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GUIDELINES FOR THE PLANNING AND CONDUCTING OF EPIDEMIOLOGICAL STUDIES ON LIVER DISEASES

by

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PLANNING OF EPIDEMIOLOGICAL STUDIES ON LIVER DISEASES

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EPIDEMIOLOGY OF ACUTE LIVER DISEASES

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INTRODUCTION

This paper has two sections. In the first we shall review the most important liver diseases and we shall examine the main clinical manifestations, laboratory findings and serological patterns, that may serve as epidemiological variables in the study of the etiology and outcome of liver diseases. In the second section we shall outline epidemiological studies that appear suitable and feasible in countries of the Eastern Mediterranean Region, and we shall consider some of the available options for the analysis.

SECTION I ACUTE VIRAL HEPATITIS - GENERAL

Viral hepatitis is a systemic viral infection in which hepatic cell necrosis and hepatic inflammation are responsible for a characteristic constellation of clinical, pathological,biochemical and immunological features. It may be caused by several viruses,but three or four of them, i.e. those of hepatitis A, hepatitis B and hepatitis non A-non B, are more important on clinical and epidemiological grounds(Table 1). Viral hepatitis is frequently a subclinical or anicteric disease, so its recognition and etiologic identification depends on antigen-antibody systems detected in the serum or the liver.

(i)Clinical features. Viral hepatitis may be distinguished into inapparent(asymptomatic), anicteric and icteric hepatitis. However, the category to which a patient may be assigned depends not only on the nature and severity of the disease but on the frequency of examination and astuteness of the examiner. Inapparent hepatitis may be suspected from aminotransferase elevation and documented by serologic markers. The symptoms of anicteric viral hepatitis are milder and of shorter duration compared to those of the icteric disease.

The clinical picture of interic viral hepatitis is well known and, usually, unrelated to its specific etiology.Symptoms usually last 2-15 days before the onset of jaundice. After an icteric period of about one to four weeks the adult patient makes an uninterrupted recovery. In children improvement is particularly rapid and jaundice mild. A rare benign variant of acute hepatitis is the "cholestatic hepatitis" in which jaundice persists 8-29 weeks and then the recovery is complete. A much more severe variant is the fulminant hepatitis, in which acute viral hepatitis results in hepatic failure, manifested by encephalopathy and often death. A useful criterion for predicting fulminant hepatitis is prothrombin activity less than 20 per cent of the control, or prothrombin time 30 sec or more (with control 10-12 sec) after administration of vitamin K.

(ii) Pathology and laboratory findings. The basic pathology of A,B and non A-non B hepatitis is virtually identical and well characterized. However, liver biopsy is rarely indicated for identification of acute viral hepatitis(except when confluent or bridging necrosis is suspected).

The two most important biochemical tests for diagnosing and monitoring acute viral hepatitis are aminotransferases and prothrombine time or prothrombine activity. Aminotransferases (SGOT, SGPT) are useful in early diagnosis and in detecting anicteric and inapparent cases. The level of the activity may have some correlation with severity of the disease but it should not be regarded as a reliable prognostic indicator. Aminotransferases decrease initially by 75 per cent per week, but the rate is not maintained and levels tend to plateau at slightly above normal limits for up to six months. In about one third of the patients, after an initial fall, a secondary rise of the serum aminotransferases has been observed. Prothrombin time is the best prognostic indicator of all the laboratory tests. Serological tests are discussed in the following sections.

VIRUS A HEPATITIS

(i) Characteristics of the virus. Hepatitis A virus (HAV) is an enterovirus of the Picornaviridae family, with diameter of 27nm and cubic symmetry. Its nucleic acid is RNA and the virus has successfully been cultivated. It can infect chimpanzees and marmosets and is resistant to many environmental factors. The virus can be detected in the stools of sufferers, from about two weeks before until one week or more after the onset of jaundice, but the number of viral particles is greatly reduced after the onset of jaundice.

Antibodies to HAV (anti-HAV) are detectable from the onset of jaundice. Total anti-HAV(IgM+IgG) in a single sample does not establish diagnosis but anti-HAV IgM class is a very good test with specificity and sensitivity approaching 100 per cent in the first two months from the onset. Small amounts of anti-HAV IgM remain positive for a year but anti-HAV IgG persistence is life-long (Figure 1).

Prognosis is good,usually with full recovery. Death is a rare event with a case-fatality ratio of less than 1 percent.Chronicity does not develop. Follow-up of large epidemics showed no long-term sequalae.

(ii) Epidemiology. The disease occurs sporadically or in epidemic form. The incubation period is 15-50 days. It is usually spread by the faecal-oral route. In Mediterranean and Middle East countries it is an hyperendemic disease. In Greece at the age of 20 the majority of the population is immune, so that the disease is uncommon in adults. The improvement of socioeconomic conditions and hygienic standards has resulted in a postponement of the average age at infection and an apparent increase of the proportion of clinical cases. Epidemiologic characteristics of hepatitis A,B and non A-non B are compared in Table 2.

VIRUS B HEPATITIS

(i) Characteristics of the virus. HBV is a DNA virus in which the intact virion has 42nm diameter. Under the electron microscopy three types of particles can be seen in hepatitis B serum:small 20nm spheres,tubules 20nm in diameter, and the 42nm

virion called Dane particle. The spheres and tubules are excess surface protein. After detergent treatment the inner 27nm core remains, containing double and single stranded DNA and DNA polymerase. The surface of HBV virion is known as hepatitis B surface antigen (HBsAg). Two antigenic activities are known in the inner core, the hepatitis B core antigen (HBcAg) and hepatitis B e antigen (HBeAg). The coat of surface material(HBsAg) is synthesized, independently of core of HBV, in the cytoplasm of infected hepatocytes. HBcAg and HBeAg have been found, using immunofluorescent techniques or electron microscopy, predominantly in the nucleus but occasionally in the cytoplasm of hepatocytes obtained from chronically infected subjects(Table 1).

(ii) Serologic diagnosis of hepatitis B. The clinically most important serological responses to hepatitis B virus are summarized in Figures 2, 3 and 4. These patterns are based on prospective follow-up of infected individuals. In practice,however,the problem is usually presented in the opposite way:"what is the infection pattern and stage, given a particular set of serological indices in a single serum sample?". Table 3 summarizes the rules allowing clinical diagnosis and epidemiologic statements on the basis of serologic findings.

(iii) Epidemiology. HBV infection has a worldwide distribution with unusually large variation in the prevalence of HBV markers in various geographic areas and between population groups within specific areas. Prevalence of HBsAg varies between less than 0.5 per cent in the U.S.A. and western Europe to more than

10 per cent in sub-Saharan Africa and Southeast Asia. Several factors have been shown to influence the risk of a person becoming a long-term HBV carrier, of which the most important is the age at infection. While the risk of an adult becoming a carrier following acute infection is between 5 and 10 per cent, in infants it may exceed 50 per cent. In chronic carriers, the titres of HBsAg usually decline with increasing age and many people eventually eliminate the virus from their body and develop protective antibody. Table 2 compares epidemiologic characteristics of various forms of viral hepatitis whereas Table 4 summarizes the patterns of hepatitis B prevalence in various countries.

NANB HEPATITIS

A significant number of cases of acute and chronic hepatitis in humans occurs in the absence of infection with any known serologically identifiable virus. These cases have been tentatively designated as non-A, non-B (NANB) hepatitis to indicate that the diagnosis is based on exclusion of infection caused by HAV or HBV. Furthermore the term non-A, non-B rather than hepatitis C was chosen to reflect the likelihood that more than one etiologic agent may ultimately be identified. Epidemiologic studies suggest that NANB shares many features with hepatitis B,including severity, relatively long incubation period in most instances, transmission by blood products or close personal contact, existence of chronic carrier state(with or without evidence of ongoing liver injury) and tendency to progress to chronic liver diseases and cirrhosis (Table 2). Recent studies suggest that a

substantial number of individuals with so-called NANB hepatitis may actually have HBV where the level of HBsAg is too low to be detected by conventional assays or is "hidden" in immune complexes.

Despite its relatively mild, often asymptomatic and anicteric presentantion during acute infection, post-transfusion NANB hepatitis has a disturbing tendency to progress to a chronic stage, perhaps even more frequently than transfusion-associated type B hepatitis. The liver histology in most chrcnic cases after post-transfusion NANB hepatitis is compatible with chronic active hepatitis but the disease is generally benign and the prognosis for the group as a whole, of patients with chronic NANB hepatitis, is considered good.

CHRONIC HEPATITIS

The exact diagnosis of chronic hepatitis is based on histologic criteria which are indicated in Table 5. The most important diagnostic entities are chronic persistent hepatitis (CPH), chronic lobular hepatitis (CLH) and chronic active hepatitis (CAH).

(i) Chronic persistent hepatitis. In many instances the etiology is unknown but it is frequently associated with viral hepatitis (HBV and NANB), excessive alcohol consumption, inflammatory bowel disease, and occasionally with infection with Entamoeba histolytica, Salmonella or Schistosoma mansoni. In clinical series CAH is more frequent than CPH. However CPH is frequently underdiagnosed and its actual prevalence is much higher. The prognosis of CPH is generally good. Nevertheless in somme cases there is progression to mild or moderate CAH or even cirrhosis.

(ii) Chronic lobular hepatitis. It is a rare condition, clinically similar to the chronic persistent hepatitis. Patients, usually males, are diagnosed after an acute viral hepatitis-like illness. Some cases may be due to non-A, non-B hepatitis, but HBsAg is absent. Serum auto-antibodies may be present. Cirrhosis does not develop.

(iii) Chronic active hepatitis. A clinical biochemical and histological entity, which has been associated with several etiological agents including hepatitis viruses (HBV,NANB), immune disorders ("lupoid" CAH), alcohol overconsumption, drug use (oxyphenacetin, isoniazid,nitrofurantoin, etc), Wilson's disease, a_1-AT deficiency, and several common viruses(rubella, cytomegalovirus) in immunosuppressed patients. Two main types have been identified. One is associated with persistence of hepatitis B infection while the other is characterized by the absence of HBsAg and has been termed "lupoid" because of the frequent association with a positive Lupus erythymatosus cell phenomenon(Table 6).

In HBsAg positive CAH the titers of HBsAg in the serum are significantly lower than in CPH or "healthy" carriers. Anti-HBc is almost always present. HBeAg in the serum has variable frequency and indicate high infectivity. A very interesting subgroup of chronic hepatitis B, from the clinical and epidemiologic point of view, is the delta (δ) antigen-positive chronic liver disease, which is very frequent in Mediterranianand Middle East regions. From hospital series in Italy and Greece, the patients with HBsAg(+)/δ(+) chronic active hepatitis, when compared to HBsAg(+)/δ(-) patients, usually are younger, have higher aminotransferases and γ-globulin values, and have a more poor prognosis.

Generally, the prognosis of the HBV- related chronic active hepatitis is variable but eventually poor. The prognosis of lupoid chronic hepatitis is extremely variable but it is much better with corticosteroid therapy.

DELTA AGENT

The delta (δ) antigen-antibody system was first detected by immunofluorescence in liver cell nuclei and serum of Italian carriers of the hepatitis B surface antigen who had chronic liver disease. Experimental evidence and extensive epidemiologic studies confirm that the δ antigen-antibody system is expressed only in subjects with circulating HBsAg, except in occasional individuals with anti-δ who have recently recovered from HBsAg/δ hepatitis. Actually, δ agent is a defective virus which needs the HBV virus for expression and replication. It has been shown that δ agent is an RNA virus with no association with a reverse transcriptase. It probably can replicate in all primate species capable of supporting replication of HBV. The δ-antigen may be detected in the liver of HBsAg carriers but not,usually, in the serum, where anti-δ is detected by enzyme immunoassays and radioimmunoassay. A specific test for anti-δ IgM class has also been developed.

The first sign of an acute B/δ hepatitis is appearence of intrahepatic δ antigen which follows invariably the appearence of HBsAg in the liver and in the serum. Depending on the virulence of δ infection,δ antigenemia may or may not be detected. It occurs, if at all, for a short period during acute infection, and parallels the peak expression of intrahepatic δ antigen. Viremia declines after a few days and it is followed by sero-

conversion to anti-δ, while δ antigen may still be present in the liver. Simultaneous infection may result in a single hepatitic episode with simultaneous expression of HBcAg and δ antigen in the liver, or in sequential expression of the two antigens, each associated with a peak of aminotransferase activity. In humans with self-limited infection, the early viremic phase is often undetectable or missed,and infection is recognized by the rising titer of anti-δ (or the low-titer δ-IgM antibody response followed by the homologous secondary IgG response). Acute B/δ infection may have no serological expression and progresses seldom to chronicity.

The course and outcome of acute δ infection in HBsAg carriers are different from those in acute B/δ co-infection. In the former case, δ-antigen is synthesized massively by HBV infected liver cells, and is shed into the blood in the form of δ-particles which contain δ-antigen encapsulated by HBsAg. Follow-up of carriers of HBsAg and retrospective analysis of pátients with HBsAg/δ hepatitis indicate that chronicity of δ develops preferentially in patients with established and continuing HBV infection. In a way reminscent of the HBc system, intrahepatic δ antigen is most abundant during the early phase of chronic infection and diminishes progressively regardless of the long-term clinical outcome. Anti-δ,however, may remain detectable for a few years after resolution of chronic infection.

Delta infection has an irregular and confusing but, nevertheless,worldwide distribution. A high prevalence of infection was initially found in Italy, particularly in the

southern part of the country, where up to 50 per cent of HBsAg carriers with chronic liver disease had anti-δ. A peculiar distribution was observed in the rest of Europe with a high prevalence in Scandinavia but a low one in other northern European countries. It appears that δ is endemic in countries of southern Europe,Africa, Middle East and South America. Interestingly, there is very little evidence of δ infection in the South East Asia despite the high prevalence of HBV infection in this region.

The δ agent follows the routes of transmission of HBV, so it is transmitted parenterally and by close contact. There is a high prevalence in drug addicts, multitransfused patients, hemodialysis patients and first degree relatives of HBV/δ carriers, but vertical transmission has not been established.

SECTION II DESCRIPTIVE EPIDEMIOLOGY OF CHRONIC LIVER DISEASES

There are no reliable routine statistics on incidence or mortality for any of the chronic liver diseases in any of the EMRO countries. Therefore, alternative ad hoc research strategies are required in order to obtain such data. The available options are: population based incidence or mortality surveys, and case or pathology series.

(i) Special incidence surveys. This design involves prospective ascertainment of all new cases of a certain group of liver diseases, in a defined population during a defined period of time. It requires coverage of all medical facilities, likely to diagnose or treat patients with these diseases, and, in addition, identification of all new clinical cases in the reference population, during the reference

time-period, who have not asked for medical help or advice. Pre-symptomatic or subclinical cases are not eligible in this design (because they represent prevalence, rather than incidence,data) unless a more complex analysis is contemplated. A special incidence survey presuposes the existence of census data, allowing the calculation of incidence rates stratified by age, sex and other relevant variables.

(ii) Special mortality surveys. This design is feasible only when the disease in question has a high fatality, and the registration of deaths is quantitatively satisfactory; it requires a special investigation of the medical aspects of every registered death. A mortality survey is optimal when it is done prospectively and is based on census data; however, it can also be done retrospectively and generate useful summary indices even in the absence of census statistics(see below the discussion on proportional indices).

(iii) Clinical or pathological series. Frequently, it is impossible to diagnose all cases arising in a well-defined population group, and it is difficult to identify the population base(catchment area) from which the index cases originate(e.g. patients in one or more hospitals, clinics or laboratories). In these instances absolute rates are impossible to calculate(there is little or no information concerning the corresponding population at risk) and the relative indices are of questionable validity(selection factors, linked to age, sex, socio-economic status, area of residence, reputation of the hospital, and nature and severity of the disease are likely to operate). Therefore,clinical

or pathological series are rarely useful for descriptive purposes, although they can provide estimates of proportional incidence and, with careful selection of the control group, they can be used effectively in analytic etiologic studies(see below).

(iv) Indices in descriptive epidemiology. In descriptive epidemiology the basic summary measurement is the "incidence rate",which describes the frequency of occurence of a particular disease in a particular population group during a particular time-period.Contrary to the notion of "risk", which may be thought of as a proportion, the "rate" has a time dimension, which gives it important conceptual and methodological properties. Most measures of mortality are in effect "rates" and, indeed, incidence rates(where the incident event is death, rather than the onset of a particular disease). When the reference population is heterogeneous with respect to age, sex, socio-economic status, etc, different(specific) rates should be given for every stratum, because the overall(crude) rate depends as much on biological forces as on the relative size of the strata. An alternative to the detailed listing of specific rates is the procedure of standardization, in which a fixed(standard) distribution is imposed on all compared populations, and freedom for variability is left only to the biological forces that determine incidence or mortality.

When the population at risk is not known, either because census statistics are not available or because selected clinical or pathological series have been used, comparisons between two or more series are still feasible by using proportional incidence(or mortality) analysis.

In proportional incidence(or mortality) analysis, what is compared is the proportion of deaths from a particular cancer (e.g. liver cancer) among all cancer deaths, or the proportion of new cases of a particular disease(e.g.cirrhosis)among all hospital admissions,etc. These comparisons are valid in so far as the rates of the corresponding denominators are equal in the two or more compared populations- a questionable assumption in many situations. Nevertheless, when absolute rates can not be calculated, proportional indices do offer an alternative which can be thought of as a useful first approximation. It should be noted that proportional indices must, and can, be standardized by age, sex, or any other relevant and available variable.

ANALYTIC EPIDEMIOLOGY OF CHRONIC LIVER DISEASES

(i) Study design. There are two main categories of studies in analytic epidemiology: cohort studies and case-control studies. In cohort studies, groups are formed on the basis of their contrasted "exposure" or "risk" characteristics(e.g.HBsAg(+) and HBsAg(-) individuals) and they are compared with respect to the frequency of future occurence of the study outcome(e.g. hepatocellular carcinoma). These studies are considered as methodologically superior, but they require large numbers of subjects, substantial resources for follow-up and considerable financial and technical support. They can be justified only when the incidence density of the outcome variable is high; this condition exists in clinical epidemiology, where interest is focused in the natural history and the prognostic factors, rather than in the etiology, of chronic diseases like chronic active hepatitis

(CAH) and hepatocellular carcinoma (HCC). By contrast, in etiologic studies, focusing, for example, on the relative importance of various hepatitis B serologic patterns in the causation of CAH or HCC, the case-control approach is methodologically equally appropriate and far more efficient than the cohort approach. The case-control design may be used even when the case series does not originate from a circumscribed or well defined population, and even when selection factors are known to operate in the formation of the case series-provided that the selection factors are not related to the exposure variables or that, if they are related, similar selection is imposed on the control series by means of individual matching or stratification.Since the nature of selection factors for hospital admission are frequently unknown it seems prudent(as well as practical) to prefer comparable hospital controls(of a group of well defined diagnoses) rather than population controls of unknown comparability. The immunological, serological and histological nature of many risk factors in chronic liver diseases facilitates the undertaking of case-control studies, since it minimizes subjective bias on the part of both the researcher and the patient.

The planning and analysis of most case-control studies is relatively simple and does not require extensive technical support or unusual statistical sophistication. Indeed,choice of specific study design and calculation of the likely to be required number of cases and controls can be done by using simple rules and by consulting computer-generated tables,

whereas analysis(with simultaneous control of several confounding variables) can be done by commercially available programs of ordinary programmable calculators, without resorting to large(or even small desk-top) computers.

EPIDEMIOLOGY OF ACUTE LIVER DISEASES

The traditional strategies for the study of the epidemiology of acute infectious diseases have been:routine notification, and investigation of the co-variates of disease incidence in epidemic settings and in sporadic cases. None of these approaches appears particularly promising for the study of viral hepatitis A, B or NANB in EMRO countries. Instead, an indirect seco-epidemiological strategy,focusing on the prevalence of anti-HAV, HBsAg, anti-HBs and anti-HBc should help to clarify several important issues, including the following:

- Overall frequency of HAV and HBV, as reflected in the overall prevalence of the corresponding serologic markers in a large sample of young adults(e.g. army recruits).

- Geographical distribution of HAV and HBV, as reflected in the corresponding distribution of the serologic markers of these viruses in a large sample of young adults(e.g. army recruits).

- Study of the age, sex and socioeconomic class distribution of HAV and HBV in a representative town-sample.

- Study of transmission patterns of HBV(and HAV) in communities at low, moderate and high risk, including consideration of vertical transmission(study of the e system,and use of serial collections) and intrafamilial spread(clustering).

- Identification and investigation of possible high risk groups (as well as groups with high potential for further transmission).

- Elementary cost-benefit and cost-effectiveness analysis for the use of hepatitis B vaccine.

- Investigation of the δ agent (anti-δ) in a sample of HBsAg(+) individuals.

- Determination, by exclusion, of the relative incidence of NANB in a consecutive series of clinical hepatitis.

- Prospective clinical study of the frequency and type of post-transfusion hepatitis (serologic markers and aminotransferases).

The detailed research specifications and objectives should be part of the study protocol, but they can be outlined only when the conditions in the field, and the situation in the particular research setting, have been carefully identified and explicitly stated.

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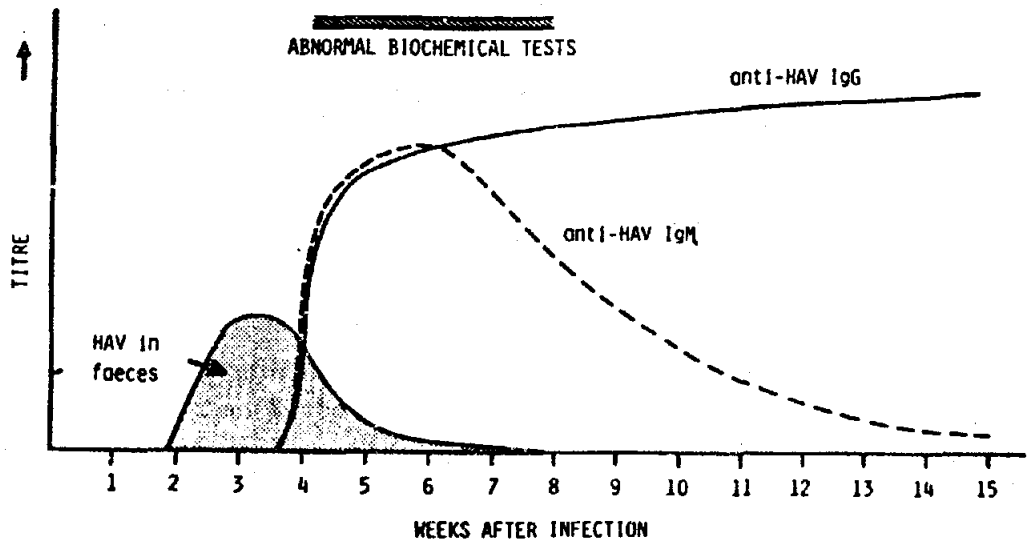
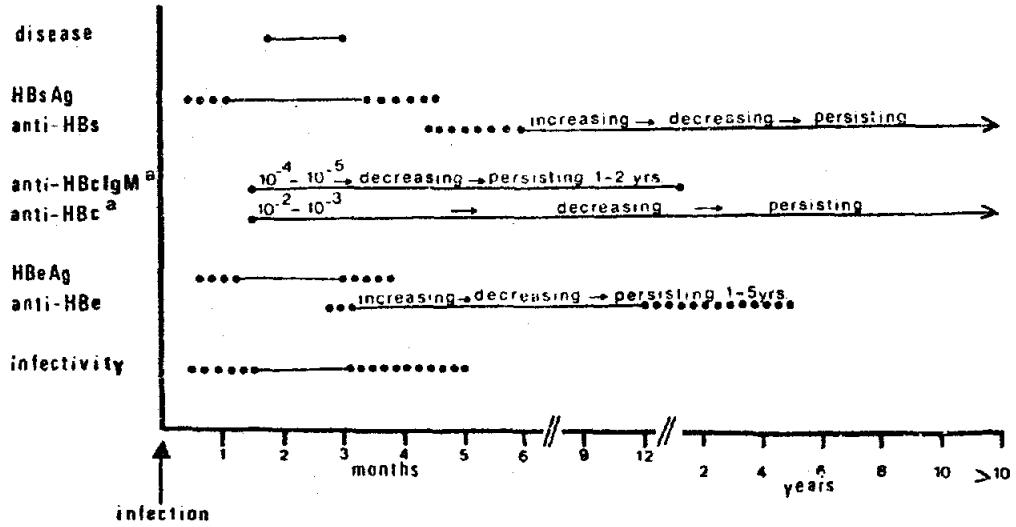
Fig.1. Typical course of hepatitis A



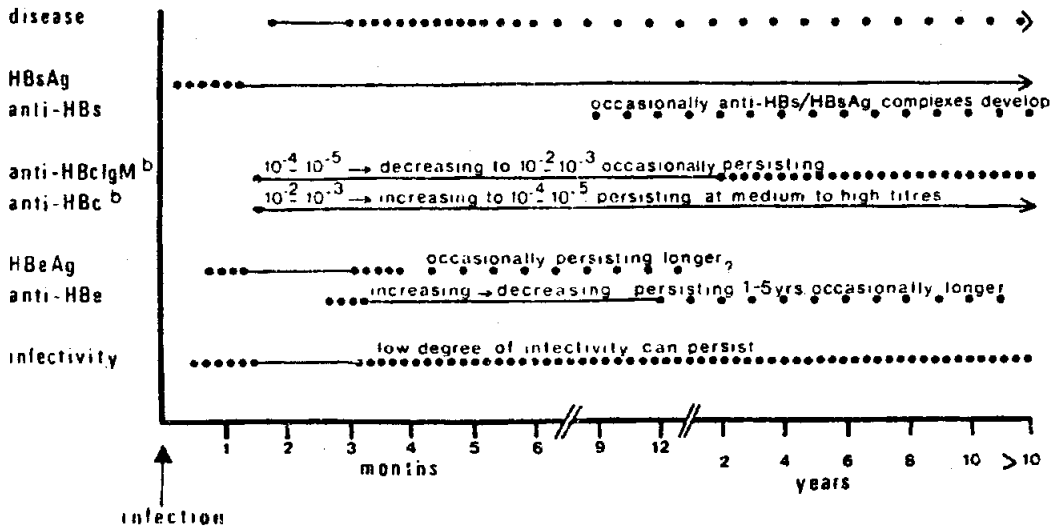
Source:Deinhardt and Gust(1982)

Fig.2. Acute hepatitis B



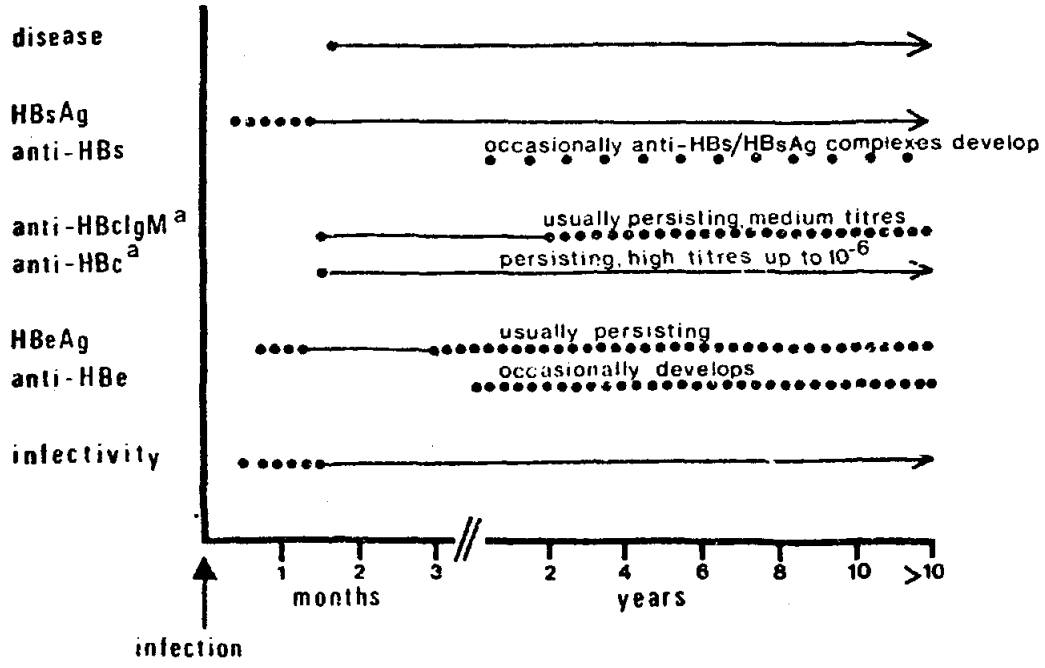
Source:Deinhardt and Gust(1982)

Fig.3. Persistent hepatitis B(healthy carriers have no or only minimal disease and usually lower anti-HBc IgM titres and are generally HBeAg-negative)



Source:Deinhardt and Gust(1982)

Fig.4. Chronic active hepatitis B



Source: Deinhardt and Gust (1982)

Table 1. Components and corresponding antibodies of the hepatitis viruses

Virus component or antibody	Definition
HA	Hepatitis A
HAV	Hepatitis A virus
HAAg	Hepatitis A virus antigen
Anti-HAV	Antibody to hepatitis A virus without defferentiation into immunoglobulin classes
Anti-HAV IgG	Antibody to hepatitis A virus of the IgG class
Anti-HAV IgM	Antibody to hepatitis A virus of the IgM class
Anti-HAV IgA	Antibody to hepatitis A virus of the IgA class
HB	Hepatitis B
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B e antigen
Anti-HBs	Antibody to hepatitis B surface antigen
Anti-HBc	Antibody to hepatitis B core antigen without differentiation into immunoglobulin classes
Anti-HBc IgG	Antibody to hepatitis B core antigen of the IgG class
Anti-HBc IgM	Antibody to hepatitis B core antigen of the IgM class
Anti-HBe	Antibody to hepatitis B e antigen
NANB	Hepatitis non-A, non-B

Source. Deinhardt and Gust (1982)

Table 2. Epidemiologic characteristics of hepatitis A, B and non A-non B

	HAV	HBV	NANB
Incubation period	15-49 days	28-180 days	1-4 weeks or 2-26 weeks
Period of infectivity	2 weeks before to 1 week after jaundice	In most cases when HBsAg is positive	Variable(?)
Infective materials			
Feces	Yes	No	?
Blood	Yes(for short period)	Yes	Yes
Urine	No.	No	?
Nasopharyngeal secretions	No	Yes(low intectivity)	?
Intestinal secretions	Probably yes	No	?
Semen	No	Yes	?
Vaginal menstrual secretions	No	Yes	?
Modes of transmission			
Water	Yes	No	Yes(?)
Milk	Yes	No	?
Food	Yes	No	?
Contact	Yes	Yes	Yes
Sexual transmission	Yes	Yes	Yes
Vertical(maternal-neonatal)	No	Yes	Yes
Intrafamiliar spread	Yes	Yes	Yes
Parenferal(transfusions,etc)	No	Yes	Yes
Animals	Non human primates	Non human primates	Chimpanzees
Insects	?	?	?
Carrier state	No	Yes	Yes

Table 3. List and interpretation of possible patterns of HBV serologic markers present in a single serum of a patient

	HBsAg	HBeAg	anti-HBc	anti-HBe	anti-HBs	Interpretation
I	+	-	-	-	-	Late incubation period of acute hepatitis B
II	+	+	-	-	-	1.Incubation period 2.Early acute HBV infection } High infectivity
III	+	+	+	-	-	1.Acute HBV infection 2.Chronic HBV infection } High infectivity
IV	+	-	+	-	-	1.Acute HBV infection 2.Chronic HBV infection
V	+	+	+	+	-	1.Acute HBV infection 2.Chronic HBV infection } Seroconversion HBeAg to anti-HBe
VI	+	-	+	+	-	1.Acute HBV infection (late stage) 2.Chronic HBV infection } Low infectivity
VII	+	-	+	+	+	1.Immune complexes HBsAg,anti-HBs, neither in excess 2.Different subtypes HBsAg and anti-HBs
VIII	-	-	+	-	-	1."Window" phase or early convalescence in acute HBV infection. 2.Chronic HBV carrier where HBsAg below detectability. 3.Remote infection with anti-HBs below detectability. 4.False positive
IX	-	-	+	+	-	1.Recent acute HBV infection 2.Chronic HBV infection with HBsAg below detectability
X	-	-	+	+	+	Recovery phase of HBV infection with persisting immunity
XI	-	-	+	-	+	Recovery of HBV infection with persisting immunity and short lived anti-HBe
XII	-	-	-	-	+	1.Immunization without infection 2.Recovery with short lived anti-HBc 3.Repeat exposure to HBsAg without infection 4.False positive
XIII	-	+	-	-	-	1.Early acute HBV infection with undetectable HBsAg 2.False positive
XIV	-	-	-	+	-	False positive
XV	-	+	+	-	+	HBV infection with circulating immune complexes of HBsAg and anti-HBs in which there is antibody excess

Source:Modified from Mushahwar et al (1981)

Table 4. Patterns of hepatitis B prevalence

Low	Intermediate	High
HBsAg,0.2-0.5%	HBsAg,2-7%	HBsAg,8-20%
Anti-HBs,4-6%	Anti-HBs,20-55%	Anti-HBs,70-95%
Childhood infection infrequent	Childhood infection frequent,neonatal infection frequent	Childhood infection highly frequent,neonatal infection highly frequent
Australia,Central Europe, North America	Eastern Europe,Japan Mediterranean,South West Asia,USSR	Some parts of China, southern Asia,tropical Africa

Source:Deinhardt and Gust (1982)

Table 5. Histologic features of chronic hepatitis

CHRONIC PERSISTENT HEPATITIS(CPH)

Inflammatory infiltration of enlarged portal tracts by lymphocytes and plasma cells. The limiting plate of liver cells between portal zones and liver cells columns is intact. Piecemeal necrosis is absent. Variable degree of focal intralobular inflammation and necrosis. Lobular architecture is preserved.

CHRONIC LOBULAR HEPATITIS (CLH)

Intralobular inflammation and necrosis while portal tracts are normal. The histological features resemble acute hepatitis but the duration is greater than three months

CHRONIC ACTIVE HEPATITIS (CAH)-MILD

Marked by the presence of piecemeal necrosis. Resembles CPH except for the presence of mild piecemeal necrosis

CHRONIC ACTIVE HEPATITIS (CAH)-MODERATE

More piecemeal necrosis, marked widening of portal tracts, with fibrosis extending irregularly outwards from the portal zones. The lobular architecture is distorted.

CHRONIC ACTIVE HEPATITIS (CAH)-SEVERE

Marked by fibrous septa extending into the liver columns with isolation of groups of liver cells in the form of rosettes. Intrahepatic bridging, either portal-central or portal-portal, is present. Small regenerating nodules are commonly seen and cirrhosis is usually diagnosed.

Table 6. Comparison of HBsAg-positive and "lupoid"chronic active hepatitis

Characteristic	CAH	Lupoid CAH
1. Age	Over 30 years(80%)	Less than 30 years(50%)
2. Sex	Males (80%)	Females (80%)
3. Onset	Usually insidious	Usually insidious
4. Asymptomatic cases	Frequent	Rare
5. Jaundice	Usually absent	Usually present but mild
6. Spider nevi and liver palms	Present in 30%	Prominent in most patients
7. Hepatomegaly	Usually present	Usually present
8. Splenomegaly or hypersplenism	Present in 20%	Present in 40-50%
9. Systemic and endocrine manifestations	Practically absent(<10%) except arthralgies	Frequently present(50-70%)
10. Increased bilirubin levels(>5mg/100ml)	5-10%	30-60%
11. Increased aminotransperases(more than five-fold)	15-25%	70-90%
12. Decreased serum albumin	20-30%	85-100%
13. Increased gamaglobulin	50%;pronounced in 10%	80%;pronounced in 40%
14. SMA and ANA	Occasionally present but transient and in low titers	Usually present,persistant and in high titers
15. LE cells	Negative	Positive in 15-35%

Source:Hadziyannis(1974)