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Hepatitis E

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Response

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Hepatitis E - an introduction

Hepatitis is a general term meaning inflammation of the liver and can be caused by a variety of different viruses such as hepatitis A, B, C, D and E. Since the development of jaundice is a characteristic feature of liver disease, a correct diagnosis can only be made by testing patients' sera for the presence of specific viral antigens and/or anti-viral antibodies.⁴⁸

Hepatitis E was not recognized as a distinct human disease until 1980, when specific tests for antibody against hepatitis A were first applied to the study of epidemic waterborne hepatitis in India. The results showed that the epidemics were not epidemics of hepatitis A. Actually, very few epidemics of waterborne disease in developing countries of Asia and Africa have been linked to hepatitis A.^{18, 40, 41}

The first experimental evidence for the existence of an additional waterborne hepatitis agent was reported in 1983.^{40, 41} This form of non-A, non-B hepatitis came to be known as Enterically transmitted non-A non-B hepatitis (ET-NANB), Epidemic non-A non-B hepatitis (ENANB), or Faecal-oral non-A non-B hepatitis, and the agent of this disease was subsequently found to be the major cause of sporadic hepatitis cases in regions where the epidemic form was known to exist.⁴¹

Warning: hepatitis E should not be confused with hepatitis C, also called parenterally transmitted non-A non-B hepatitis (PT-NANBH), or B-like non-A non-B hepatitis.

What causes the disease?

Hepatitis E is caused by infection with the hepatitis E virus (HEV), a nonenveloped, positive-sense, single-stranded RNA virus.

Originally classified within the family of caliciviruses, HEV is now unclassified.^{17, 39}

How is HEV spread?

Just like HAV, HEV is transmitted from person-to-person via the faecal-oral route.^{10, 18, 40}

Hepatitis E is a waterborne disease, and contaminated water or food supplies have been implicated in major outbreaks.^{10, 19}

There is a possibility of zoonotic spread of the virus, since several non-human primates, pigs, cows, sheep, goats and rodents are susceptible to infection.^{18, 41}

Who is susceptible to infection?

People who never have contracted HEV are at risk of infection.

The risk factors for HEV infection are related to resistance of HEV to environmental conditions, poor sanitation in large areas of the world, and HEV shedding in faeces.

Where is HEV a problem globally?

Hepatitis E has a restricted distribution: epidemics of hepatitis E have been found in much of Central and South-East Asia, North and West Africa, and in Mexico, confined to geographic areas where faecal contamination of drinking water is common.¹⁰

However, the application of recently developed serologic tests has revealed anti-HEV in every country in which it has been sought, including developed countries like the United States (US), in which the disease virtually does not occur.⁴⁰

It is not clear whether such antibodies represent missed diagnoses of hepatitis E, asymptomatic infections, infections with attenuated strains of HEV, antibodies that cross-react with an as yet unrecognized agent, or some type of nonspecificity of the existing assays.

Possible reservoirs of HEV in the mentioned regions could be found in animals like monkeys, pigs, cows, rodents, sheep or goats. In fact, all these species are susceptible to infection with HEV.^{14, 18, 26, 41, 53, 54}

When is a HEV infection life-threatening?

Hepatitis E is a mild to moderate disease in severity (mortality rate of 0.4-4.0%) except in pregnancy, where the mortality rate is progressively higher in each succeeding trimester and may reach 20%.

Why is there no treatment for the acute disease?

Hepatitis E is a viral disease, and as such, antibiotics are of no value in the treatment of the infection.

There is no hyperimmune E globulin available for pre- or postexposure prophylaxis.

HEV infections are usually self-limited, and hospitalization is generally not required. No available therapy is capable of altering the course of acute infection.

The hepatitis E virus HEV

HEV causes self-limited acute viral hepatitis in adults aged 15-40.

HEV is a nonenveloped, spherical, positive-stranded RNA virus. Several different strains have been isolated, partially characterized and molecularly cloned (1990-92).^{20, 41, 44, 49, 53} Although originally classified within the family of caliciviruses, they are now unclassified.^{17, 39}

Replication in cell culture was first reported in 1993; yields of virus are generally very low.¹⁸ In natural infections, the virus replicates in hepatocytes.⁴⁸ *In vivo* infected macaque hepatocytes support HEV replication after isolation and placement into tissue culture.⁵⁰

Man is the natural host for HEV, but certain non-human primates, e.g. chimpanzees, cynomolgus monkeys, rhesus monkeys, pigtail monkeys, owl monkeys, tamarins and African green monkeys are reported to be susceptible to natural infection with human strains of HEV.^{10, 26, 32, 41, 44, 48, 56}

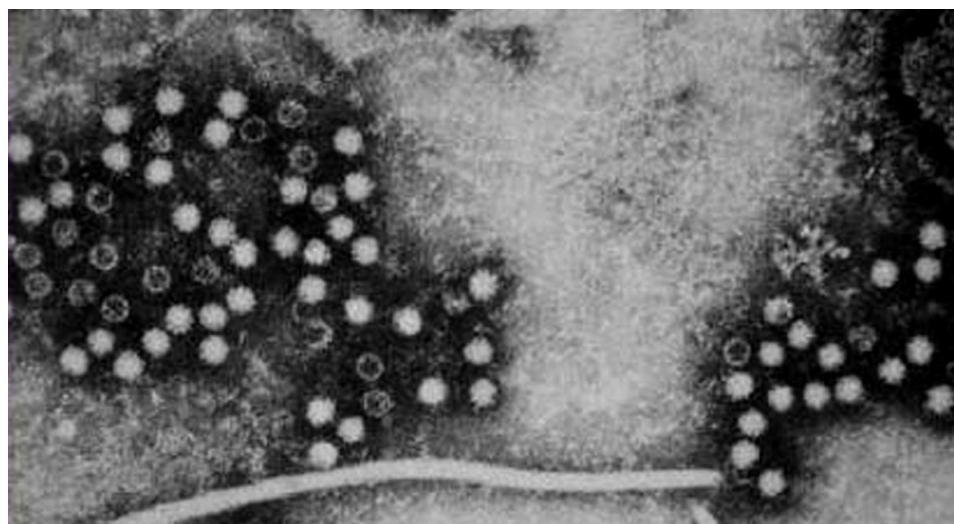
Transmission of human strains of HEV to swine has been reported for the US-2 strain of human HEV, but could not be shown for the Sar-55 and Mex-14 strains.^{32, 35}

A swine strain of HEV has been isolated, identified and characterized and subsequently shown to infect rhesus monkeys and chimpanzees, experimental surrogates of humans. This ability to cross species barriers puts humans at risk for infection with swine HEV.^{32, 33}

In endemic areas, naturally acquired anti-HEV has been found in 42 – 67% of cows, sheep and goats.^{12, 14}

Recent studies show evidence of widespread HEV or HEV-like infection in rodents in the US (prevalence rate of 60% in rats), raising the question of transmission, reservoirs, and strains of HEV in developed countries.^{13, 24, 47}

Electron Microscopy (EM) picture



From: Centers for Disease Control and Prevention (CDC), Atlanta, USA.¹¹
http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_e/slide_1.htm

Electron microscopy picture of human hepatitis E virus.

Morphology and physicochemical properties

HEV is a small and structurally simple RNA animal virus.

The virion is nonenveloped and, with a diameter of 27-34 nm, is composed entirely of viral protein and RNA. Electron microscopy (EM) analyses show spherical particles of possible icosahedral symmetry, with indefinite surface substructure, resembling the caliciviruses.^{18, 41}

Morphologically, HEV is similar to Norwalk virus, a member of the calicivirus family, although the sequence of HEV most closely resembles the sequence of rubella virus, a togavirus, and beet necrotic yellow vein virus, a plant furovirus.^{18, 41, 48}

Full virions have a buoyant density of 1.29 g/cm³ in potassium tartrate/glycerol gradients and a sedimentation coefficient of 183 S in neutral sucrose gradients, empty capsids of 165 S under the same conditions.^{9, 10, 41}

Genome and proteins

The hepatitis E genome consists of a linear, single-stranded, positive-sense RNA (that is, mRNA) of approximately 7.5 kb containing a 3' poly(A) tail and short 5' and 3' noncoding (NC) regions.^{10, 18, 19, 41}

Three overlapping open reading frames (ORFs) exist, and all three coding frames are used to express different proteins.^{10, 29, 41}

ORF1 (5 kb) is located towards the 5' end of the genome and encodes a polyprotein of about 1690 amino acids that probably undergoes post-translational cleavage into multiple nonstructural proteins required for virus replication, including a methyltransferase, a putative papain-like cysteine protease, an RNA helicase and an RNA-dependent RNA polymerase.^{18, 19, 29, 41}

ORF2 does not overlap with ORF1; it is located at the 3'-end of the genome and encodes the principal and probably only structural protein. It is a capsid protein of 660 amino acids (71 kDa).^{18, 19, 29, 41, 56}

ORF3 begins with the last nucleotide of ORF1; it overlaps extensively with ORF2 and is the shortest of the open reading frames, encoding a small immunogenic 123 amino acid phosphoprotein (14.5 kDa) which associates with the cytoskeleton, suggesting a possible role in the assembly of virus particles.^{18, 29, 41, 65}

The genomes of several HEV strains from different parts of the world have been sequenced and compared. Overall, they appear to fall into four major genetic groups:

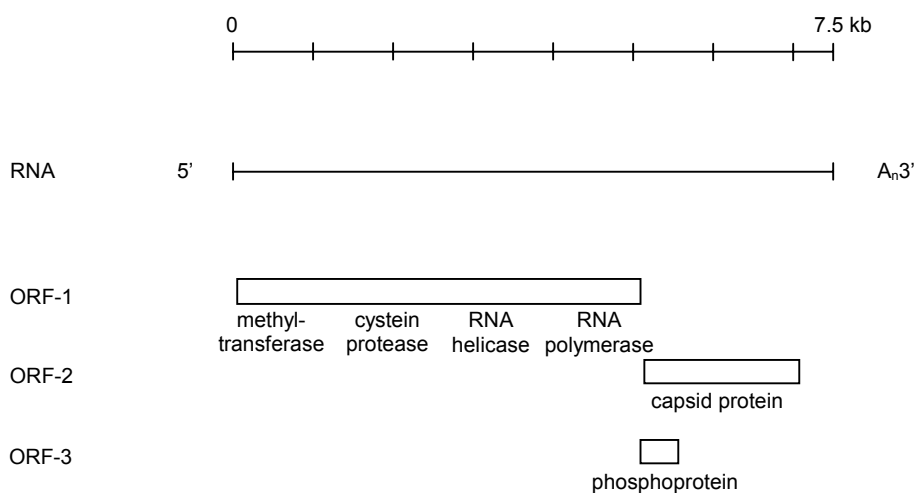
- 1 - South-East Asian (Burmese, some Indian strains), North and Central Asian (strains from China, Pakistan, Kyrgyzstan, and a few from India), and North African strains form one somewhat heterogeneous genotype,
- 2 - the single North American (Mexico) isolate comprises a second,
- 3 - the US and swine isolates comprise a third and
- 4 - a subset of isolates from China and most isolates from Taiwan comprise a newly described fourth group.

Genetically heterogeneous isolates from several European countries have been designated new genotypes, but, at this time, probably should be grouped with the US isolates into a large, heterogeneous

group.^{9, 18, 20, 41, 44, 46, 53} Two novel isolates of HEV have recently been described in Argentina. Distinct from all previously described isolates, they represent two diverse subtypes of a new genotype of HEV.⁴⁷

The genome of swine HEV, an animal strain of HEV, has recently been identified and characterized. The putative capsid gene (ORF2) of swine HEV shares about 80% sequence identity at the nucleotide level and about 92% identity at the amino acid level with that of human HEV strains. The small ORF3 of swine HEV has about 84% nucleotide sequence identity and about 80% amino acid identity with human HEV strains.³³

Genetic map



Organization of the genome of HEV. The positive-sense single-stranded RNA genome of the prototype strain of HEV, recovered in Myanmar, consists of a 5' NC region of 27 nucleotides, followed by an ORF (ORF1) of 5079 bases. A second ORF (ORF2) begins in coding frame two, 38 nucleotides 3' of the termination of ORF1 and consists of 1980 nucleotides. A 65-nucleotide 3' NC region is contiguous with the termination of ORF2 and is terminated by a 3' stretch of 150 to 200 or more adenosine residues. A third ORF, 369 nucleotides in length, overlaps ORF1 by one nucleotide at its 5' end and extends into ORF2 in coding frame three. The HEV genome is capped. The three open reading frames (ORFs) expressed during infection are shown. Putative functions (protein products of each ORF) are labelled beneath.^{9, 10, 20, 25, 29, 48, 53}

Comparison of amino acid sequences of different HEV strains

A

Sar55	MRPRPILLLLMFLPMLPAPPQPGRRRRGGSGGGFWGDRVDSQFFAIPIYHPTNFPADVTAAGAGPRVVRQPARPLGSAWRDQAQPPAAASRRRPTTAGAAPLTAVAFAHDTF	120
MexicoL...F.L.....T.....T.....A.S.S..L.....T.....S.....A.....A.....S	120
KS2-87V.....A.....	120
BurmaV.....	120
MadrasS.....P.....	120
Uigh179I.V.....H.....T.....	120
HEV037H.....T.....	120
Hyderabad	.G...F...L.....N.....V.....	120
NE8LV.....	120
HetianA.....	120
Swine HEV	..AV...FVL.....A.....C.N..A.....L.....A..V.SQP...D.P..P.....S...ST.P..SAP.....S.P..A	120
Sar55	FVPDVSRRGAILRRQYNLSTSPLTSSVATGTLNVLVYAAPLSPLLPLQDGNTHIMATEASNYAQYRVARATIRYRPLVFNVAAGVYSAISFWFQTTTPTSDVMSITSTDRILVQPGI	240
MexicoS.....N.P.....	240
KS2-87N.P.....	240
Burma	240
MadrasG.....	240
Uigh179G.....	240
HEV037P.....	240
HyderabadP.....	240
NE8LA.....V.....	240
HetianH.....V.....	240
Swine HEVA.....N.....V.....	240
Sar55	ASELVIPSERLHYRNQGWRSVETSGVAEEBATSGLVMLCIHGSPVNSYNTPTYPYTGALGLLDFALELFRNLTPGNTNTRVSRYSSTARHLLRRGADGTAEITTTAATRFMKDLYFTSTNG	360
MexicoTC.....SA.....H..GL.....	359
KS2-87L.....	360
BurmaL.....	360
MadrasV.....T.....	360
Uigh179L.....F.....	360
HEV037L.....F.....	360
Hyderabad	360
NE8LH.....	360
HetianT.....	360
Swine HEVT.....H..G.....	360
Sar55	VGEIGRGIALTLFNLADTLGLLPTLTISSAGGOLFYSRPFVVSANGEPTVKLYTSVENAQDQKIAIPHDIDLGESRVVIQDYDNQHEQDRPTSPAPSRPFVLRANDVLWLSLTAABY	480
MexicoV.....D.....	479
KS2-87D.....	480
BurmaR.....A.....	480
MadrasR.....A.....	480
Uigh179R.....A.....	480
HEV037N.....	480
HyderabadH.....	480
NE8LH.....	480
HetianT.....D.....	480
Swine HEVV.....T.....D.....	480
Sar55	DQSTYGSSTGPVYVSDSVTLVNVATGAQAVARSLDWTKVLIDGRPLSTIQQYSKTFVPLRGLKLSFWEAGTTKAGYPYNYNTTASDQLLVENAGHRVAISTYTTSLGAGPVSISAVAV	600
MexicoI.....P.VE.....I.I.....R.....A.....A.....	599
KS2-87I.....P.VE.....I.I.....R.....A.....A.....	600
BurmaC.....I.....A.....	600
MadrasC.....I.....A.....	600
Uigh179C.....I.....A.....	600
HEV037C.....I.....A.....	600
HyderabadA.....P.....I.....R.P.....	600
NE8LA.....P.....I.....R.P.....	600
HetianT.....N.M...T.....S.....T.....Y.....I.I.....T...G.....	600
Swine HEVT.....N.M...T.....S.....T.....Y.....I.I.....T...G.....	600
Sar55	LAPHVLLALLETMDYPARAHTFDDEFCPECRPLGLQGCAPQSTVAELQRLMKVGTREL	660
Mexico	..R.A.....F..G.....D.....A.....G.....V.....	659
KS2-87	..T..A.....L.....	660
Burma	..A.....L.....	660
Madras	..A.....L.....	660
Uigh179	..A.....L.....	660
HEV037	..A.....L.....	660
Hyderabad	.G...A...L...C.....	660
NE8L	..A.....L...C.....	660
Hetian	..A.....V.....T.....I.....S.....	660
Swine HEV	..A...V...V.....T.....I.....S.....	660

B

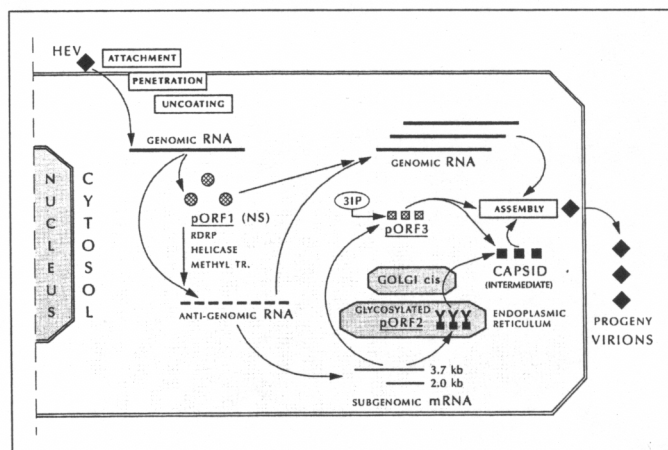
Sar55	MNNSFAAPMGSRPCALGLFCCSSCFCLCCPRHRPVSRLAAVVGAAAVPVVSGVTGLILSPSQSIFIQPTSPFMSPLRPGLDLVFANFPDHSAPLGVTRPSAPLPHVDLPQLGPRR	123
MexicoW.....P.....L.QTL.....A...Q.G.L...EI.....P.A...P.L..	123
KS2-87P.....P.....QTL.....A...Q.G.L...EI.....P.A...P.L..	123
BurmaW.....S.....L.....A.....	123
MadrasW.....S.....L.....A.....	123
Uigh179W.....S.....L.....A.....	123
HEV037W.....S.....L.....A.....	123
Hyderabad	.D.....W.....S.....R.....S.....A.....	123
NE8LD.....S.....Q.....	123
HetianS.....A.....T.....P.....L...FHN...EFALDSR.APL...S...P...L...123	123
Swine HEVS.....A.....T.....P.....L...FHN...EFALDSR.APL...S...P...L...123	123

From: Meng X-J et al. A novel virus in swine is closely related to the human hepatitis E virus. *Proceedings of the National Academy of Sciences USA*, 1997, 94:9860-9865,³³ "Copyright (1997) National Academy of Sciences, U.S.A.", with permission.

Alignment of the amino acid sequences of ORFs2 (A) and 3 (B) of swine HEV with human strains of HEV. The sequence of Sar55 strain is shown on top, and only differences are indicated. Deletions are indicated by a minus. The putative hypervariable region (HVR) in the ORF3 is indicated by asterisks. Sequences used in this alignment are Burma⁴⁹, Mexico²⁰, NE8L (Myanmar⁷), Hyderabad (India³⁷), Madras (India, GenBank accession no.X99441), HEV037 (isolate from a case of fulminant hepatitis, GenBank accession no.X98292), Sar55 (Pakistan⁵³), KS2-87 (China⁶⁴), Hetian (China, GenBank accession no.L08816), and Uigh179 (China⁸).^{20, 33}



Model of HEV replication



From: Krawczynski K, Mast EE, and Perdy MA. Hepatitis E : an overview. In: Rizzetto M, Purcell RH, Gerin JL, and Verme G, eds. *Viral hepatitis and liver disease*, Turin, Minerva Medica, 1997:305-312.28 "Copyright (1997) Edizioni Minerva Medica, Italy", with permission.

Model of HEV replication. HEV: hepatitis E virus. pORF1, 2, 3: proteins encoded by open reading frames 1, 2, 3. 3IP: host protein reacting with protein encoded by ORF3.²¹ The evidence supporting the existence of HEV subgenomic mRNA derives from Yarbough et al.⁶³, and the data suggesting the compartmentalization of glycosylated pORF2 were generated by Jameel et al.²¹. The model represents an extension and modification of the HEV replication strategy proposed by Reyes et al.^{43, 28}

Antigenicity

All HEV strains studied to date (1998) appear to comprise a single serotype.^{29, 40, 41}

Major epitopes appear to exist near the carboxyl ends of ORF2 and ORF3. Epitopes contained in ORF2 are more conserved (90.5%) than epitopes contained in ORF3 (73.5%) in different strains.⁴¹

Western blot data indicate that type (virus)-specific epitopes exist and can be used to differentiate serologically different isolates.^{10, 19}

Serologic tests for anti-HEV based upon expressed ORF2 sequences are more sensitive for detecting IgM and IgG anti-HEV than are tests based upon antigens containing ORF3 sequences. In fact, proteins expressed from ORF2 measure antibodies that correlate with protection against hepatitis E, whereas no such correlation has been shown for antibodies to ORF3.¹⁶

Antibodies to swine HEV cross-react with capsid antigens from strains of human HEV.

No serologic or hybridizing cross-reactivity between HEV and other viral hepatitis agents, including hepatitis A virus (HAV), has been observed.

Stability

HEV is extremely sensitive to high salt concentrations (CsCl).^{9, 10}

HEV should be stored as cold as possible, although it is rapidly degraded when freeze-thawed. The virus is sensitive to degradation by proteolytic enzymes.^{9, 10, 52}

HEV is excreted from the liver via the common bile duct into the duodenum of the small intestine. Survival in the gastrointestinal tract suggests relative stability to acid and mild alkaline conditions.^{10, 18, 23, 41}

The amount of infectious virions shed in the faeces during infection is low, consistent with the low rates of secondary spread during epidemics.¹⁸

Virions remain unaltered after exposure to trifluorotrchloroethane.⁴¹

Outbreaks of HEV have been successfully controlled by chlorination of water supplies. Iodinated disinfectants or autoclaving destroys the virus.⁵²

For transportation, specimens containing HEV should be kept frozen in dry ice (solid CO₂, -70°C), or preferably in liquid N₂ (-120°C).⁵²

The disease

Hepatitis E virus causes acute sporadic and epidemic viral hepatitis. Symptomatic HEV infection is most common in young adults aged 15-40 years and is uncommon in children. Although HEV infection is frequent in children, it is mostly asymptomatic and anicteric.⁵

The clinical presentation of hepatitis E is comparable to hepatitis A.

The incubation period following exposure to HEV ranges from 3 to 8 weeks, with a mean of 40 days.^{29, 40, 41}

Typical signs and symptoms of hepatitis include jaundice, anorexia, hepatomegaly, abdominal pain and tenderness, nausea and vomiting, and fever, although the disease may range in severity from subclinical to fulminant.^{10, 29}

Peak viremia and peak shedding of HEV into the faeces occurs during the incubation period and early acute phase of disease. Detection of HEV antigens in the liver generally parallels viremia and faecal shedding of virus.^{41, 52}

The highest rate of clinically evident disease is typically observed in young to middle-age adults. Lower disease rates in younger age groups may be the result of anicteric or/and subclinical HEV infections.¹⁸

The severity of an HEV infection is generally greater than the severity of an HAV infection.⁴¹

In general, hepatitis E is a self-limiting viral infection followed by recovery.

Occasionally, a fulminant form of hepatitis develops, with mortality rates ranging between 0.5% - 4.0% of the overall population of patients.

Fulminant hepatitis cases in pregnancy may reach a mortality rate of 20% in the 3rd trimester. Premature deliveries with high infant mortality of up to 33% are also observed.^{10, 29, 40, 41, 48} The reason for this high mortality is not clear yet. Some of the complications of pregnancy are toxemia with hypertension, proteinuria, edema, and kidney lesions. By directly or indirectly affecting the kidneys, HEV might precipitate eclampsia and lead to increased mortality in pregnant women.⁶

Common cholestatic jaundice can persist for several weeks.

No evidence of chronic inflammation or of a healthy chronic carrier state has been detected, and no recurrence of hepatitis E has been reported.^{29, 40, 41}

Association with hepatocellular carcinoma or persistent viremia are not features of HEV infection.⁴⁸

Coinfection of young children with HEV and HAV may lead to severe forms of disease, including acute liver failure.

Diagnosis

Since cases of hepatitis E are not clinically distinguishable from other types of acute viral hepatitis, diagnosis is made by biochemical assessment of liver function (laboratory evaluation of: urine bilirubin and urobilinogen, total and direct serum bilirubin, ALT and AST, alkaline phosphatase, prothrombin time, total

protein, albumin, IgG, IgA, IgM, complete blood count). Acute hepatitis E is diagnosed when the presence of IgM anti-HEV is detected.^{41, 52}

Storage of serum samples is acceptable for several days at 4°C, although anti-HEV will be preserved at –20°C, and a temperature of –70°C should be preferred when viremia is suspected.⁴²

Hepatitis E should be suspected in outbreaks of waterborne hepatitis occurring in developing countries, especially if the disease is more severe in pregnant women, or if hepatitis A has been excluded. If laboratory tests are not available, epidemiologic evidence can help in establishing a diagnosis.¹⁸

HEV RNA can be detected in acute phase faeces by PCR in approximately 50% of cases. Immune electron microscopy is positive in only about 10% of cases.⁴¹

The viral proteins pORF2 and pORF3 have been expressed in various recombinant systems and form the basis for diagnostic tests and vaccine studies. To confirm the results of EIA or ELISA tests, Western blot assays to detect IgM and IgG anti-HEV in serum can be used, along with polymerase chain reaction (PCR) tests for the detection of HEV RNA in serum and stool, immunofluorescent antibody blocking assays to detect antibody to HEV antigen in serum and liver, and immune electron microscopy to visualize viral particles in faeces.^{9, 18, 19, 22, 30, 36, 41, 48, 52, 55, 56}

Host immune response

Viremia in bile and serum and shedding of HEV in faeces reach their peak during the incubation period and keep constant levels in the acute phase of the disease. At the same time, HEV antigens can be detected in the liver.

The period of infectivity after acute infection has not been determined, but virus excretion in faeces has been demonstrated up to 14 days after onset of jaundice.

Viremia precedes the major peak in ALT activity.

Virus excretion in stools continues for up to 14 days after onset of illness, then disappears during the recovery phase.

Antibodies to HEV (IgM and IgG) develop at the time symptoms occur, usually before the development of jaundice.^{41, 48} IgM anti-HEV precedes the IgG anti-HEV by a few days.⁴

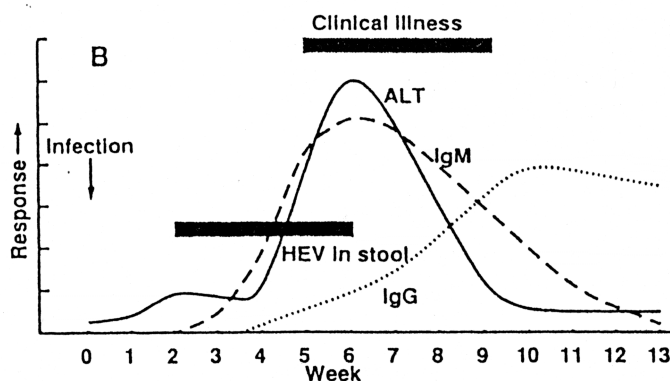
Viremia may persist after appearance of serum antibodies.

IgM anti-HEV titres decline rapidly during early convalescence.⁴⁸

IgG anti-HEV have been shown to persist for long periods of time (>14 yrs) and provide protection against subsequent infections.^{27, 29}

Monkeys infected with human HEV are protected against new challenge with homologous or heterologous strains from Asian and African countries. However, the immunity is incomplete since only the clinical disease seems to be prevented, while the virus is still excreted in stools.³⁸

Typical serologic course



From: Robertson BH and Bradley DW. Enterically transmitted hepatitis. In: Lennette EH, Lennette DA, and Lennette ET, eds. *Diagnostic Procedures for Viral, Rickettsial, and Chlamydial Infections*, 7th ed. Washington, DC, American Public Health Association, 1995:361-373,45 "Copyright (1995) American Public Health Association", with permission.

Summary of clinical, biochemical, and serologic findings in acute hepatitis E.

Prevalence

The highest prevalence of infection occurs in regions where low standards of sanitation promote the transmission of the virus.²⁹

The prevalence of antibody to HEV in suspected or documented endemic regions has been much lower than expected (3 - 26%).⁴¹

Screening of blood donors in central Europe and North America has shown a prevalence of anti-HEV antibodies of 1.4 - 2.5%, in South Africa of 1.4%, in Thailand of 2.8%, in Saudi Arabia of 9.5%, and in Egypt of 24.0%.

The prevalence of antibody to HEV in non endemic regions (like the US) has been much higher than anticipated (1 - 3%).^{41, 51}

HEV infections account for >50% of acute sporadic hepatitis in some high endemic areas.

Pathogenesis

In monkeys, viral replication apparently causes liver damage. The immune response successfully eliminates viremia and shedding of virus in faeces, while not inducing much damage to the liver. Seroconversion marks the clearing of virus from faeces and blood and is correlated with resolution of disease.⁵⁴

As with hepatitis A, virus is detected in bile, liver and faeces before the onset of liver function abnormalities.⁴⁸
Severe or fulminant cases may show submassive and massive hepatic necrosis.^{10, 48}

Transmission

HEV is spread by the oral-faecal route. This enterically transmitted virus has been implicated in several food and waterborne outbreaks.⁴⁰

Consumption of faecally contaminated drinking water has given rise to epidemic cases, and the ingestion of raw or uncooked shellfish has been the source of sporadic cases in endemic areas.⁴¹

The low amount of intact HEV particles present in patient stools accounts for the generally lower rate of person-to-person transmission of hepatitis E when compared with that of hepatitis A.¹⁰

Naturally acquired HEV antibodies have been detected in primates, rodents and swine.^{26, 41} Swine HEV cross-reacts with antibodies to the human HEV capsid antigen.³³

Human hepatitis E has been transmitted under laboratory conditions to various species of primates, domestic pigs, lambs and laboratory rats.^{9, 32, 41, 54, 57}

Species specific HEV has been demonstrated in pigs with the identification of swine HEV. Swine HEV is distinct, but closely related to human HEV strains. While specific-pathogen-free pigs can be experimentally infected with the US-2 strain of human HEV, it is still not known whether swine HEV can infect humans, although it can infect chimpanzees under experimental conditions. Until then, swine HEV raises a potential public health concern for zoonosis and xenozoonosis following xenotransplantation with pig organs.^{32, 33}

A zoonotic spread of HEV is not excluded, since monkeys, pigs, cows, rodents, sheep and goats are susceptible to infection with HEV (possible non-human reservoir of virus).^{14, 18, 26, 41, 53, 54}

Although hepatitis E is not endemic in the US and other developed countries, anti-HEV has been found in a significant proportion, up to 28% in some areas, of healthy individuals in these countries.⁵¹ Subclinical infection of humans with swine HEV (possible non-human reservoir of virus) might explain the relatively high prevalence of anti-HEV in healthy individuals in areas where hepatitis E is not endemic.^{33, 60}

Most cases of acute hepatitis E in the US, central and western Europe have been reported among travellers returning from high HEV-endemic areas, although a few have occurred in individuals who have not left their country. It appears, therefore, that some HEV is imported into industrialized countries and some is probably endemic, possibly as a zoonosis.²⁹

The occurrence of sporadic HEV infections in humans may maintain transmission during inter epidemic periods.

Regardless of whether HEV is endemic in the respective human population, hepatitis E is enzootic in pigs, probably worldwide.³⁴

There is no evidence for sexual transmission or for transmission by transfusion.⁴

Risk groups

Here is a list of groups of people who are at risk of contracting HEV:

- persons residing in areas where extended community outbreaks exist
- international travellers to regions of the world where HEV is endemic
- refugees residing in overcrowded temporary camps following catastrophies, especially in Sudan, Somalia, Kenya and Ethiopia
- persons who have chronic liver disease
- possibly persons working with non-human primates, pigs, cows, sheep and goats

Surveillance and Control

Surveillance and control procedures should include

- provision of safe drinking water and proper disposal of sanitary waste
- monitoring disease incidence
- determination of source of infection and mode of transmission by epidemiologic investigation
- detection of outbreaks
- spread containment

Endemicity

Data on the endemicity of HEV infection have predominantly been collected in areas where outbreaks have been reported. As an exception, seroprevalence studies carried out in Egypt, where outbreaks of HEV have not been noted, showed rates of up to 60%, suggesting that most infections occurred early in life and were asymptomatic or mild.¹⁵

Outbreaks have been reported from Algeria, Bangladesh, Borneo, China, Egypt, Ethiopia, Greece, India, Indonesia, Iran, Côte d'Ivoire, Jordan, Libya, Mexico, Myanmar, Nepal, Nigeria, Pakistan, southern Russia, Somalia, eastern Sudan, and The Gambia.^{10, 18}

Most outbreaks have occurred following monsoon rains, heavy flooding, contamination of well water, or massive uptake of untreated sewage into city water treatment plants.^{10, 28, 48}

Incidence/Epidemiology

Outbreaks of hepatitis E are more common in parts of the world with hot climates and are rare in temperate climates.

Outbreaks are mainly associated with faecally contaminated drinking water; exceptions are food-borne epidemics (raw or uncooked shellfish).

HEV was first identified in India, and has since been recognized in the Middle and Far East, in northern and western Africa, the central Asian Republics of the former Soviet Union, in China and Hong Kong SAR.²⁹

Epidemic and sporadic cases have been reported from southeast and central Asia, the Middle East, northern and western Africa and North America (Mexico).^{40, 41}

30 000 cases were reported in New Delhi, India, (1955 - 1956) after the flooding of the river Yamuna and contamination of the city's drinking water.⁵⁸

20 000 cases occurred in Mandalay, Myanmar, (1976-1977) with 18% case fatality rate in infected pregnant women.¹⁰

52 000 cases were reported in Kashmir, India, in 1978.²⁷

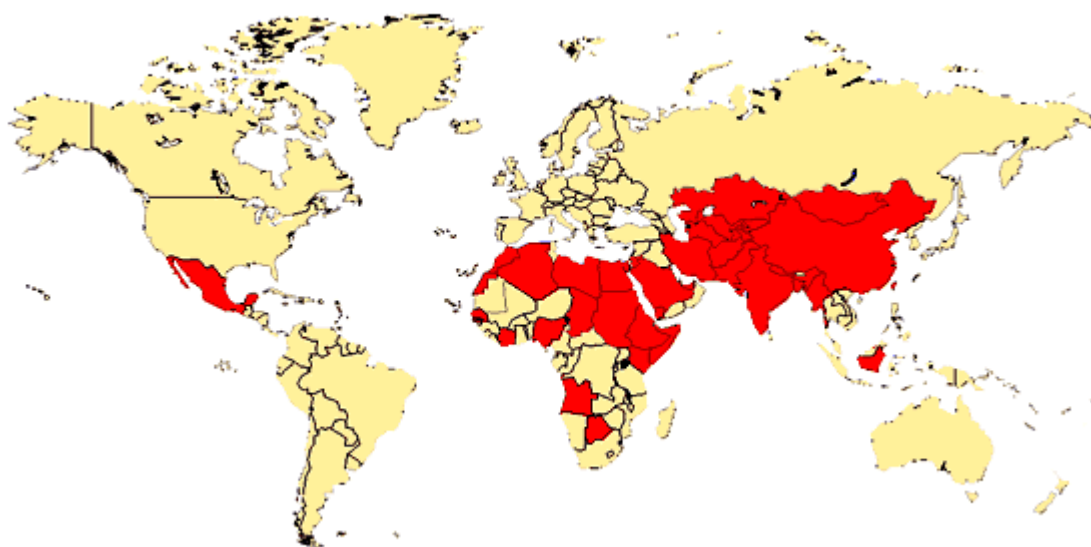
100 000 cases were reported in China between 1986 and 1988.⁴⁸



11 000 cases occurred in Somalia, and about 4 000 cases were reported in Mexico between 1988 and 1989.

Low incidence is reported in Italy and Spain (1995).^{29, 31}

Epidemiology map



Source: Centers of Disease Control and Prevention (CDC), Atlanta, USA.¹¹
http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_e/slide_5.htm

Geographic distribution of hepatitis E.^{11, 41} (Note: The map of HEV infection generalizes available data and patterns may vary within countries.)

Trends

Hepatitis outbreaks occurring in Europe prior to the 20th century, and believed to be hepatitis A, had the epidemiologic characteristics of hepatitis E.^{40, 41}

HEV, more labile and shed in lower titres than HAV, may have disappeared from more industrialized countries in the recent past, just as HAV is currently diminishing in importance in these countries.⁴¹

Immune prophylaxis

There is no available immunoglobulin (IG) prophylaxis at present.

IG prepared from donors in non-HEV-endemic countries does not prevent infection.^{41, 48}

The efficacy of IG prepared from donors in HEV-endemic areas is unclear, although convalescent human sera have given promising preliminary results for passive protection.¹⁰

Experimental immune prophylaxis against HEV based on recombinant antigens appears to confer short-term protection and may be useful for pregnant women in endemic areas and travellers coming into these regions.

Vaccines

At present, no commercially available vaccines exist for the prevention of hepatitis E. However, several studies for the development of an effective vaccine against hepatitis E are in progress.^{41, 55, 61, 62}

- *Recombinant vaccines*

A 55 kDa recombinant HEV-derived ORF2 protein has been used to vaccinate rhesus monkeys against different strains of hepatitis E. Although primates could still be infected, the vaccine protected them from the symptoms of disease.^{55, 62}

- *Subunit HEV vaccines*

The direct intramuscular injection of purified plasmid DNA containing the full-length ORF2 of HEV has induced a prolonged humoral immune response (>12 months) to the expressed structural protein ORF2 in 80% and 100% of two separate groups of challenged mice, respectively.¹⁹

Because swine HEV is immunologically cross-reactive with human HEV and their capsid genes are very conserved, swine HEV may prove useful as an attenuated vaccine for immunization against human hepatitis E through the “Jennerian” approach.³³

Prevention and Treatment

Since antivirals have never been as successful for the treatment of viral infections as antibiotics have been for the treatment of bacterial infections, prevention of viral diseases remains the most important weapon for their control.

Prevention

As almost all HEV infections are spread by the faecal - oral route, good personal hygiene, high quality standards for public water supplies and proper disposal of sanitary waste have resulted in a low prevalence of HEV infections in many well developed societies.²⁹

For travellers to high endemic areas, the usual elementary food hygiene precautions are recommended. These include avoiding drinking water and/or ice of unknown purity and eating uncooked shellfish, uncooked fruits or vegetables that are not peeled or prepared by the traveller.

Vaccines or specific IG preparations are currently under development.⁴⁸

Treatment

As no specific therapy is capable of altering the course of acute hepatitis E infection, prevention is the most effective approach against the disease.^{41, 48}

As with hepatitis A, hepatitis E patients generally do not require hospitalization.⁴⁸

Admission is required for fulminant hepatitis and should be considered for infected pregnant women.⁴⁸

Guidelines for epidemic measures

1. Determination of mode of transmission.
2. Identification of the population exposed to increased risk of infection.
3. Elimination of common source of infection.
4. Improvement of sanitary and hygienic practices to eliminate faecal contamination of food and water.

Future considerations

The development of more sensitive and more specific serologic tests for IgM and total anti-HEV antibodies will provide insight into the epidemiology of the disease.

The manufacture of hyperimmune E globulin and the production of a vaccine are essential for the control of the disease.

There is a need for determining the durability of anti-HEV neutralizing antibody after natural infection or vaccination.

The development of differential diagnostic tests to distinguish between infections with swine HEV and human HEV is necessary.³³



The pathogenesis of the disease, especially in infected pregnant women, needs to be elucidated.

International measures should be established.



Glossary

albumin a water soluble protein. Serum albumin is found in blood plasma and is important for maintaining plasma volume and osmotic pressure of circulating blood. Albumin is synthesized in the liver. The inability to synthesize albumin is a predominant feature of chronic liver disease.

alkaline phosphatase any of group of phosphatases showing activity at alkaline pH, which are normally measured collectively in blood serum. Serum levels are elevated in various conditions, among which are hepatobiliary disorders.

ALT alanine aminotransferase an enzyme that interconverts L-alanine and D-alanine. It is a highly sensitive indicator of hepatocellular damage. When such damage occurs, ALT is released from the liver cells into the bloodstream, resulting in abnormally high serum levels. Normal ALT levels range from 10 to 32 U/l; in women, from 9 to 24 U/l. The normal range for infants is twice that of adults.

amino acids the basic units of proteins, each amino acid has a NH-C(R)-COOH structure, with a variable R group. There are altogether 20 types of naturally occurring amino acids.

antibody a protein molecule formed by the immune system which reacts specifically with the antigen that induced its synthesis. All antibodies are immunoglobulins.¹

antigen any substance which can elicit in a vertebrate host the formation of specific antibodies or the generation of a specific population of lymphocytes reactive with the substance. Antigens may be protein or carbohydrate, lipid or nucleic acid, or contain elements of all or any of these as well as organic or inorganic chemical groups attached to protein or other macromolecule. Whether a material is an antigen in a particular host depends on whether the material is foreign to the host and also on the genetic makeup of the host, as well as on the dose and physical state of the antigen.¹

AST aspartate aminotransferase the enzyme that catalyzes the reaction of aspartate with 2-oxoglutarate to give glutamate and oxaloacetate. Its concentration in blood may be raised in liver and heart diseases that are associated with damage to those tissues. Normal AST levels range from 8 to 20 U/l. AST levels fluctuate in response to the extent of cellular necrosis.¹

bilirubin is the chief pigment of bile, formed mainly from the breakdown of haemoglobin. After formation it is transported in the plasma to the liver to be then excreted in the bile. Elevation of bile in the blood causes jaundice.⁵⁹

capsid the protein coat of a virion, composed of large multimeric proteins, which closely surrounds the nucleic acid.¹

cholestasis impairment of bile flow at any level from the canaliculus to the duodenum. The clinical condition resulting therefrom, characterized by jaundice and pruritus, is due to the accumulation in blood and tissues of substances normally secreted in bile, particularly bilirubin, bile salts, and cholesterol.¹

codon the smallest unit of genetic material that can specify an amino acid residue in the synthesis of a polypeptide chain. The codon consists of three adjacent nucleotides.

complete blood count chemical analysis of various substances in the blood performed with the aim of a) assessing the patient's status by establishing normal levels for each individual patient, b) preventing disease by alerting to potentially dangerous levels of blood constituents that could lead to more serious conditions, c) establishing a diagnosis for already present pathologic conditions, and d) assessing a patient's progress when a disturbance in blood chemistry already exists.

edema the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body, usually referring to demonstrable amounts in the subcutaneous tissues. It may be localized, due to venous or lymphatic obstruction or increased vascular permeability, or systemic, due to heart failure or renal disease.³

eclampsia convulsions occurring in a pregnant or puerperal woman, associated with preeclampsia, i.e., with hypertension, proteinuria, or edema.³

endemic continuously prevalent in some degree in a community or region.⁵⁹

enzootic descriptive of an infection which is continuously prevalent in an animal community, although it may not cause obvious morbidity or may effect few members of the community at any one time.⁵⁹

enzyme any protein catalyst, i.e. substance which accelerates chemical reactions without itself being used up in the process. Many enzymes are specific to the substance on which they can act, called substrate. Enzymes are present in all living matter and are involved in all the metabolic processes upon which life depends.⁵⁹

epidemic an outbreak of disease such that for a limited period a significantly greater number of persons in a community or region suffer from it than is normally the case. Thus an epidemic is a temporary increase in incidence. Its extent and duration are determined by the interaction of such variables as the nature and infectivity of the casual agent, its mode of transmission and the degree of preexisting and newly acquired immunity.⁵⁹

epitope or antigenic determinant. The small portion of an antigen that combines with a specific antibody. A single antigen molecule may carry several different epitopes.¹

genome the total genetic information present in a cell. In diploid cells, the genetic information contained in one chromosome set.¹

genotype the genetic constitution of an individual.²

hepatocytes liver cells.¹

humoral pertaining to the humors, or certain fluids, of the body.¹

IgA antibodies IgA is the major class of antibodies in external secretions, such as saliva, tears, bronchial and intestinal mucus. IgA has antiviral properties. Its production is stimulated by aerosol immunizations and oral vaccines.

IgG antibodies IgG is the most abundant of the circulating antibodies. It readily crosses the walls of blood vessels and enters tissue fluids. IgG also crosses the placenta and confers passive immunity from the mother to the fetus. IgG protects against bacteria, viruses, and toxins circulating in the blood and lymph.

IgM antibodies IgMs are the first circulating antibodies to appear in response to an antigen. However, their concentration in the blood declines rapidly. This is diagnostically useful, because the presence of IgM usually indicates a current infection by the pathogen causing its formation. IgM consists of five Y-shaped monomers arranged in a pentamer structure. The numerous antigen-binding sites make it very effective in agglutinating antigens. IgM is too large to cross the placenta and hence does not confer maternal immunity.

immunoglobulin (IG) a sterile preparation of concentrated antibodies (immunoglobulins) recovered from pooled human plasma processed by cold ethanol fractionation. Only plasma that has tested negative for a)

hepatitis B surface antigen (HBsAg), b) antibody to human immunodeficiency virus (HIV), and c) antibody to hepatitis C virus (HCV) is used to manufacture IG. IG is administered to protect against certain diseases through passive transfer of antibody. The IGs are broadly classified into five types on the basis of physical, antigenic and functional variations, labelled respectively IgM, IgG, IgA, IgE and IgD.

immunogenic capable of eliciting an immune response.

incidence the number of cases of a disease, abnormality, accident, etc., arising in a defined population during a stated period, expressed as a proportion, such as x cases per 1000 persons per year.¹

jaundice is a yellow discoloration of the skin and mucous membranes due to excess of bilirubin in the blood, also known as icterus.⁵⁹

lymphocyte a leukocyte of blood, bone marrow and lymphatic tissue. Lymphocytes play a major role in both cellular and humoral immunity. Several different functional and morphologic types have been recognized, i.e. the small, large, B-, and T-lymphocytes, with further morphologic distinction being made among the B-lymphocytes and functional distinction among T-lymphocytes.¹

nucleotide a molecule formed from the combination of one nitrogenous base (purine or pyrimidine), a sugar (ribose or deoxyribose) and a phosphate group. It is a hydrolysis product of nucleic acid.¹

peptide a compound of two or more amino acids linked together by peptide bonds. Peptides of more than 10 amino acid residues are called polypeptides.

plasma the liquid matrix in which the blood cells and blood proteins are suspended in. It contains an extensive variety of solutes dissolved in water. Water accounts for about 90% of blood plasma.

plasmid a small, circular DNA molecule, separate from the bacterial chromosome, capable of independent replication.

pleomorphic distinguished by having more than one form during a life cycle.¹

polymerase an enzyme which catalyzes the replication of DNA (DNA polymerase) or RNA (RNA polymerase).

prevalence is the number of instances of infections or of persons ill, or of any other event such as accidents, in a specified population, without any distinction between new and old cases.⁵⁹

prophylaxis is the prevention of disease, or the preventive treatment of a recurrent disorder.⁵⁹

protein large molecule made up of one or more polypeptide chains of usually more than 100 amino acids. Biologically important as enzymes, structural protein and connective tissue.

proteinuria the presence of an excess of serum proteins in the urine.³

prothrombin time a test used to measure the activity of clotting factors I, II, V, VII, and X. Deficiency of any of these factors leads to a prolongation of the prothrombin time. The test is basic to any study of the coagulation process, and it helps in establishing and maintaining anticoagulant therapy.

self-limited denoting a disease that tends to cease after a definite period; e.g., hepatitis A.²

seroconversion the production in a host of specific antibodies as a result of infection or immunization. The antibodies can be detected in the host's blood serum following, but not preceding, infection or immunization.¹

serotype a subgroup within a species, defined by reaction of one or more antigens with the corresponding antiserum.¹

serum is the clear, slightly yellow fluid which separates from blood when it clots. In composition it resembles blood plasma, but with fibrinogen removed. Sera containing antibodies and antitoxins against infections and toxins of various kinds (antisera) have been used extensively in prevention or treatment of various diseases.⁵⁹

titre a measure of the concentration or activity of an active substance.

toxemia any condition resulting from the spread of toxins by the bloodstream.³

translation the process of forming a specific protein having its amino acid sequence determined by the codons of messenger RNA. Ribosomes and transfer RNA are necessary for translation.¹

urobilinogen also stercobilinogen. A colorless, reduced form of stercobilin, in which the pyrrole rings are joined by -CH₂- groups. It is oxidized by air to the colored stercobilin.¹

vaccine an antigenic preparation used to produce active immunity to a disease to prevent or ameliorate the effects of infection with the natural or "wild" organism. Vaccines may be living, attenuated strains of viruses or bacteria which give rise to inapparent to trivial infections. Vaccines may also be killed or inactivated organisms or purified products derived from them. Formalin-inactivated toxins are used as vaccines against diphtheria and tetanus. Synthetically or genetically engineered antigens are currently being developed for use as vaccines. Some vaccines are effective by mouth, but most have to be given parenterally.^{1, 59}

viremia the presence of viruses in the blood, usually characterized by malaise, fever, and aching of the back and extremities.³

virion a structurally complete virus, a viral particle.¹

virus any of a number of small, obligatory intracellular parasites with a single type of nucleic acid, either DNA or RNA and no cell wall. The nucleic acid is enclosed in a structure called a capsid, which is composed of repeating protein subunits called capsomeres, with or without a lipid envelope. The complete infectious virus particle, called a virion, relies on the metabolism of the cell it infects. Viruses are morphologically heterogeneous, occurring as spherical, filamentous, polyhedral, or pleomorphic particles. They are classified by the host infected, the type of nucleic acid, the symmetry of the capsid, and the presence or absence of an envelope.¹

xenozoonosis the inadvertent transmission of pathogens from animal organs to human recipients.

xenotransplantation animal organ and tissue transplantation into humans.

zoonosis a disease of animals that is capable of afflicting man.¹

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