the occurrence of autoantibodies against triosephosphate isomerase and the reactivation of latent persistent Epstein-Barr virus infection. *J Med Virol* **50:** 272-5, 1996.
189. Lyons, DJ, JM Gilvarry and JF Fielding: Severe haemolysis associated with hepatitis A and normal glucose-6-phosphate dehydrogenase status. *Gut* **31:** 838-9, 1990.
190. Tibble, JA, A Ireland and JR Duncan: Acute auto immune haemolytic anaemia secondary to hepatitis A infection. *Clin Lab Haematol* **19:** 73-5, 1997.
191. Domenech, P, A Palomeque, A Martinez-Gutierrez, N Vinolas, E Vela and R Jimenez: Severe aplastic anaemia following hepatitis A. *Acta Haematol* **76:** 227-9, 1986.
192. Cohen, O, D Mevorach, Z Ackerman and R Oren: Thrombocytopenic purpura as a manifestation of acute hepatitis A. *J Clin Gastroenterol* **17:** 166-7, 1993.
193. Simmons, J, L Stein and A Kaufman: Pure red cell aplasia and hepatitis A. *South Med J* **86:** 1274-6, 1993 Nov.
194. Mourani, S, SM Dobbs, RM Genta, AK Tandon and B Yoffe: Hepatitis A virus-associated cholecystitis. *Ann Intern Med* **120:** 398-400, March 1, 1994.
195. Dan, M and R Yaniv: Cholestatic hepatitis, cutaneous vasculitis, and vascular deposits of immunoglobulin M and complement associated with hepatitis A virus infection. *Am J Med* **89:** 103-4, 1990.
196. Geltner, D, Y Naot, O Zimhoni, S Gorbach and Y Bar-Khayim:

Acute oliguric renal failure complicating type A nonfulminant viral hepatitis. A case presentation and review of the literature. *J Clin Gastroenterol* **14:** 160-2, 1992.
197. Chio, F Jr and AA Bakir: Acute renal failure in hepatitis A. *Int J Artif Organs* **15:** 413-6, 1992.
198. Zikos, D, KS Grewal, K Craig, JC Cheng, DR Peterson and KA Fisher: Nephrotic syndrome and acute renal failure associated with hepatitis A virus infection. *Am J Gastroenterol* **90:** 295-8, 1995.
199. McCann 2nd, UG, F Rabito, M Shah, 3CR Nolan and M Lee: Acute renal failure complicating nonfulminant hepatitis A. *West J Med* **165:** 308-310, 1996.
200. Faust, RL and N Pimstone: Acute renal failure associated with nonfulminant hepatitis A viral infection. *Am J Gastroenterol* **91:** 369-72, 1996.
201. Lin, CC, CH Chang, SH Lee, SS Chiang and AH Yang: Acute renal failure in non-fulminant hepatitis A. *Nephrol Dial Transplant* **11:** 2061-2066, 1996.
202. Davis, TV and EB Keeffe: Acute pancreatitis associated with acute hepatitis A. *Am J Gastroenterol* **87:** 1648-50, 1992 .
203. Pelletier, G, D Elghozi, C Trepo, C Laverdant and JP Benhamou: Mononeuritis in acute viral hepatitis. *Digestion* **32:** 53-6, 1985.
204. Safadi, R, T Ben-Hur and D Shouval: Mononeuritis multiplex: a rare complication of acute hepatitis A. *Liver* **16:** 288-9, 1996.
205. Tabor, E: Guillain-Barré syndrome and other neurologic syndromes in hepatitis A, B, and non-A, non-B. *J Med Virol* **21:** 207-16, 1987.
206. Davis, LE, JE Brown, BH Robertson, B Khanna and LB Polish: Hepatitis A post-viral encephalitis. *Acta Neurol Scand* **87:** 67-9, 1993.
207. Thomas, WJ, P Bruno and K Holtzmuller: Hepatitis A virus anicteric encephalitis coexistent with hepatitis C virus infection. *Am J Gastroenterol* **88:** 279-81, 1993.
208. Breningstall, GN and KK Belani: Acute transverse myelitis and brainstem encephalitis associated with hepatitis A infection. *Pediatr Neurol* **12:** 169-71, 1995.
209. Repsher, LH and RK Freebern: Effects of early and vigorous exercise on recovery from infectious hepatitis. *N Eng J Med* **281:** 1393-1396, 1969.
210. Stokes Jr., J and JR Neefe: The prevention and attenuation of infectious hepatitis with gamma globulin (preliminary note). *JAMA* **127:** 144-145, 1945.
211. McKhann, CF: The prevention and modification of measles. *JAMA* **109:** 234, 1937.
212. Cohn, EJ, JL Oncley, LE Strong, WL Hughes Jr. and SH Armstrong: Chemical, clinical, and immunological studies on the products of human plasma fractionation. I. The characterization of the protein fractions of human plasma. *J Clin Invest* **23:** 417-432, 1944.
213. Stokes Jr., J, EP Maris and SS Gelliss: Chemical, clinical, and immunological studies on the products of human plasma fractionation. XI. Use of concentrated normal human serum gamma globulin (human immune serum gobulin) in the prophylaxis and treatment of measles. *J Clin Invest* **23:** 531-540, 1944.
214. Ordman, CW, CG Jennings Jr. and CA Janeway: Chemical, clinical, and immunological studies on the products of human plasma fractionation. XII. Use of concentrated normal human serum gamma globulin (human immune serum gobulin) in the prevention and attenuation of measles. *J Clin Invest* **23:** 541-549, 1944.
215. Gellis, SS, J Stokes Jr. and GM*eal* Brother: The use of human immune serum globulin (gamma globulin) in infectious (epidemic) hepatitis in the Mediterranean theater of operations. I. Studies on prophylaxis in two epidemics of infectious hepatitis. *JAMA* **128:** 1062-1063, 1945.
216. Havens Jr., WP and JR Paul: Prevention of infectious hepatitis with gamma globulin. *JAMA* **129:** 270-272, 1945.
217. Stokes Jr., J, JA Farquhar and ME*eal* Drake: Infectious hepatitis: length of protection by immune serum globulin (gamma globulin) during epidemics. *JAMA* **147:** 714-719, 1951.
218. Winokur, PL and JT Stapleton: Immunoglobulin prophylaxis for hepatitis A. [Review] [84 refs]. *Clin Infect Dis* **14:** 580-6, 1992.
219. Behrens, RH and JF Doherty: Severe hepatitis A despite passive immunisation. *Lancet* **341:** 972, 1993.
220. Zaaijer, HL, A Leentvaar-Kuijpers, H Rotman and PN Lelie: Hepatitis A antibody titres after infection and immunization: implications for passive and active immunization. *J Med Virol* **40:** 22-7, 1993.
221. Hopkins, R: HBsAg-negative blood donors with a history of jaundice as a source of plasma for preparation of hyperimmune hepatitis type A globulin. *J Infect* **3:** 166-171, 1981.
222. Sjogren, MH, CH Hoke, LN Binn, KH Eckels, DR Dubois, L Lyde, A Tsuchida, S Oaks Jr, R Marchwicki, W Lednar, R Chloupek, J Ticehurst, and WH Bancroft: Immunogenicity of an inactivated hepatitis A vaccine. *Ann Intern Med* **114:** 470-1, 1991.
223. Midthun, K, E Ellerbeck, K Gershman, G Calandra, D Krah, M McCaughtry, D Nalin and P Provost: Safety and immunogenicity of a live attenuated hepatitis A virus vaccine in seronegative volunteers. *J Infect Dis* **163:** 735-9, 1991.
224. Andre, FE, E D'Hondt, A Delem and A Safary: Clinical assessment of the safety and efficacy of an inactivated hepatitis A vaccine: rationale and summary of findings. *Vaccine* **10:** S160-8, 1992.
225. Werzberger, A, B Mensch, B Kuter, L Brown, J Lewis, R Sitrin, W Miller, D Shouval, B Wiens, G Calandra, J Ryan, P Provost and D Nalin: A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Eng J Med* **327:** 453-457, 1992.
226. Innis, BL, R Snitbhan, P Kunasol, T Laorakpongse, W Poopatanakool, CA Kozik, S Suntayakorn, T Suknuntapong, A Safary and JW Boslego: A field efficacy trial of inactivated hepatitis A vaccine among children in Thailand. *Vaccine* **10:** S159, 1992.
227. Príkazsky, V, V Oleár, A Cernoch, A Safary and FE Andre: Interruption of an outbreak of hepatitis A in two villages by vaccination. *J Med Virol* **44:** 457-9, 1994.
228. McMahon, BJ, M Beller, J Williams, M Schloss, H Tanttila and L Bulkow: A program to control an outbreak of hepatitis A in Alaska by using an inactivated hepatitis A vaccine. *Arch Pediatr Adolesc Med* **150:** 733-9, 1996.
229. Green, MS, D Cohen, Y Lerman, M Sjogren, LN Binn, S Zur, R Slepon, G Robin, C Hoke, W Bancroft and: Depression of the immune response to an inactivated hepatitis A vaccine administered concomitantly with immune globulin. *J Infect Dis* **168:** 740-3, 1993.
230. Ambrosch, F, G Wiedermann, FE André, A Delem, H Grepor, H Hofmann, E D'Hondt, M Kundi, J Wynen and Ch Kunz: Clinical and immunological investigation of a new combined hepatitis A and hepatitis B vaccine. *J Med Virol* **44:** 452-456, 1994.
231. Gardner, P, T Eickhoff, GA Poland, P Gross, M Griffin, FM LaForce, W Schaffner and R Strikas: Adult immunizations. *Ann Intern Med* **124:** 35-40, 1996.
232. Lee, SD, CY Chan, MI Yu, YJ Wang, FY Chang, KJ Lo and A Safary: Safety and immunogenicity of inactivated hepatitis A vaccine in patients with chronic liver disease. *J Med Virol* **52:** 215-218, 1997.

233. Keeffe, EB, S Iwarson, BJ McMahon, KL Lindsay, RS Koff, M Manns, R Baumgarten, M Wiese, M Fourneau, A Safary, R Clemens and DS Krause: Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology* **27:** 881-886, 1998.
234. Hess, G, R Clemens, U Bienzle, C Schonfeld, B Schunck and HL Bock: Immunogenicity and safety of an inactivated hepatitis A vaccine in anti-HIV positive and negative homosexual men. *J Med Virol* **46:** 40-2, 1995.
235. Neilsen, GA, NJ Bodsworth and N Watts: Response to hepatitis A vaccination in human immunodeficiency virus-infected and -uninfected homosexual men. *J Infect Dis* **176:** 1064-7, 1997.
236. Bryan, JP and M Nelson: Testing for antibody to hepatitis A to decrease the cost of hepatitis A prophylaxis with immune globulin or hepatitis A vaccines. *Arch Intern Med* **154:** 663-8, 1994.
237. Steffen, R, MA Kane, CN Shapiro, N Billo, KJ Schoellhorn and P van Damme: Epidemiology and prevention of hepatitis A in travelers . *JAMA* **272:** 885-9, 1994.
238. Van Doorslaer, E, G Tormans and P Van Dammes: Cost-effectiveness analysis of vaccination against hepatitis A in travellers. *J Med Virol* **44:** 463-469, 1994.
239. Dalton, CB, A Haddix, RE Hoffman and EE Mast: The cost of a food-borne outbreak of hepatitis A in Denver, Colo. *Arch Intern Med* **156:** 1013-6, 1996
240. Lemon, SM and CN Shapiro: The value of immunization against hepatitis A. *Infect Agents Dis* **3:** 38-49, 1994 Feb.
241. Das, A: An economic analysis of different strategies of immunization against hepatitis A virus in developed countries. *Hepatology* **29:** 548-552, 1999.
242. Bottiger, M, B Christenson and L Grillner: Hepatitis A immunity in the Swedish population. A study of the prevalence of markers in the Swedish population. *Scand J Infect Dis* **29:** 99-102, 1997.
243. Bernal, W, HM Smith and R Williams: A community prevalence study of antibodies to hepatitis A and E in inner-city London. *J Med Virol* **49:** 230-4, 1996.
244. Morales, JL, L Huber, S Gallego, G Alvarez, J Diez-Delgado, A Gonzalez, L Aguilar and R Dal-Re: A seroepidemiologic study of hepatitis A in Spanish children. Relationship to age and socio-environmental factors. *Infection* **20:** 194-196, 1992.
245. Stroffolini, T, M Chiaramonte, E Franco, M Rapicetta, D De Mattia, I Mura, R Trivello, A Giammeco, G Rigo and B Scarpa: Baseline seroepidemiology of hepatitis A virus infection among children and teenagers in Italy. *Infection* **19:** 97-100, 1991.
246. Hawkins, RE, JD Malone, LA Cloninger, PJ Rozmajzl, D Lewis, J Butler, E Cross, S Gray and KC Hyams: Risk of viral hepatitis among military personnel assigned to US Navy ships. *J Infect Dis* **165:** 716-9, 1992.
247. Hodges, M, E Sanders and C Aitken: Seroprevalence of hepatitis markers; HAV, HBV, HCV and HEV amongst primary school children in Freetown, Sierra Leone. *West Afr J Med* **17:** 36-7, 1998.
248. Bowden, FJ, BJ Currie, NC Miller, SA Locarnini and VL Krause: Should aboriginals in the "top end" of the Northern Territory be vaccinated against hepatitis A?. *Med J Aust* **161:** 372-3, 1994.