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Hepatitis Delta

World Health Organization
Department of Communicable Disease Surveillance and
Response

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Hepatitis Delta - 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 antigens and anti-viral antibodies.

In 1977, a previously unrecognized nuclear antigen was detected in hepatocytes of patients with chronic hepatitis B. The antigen resembled hepatitis B core antigen (HBcAg) in its subcellular localization. Its presence was always associated with hepatitis B virus (HBV) infection, but it rarely coexisted with HBcAg. It was termed "delta antigen". Patients with delta antigen develop anti-delta antibodies.^{14, 21, 22}

In 1980, the delta antigen was recognized to be the component of a novel virus that was defective and required coinfection with HBV for its replication. The hepatitis delta virus (HDV) was shown to rely on HBV for transmission because it used the hepatitis B surface antigen (HBsAg) as its own virion coat.^{14, 21, 25}

The viruslike delta agent was subsequently shown to be associated with the most severe forms of acute and chronic hepatitis in many HBsAg-positive patients. The disease it caused was designated delta or type D hepatitis.

What causes the disease?

Hepatitis D or delta hepatitis is caused by the hepatitis delta virus (HDV), a defective RNA virus. HDV requires the help of a hepadnavirus like hepatitis B virus (HBV) for its own replication.

How is HDV spread?

HDV is transmitted percutaneously or sexually through contact with infected blood or blood products.

Blood is potentially infectious during all phases of active hepatitis D infection. Peak infectivity probably occurs just before the onset of acute disease.

Who is at risk for infection?

Chronic HBV carriers are at risk for infection with HDV.

Individuals who are not infected with HBV, and have not been immunized against HBV, are at risk of infection with HBV with simultaneous or subsequent infection with HDV.

Since HDV absolutely requires the support of a hepadnavirus for its own replication, inoculation with HDV in the absence of HBV will not cause hepatitis D. Alone, the viral genome indeed replicates in a helper-independent manner, but virus particles are not released.

Where is HDV a problem globally?

The hepatitis delta virus is present worldwide and in all age groups.^{14, 21}

Its distribution parallels that of HBV infection, although with different prevalence rates (highest in parts of Russia, Romania, Southern Italy and the Mediterranean countries, Africa and South America). In some HBV-prevalent countries such as China, HDV infection is disproportionately low.¹⁴

The natural reservoir is man, but HDV can be experimentally transmitted to chimpanzees and woodchucks that are infected with HBV and woodchuck hepatitis virus, respectively.^{19, 21, 24}

When is a HDV infection life-threatening?

HDV infection of chronically infected HBV-carriers may lead to fulminant acute hepatitis or severe chronic active hepatitis, often progressing to cirrhosis.

Chronic hepatitis D may also lead to the development of hepatocellular carcinoma.¹¹

Why is there no treatment for the disease?

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

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

Disease conditions may occasionally improve with administration of α -interferon.^{15, 21, 25}

Since no effective antiviral therapy is currently available for treatment of type D hepatitis, liver transplantation may be considered for cases of fulminant acute and end-stage chronic hepatitis D.

The hepatitis Delta virus HDV

The genome of HDV is unrelated to the genomes of hepadnaviruses, of which hepatitis B virus (HBV) is a member. HDV is therefore not a defective-interfering particle of HBV, and should be considered as a satellite virus, a natural subviral satellite of HBV.^{10, 11, 14, 25}

Important parallels can be drawn between HDV and certain subviral agents of plants, especially the viroids, with respect to genome structure and replication mechanisms. Because of the many differences however, HDV has been classified into the separate genus Deltavirus.^{13, 18, 25}

The genome of HDV was cloned and sequenced in 1986.²⁷ HDV is a replication defective, helper (HBV) dependent ssRNA virus that requires the surface antigen of HBV (HBsAg) for the encapsidation of its own genome. The envelope proteins on the outer surface of HDV are entirely provided by HBV.^{16, 18, 25}

The outer envelope of HDV particles actually contains lipid and all three forms (S, M, and L) of HBV surface antigen (HBsAg), but predominantly the major form of HBsAg with very few middle (pre S1) and large (pre S2) proteins. This proportion (95:5:1 of S:M:L) is different from that found in HBV particles.^{13, 14, 25}

There is no evidence that the HBV-derived envelope proteins are additionally modified when they become the envelope of HDV.²¹

The internal, nucleocapsid structure of HDV is composed of the viral single stranded RNA genome and about 60 copies of delta antigen, the only HDV-encoded protein, in its large and small forms.^{13, 25}

Synthesis of HDV results in temporary suppression of synthesis of HBV components.¹³

HDV does not infect established tissue culture cell lines. Complete viral replication cycles in vitro are limited to primary hepatocytes, generally of woodchucks or chimpanzees, that are coinfecting with a hepadnavirus or cotransfected with hepadnavirus cDNA. When experimental conditions meet these requirements, infectious HDV particles are produced.^{13, 14, 21}

In nature, HDV has only been found in humans infected with HBV. Experimentally, it can be transmitted to chimpanzees and woodchucks in the presence of HBV or woodchuck hepatitis virus (WHV), respectively.^{13, 18, 19, 21, 24, 25}

Hepatitis Delta virus replication cycle

To replicate efficiently, a virus requires the cooperation of the host cell at all stages of the replicative cycle: attachment, penetration, uncoating, provision of appropriate metabolic conditions for the synthesis of viral macromolecules, the final assembly of viral subunits and the release of new virions. HDV also requires the presence of a helper hepadnavirus to provide the protein components for its own envelope.

How HDV enters hepatocytes is still not known, but it may involve the interaction between HBsAg-L and a cellular receptor. The incoming HDV RNA is then transported into the nucleus, the site of genome replication, probably by the small form of delta antigen, HDAg-S. Binding of HDAg to RNA also protects the HDV RNAs from degradation.^{13, 14, 25}

HDV RNA replication is carried out by cellular RNA polymerase II, without a DNA intermediate, and without the help of HBV. Replication proceeds via a double rolling-circle model. The genomic strand which is of negative polarity yields an oligomeric linear structure with site-specific autocatalytic cleavage and ligation. This structure generates circles of the opposite positive strand polarity, which again replicate in

the same way and produce the genomic negative RNA. The only functional open reading frame which codes for the two HDV structural phosphoproteins occurs in the antigenomic strand at one end of the HDV RNA rod. It is 800 bases long and terminates at a polyadenylation site.^{10, 13, 14, 17, 18, 25}

RNA transcription is regulated: initially, mRNA(s) is(are) transcribed from the incoming minus-strand genome and later, after the translation of the mRNA to make essential replication proteins, there is a switch in the mode of RNA-directed RNA synthesis to facilitate replication of the RNA genome.^{13, 25}

Translation of the 800 b RNA transcript yields a small (p24) and a large (p27) form of HDAg. These two proteins, known as short (HDAg-S) and long form (HDAg-L) of HDAg, have very different functional roles during viral replication. The HDAg-S is a transactivator of HDV RNA replication, while the HDAg-L inhibits RNA synthesis and initiates virion assembly with HBsAg.^{8, 10, 13, 14, 21, 23, 25}

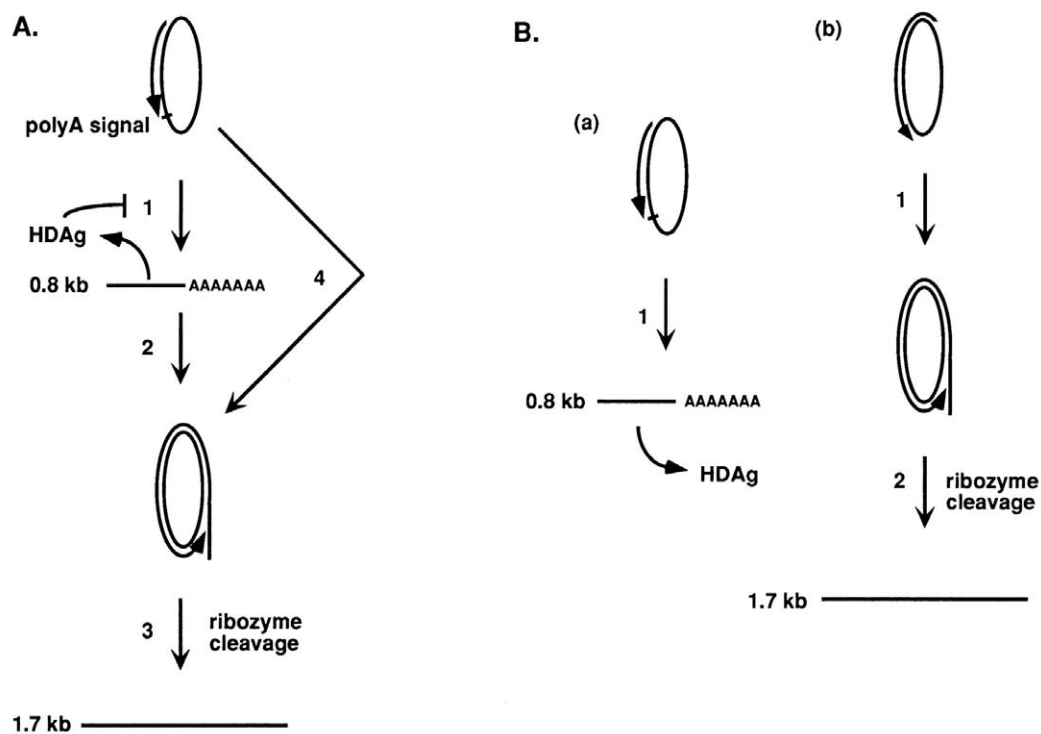
The production of HDAg-S, as opposed to HDAg-L, depends on the extent of HDV RNA editing. A specific modification at nucleotide position 1012 from A to G changes the UAG stop codon of the transcript to UGG (tryptophan), allowing translation to continue for another 19 amino acids. The target of editing is the antigenomic strand; the adenosine is converted to guanosine via inosine by a cellular double-stranded RNA adenosine deaminase. The intracellular ratio of p24/p27 will determine the extent of viral replication, assembly and transport.^{5, 10, 13, 20, 25}

Since HDV particles consist of HBsAg, HDAg-S and HDAg-L, and RNA, they are assembled only in the presence of the helper virus, HBV. HBsAg and HDAg-L are necessary and sufficient for virus assembly, whereas HDV RNA or HDAg-S are not required, but are certainly present, in viral particles.²⁵ The basis of selectivity of RNA packaging *in vivo* is not yet clear, and although HDAg can interact with both genomic- and antigenomic-sense HDV RNA, only genomic-sense RNA is found in viral particles.^{13, 23, 25}

The primary initiation event for HDV assembly is the interaction of HDAg-L with HBsAg, which is determined by the presence of the C-terminal 19 amino acids of HDAg-L and the prenylation of the cysteine residue 211 on HDAg-L.^{9, 25} However, HDAg is localized in the nuclei, and HBsAg is present in the cytoplasm of the infected cells. How these two proteins in different cellular compartments come into direct contact remains a puzzling issue.^{12, 13}

A speculation is that the genomic RNA, assembled into a ribonucleoprotein (RNP) involving both HDAg-S and HDAg-L, interacts with HBsAg already inserted in the membranes of the endoplasmic reticulum. This would then be followed by the passage of assembled particles onto the Golgi apparatus, and the release of virions from the cell, without direct toxicity.^{13, 25}

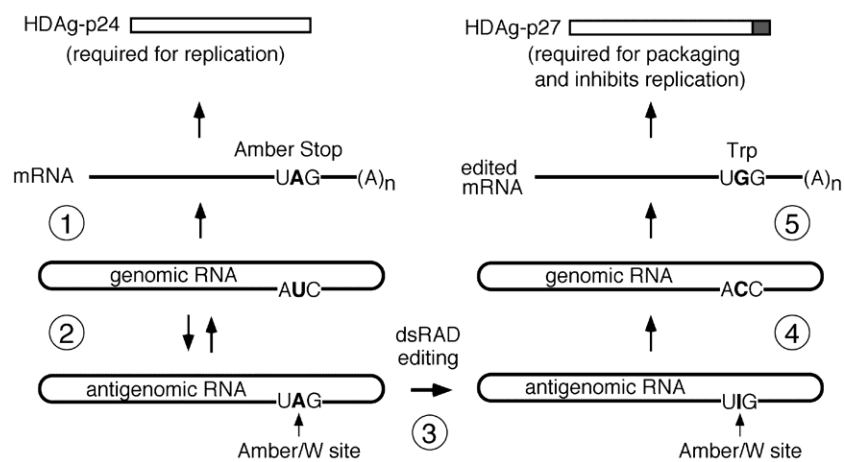
Genome replication model



From: Modahl LE and Lai MMC. Transcription of Hepatitis Delta antigen mRNA continues throughout hepatitis Delta virus (HDV) replication: a new model of HDV RNA transcription and replication. *Journal of Virology*, 1998, 72(7):5449-5456,¹⁷ "Copyright (1998) American Society for Microbiology", with permission.

Proposed models of HDV RNA transcription and replication. (A) The previously accepted model of HDV RNA transcription and replication. The initial product of replication from the genomic HDV RNA template is the 0.8 kb HDAg-encoding mRNA (arrow 1). HDAg produced from this mRNA suppresses the HDV polyadenylation signal, allowing synthesis of multimeric RNA (arrow 2), which is processed into full-length antigenomic HDV RNA (arrow 3). Subsequent rounds of replication bypass the polyadenylation signal due to the presence of HDAg and directly synthesize full-length antigenomic HDV RNA (arrow 4). (B) Proposed new model for HDV RNA transcription and replication. The syntheses of 0.8 kb mRNA (a) and 1.7 kb monomer RNA (b) are independent and occur in parallel.^{17, 25}

A model for RNA editing of HDV



Reprinted by permission from *Nature* (Polson AG, et al. RNA editing of hepatitis delta virus antigenome by dsRNA-adenosine deaminase. *Nature*, 1996, 380:454-456²⁰) copyright (1996) Macmillan Magazines Ltd. (<http://www.nature.com>).

A model for RNA editing of HDV. (1) Replication-competent genomes are transcribed to produce an mRNA encoding HDAg-p24. (2) HDAg-24 enables replication of the genome by RNA polymerase II, generating antigenomic RNA. (3) dsRAD (double-stranded-RNA-adenosine deaminase) acts on antigenomic RNA to convert the adenine at the amber/W site to an inosine. (4) Like G, inosine prefers to pair with C; thus, after replication, the genome has a C at the amber/W site instead of a U. (5) The edited genome is transcribed to yield an mRNA encoding HDAg-p27. HDAg-p27, which contains a 19-amino-acid extension (shaded), inhibits replication and helps packaging of the HDV genome by HBV surface antigen.²⁰

Morphology and physicochemical properties

HDV virions are 36 - 43 nm, roughly spherical, enveloped particles with no distinct nucleocapsid structure. They do not have distinct spikes on their outer surface and are possibly icosahedral.^{13, 14, 25}

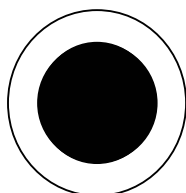
When the virus particle is disrupted with nonionic detergents, an internal nucleocapsid is released and HDAg becomes detectable.^{13, 25}

The 19 nm nucleocapsid contains about 60 copies of HDAg in its two forms (24 and 27 kDa) and HDV genomic RNA.²⁵

The buoyant density of HDV particles is 1.25 g/cm³ in CsCl gradients.^{13, 14, 18}

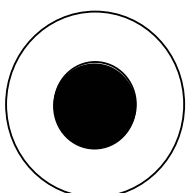
Schematic representation of viral particles found in serum of HBV - HDV infected people

Infectious HBV particle:



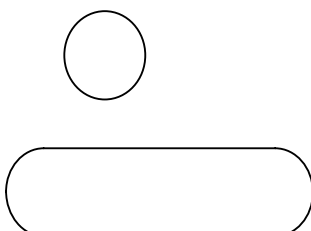
- 42 nm outer envelope containing lipid and three forms of HBsAg
- 27 nm nucleocapsid containing 180 copies of core protein and reverse transcriptase and HBV DNA

Infectious HDV particle:



- 36 - 43 nm outer envelope containing lipid and three forms of HBsAg
- 19 nm nucleocapsid containing 60 copies of delta antigen and HDV genomic RNA

Empty noninfectious particles:



- 22 nm filaments and spheres made of lipid and mainly one form of HBsAg

From: Taylor JM, Hepatitis Delta virus and its replication. In: Fields Virology, 3rd ed. Philadelphia, Lippincott – Raven, 1996:2809-2818,²⁵ with permission (<http://lww.com>).

Genome and proteins

The HDV genome is a single, negative stranded, circular RNA molecule nearly 1.7 kb in length containing about 60% C+G.^{13, 14, 18, 25}

HDV RNA is the only animal virus known to have a circular RNA genome.¹³

A high degree of intramolecular complementarity allows about 70% of the nucleotides to be basepaired to each other to form an unbranched, double-stranded, stable, rod-shaped structure.^{10, 13, 14, 18}

So far, about 14 different HDV isolates from different parts of the world have been sequenced, and all range from 1670 to 1685 nucleotides in length. Based on sequence similarities, HDV isolates can be classified into three genotypes.¹³

Genotype I is the most predominant one in most areas of the world, and is associated with a broad spectrum of chronic HDV disease. Originally found in a Japanese isolate, genotype II has been found recently to predominate in Taiwan. Disease associated with genotype II might be less severe than genotype I. Genotype III is associated with outbreaks in Venezuela and Peru. It is responsible for more severe disease in the northern South American regions.^{5, 10, 11, 13}

The genome contains several sense- and antisense open reading frames (ORFs), only one of which is functional and conserved. The RNA genome is replicated through an RNA intermediate, the antigenome.^{13, 14, 18}

The genomic RNA and its complement, the antigenome, can function as ribozymes to carry out self-cleavage and self-ligation reactions.^{13, 18, 25}

A third RNA present in the infected cell, also complementary to the genome, but 800 b long and polyadenylated, is the mRNA for the synthesis of the delta antigen (HDAg).^{14, 18, 25}

The one and only protein expressed by HDV, the hepatitis delta antigen HDAg, is not exposed on the virion outer surface, but is present in the internal nucleocapsid.^{13, 14, 18}

The protein is seen as two species, of 24kD and 27kD. The two species are identical, but the 27kD protein has a 19 aa longer C-terminus. The short form (195 amino acids, HDAg-S), synthesized first, is required for RNA replication; the long form (214 amino acids, HDAg-L), becoming detectable after prolonged replication, suppresses viral RNA replication and is required for packaging of the HDV genome by HBsAg.^{13, 14, 18, 21, 23}

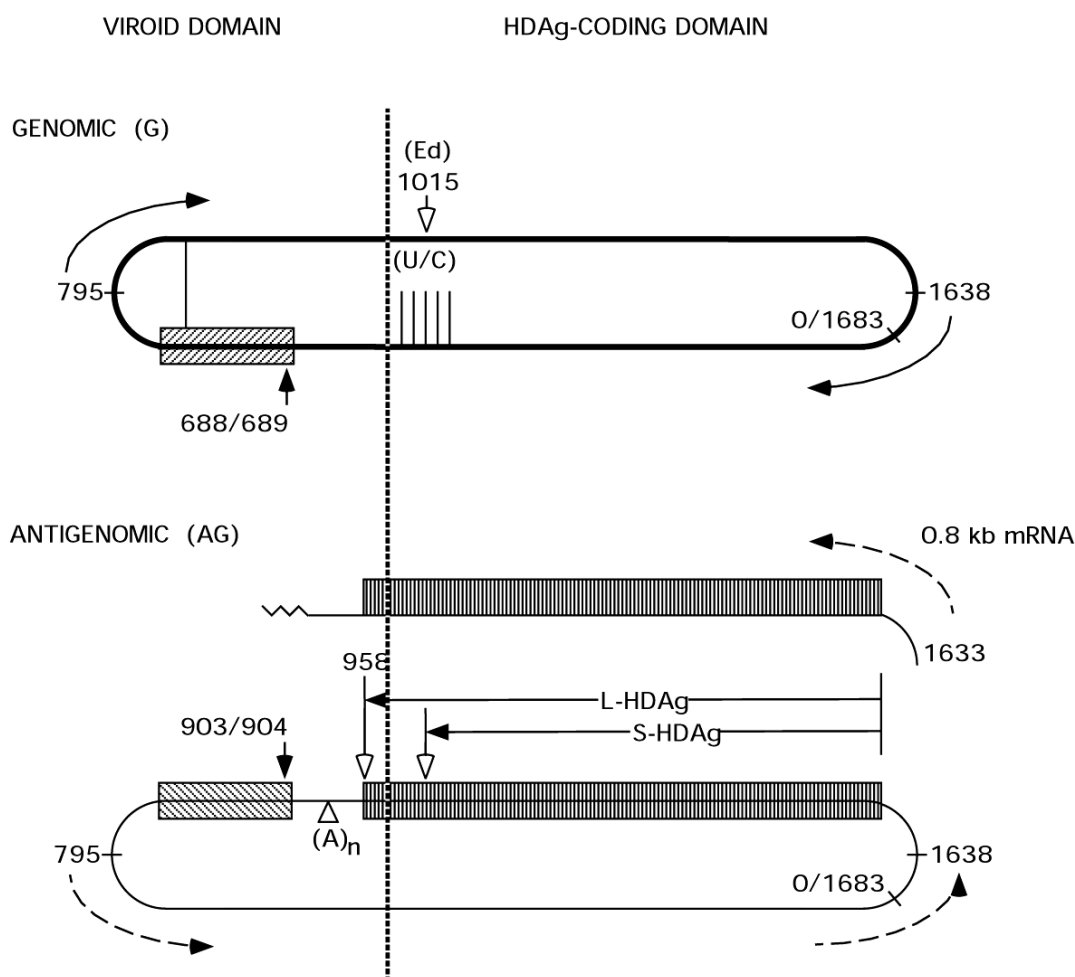
The relative ratios of these two species vary from patient to patient. Two separate ORFs on different RNAs encode HDAg-S and HDAg-L. A single nucleotide at the termination codon for HDAg-S is altered by a specific posttranscriptional RNA editing event in some RNAs, so that the ORF extends for 19 additional amino acids.¹³

HDAg is a non-glycosylated phosphoprotein.^{13, 21, 25} It has an RNA-binding activity and appears to bind specifically to HDV RNA in the virus particle.²⁸ In infected cells, HDAg is localized in the nuclei.^{13, 14, 25}

Functional domains present in HDAg include the nuclear localization signal located within the N-terminal one-third of the protein, the RNA-binding motif present in the middle one-third of the protein and a third domain, consisting of the C-terminal 19 amino acids, possibly involved in interactions with the HBsAg during virion assembly, and in the inhibition of HDV RNA assembly.^{13, 14, 25}

The other protein present in HDV particles is HBsAg. This protein is derived from the coinfection with HBV and is essential for HDV virion assembly and virus transmission.

The three RNAs of HDV present in the infected cell



From: Lai MCC. *The molecular biology of hepatitis Delta virus*. *Annual Review of Biochemistry*, 1995, 64:259-286.¹³ "With permission, from the *Annual Review of Biochemistry*, Volume 64 ©1995 by Annual Reviews <http://www.AnnualReviews.org>".

Schematic diagrams of the structure of HDV RNA. The antigenomic RNA and mRNA are detected only in the cells. The nucleotide numbers are according to Reference ¹⁶ and represented in genomic orientation even on the antigenomic strand. The genomic RNA is represented in clockwise orientation, while antigenomic RNA is counterclockwise. Nucleotides 688/689 and 903/904 are ribozyme cleavage sites for genomic and antigenomic RNAs respectively. The hatched boxes represent the ribozyme domain. Nucleotide 1015 (Ed) denotes RNA editing site. (A)_n represents polyadenylation signal. The UV cross-linking site is indicated by a vertical line in the viroid domain.¹³

Comparison of HDV genotypes

Hepatitis Delta Virus Genotypes					
	Genetic distance (%) between isolates of genotype:			Associated Disease?	Locations
	I	II	III		
I	8 (1 - 15)	23 (21 - 26)	31 (29 - 33)	moderate to severe	North America, Asia Middle East, Europe
II		7 (5 - 8)	33 (32 - 34)	moderate	East Asia
III			5 (1 - 7)	severe	South America

From: Casey JL et al. *Molecular biology of HDV: analysis of RNA editing and genotype variations*. In: *Viral Hepatitis and Liver Disease*, Turin, Edizioni Minerva Medica, 1997:290-294,⁵ with permission.

1. Genetic variability, tentative disease associations, and geographic distributions of HDV genotypes I, II, and III.⁵

Comparison of HDV Genotypes I and III		
	Genotype I	Genotype III
Virion Formation		
Transfected cells (day 10)	≤5 %	10 %
Transfected cells (day 13)	2 %	20 %
Secretion of HDAg-p27 with HBsAg (ayw)	+++	+
RNA Editing		
Serum virion RNA	30%	15%
Virion RNA from transfected cell medium	18%	10%
Modified by purified dsRAD	yes	?
Target structure	base-paired	uncertain
Support of HDAg(-) RNA Replication		
HDAg-p24 (I)	+++	+/-
HDAg-p24 (III)	-	+++

From: Casey JL et al. *Molecular biology of HDV: analysis of RNA editing and genotype variations*. In: *Viral Hepatitis and Liver Disease*, Turin, Edizioni Minerva Medica, 1997:290-294,⁵ with permission.

2. Comparison of virion formation, RNA editing and RNA replication for HDV genotypes I and III.⁵

Antigenicity

The intact virus particle is reactive with anti-HBsAg antibody, but not with anti-HDAg antibody.

Despite the sequence heterogeneity observed in HDV isolates from different geographical regions, there appear to be no serological differences among these isolates.¹⁴

All HDV are antigenically related, and antibodies to HDAg do not neutralize HDV.²¹

Surface epitopes unique to HDV have not been detected.

Under experimental conditions, HDV can use different hepadnaviruses as helpers. In each case, the envelope of HDV has both the physical and antigenic characteristic of the helper virus.

Stability

Because of its double-strandedness, the HDV RNA is relatively stable.

The hepatitis delta virus survives dry heat at 60°C for 30h.¹⁴

The disease

An HDV infection absolutely requires an associated HBV infection. The outcome of disease largely depends on whether the two viruses infect simultaneously (coinfection), or whether the newly HDV-infected person is a chronically infected HBV carrier (superinfection).

Coinfection of HBV and HDV (simultaneous infection with the two viruses) results in both acute type B and acute type D hepatitis. The incubation period depends on the HBV titre of the infecting inoculum. Depending on the relative titres of HBV and HDV, a single bout or two bouts of hepatitis may be seen. Coinfections of HBV and HDV are usually acute, self-limited infections. The chronic form of hepatitis D is seen in less than 5% of HBV - HDV coinfecting patient.^{10, 21}

Acute hepatitis D occurs after an incubation period of 3 - 7 weeks, and a preicteric phase begins with symptoms of fatigue, lethargy, anorexia and nausea, lasting usually 3 to 7 days. During this phase, ALT and AST activities become abnormal. The appearance of jaundice is typical at the onset of the icteric phase. Fatigue and nausea persist, clay-colored stools and dark urine appear, and serum bilirubin levels become abnormal. In patients with acute, self-limiting infection, convalescence begins with the disappearance of clinical symptoms. Fatigue may persist for longer periods of time.^{14, 21}

Superinfection of HBV and HDV (HDV infection of a chronically infected HBV carrier) causes a generally severe acute hepatitis with short incubation time that leads to chronic type D hepatitis in up to 80% of cases. Superinfection is associated with fulminant acute hepatitis and severe chronic active hepatitis, often progressive to cirrhosis.^{14, 21}

During the acute phase of HDV infection, synthesis of both HBsAg and HBV DNA are inhibited until the HDV infection is cleared.¹⁴

Fulminant viral hepatitis is rare, but still about 10 times more common in hepatitis D than in other types of viral hepatitis. It is characterized by hepatic encephalopathy showing changes in personality, disturbances in sleep, confusion and difficulty concentrating, abnormal behavior, somnolence and coma. The mortality rate of fulminant hepatitis D reaches 80%. Liver transplantation is indicated.^{14, 21}

Chronic viral hepatitis D is usually initiated by a clinically apparent acute infection. Symptoms are less severe than in acute hepatitis, and while serum ALT and AST levels are elevated, bilirubin and albumin levels and prothrombin time may be normal. In chronic hepatitis D, the HBV markers are usually suppressed.^{13, 14, 21}

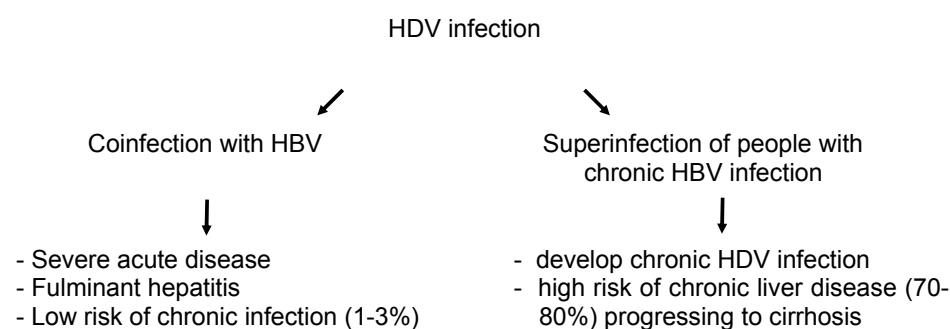
Progression to cirrhosis usually takes 5 - 10 yrs, but it can appear 2 years after onset of infection. About 60 to 70% of patients with chronic hepatitis D develop cirrhosis. A high proportion of these patients die of hepatic failure.²¹

Hepatocellular carcinoma (HCC) occurs in chronically infected HDV patients with advanced liver disease with the same frequency as in patients with ordinary hepatitis B. HCC may actually be more a secondary effect of the associated cirrhosis than a direct carcinogenic effect of the virus.

Taken together, three phases of chronic hepatitis D have been proposed: a) an early active phase with active HDV replication and suppression of HBV, b) a second moderately active one with decreasing HDV and reactivating HBV, c) a third late one with development of cirrhosis and hepatocellular carcinoma caused by replication of either virus or with remission resulting from marked reduction of both viruses.¹⁰

The mortality rate for HDV infections lies between 2% and 20%, values that are ten times higher than for hepatitis B.²¹

Scheme of infection and clinical features



Diagnosis

Hepatitis D should be considered in any individual who is HBsAg positive or has evidence of recent HBV infection.²¹

The diagnosis of acute hepatitis D is made after evaluation of serologic tests for the virus. Total anti-HDV are detected by commercially available radioimmunoassay (RIA) or enzyme immunoassay (EIA) kits.^{10, 21}

The method of choice for the diagnosis of ongoing HDV infection should be RT-PCR, which can detect 10 to 100 copies of the HDV genome in infected serum.^{10, 11, 18, 21}

- acute HBV-HDV coinfection:
 - appearance of HBsAg, HBeAg and HBV DNA in serum during incubation
 - appearance of anti-HBc at onset of clinical disease
 - appearance of IgM anti-HD, HDV RNA, HDAg in serum
 - anti-HDV antibodies develop late in acute phase and usually decline after infection to subdetectable levels
 - if HDAg is detectable early during infection, it disappears as anti-HDV appears
 - all markers of viral replication disappear in early convalescence, and both IgM and IgG anti-HD disappear within months to years after recovery

- HBV-HDV superinfection:
 - usually results in persistent HDV infection
 - HDV viremia appears in serum during preacute phase
 - high titres of IgM and IgG anti-HDV are detectable in acute phase, persisting indefinitely
 - titre of HBsAg declines when HDAg appears in serum
 - progression to chronicity is associated with persisting high levels of IgM anti-HD and IgG anti-HD
 - HDAg and HDV RNA remain detectable in serum and liver
 - viremia is associated with active liver disease

Each of the markers of HDV infection, including IgM and IgG antibodies, disappears within months after recovery. In contrast, in chronic hepatitis D, HDV RNA, HDAg, and IgM and IgG anti-HD antibodies persist.^{14, 18}

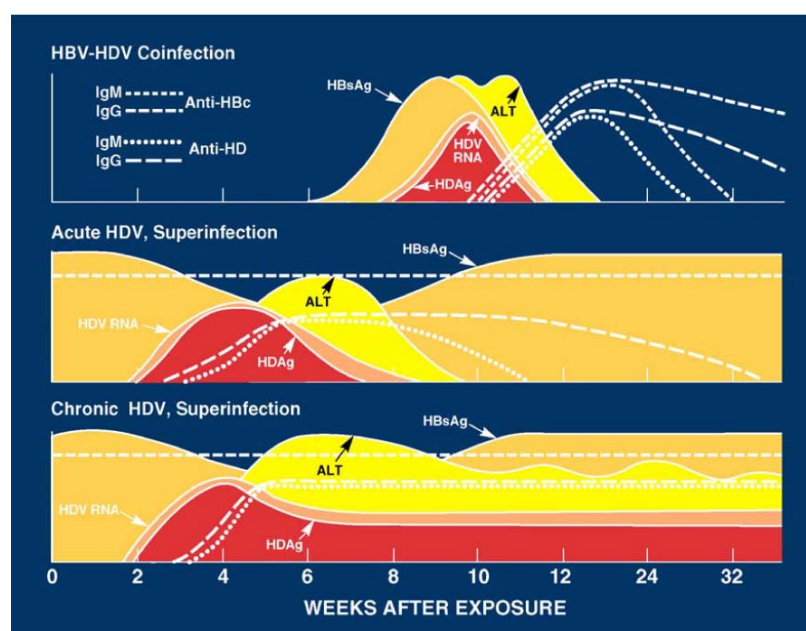
Host immune response

Both humoral and cellular immunity are induced in patients infected with HDV.^{14, 21}

These immune responses may provide protection from HDV re-infection, or simply modulate clinical symptoms. However, second cases of hepatitis D have not been reported.^{14, 21}

Anti-HD antibodies do not always persist after acute infection is cleared. The serological evidence of past HDV infection is therefore not easy to demonstrate.¹⁴

Typical serologic course



From: Purcell RH and Gerin JL, Hepatitis Delta virus. In: Fields Virology, 3rd ed. Philadelphia, Lippincott – Raven, 1996:2819-2829,²¹ with permission (<http://lww.com>).

The serological patterns of type D hepatitis: coinfection and superinfection. **Top:** Coexistent acute hepatitis B and hepatitis D. **Middle:** Acute hepatitis D superimposed on a chronic hepatitis B virus infection. **Bottom:** Acute hepatitis D progressing to chronic hepatitis, superimposed on a chronic hepatitis B virus infection.²¹

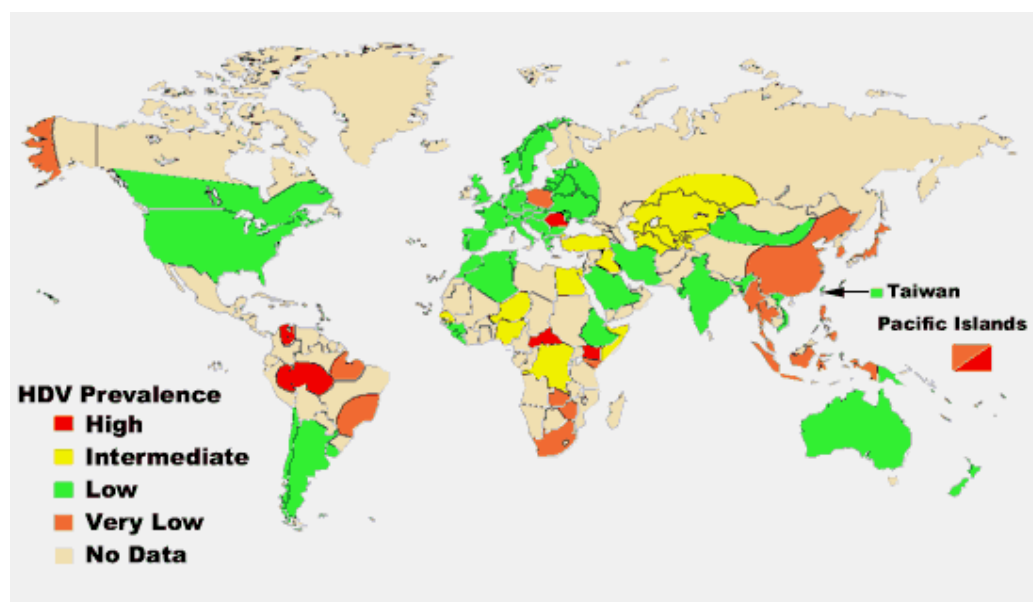
Prevalence

Areas of high prevalence include the Mediterranean Basin, the Middle East, Central Asia, West Africa, the Amazon Basin of South America and certain South Pacific islands.^{13, 14, 21}

Severe, often fatal, acute and chronic type D hepatitis occurs among indigenous people of Venezuela, Colombia, Brazil, and Peru, all regions with high chronic HDV infection rates.²¹

Hepatitis D is less common in Eastern Asia, but is present in Taiwan, China and India.²¹

Worldwide distribution of HDV infection



From: Centers for Disease Control and Prevention (CDC), Atlanta, USA.⁶
http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_d/slide_6.htm

Pathogenesis

Infection with both HBV and HDV is associated with more severe liver injury than HBV infection alone.¹³

Pathologic changes in hepatitis D are limited to the liver, the only organ in which HDV has been shown to replicate. The histologic changes consist of hepatocellular necrosis and inflammation.²¹

HDV genome replication is not acutely cytopathic, and both humoral and cellular immune mechanisms may be involved in the pathology of hepatitis D. More experimental data are needed to unravel the underlying mechanisms of HDV-induced disease.^{10, 14, 21, 25}

HBV is an essential cofactor in the evolution of hepatocellular damage.^{7, 10}

Transmission

Transmission is similar to that of HBV:

- bloodborne and sexual
- percutaneous (injecting drug use, haemophiliacs)
- permucosal (sexual)
- rare perinatal

Superinfections increase the chance of HDV spread, and at the peak of an acute infection, the amount of HDV in the serum can exceed 10^{12} RNA-containing particles per ml.²⁵

During an HDV superinfection, the titre of HDV reaches a peak between 2 and 5 weeks postinoculation, after which it declines in 1 to 2 weeks.²⁵

The probability of being productively coinfecting, with the coinfection resulting in clinical disease, depends on both the relative and absolute amounts of the two inoculated viruses.²⁵

The main route of transmission is infected blood and blood products.

Risk groups

Here is a list of groups of people who are at risk of contracting HDV:²¹

- intravenous drug users using HDV-contaminated injection needles
- promiscuous homosexual and heterosexual groups (although HDV infections are less frequent than HBV or HIV infections)
- people exposed to unscreened blood or blood products
- °haemophiliacs
- °persons with clotting factor disorders

° the risk has decreased in recent years due to better control of blood sources

Incidence/Epidemiology

Seroprevalence studies of anti-HD in HBsAg-positive patients has shown a worldwide but not uniform distribution.²¹

Epidemics of HDV infections have been described in the Amazon Basin, the Mediterranean Basin and Central Africa.

Two epidemiologic patterns of hepatitis D infections exist: in Mediterranean countries infection is endemic among HBV carriers, and the virus is transmitted by close personal contact. In Western Europe and North America, HDV is confined to persons exposed to blood or blood products, like e.g. intravenous drug addicts sharing unsterilized injection needles.

Worldwide, more than 10 million people are infected with HDV.^{10, 11}

Trends

New foci of high HDV prevalence continue to be identified as in the case of the island of Okinawa in Japan, of areas of China, Northern India and Albania.¹⁰

There is a decreasing prevalence of both acute and chronic hepatitis D in the Mediterranean area and in many other parts of the world, which has been attributed to a decline in the prevalence of chronic HBsAg carriers in the general population.¹⁰

Immune prophylaxis

Immune prophylaxis against HDV is achieved by vaccination against HBV because HDV uses the envelope proteins of HBV. This mode of prevention is possible only for coinfections in HBV susceptible individuals.^{10, 21}

Immune globulin (IG), hepatitis B (HB) specific IG and HB vaccine do not protect HBV carriers from infection with HDV.

Vaccines

No vaccines exist against HDV; however, vaccination against HBV of patients who are not chronic HBV carriers, provides protection against HDV infection.

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

Since HDV is dependent on HBV for replication, control of HDV infection is achieved by targeting HBV infections. All measures aimed at preventing the transmission of HBV will prevent the transmission of hepatitis D. HBV vaccination is therefore recommended to avoid HBV-HDV coinfection.¹⁴

However, there is no effective measure to prevent HDV infection of chronic HBV carriers, and prevention of HBV-HDV superinfection can only be achieved through education to reduce risk behaviors.^{14, 21}

Promising research results indicate that in some woodchucks immunized with recombinant purified HDAg-S complete protection is possible.

Hepatitis B IG and HB vaccine do not protect HBV carriers from infection by HDV.

Treatment

Currently there is no effective antiviral therapy available for treatment of acute or chronic type D hepatitis.²¹

For infected patients, massive doses of α -interferon (9 million units three times a week for 12 months or 5 million units daily for up to 12 months) have yielded remissions, but most patients remained positive for HDV RNA despite the improved disease conditions.²¹

The effect of interferon is considered to be most likely an indirect one, possibly via an effect on the helper hepadnavirus and/or on the immune response to the infections.²⁵

Acyclovir, ribavirin, lamivudine and synthetic analogues of thymosin have proved ineffective.¹⁰

Immunosuppressive agents do not have any effect on hepatitis D.^{14, 21}

Liver transplantation has been helpful for treating fulminant acute and end-stage chronic hepatitis.^{11, 21} In one study, the 5-year survival rate of transplant patients for terminal delta cirrhosis was 88% with reappearance of HBsAg only in 9% under long-term anti-HBs prophylaxis.¹⁰

Guidelines for epidemic measures

- 1) When two or more cases occur in association with some common exposure, a search for additional cases should be conducted.
- 2) Introduction of strict aseptic techniques. If a plasma derivative like antihemophilic factor, fibrinogen, pooled plasma or thrombin is implicated, the lot should be withdrawn from use.
- 3) Tracing of all recipients of the same lot in search for additional cases.

Future considerations

Whether or not immunization with HDAg can confer protection against superinfection or slow the progression of liver disease in the over 350 million HBV carriers who are at risk of contracting type D hepatitis, needs to be determined.²¹

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.

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

antigenome RNA molecule complementary to the viral single stranded RNA genome.

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 hemoglobin. 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.²⁶

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

carcinoma a malignant epithelial tumour. This is the most frequent form of cancer.

cDNA complementary DNA. DNA synthesized by RNA-directed DNA polymerase as a copy of RNA, usually isolated mRNA or viral genomic RNA. It differs in sequence from eukaryotic chromosomal DNA by the absence of introns.

cirrhosis a chronic disease of the liver characterized by nodular regeneration of hepatocytes and diffuse fibrosis. It is caused by parenchymal necrosis followed by nodular proliferation of the surviving hepatocytes. The regenerating nodules and accompanying fibrosis interfere with blood flow through the liver and result in portal hypertension, hepatic insufficiency, jaundice and ascites.

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.

cytopathic effects include morphological changes in the cell appearance (rounding up of cells), agglutination of red blood cells (haemagglutination assay with influenza-virus), zones of cell lysis on monolayers of tissue culture or finally immortalization of animal cell lines (foci formation).

cytoplasm the protoplasm of the cell which is outside of the nucleus. It consists of a continuous aqueous solution and the organelles and inclusions suspended in it. It is the site of most of the chemical activities of the cell.

encephalopathy an acute reaction of the brain to a variety of toxic or infective agents, without any actual inflammation such as occurs in encephalitis.¹

endemic continuously prevalent in some degree in a community or region.²⁶

endoplasmic reticulum a network or system of folded membranes and interconnecting tubules distributed within the cytoplasm of eukaryotic cells. The membranes form enclosed or semienclosed spaces. The endoplasmic reticulum functions in storage and transport, and as a point of attachment of ribosomes during protein synthesis.

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 matters and are involved in all the metabolic processes upon which life depends.^{1, 26}

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.²⁶

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

fulminant describes pathological conditions that develop suddenly and are of great severity.¹

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

Golgi apparatus a cytoplasmic organelle which is composed of flattened sacs resembling smooth endoplasmic reticulum. The sacs are often cup-shaped and located near the nucleus, the open side of the cup generally facing toward the cell surface. The function of the Golgi apparatus is to accept vesicles from the endoplasmic reticulum, to modify the contents, and to distribute the products to other parts of the cell or to the cellular environment.

hepadnavirus family of single stranded DNA viruses of which hepatitis B virus (HBV) and woodchuck hepatitis virus (WHV) are members.

hepatocytes liver cells.¹

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

icterus jaundice.

IgA antibodies 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): is 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, and labelled respectively IgM, IgG, IgA, IgE and IgD.

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

interferon a class of proteins possessing antiviral and antitumour activity produced by lymphocytes, fibroblasts and other tissues. They are released by cells invaded by virus and are able to inhibit virus multiplication in noninfected cells. Interferon preparations have been shown to have some clinical effect as antiviral agents. The preparations so far available have produced side effects, such as fever, lassitude, and prostration, not dissimilar from those accompanying acute virus infection itself.¹

jaundice is a yellow discoloration of the skin and mucous membranes due to excess of bilirubin in the blood, also known as icterus.²⁶

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 must be 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

necrosis death of tissue.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

nucleus a membrane-bounded compartment in an eukaryotic cell which contains the genetic material and the nucleoli. The nucleus represents the control center of the cell. Nuclei divide by mitosis or meiosis.

peptide a compound of two or more amino acids linked together by peptide bonds.²⁶

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

prenylation the enzymic addition of prenyl moieties to proteins as a post-translational modification.

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.²⁶

prophylaxis is the prevention of disease, or the preventive treatment of a recurrent disorder.²⁶

protein large molecule made up of many amino acids chemically linked together by amide linkages. Biologically important as enzymes, structural protein and connective tissue.

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.

reverse transcriptase RNA-directed DNA polymerase. Enzyme that synthesizes DNA according to instructions given by an RNA template.

ribozyme an RNA molecule with catalytic activity.

RT-PCR reverse transcriptase - polymerase chain reaction. A technique commonly employed in molecular genetics through which it is possible to produce copies of DNA sequences rapidly.

self-limited denoting a disease that tends to cease after a definite period; e.g., pneumonia.³

sense and antisense strands of the two strands that comprise the double helix of a DNA molecule, only sense strand contains a sequence of nucleotides that can be read out to form a protein. The complementary strand, termed the antisense strand, has a sequence of nucleotides that, if read out, would give either a garbled or a totally lacking messenger RNA.² An artificial, antisense, single stranded RNA molecule of messenger RNA or of some other specific RNA transcript of a gene can hybridize with the specific RNA and thus interfere with the latter's actions or reactions.

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.²⁶

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

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

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, 26}

viremia the presence of viruses in the blood, usually characterized by malaise, fever, and aching of the back and extremities.⁴

virion a structurally complete virus, a viral particle.¹

viroid any of a class of infectious agents consisting of a single-stranded closed circular RNA lacking a capsid. The RNA does not code for proteins and is not translated; it is replicated by host cell enzymes. Viroids are known to cause several plant diseases.

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, must rely 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



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