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Hepatitis viruses: Changing patterns of human disease

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ABSTRACT   Viral hepatitis is a disease of antiquity, but evidence for more than one etiologic agent has been recognized only since the 1940s, when two viruses (hepatitis A virus and hepatitis B virus) were thought to account for all disease. In the past 20 years, three additional hepatitis agents (hepatitis C virus, hepatitis D virus, and hepatitis E virus) have been discovered, and there is evidence for at least one additional virus. Each of the five recognized hepatitis viruses belongs to a different virus family, and each has a unique epidemiology. The medical impact of these viruses on society has been strongly influenced by changes in human ecology. This has resulted in some cases in diminished disease and in others in increases in the incidence of disease.

Viral hepatitis is caused by at least five distinct viruses. Each belongs to an entirely different family of viruses, and they have very little in common except the target organ they affect, the liver, and a certain degree of shared epidemiology. Each of the five viruses has a world-wide distribution. In general, the regional incidence rates for each virus are lowest in the Western Hemisphere and northern regions and highest in the Eastern Hemisphere and tropical regions. Thus, the incidence of infection with these five viruses is generally lowest in industrialized and developed countries and highest in less-developed regions. Two of the viruses [hepatitis A virus (HAV) and hepatitis E virus (HEV)] are spread principally by fecal–oral means and three [hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV)] are spread principally by exposure to blood, although HBV is frequently spread by unprotected sex. Although it has been sought, arthropod-borne or other vector-mediated transmission of the blood-borne hepatitis viruses has not been found. Other viruses, principally from the families *Arenaviridae, Bunyaviridae, Flaviviridae, Filoviridae,* and *Herpesviridae,* also cause hepatitis as part of systemic diseases, but these are generally not grouped with the hepatitis viruses.

Changes in human ecology and behavior have had discernable effects on the epidemiology of the hepatitis viruses in different ways and to different degrees. Following is a brief summary of each virus and how it has interacted with its host. In some cases the view is but a glimpse because the existence of three of the five viruses has been recognized for less than 20 years.

Hepatitis A Virus

History. HAV may be traced back to epidemics of "campaign jaundice" that afflicted the armies of the Middle Ages and that has continued to be a serious problem up to and including the Korean and Vietnamese conflicts (see ref. 1). The first civilian epidemics of hepatitis were recorded in Europe in the 17th and 18th centuries. The differentiation of hepatitis A, then called infectious hepatitis, from hepatitis B, then called serum hepatitis, came principally from studies in volunteers in Europe and the United States from the 1940s through the 1960s. It was not until the 1970s that HAV was transmitted to laboratory animals (marmoset monkeys and chimpanzees), and the virus was isolated in cell culture in 1979 (2). It remains the only one of the five hepatitis viruses that has been unequivocally isolated and serially propagated in cell culture. Effective inactivated whole virus vaccines have been developed. The first was licensed in Europe in 1991 and two inactivated hepatitis A vaccines should be licensed in the United States within the next 1 or 2 years.

Epidemiology. HAV is commonly transmitted by the fecal–oral route, either by person-to-person spread (the most common) or in common-source epidemics caused by contamination of food or water. Viremia occurs during the incubation period and the early acute phase of hepatitis A, and transmission by transfusion or recently by contaminated commercial factor VIII (3) has been reported, but such blood-borne transmissions are rare.

Virology. HAV is classified in the family *Picornaviridae,* genus *Hepatovirus.* Based on genomic sequence heterogeneity, seven genotypes of HAV have been identified, but one serotype comprises all of these (4). The infectivity titer of HAV in the feces may be as high as 10^9 infectious doses per gram (5). Viremias lasting as long as several weeks and with titers as high as 10^5 infectious doses per ml of blood have been recorded (3, 5).

Clinical Characteristics. The incubation period of hepatitis A averages 25 days. Hepatitis A is generally mild to moderate in severity, with a mortality rate of 0.2% or less, and never becomes chronic. However, inapparent infection with shedding of virus may persist for up to 6 months in neonates.

Changing Patterns. The epidemiology of HAV is highly influenced by personal and public hygiene. Hepatitis A has diminished in importance over the past several decades in developed and industrialized countries of northern and western Europe and North America (6). A gradient from northern to southern Europe exists, in which hepatitis A is almost nonexistent in Scandinavian countries but is still present, albeit with diminishing importance, in the Mediterranean countries of Europe. A similar pattern of diminishing incidence of hepatitis A has been seen in other developed and transitional regions, including Australia, China, Japan, and Hong Kong, but HAV infection remains highly endemic in many other regions of Central and Southeast Asia, Africa,

Abbreviations: HAV, HBV, HCV, HDV, HEV, hepatitis A, B, C, D, and E viruses; NANB, non-A, non-B; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus.

and Central and South America. As with other picornaviruses such as poliovirus, infection of the very young is usually inapparent, and disease becomes progressively more severe with increasing age. Thus, as the mean age of infection increases with improved sanitation, clinical hepatitis paradoxically becomes more apparent rather than less apparent.

In the United States, hepatitis occurred as recurring epidemics through the 1970s, with 7- to 10-year periodicity (7). When serologic tests for HAV infection became available, HAV was identified as the principal cause of these epidemics, and until the 1980s it remained the type of viral hepatitis most frequently reported to the Centers for Disease Control. Since the last epidemic in the early 1970s, HAV has diminished in importance in the United States but recently has leveled off and is still responsible for ≈30% of reported clinical hepatitis in this country (8). The changing epidemiology of HAV is thought to be the result of better sanitation, principally in the form of improved treatment of water and sewage and improved personal hygiene. Consequently, the epidemiology of HAV has changed from one of diffuse person-to-person spread to one of association with specific high-risk groups. Thus, based on data from the Centers for Disease Control, international travel to areas of HAV endemicity, exposure to very young children (often in the setting of day-care facilities), drug abuse, and homosexual activity collectively accounted for ≈50% of cases of hepatitis A studied (7). Not specifically listed but often cited as a cause of hepatitis A is ingestion of raw or undercooked shellfish, the cause of a massive epidemic of hepatitis A in Shanghai in 1988 (9). Approximately a third of hepatitis A cases have no identifiable risk factor. Thus, hepatitis A has become a more up-scale disease in the United States, with proclivities for "yuppie" lifestyles, but it remains a serious endemic problem especially among Native Americans on or near reservations in the western United States. Hepatitis A in such settings accounts for much of the excess incidence of this disease in the western states in recent years. It also is a periodic problem among native populations in Alaska.

Hepatitis B Virus

History. The first report of what must surely have been hepatitis B was that of Lürman who reported on an epidemic of hepatitis that occurred in shipyard workers in Bremen following vaccination against smallpox with glycerinated lymph of human origin in 1883 (see ref. 1). Serum hepatitis (hepatitis B) rose in importance in parallel with the increasing use of syringes and needles for the treatment of syphilis during the first-half of the 20th century. Similar disease occurred in diabetics who were given insulin with improperly sterilized syringes and needles. Epidemics of hepatitis, some quite large, followed the administration of yellow fever vaccines that had been stabilized by the addition of human serum. Eventually, the association of hepatitis B specifically with blood and blood products was recognized and its distinctness from hepatitis A documented in volunteer studies. Hepatitis B was first transmitted to laboratory animals (the chimpanzee) in the 1970s. Although HBV has never been isolated and serially propagated in cell culture in any practical system, the first hepatitis B vaccine was licensed in the United States in 1981. This unique vaccine was prepared from viral envelope protein [hepatitis B surface antigen (HBsAg)] that was purified from the plasma of chronically infected individuals. Although safe and highly efficacious, the plasma-derived vaccine was replaced with a recombinant vaccine prepared in yeast, in part because the principal source of HBsAg-positive plasma for the manufacture of vaccine was from the same population that subsequently was at highest risk of contracting AIDS.

Epidemiology. Transmission of HBV is principally by exposure to blood or blood products, but transmission by unprotected sex (both homosexual and heterosexual) is also common. In Asia, perinatal transmission from the infected mother to her offspring is an important mode of spread, whereas horizontal transmission among very young children is more important in Africa.

Virology. HBV is classified in the family *Hepadnaviridae*, genus *Orthohepadnavirus*. Based upon genomic heterogeneity, five genotypes of HBV have been identified, but one serotype comprises all of these (10). The infectivity titer of HBV in blood may be 10^8 or more infectious doses per ml (11). The virus has been found in saliva and serum and this may contribute to its sexual transmission.

Clinical. The incubation period of hepatitis B averages 75 days. The disease is usually moderate but may be severe, with a mortality rate of 0.2% to 2%. Disease is less likely to be clinically severe but more likely to become chronic in the very young: >90% of infected newborns develop chronic infection, and this progressively diminishes to 6 years of age, when the adult chronicity rate of 2–7% is reached (12).

Changing Patterns. Since serologic tests for the detection of HBV infection were first applied in the mid-1960s the incidence of hepatitis B progressively increased until the mid-1980s, when it reached a plateau and began to decrease slightly, probably as a result of intensive efforts to control the spread of human immunodeficiency virus (HIV) in the same high-risk populations. Hepatitis B vaccine appears to have had little impact on the incidence of hepatitis B (13). The rise in incidence of hepatitis B during the 1960s, 1970s, and 1980s is believed to have been due principally to changing lifestyles within components of the U.S. population. Specifically, the increase in unprotected sex, both homosexual and heterosexual, and the rise in the drug culture, especially the increased use of illicit parenteral drugs, are thought to have been the most important factors in the spread of HBV. Thus, the more recent epidemic of HIV infection among these high-risk populations is an echo of the earlier epidemic of hepatitis B. It is not surprising that many researchers with experience in studying HBV made the transition to the study of HIV and its epidemiology early in the epidemic of AIDS.

Other subsets of the population who were at high risk of acquiring hepatitis B have fared better. Indigenous populations in Alaska, in whom the incidence of hepatitis B was quite high, received universal pediatric and adult vaccination with hepatitis B vaccine. A spectacular decrease in the incidence of hepatitis B has been observed, demonstrating that control of this disease by immunoprophylaxis is possible if carried out appropriately (14). Recipients of blood and blood products were two other groups in whom hepatitis B was a serious risk. During the 1960s, up to 10% of recipients of massive blood transfusion developed transfusion-associated hepatitis B, and >80% of hemophiliacs were infected with HBV that contaminated commercial lots of pooled clotting factors. Conversion to an all-volunteer blood donor population and mandated screening of donors for serologic markers of HBV infection have virtually eradicated transfusion-associated hepatitis B. Similarly, serologic screening, coupled with incorporation of inactivation steps in the manufacture of commercial clotting factors and vaccination of hemophiliacs with hepatitis B vaccine have virtually eliminated HBV infection among this population. However, control of hepatitis B in the general population of the United States will require universal vaccination in addition to continuing efforts to interdict transmission of HBV within the identified high-risk populations (13).

Hepatitis C Virus

History. The existence of a third type of viral hepatitis was not appreciated until 1975, when the application of recently

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developed diagnostic tests for hepatitis A and hepatitis B to stored samples of prospectively studied cases of transfusion-associated hepatitis revealed that most of the cases were neither hepatitis A nor hepatitis B (15). The proportion of such "non-A, non-B" (NANB) cases increased from ≈65% before screening for HBV markers was instituted to >90% as HBV carriers were excluded from the blood donor population (16). The "new" hepatitis had an average incubation period of ≈7–10 weeks, which is intermediate between those of hepatitis A and hepatitis B and similar to the mean incubation period of all cases of transfusion-associated hepatitis in the 1950s and 1960s, suggesting that NANB hepatitis had also been the principal cause of transfusion-associated hepatitis in the past (17). Although NANB hepatitis was transmitted to chimpanzees in 1978, thus establishing its infectious nature, it was not until 1989 that the virus itself was identified. Indirect evidence of the nature of the virus had been obtained by experiments in chimpanzees: it had been shown to be inactivated by lipid solvents and therefore was probably an enveloped virus, and its size had been estimated at between 30 and 60 nm in diameter. However, in 1989 a small piece of the viral RNA was reverse-transcribed, cloned, and sequenced, and this resulted in the subsequent cloning and sequencing of the entire genome (18). The virion was only recently tentatively visualized by electron microscopy (19). Nevertheless, all of the viral proteins encoded by the HCV genome have been expressed, and some of these serve as the basis for currently licensed serologic tests for antibody to HCV.

Epidemiology. HCV is commonly transmitted via blood and blood products. Its transmission by other routes, such as unprotected sex, perinatal transmission from infected mother to offspring, etc., have been proposed but remain controversial and probably of minor importance. However, >40% of cases of hepatitis C in the United States have no recognizable risk factor (20).

Virology. HCV is classified in the family *Flaviviridae*, in a separate as-yet-unnamed genus. Based on genomic sequence heterogeneity, 6 major and >12 minor genotypes of HCV have been identified (21). The major genotypes differ from one another to the same degree that other RNA viruses belonging to separate subgenera differ; minor genotypes differ to about the degree that different serotypes of other RNA viruses differ from one another. This suggests that multiple serotypes of HCV exist, but the lack of a convenient *in vitro* assay system and the failure to demonstrate lasting immunity following infection of chimpanzees, even when the virus used for rechallenge is the same as the original inoculum, suggest that serotypic variation is a prominent feature of HCV. The infectivity titer of HCV in the blood may be as high as 10^6 infectious doses per ml but is usually much lower, especially in cases of chronic infection, apparently because of complexing of virus to antibody (22, 23). Detection by polymerase chain reaction of HCV genomic RNA in other body fluids has been reported, but it is unclear whether this represents infectious virus.

Clinical Characteristics. The incubation period of hepatitis C averages 50 days. Acute hepatitis A is generally a mild disease with a mortality rate of <1%. However, >50% of acute cases progress to chronicity, and some of these will eventually progress to cirrhosis or hepatocellular carcinoma or both.

Changing Patterns. Insufficient time has passed since its discovery for us to have a clear picture of the ecology of HCV. Only ≈0.3% of the normal blood donor population of the United States has antibody to HCV, but the prevalence of anti-HCV in inner city populations may be >50-fold higher (24). The same inner city populations have very high prevalences of antibody to HBV and HIV, undoubtedly reflecting the high-risk lifestyles of these groups. However, since

NANB hepatitis has been reported as a separate entity beginning in the early 1980s, some trends in relative importance of risk factors have emerged (25). Transfusion-associated NANB hepatitis is virtually disappearing as a result of the current comprehensive screening program that tests specifically for infections with HBV, HCV, and HIV and excludes all who identify themselves as members of high-risk populations. Intravenous drug use as a risk factor has also diminished in relative importance, probably because of efforts to control AIDS in such populations. However, control of NANB hepatitis (principally hepatitis C) in the general population will probably require the development of effective hepatitis C vaccines and their appropriate use.

The impact of hepatitis C in other countries is still being sorted out. Hepatitis C virus has a world-wide distribution, but, surprisingly, the prevalence of anti-HCV is on the order of 1% in most developed countries and <10% in most developing countries surveyed to date. An exception is Egypt, where the prevalence of anti-HCV is ≈10–20% (26). Much is yet to be learned about the ecology of HCV. For instance, several of the genotypes of HCV have world-wide distributions but others appear to be limited to certain regions or even countries (21). A possible connection between certain genotypes of HCV and the clinical course of infection has been reported but not confirmed. Similarly, certain genotypes of HCV appear to be more susceptible to therapy with interferon than others (27). Finally, coinfection, superinfection, and reinfection with different strains of HCV probably occur as well as the emergence of genetic variants (thought to be neutralization-escape mutants of the virus) over time in chronically infected individuals (28–32). Thus, many of the same phenomena observed in infections with HIV, another highly heterogeneous and mutable virus, have been observed in HCV infections. This bodes ill for the rapid development of an effective hepatitis C vaccine, although the first successful steps toward vaccine development have been taken (33).

Hepatitis D Virus

History. The first evidence for the existence of HDV came in 1978 when a previously unrecognized intranuclear antigen was detected by immunofluorescence in liver biopsies from Italian patients with chronic HBV infection. First thought to be another antigenic specificity of HBV, the antigen was eventually shown to be associated with the capsid protein of a previously unrecognized virus, subsequently called "hepatitis delta virus" (HDV) (34). The virus was shown to be defective, requiring a helper function from HBV, probably because HDV is enveloped with the envelope of HBV. The transmissible nature of HDV was established in 1980 by transmission of the virus to HBV-infected chimpanzees.

Epidemiology. HDV is commonly transmitted by blood and blood products. Perinatal transmission has been reported but is rare, probably because the perinatal transmission of HBV is uncommon in regions where HDV is prevalent. HDV has been found in indigenous populations of South America, Africa, and certain parts of Central and Southeast Asia, where it has caused outbreaks of severe and often fatal hepatitis. Its modes of spread in such indigenous populations are poorly understood but may include inapparent exposure to blood and, in some cases, sexual transmission. In developed countries, hepatitis D is largely restricted to certain high-risk populations, principally users of illicit parenteral drugs.

Virology. HDV is the most unusual of the hepatitis viruses. It does not resemble any other known animal virus and has been classified with the plant virus satellites, agents that are also related to viroids of plants. Based upon the genetic heterogeneity of the agent's single-stranded circular RNA

genome, three genotypes have been described (35). It is not clear how many serotypes exist, since the virus is enveloped with the envelope of HBV (HBsAg), from which it probably takes its serologic specificity. HDV achieves extraordinarily high titers (10^{11} infectious doses per ml) in the blood of infected individuals (36).

Clinical Characteristics. The incubation period of HDV averages 35 days. Disease may occur as a coinfection with HBV or as a superinfection of a chronic HBV infection. In either case, hepatitis D is usually severe, being associated in coinfections with fulminant hepatitis and a high mortality and in superinfections with rapidly progressive, often fatal, subacute or chronic hepatitis. Overall, the mortality rate is 2–20%. Chronicity follows 1–3% of coinfections and 70–80% of superinfections.

Changing Patterns. As with HCV, little is known about the long-term changes in the ecology of HDV. Epidemics of severe hepatitis D in indigenous populations of Venezuela, Colombia, Brazil, and Peru are only recent manifestations of a disease that has been present for many decades as documented by retrospective analysis of stored liver tissue and the recent demonstration that South American strains of HDV are genetically different from other strains. In contrast, HDV has been introduced relatively recently into the populations of developed countries. Specifically, epidemics of hepatitis D appeared in populations of parenteral drug users in the 1970s in Norway, Sweden, Greece, and Australia and in the 1980s in Ireland and Poland (37–41). HDV infection has also been prevalent in U.S. drug abusers at least since the 1970s. However, unlike HBV and HIV, HDV has not spilled over appreciably from illicit drug-user populations to sexually promiscuous populations. Interestingly, hepatitis D has diminished in importance in the general population of southern Italy, where its medical importance as a highly endemic virus was first appreciated in the 1970s (42). Effective use of hepatitis B vaccines should eventually control hepatitis D in parallel with the control of hepatitis B, but individuals who are already chronically infected with HBV (estimated at >300 million worldwide) will continue to be at risk of contracting hepatitis D.

Hepatitis E Virus

History. Hepatitis E was not recognized as a unique human disease until 1980, when serologic tests for the diagnosis of hepatitis A and hepatitis B were applied to stored clinical samples collected during water-borne epidemics of viral hepatitis in India (43, 44). Among these was the massive epidemic of hepatitis that occurred in Delhi, India, in 1955–1956 following contamination of a major water treatment plant with raw sewage. The epidemic had been cited previously as a classical example of water-borne hepatitis A, but the subsequent discovery that hepatitis A was highly endemic in Indian populations, with HAV infecting almost 100% of the population by the age of 5–10 years, made it difficult to accept that the Delhi epidemic and other water-borne epidemics that occurred principally in young adults were caused by HAV. Indeed, virtually 100% of stored serum samples from such epidemics were found to contain IgG anti-HAV but not IgM anti-HAV—strong evidence for past HAV infection with resultant immunity and therefore evidence for the existence of a previously unrecognized hepatitis agent as the cause of the epidemics. HEV was first visualized in 1983 and transmitted to a human volunteer and cynomolgus monkeys, thus establishing its etiologic role in enterically transmitted NANB (ET-NANB) hepatitis (45). Because HEV could not be grown in cell culture and the amount of virus recoverable from natural infections of man or experimental infections of primates was quite small, progress in understanding hepatitis E was slow. However, in 1990 the genome of HEV was

cloned, and viral antigens encoded by this RNA genome were expressed by recombinant DNA technology (46). This resulted in the development of specific and sensitive serologic tests that have permitted rapid expansion of our knowledge of the epidemiology of this virus.

Epidemiology. HEV is transmitted by the fecal–oral route. Although it is best known from water-borne epidemics of hepatitis E, it also accounts for much sporadic disease in countries where it is endemic. Hepatitis E has a restricted distribution: disease with the epidemiologic characteristics of hepatitis E has been found in much of Central and Southeast Asia, northern and western Africa, and, to a limited extent, in Mexico. However, the application of recently developed serologic tests has revealed anti-HEV in every country in which it has been sought, including developed countries in which the disease virtually does not occur. For example, 1–5% of normal blood donors in the United States have been found to be positive for anti-HEV, a prevalence of antibody 10 times higher than that for anti-HCV (47). It is not clear whether such antibody represents missed diagnoses of hepatitis E, infection with an attenuated strain of HEV, antibody that cross-reacts with an as-yet-unrecognized agent, or some type of nonspecificity of the existing assays.

Virology. HEV is presently unclassified. Its genomic organization most closely resembles that of the caliciviruses, but it is not identical; the sequence of, for example, the putative RNA polymerase gene of HCV more closely resembles that of the togavirus-like polymerases than that of the caliciviruses and picornaviruses (48). Based on genomic sequence heterogeneity, three genotypes of HCV have been identified, but one serotype appears to comprise all of these. The infectivity titer of HEV in feces probably does not exceed 10^7 infectious doses per g, 2 orders of magnitude less than peak fecal titers of HAV. A viremia occurs during the incubation period of hepatitis E, but the titer of virus present has not been determined.

Clinical Characteristics. The incubation period of hepatitis E averages 40 days. Hepatitis E is a mild-to-moderate disease in severity (mortality rate of 0.2–1%) except in pregnancy, where the mortality rate is progressively higher in each succeeding trimester and may reach 20%. Hepatitis E appears never to become chronic.

Changing Patterns. The epidemiology and virology of hepatitis E suggest that HEV is less readily transmitted than HAV, and recent seroepidemiologic data confirm this: in populations where virtually 100% of the population was infected with HAV by the age of 5–10 years, a relatively small proportion of the population in an endemic region had anti-HEV (V. A. Arankalle, S. A. Tsarev, M. S. Chadha, D. W. Alling, S. U. Emerson, K. Banerjee, and R.H.P., unpublished data). The relatively low prevalence of anti-HEV in at-risk populations could explain the recurring epidemics among young adults. The study cited above took place in a population in which neither HAV nor HEV was diminishing in importance over time. However, it is likely that in transitional populations in which HAV is diminishing in importance, HEV, if ever present, diminished in importance at an earlier date. Some epidemiologic evidence for this comes from a review of the early literature on epidemic hepatitis during the last century (49). Such reports of epidemic hepatitis in Europe and elsewhere described a disease afflicting predominantly young adults and associated with fulminant hepatitis in pregnant women. As we have seen, age-specific antibody profiles of HAV in many countries now industrialized point to a prevalence of anti-HAV that may have been virtually 100% during the last century. It is possible, therefore, that "infective hepatitis," occurring as sporadic and epidemic cases among adults in Europe and elsewhere before the 20th century, may have actually been hepatitis E, not hepatitis A, as has been supposed. It will be

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important to determine age-specific antibody profiles for populations of currently industrialized countries to determine if this can be confirmed and to determine if the anti-HEV currently detected in such populations represents the traces of a former time.

More recent interactions between changing human culture and HEV were seen in epidemics of hepatitis E that occurred among refugees living under substandard conditions in Ethiopia and Somalia in the 1980s (50). Those epidemics could be traced directly to overcrowding, substandard living conditions, and nonexistent sanitation. Such epidemics are likely to occur in the future if HEV is introduced into similar environments that are conducive to explosive spread of fecal–orally transmitted viruses. It was surprising, for example, that hepatitis E epidemics did not occur during the recent Gulf war, since the Norwalk agent, a fecal–orally transmitted calicivirus, did cause significant disease. Perhaps only the absence of HEV from the war zone prevented an epidemic.

Interactions of the Hepatitis Viruses

Not only do changes in the culture of populations alter the epidemiology of the hepatitis viruses, but interactions among the viruses and their hosts further modify the ecology of viral hepatitis. The obligatory interaction between HDV and HBV, leading to much more severe disease, also results in suppression of replication of HBV by mechanisms that are not completely understood but may be related to the expression or action of interferon (51). Similar suppression of replication of HBV by HAV and HCV has been reported and dual infections of hepatitis viruses are thought usually to result in more severe disease than single infections. One example of this is an epidemic of severe, in some cases fatal, hepatitis B that occurred in Edinburgh, Scotland, in 1969–1970 (52). Long an enigma because other similar blood-borne epidemics of hepatitis B had not resulted in such catastrophic outcomes, the reason for the severity of this outbreak has been doggedly pursued by one of the original investigators, B. Marmion. Over the years, a variety of possible explanations, including coinfection with HDV, were ruled out. Recently, Marmion and his colleagues have provided convincing evidence that the severe hepatitis B in Edinburgh was associated with dual infection with HCV (B. Marmion, personal communication).

Other Hepatitis Viruses

Approximately 10% of transfusion-associated hepatitis and ≈4% of community-acquired hepatitis in the United States cannot be ascribed to any of the five recognized hepatitis viruses. It has been proposed that these cases may be caused by a previously unrecognized hepatitis virus, but attempts to transmit an agent from such patients to primates have yielded equivocal or negative results. Additional studies must be carried out to determine whether these cases are indeed caused by a new agent or whether their etiology may be noninfectious.

More convincing evidence for an additional, water-borne hepatitis agent has come from recent studies in Asia, where at least two water-borne epidemics of hepatitis appear not to have been caused by any of the recognized hepatitis viruses (53, 54). Thus, the epidemiology of viral hepatitis continues to evolve.

Conclusions

In summary, changes in human culture have had profound effects on the epidemiology and public health impact of the hepatitis viruses. In some cases, this has been a positive influence; in others it has been negative. For example,

progressive improvement in public and personal hygiene over the last century has diminished the medical importance of hepatitis A and, possibly, at an earlier time, hepatitis E. Lapses in sanitation, through war, such as happened in Somalia, or through changing social mores, as has happened among certain groups in the United States, has resulted in increased disease caused by the fecal–orally transmitted hepatitis viruses, confirming the need for constant vigilance.

Similarly, increased sexual promiscuity, whether homosexual or heterosexual, and increasing use of illicit parenteral drugs has resulted in infection with the blood-borne hepatitis viruses in epidemic proportions. These epidemics were the forerunners of the current HIV epidemic. In most cases, these changes could have been predicted by simple epidemiology, had we the knowledge about the viruses that we now possess. However, preventing outbreaks of disease that are caused by changes in behavior patterns has never been simple or effective, and making an impact on ongoing disease by methods that rely upon changing the behavior of at-risk populations is a difficult and frustrating chore. It is one of the reasons why vaccines, although initially expensive, prove in the long run to be among the most cost-effective of all medical interventions.

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