5. HEPATITIS, CIRRHOSIS
AND BILIARY DISEASES

The liver plays a crucial role in the body's metabolism, participating directly or indirectly in all of the pathological phenomena likely to affect the human body and the body's homeostasis.

In a nutshell, the liver is at the crossroads of body functions. It also acts as a filter of the portacaval system preventing the entry of micro-organisms and parasites, such as viruses, bacteria, spirochaetes, protozoa (amoebae) and plasmodia, helminths (echinococci, schistosomes and flukes).

In the tropics, the liver is exposed to numerous and frequent assaults. This situation can lead to acute, or chronic infections and autoimmune disorders. Such disorders can be latent as well as symptomatic. The hepatic viruses, who were too long overlooked, deserve particular attention, considering that their incidence is rising steadily.

To get a clear picture of the liver disease in Africa, there are two problems. On the one hand, the African patient usually does not go to the doctor unless his complaints become very serious, with the result that morbidity statistics usually do not reflect the actual situation. On the other hand, Europeans living in Africa were seeking medical help for liver failure, weak liver, and tropical liver, which are general diagnoses with imprecise boundaries representing many indistinct complaints.

A particular problem concerns jaundice. Virchow considered the acute form to be a catarhal icterus of the biliary tract. This anatomo-pathological point of view has for some time dominated the ideas concerning this condition, which was characterized by a yellow colouring of the skin, sclera, and mucous membranes, dark brown urine, and discoloration of the faeces in the case of biliary tract obstruction. This catarhal icterus was thought to be caused by a functional disorder of the liver's biliary tract without an accompanying liver disorder as such.

The important advances made by medical chemistry in the 19th century, which was the great era of experimental physiology and the introduction of the test tube, made it possible to study bilirubin, which colours the bile golden yellow and is the product of the transformation of haemoglobin by the reticuloendothelial system, as discovered by Aschoff. Gmelin's nitric-nitrous acid test was followed by several other attempts to develop more precise tests. Ehrlich's diazoreaction enabled Hymans Van den Bergh to differentiate immature bilirubin, which is still coupled to a globin and yields an indirect reaction, from free or unconjugated bilirubin, which will be conjugated to glucuronide by the liver cells and then be detected by the direct Hymans Van den Bergh reaction. This distinction proved very useful to distinguish inflammatory from obstructive processes.

Attention then turned to the study of other hepatic functions. Serum protein alterations were revealed by opacification and flocculation tests and analysed by electrophoresis. The presence of excess amounts of hepatic enzymes (alkaline phosphatases and amino-transferases, previously called transaminases) and elimination tests (such as Bromsulphthalein or BSP), gave instant snapshots that were useful for evaluating the liver function. Liver biopsies, often combined with laparoscopy, provided very useful histopathological information under ordinary light microscope or electron microscope for a clinical diagnosis. Ultrasound detection became a particularly advantageous complement to X-ray examinations.

The milestones laid by clinical observations and their epidemiological analysis made it possible to distinguish infectious hepatitis or hepatitis A from serum hepatitis or hepatitis B. Hepatitis A, which is transmitted by the faecal-oral chain, is endemic in Africa and occurs in epidemic waves at variable intervals. Its connection with poor faecal hygiene proves it to be a childhood disease. The hepatitis A endemicity is hardly visible, yet it is enough for individuals from areas with satisfactory hygiene and/or belonging to privileged segments of the native population to enter in contact with this circulating virus for sporadic cases or small family epidemics to arise. This risk becomes a reality each time armies set off on a campaign in an endemic area. Larrey, for example, described such cases during the Napoleonic Wars in North Africa and more than 25,000 cases were recorded in the US Army's health statistics during World War II.

Hepatitis B occurs at levels of very high endemicity reaching 20 to 50% or higher in some areas. In such environments the virus carried in the blood constitutes already a serious risk for a
child from the time of its birth; this risk is maintained by traditional interventions such as circumcision, tattooing and sexual activity. This hepatitis B, which is linked to blood, blood products, and unclean instruments, belongs to the group of viral infections with long incubation periods, with an ever rising importance. It is useful to recall that the fulminant form of hepatitis B is not due to the particular virulence of the virus, but to an excess in immune reaction of the patient's T lymphocytes.

The Hepatitis C virus was discovered in 1989, as the major cause of the formerly classified hepatitis as non-A non-B. Its epidemiology is not yet entirely known. But, as with B hepatitis, the number of asymptomatic carriers of the virus, the frequent evolution towards chronic hepatitis and cirrhosis, and the links of these two hepatitis with hepatocarcinoma, have made evident that viral hepatitis was a very serious public health problem, for at least half a century.

The risks of toxic hepatitis caused by chlorinated compounds (CCl4, chloroform, and pesticides), mercury, antimony, bismuth, phosphorus, and arsenic are known. Stokes and his co-workers had already stressed in 1920, that the jaundice seen after the administration of arsenic compounds (given to treat yaws, syphilis, and sleeping sickness) was not purely toxic, but was also linked to unclean needles.

Plant materials, especially mycotoxins, also cause hepatotoxicity. The notorious mycotoxin of Ammanites phalloides has ceded its leading position to Aspergillus flavus and aflatoxin.

All this should not make us forget tuberculosis, Q fever, granulomatous diseases, amoebiasis, hepatic metastases and other aetiologies of liver disease.
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HEPATITIS, CIRRHOSIS AND BILIARY DISEASES

HISTORICAL BACKGROUND

a. Jaundice

Jaundice (icterus) is a symptom known since the time of Hippocrates, which is since the fifth century BC. The Arab doctors drew attention to the yellow colour of the sclera. However, the relationship between jaundice and hepatitis was not established until much later.

The seriousness of jaundice did not escape the notice of observers who accompanied the explorers of tropical Africa or the armies, above all those of Napoleon. But its origin remained a mystery. Epidemics of jaundice were reported as early as the first century AD (Decree of Cappadocia).

Larrey (1812), in his observations about the cases of hepatitis he saw in Egypt, tried to track down their possible causes; he cited the combination of heavy drinking (wine and strong liquor) and the heat, the bitter unhealthy water of the garrisons, which led to gallbladder obstruction, the carrying out of too many mercury skin massages for the treatment of venereal diseases, exhaustion, and improperly administered bleedings, etc. He also noted that the liver could discharge pus, that could only be drained off after reaching a mature state.

The development of jaundice was a sign which led to serious apprehension, which in the event of an epidemic resulted in real terror. Due to the lack of diagnostic means, epidemic icteric conditions such as yellow fever and also secondary jaundice, were linked up to well-known diseases, such as malaria, haemoglobinuria (black water fever), relapsing tick fever, leptospirosis, typhoid fever, lobar pneumonia, hepatic amoebiasis, cirrhosis and cancer.

The discovery in 1886 of the agent responsible for Weil’s relapsing jaundice, a leptospirosis, led to many other discoveries, among which the yellow fever virus and viral hepatitis as a start. The identification of these viruses was a difficult task as was the refinement of the virological techniques themselves, due to the lack of sensitive laboratory animals and sensitive cell lines.

A few misunderstood observations of viral hepatitis could have influenced the way of thinking of that time. A. Lurmans (1888) observed a jaundice epidemic among shipyard workers at Bremen, after they were vaccinated with humanized lymph containing human serum. In a detailed study of catarrhal icterus E.A. Cockayne (1912) observed that this term covered at least 2 or 3 aetiologies (including leptospirosis), and indisputably two clinical varieties. He pointed out their infectious nature and suggested the name infectious jaundice. In a Swedish clinic for diabetics, A. Flauent et al. (1926) observed an epidemic of icterus and attributed the cause to have come from the syringes and needles used at the time; they also pointed out the lengthy incubation period. In 1937, G. Findlay and F. MacCallum reported some cases of jaundice after yellow fever vaccinations with a vaccine to which human serum had been added.

Infectious jaundice does not appear to have attracted the attention of specialists in tropical diseases before the 1914-1918 war. The cases of so-called infectious hepatitis described in Senegal and the Sudan from 1915 on were called camp jaundice as the infections erupted in small epidemics. Other micro-epidemics were caused by leptospiroses. The possibility of various aetiologies was often the origin of confusions. Babet (1942) contributed with others to a first classification based on histopathological criteria.

On examination of the Belgian literature of tropical medicine, one becomes aware of the fact that no mention of epidemic hepatitis was made before 1914. This state of affairs was obviously due to the lack of the existence of an adequate medical coverage before the period in question. This remark is valid also for the other tropical African territories.

However, after the First World War one began to track down the epidemics of hepatitis and one tried to determine their aetiologies. Indeed, each new epidemic brought about its shares of surprises: one began by isolating the recurring spirochaetes in the blood and the leptospiroses in the urine of icteric patients; it was noticed that pneumonia of Africans was often accompanied by hepatitis and jaundice; yellow fever was isolated as a cause of hepatitis, on the basis of highly evocative histopathological liver lesions found in the deceased subjects (a trabecular disorganization of the hepatic lobule with steatosis and Councilman bodies).

These observations apply equally well to the Belgian Congo as to Rwanda and Burundi. Kadaner and Corti (1933) observed cases of jaundice caused by leptospiroses in Kisangani (previously called Stanleyville); Jadin and Arnald (1938) described an atypical yellow fever at Zongho (Ubangi), that was later identified as acute yellow atrophy (Babet, 1942); Van Riel (1939) revealed the existence of a focus of leptospirosis, causing serious, sometimes fatal, jaundice.

The notion of viral hepatitis as seen today did not apply automatically to Africa. In epidemics the diagnosis of the cause had been carried out by exclusion, for yellow fever, spirochaetes or borrelia.
It was not until the second World War that the subject matter of viral hepatitis was brought into question. A group of doctors from the British Health Services published a report in 1943, on the appearance of jaundice in schoolchildren after the administration of serum from convalescent measles patients, or in patients who received plasma transfusions, and as a follow-up of yellow fever vaccinations. The causative agent however had still not been isolated, but the person-to-person transmission of the infection was observed and consequently confirmed in 1944, by experiments carried out on volunteers. By 1947 the distinction between epidemic viral hepatitis, called hepatitis A, and a non-epidemic serum hepatitis, called hepatitis B, had become clear.

The inability to cultivate the virus and the lack of the possibility of inoculating a laboratory animal, explain why it took so long to detect the viral cause of hepatitis.

For a long time the epidemic forms of viral hepatitis were diagnosed only after it had been possible to rule out the diagnoses of yellow fever, spirochaetosis, and relapsing fever.

Beheyt (1953) has frequently observed cases of jaundice among the Congolese; these cases had long been classified as catarrhal or toxic icterus. This latter cause was often attributed to the use of traditional mysterious remedies, as well as intoxication by arsenic compounds and bismuth salts. During the in-depth study of 249 cases in Leopoldville (Kinshasa) in 1951, Beheyt came to the conclusion that apart from the aetiologies already cited, the icterus were linked either with viral epidemic hepatitis or homologous serum hepatitis.

In 1967, Dentley and his co-workers managed to isolate the hepatitis A virus in chimpanzees and in marmosets. The hepatitis B virus required a long but fascinating detour. Blumberg and his co-workers had noticed during a study of serum lipoproteins that the serum of a haemophilic patient who had received multiple transfusions, contained an antibody that reacted with an antigen detected in the serum of an Australian. A series of investigations culminated in the identification of this Australia antigen as being the surface antigen of the B virus particle, that is, HBs.

b. Cirrhosis

In the first decades of the twentieth century, African patients tended to turn more readily to traditional healers rather than to doctors, especially for chronic diseases. As a result, many health problems had still to await the moment of scientific explorations.

The physicians working in the Belgian Congo, and in Ruanda-Urundi or in tropical Africa, were affected by the frequent association of primary liver cancer with cirrhosis as was brought to light by carrying out routine autopsies. Cirrhosis was not frequently scientifically studied.

In the past the department for internal medicine in teaching hospitals was breaking down the aetiology of cirrhosis to only one outstanding factor, namely alcohol abuse if the patient was a Christian, and malaria if he was a Muslim. The role of malarial cirrhosis was first of all incriminated and is now based on the accumulation of risk factors and on contradictory conclusions which have no scientific basis. But the cirrhosis due to malaria appears to be a rational extension of the liver involvement from the onset of this disease.

When all is said and done, malnutrition, parasitic disorders of the digestive tract, viral hepatitis, chronic alcohol abuse, and other toxic factors were incriminated in turn with more or less conviction, depending on the period and the up date in medical theories. Pages 944-948 review the development of ideas concerning the aetiology of liver cirrhosis.

Moreover advances in epidemiology and immuno-histochemistry have recently made it possible to elucidate the major role of hepatitis viruses (HBV and NANBH) in the genesis of post-necrotic cirrhosis. These advances have also shown that whatever the cause of hepatitis, the risk for the development of hepato-cellular cancer is high (in 10 to 20% of the cases). Conclusive studies have been conducted in Kenya and Uganda, but studies in many other parts of the world, have remained limited and even non existant in many other regions, particularly in Central Africa. Other aetiological factors, such as alcohol and various hepatotoxic substances, including aflatoxin, have been described and suggest the existence of dietary or environmental influences that may contribute to the genesis of cirrhosis, so frequent in tropical Africa.
MAJOR CHALLENGES

1. Hepatitis

The notion hepatitis covers conditions affecting the hepatocyte. While the diagnosis is usually made on the basis of its most familiar and spectacular symptom, jaundice, it should be stressed that, in Central Africa even more than in other parts of the globe, not every icterus is a sign of hepatitis and not every hepatitis is preceded by a jaundice. Furthermore, jaundice is not always visible. The melanin of the skin masks the icteric condition, while the sclera of the eye of the African population often presents coloured patches which do not facilitate the diagnosis.

Jaundice may accompany hepatitis, but, in Central Africa, a pre- or post-hepatic jaundice can also often be seen: pre-hepatic jaundice has as main cause malaria which leads up to the increased production of bilirubin due to massive lyses of the RBCs during attacks of malaria; post-hepatic jaundice, often found in the industrialized world, is rare in the tropics, and is due to an obstruction of the biliary duct by a gall stone or to a compression by a neoplasm, for example of the head of the pancreas, or by the infectious or neoplastic choleodochus stenosis.

On the other hand the main cause of hepatitis depends on viral infections, with symptoms of fever, asthenia and anorexia, that make part of the clinical picture for numerous and frequent diseases in the tropics. To this must be added the fact that the people affected during epidemics include a variable but not insignificant proportion of patients without icterus who are perfectly capable of transmitting the infection; therefore it was understandable that the notion of an epidemic disease could not immediately come to the mind of the too rare medical research-workers at the beginning of the century. But from 1970 on, the progress of virology has lead to the recognition of the existence of 5 viruses as being the origin of hepatitis.

1.1. Viruses of hepatitis

1.1.1. Hepatitis A Virus

Hepatitis A virus (HAV) is a spherical virus, with an icosahedral symmetry of 27 nm containing RNA, and belonging to the picornavirus group. The virion has an envelope or capsid formed by at least 3 major polypeptide structures. Its genome is made up of a single strand of RNA comprising some 7,500 nucleotids, ending with a polyadenylc acid. This organisation of the genome is similar to the arrangement in other picornaviruses. The RNA is the infectious element.

This virus withstands heat fairly well and its replication is not easily inhibited by various agents; however, its infective strength is weakened after remaining for a period of 4 weeks at room temperature.

HAV is inactivated by ultraviolet light, by heating at 100°C for at least 5 minutes, and by contact with a 1:4,000 formaldehyde solution. HAV multiplies in cell cultures, without producing a cyto-pathogenic effect nor inhibiting macromolecular synthesis in the host cell. The HAV strains that have been collected from various parts of the world, show that they all belong to just one serotype.

1.1.2. Hepatitis B Virus (HBV)

Hepatitis B virus (HBV) is a DNA virus belonging to the HepAdNA group. This 42 nm diameter virus has a more complex structure than HAV. Its double shell includes an outer shell of lipoprotein, which is produced in excess and is encountered in the carrier’s serum as hepatitis B surface antigen, HBsAg, or Australia antigen. The inner coat or nucleocapsid surrounds the 27 nm core. The core is made up of circular double-strand DNA of 3,200 nucleotids and a DNA-dependent polymerase which is used for viral replication. The viral genome can incorporate itself into the host cell’s genome. The virus can survive for hours on outside surfaces, even after desiccation.

The HBV virion has three antigens:
- the first one is the surface antigen or HBsAg (Australia antigen), destroyed by heating at 80°C for 30 minutes; it has one common determinant a, and four specific determinants, d, y, w, and r; their combinations allow to distinguish between different subtypes, which is very important for epidemiological studies. HBsAg appears very early in the infection, even before liver function tests become abnormal; it is thus the first indicator of an active infection and persists throughout the clinical illness;
- the core antigen or HBeAg is present only in the infected hepatocytes; it never circulates in the blood. It has no variants.
- HBeAg is demonstrated only in patients carrying HBsAg. It is believed to be a form of HbcAg that undergoes a transformation upon leaving the hepatocyte. HBeAg circulates in the bloodstream, and its level in blood correlates closely with the latter's capacity for infection. The presence of this antigen is of great practical importance, for it means that the virus is still replicating and the patient is still infectious.

1.1.3. Hepatitis D Virus (HDV or Delta virus)

In 1977 a group of scientists working under Rizetto found a new RNA viral particle, which they named the delta antigen, in hepatocytes infected with hepatitis B virus. What is now known as hepatitis D virus (HDV) is one of the smallest known viruses (35-37 nm) which needs HBs antigen for its replication and expression. Its RNA single-strand genome of 1,700 nucleotides is surrounded by a specific protein, HDAg. This delta nucleus is encased in an outer envelope of HBsAg without which the virus is incomplete and cannot survive nor replicate. It is cytopathogenic and is transmitted parenterally.

1.1.4. Hepatitis C Virus (HCV)

The recent discovery of the hepatitis C virus is the fruit of very sophisticated molecular biology techniques. It is a single-strand RNA virus of about 10,000 nucleotides, the capsid of which is icosahedral, and has an envelope. The virus has a diameter of 60 nm, is heat resistant, but is destroyed by detergents and chloroform and is not incorporated in the cell genome. It can also be transmitted parenterally.

1.1.5. Hepatitis E Virus (HEV)

The hepatitis E virus is responsible for most of the enterally-transmitted cases of non-A, non-B hepatitis. It is approximately 32 nm in diameter virus (one of the smallest known viruses) which has no envelope. Its genome has just been cloned and sequenced, thereby paving the way for the development of a routine serological test and perhaps even a vaccine. It consists of a 7,600-nucleotide single strand of RNA and belongs to the Calicivirus family.

1.2. Pathogenesis

1.2.1. Hepatitis A

HAV is characterized by a short period of viraemia. Viral excretion in the stools can start two weeks before the onset of the disease and is particularly abundant towards the end of the incubation period and the start of the disease. The virus is usually no longer found in the faeces after the third week of illness. It was demonstrated in chimpanzees that HAV antigen is already inside the hepatocytes when the virus is excreted in the stools.

Investigators have shown that only 5 to 10% of the hepatocytes are infected in the initial phase (IP) and that the virus particles gather in the intracytoplasmic vesicles. The virus passes from the hepatocytes into the bile, and then into the intestine, to be excreted with the stools.

The liver cell damage seems to develop in two phases:

1. The first phase, which coincides with the faecal shedding of HAV, is characterized by elevated hepatocyte enzyme secretion but is free of histopathological lesions. When the transaminases reach their peak level the virus is no longer found in the blood.

2. The second phase is represented by the production of anti-HAV antibody triggering immune reactions (hepatic mononuclear lymphocyte infiltration and liver cell necrosis).

HAV antigen is present, as shown by IF, not only in hepatocytes and Kupffer cells, but also in the abdominal lymph nodes, the spleen, and the kidneys. In the last organ immune complexes may be found along the basal membrane of the glomeruli.

The humoral response is rapid. Antibodies appear early, towards the end of the first week of the acute phase. They consist of specific anti-HAV IgM antibodies which remain for only a brief period not exceeding six months, except in extended or relapsing forms and in immuno-suppressed patients, in whom they may persist much longer. They are then replaced by anti-HAV IgG antibodies, which reach peak levels one to two months after the onset of the disease and persist at a residual level usually for the rest of the patient’s life. These antibodies immunize the subject against reinfection.

1.2.2. Hepatitis B

The host’s response to hepatitis B infection may take different forms:

1) The most frequently encountered hepatitis B infection in adults (90%) is self-limiting. Histological changes prevail in the centre of the liver lobule. The hepatocyte varies in size and there is a marked degeneration, with an eosinophilic necrosis in some cells. At the same time, there are signs of cellular regeneration, and inflammatory reaction of the mesenchyme, which leads to complete normal
reconstitution. There is usually neither steatosis nor marked bile-stasis. HBs antigen is the first viral marker to appear in the blood. It is detectable in one or two weeks but sometimes in eleven or twelve weeks after exposure to the hepatitis B virus. The clinical signs generally appear after four weeks. HBsAg persists in the blood for around one to six weeks. HBe antigen usually appears a few days after HBsAg. The HBeAg levels decrease gradually during the ten weeks following the onset of the symptoms. The patients who remain HBeAg-positive for more than ten weeks are likely to become chronic carriers, and the presence of this antigen is a sign of viral replication. Anti-HBe antibody appears in most patients at the moment HBeAg disappears and persists, as a rule, for one to two years after the hepatitis B has been cured.

Anti-HBc antibodies (against the core of the virus) can usually be detected some three to four weeks after the appearance of the HBsAg. They are first of all of the IgM-type, then of the IgG-type and persist in the blood several years after hepatitis has been cured.

Anti-HBs anti-bodies generally appear after complete disappearance of HBsAg, and testify for recovery.

2) In fulminant B viral hepatitis, massive cellular necrosis usually leads to liver atrophy.

3) The evolution towards chronicity can develop in two forms:
- In persistent chronic hepatitis, there is parcellar cytolysis and inflammatory infiltrate of portal tracts, without marked alteration of liver architecture nor important fibrosis. HBsAg persists in the serum without the appearance of anti-HBs antibody. This evolutive type is rarely severe, but it can be re-activated.
- In chronic active hepatitis, histological changes are very important: diffuse and evolutive portal and periportal fibrosis with extensive hepatocytic necrosis. Hbs and HBe antigens persist in serum as well as ADN of HBV, testifying for its active replication.

HBV does not seem to be directly cyto-pathogenic. Clinical signs and evolution appear to be closely linked to the immune response, especially to cytotoxicity of some lymphocytes towards infected cells.

4) Chronic HBsAg carriers

About one third of the patients who carry HBsAg for more than 20 weeks, usually remain infected for the rest of their lives and are chronic HBsAg carriers. About a quarter of them carry HBeAg and are thus highly contagious. HBeAg disappears after some two to seven years in about 45% of these patients, and then anti-HBe antibodies appear. Those carriers (HBsAg+, anti-HBe+) can be considered as chronic healthy HBsAg carriers. They have neither clinical nor biological signs (Dive, 1993): ALT and AST (Alanine and Aspartate amino-transferase, or transaminases) are in the normal range, and have neither HBeAg nor ADN of VHB in the serum. Histological examination of their liver appears to be normal, except that numerous hepatocytes show an homogenous cytoplasm (ground glass hepatocytes) due to the presence of large amounts of HBsAg and hyperplasia of endoplasmic reticulum. The HBsAg level decreases at the rate of about 2% per year.

5) HBsAg-negative persistent infection

A minority of patients may display persistent hepatitis B virus infections and transmit the infection whilst remaining HBsAg-negative. These patients usually have high anti-HBc antibody titres.

6) Interactions between hepatitis B and other factors:

During a treatment of corticosteroids HBsAg may reappear. The same phenomenon has been described in HIV carriers.

1.2.3. Hepatitis D (Delta)

Given the absolute need of Hepatitis D virus for HBsAg (surface antigen) to replicate and to be expressed, hepatitis D infection is seen only in HBsAg carriers. Hepatitis D antigenaemia, which lasts only a few days, is seldom ascertained. The diagnosis thus relies on detection of anti-HD antibodies belonging to the IgM class of immunoglobulins, which are inconsistently followed by IgG antibodies. Hepatitis D antibodies are found in two situations:
- hepatitis B + D co-infections: the hepatitis D virus infection is observed in one-third of fulminating hepatitis B cases;
- hepatitis D superinfections in chronic hepatitis B virus carriers: such super-infections may lead to chronic liver disease. The Delta particle appears to be responsible for 2/3 of the cases of fulminating hepatitis occurring in chronic HBsAg carriers.

1.2.4. Hepatitis C

Studies on post-transfusional non-A, non-B hepatitis have revealed the frequency of asymptomatic infections, the possibility of fulminating forms, and the frequent development of chronic liver disease leading to cirrhosis and liver cancer. Prospective studies of subjects who received a transfusion have revealed that antibody production often lags behind the transaminase peak. Antibodies are detected in 55% of patients during the first month after infection, but in half of the cases seroconversion does not occur until the second to twelfth month.
1.2.5. *Hepatitis E*

The hepatitis E virus can be transmitted to monkeys from the faecal material of contaminated subjects, provoking an increased level of transaminases while the virus becomes detectable in the liver, bile and stools. In the sera of infected people and monkeys anti-HVE neutralizing antibodies have been detected. These antibodies were able to react with the viral particles present in the faeces of patients from different parts of the world.

1.3. Transmission

1.3.1. *Hepatitis A*

While the chimpanzee is susceptible to become infected, the human population is considered the virus’s only reservoir. Hepatitis A infection is contracted through food and water that have been contaminated by faecal material of infected individuals. In other words, poor faecal hygiene is the major source of contamination.

Tropical Africa provides, by the lack of hygiene or incorrect use of latrines, the ideal conditions for the transmission of hepatitis A, which occurs predominantly by the faecal-oral route. This explains why hepatitis A occurs as small family epidemics. Like other intestinal micro-organisms, HAV can also be transmitted by sexual intercourse by oral-anal contact in homosexuals. Vertical transmission from mother to child is extremely rare or nonexistent. The viraemic period is so short that infection through blood transfusions is possible only in very exceptional circumstances.

1.3.2. *Hepatitis B*

Hepatitis B transmission is explained by many facts; it is especially bound to the length of the incubation period (two to six months) while serum is already infectious during the second part of this period, to the very high infectious titre of blood (0.0001 ml plasma can transmit HBV), and to the frequency of healthy carriers.

Hepatitis B is thus first and foremost transmitted parenterally by blood and blood products: it was formerly called *serum hepatitis*. However, HBsAg has been found in almost all body fluids, whereas the presence of infectious HBV particles was detected only in blood, saliva, and vaginal secretions.

Hepatitis B can also be transmitted by sexual intercourse and vertically from mother to child as well as horizontally between young children.

1. Transmission by blood and blood products

Since blood donors in Africa are not usually tested for hepatitis B, almost all transfusions of blood or blood products carry a risk of infection. There are also risks connected with certain traditional ritual practices such as circumcision, scarifications, and tattooing, which are often performed under rather poor hygiene conditions. The failure to sterilize needles between injections is often the origin of a chain of transmission between patients. Thus, some dispensaries can be really infection distribution centres. Health professionals might become infected when they accidentally prick themselves with contaminated needles or if cuts come in contact with infected blood. Drug addicts who share unsterilized needles and syringes are at a great risk of infection.

2. Sexual transmission

Since HBV may be present in semen and vaginal secretions the infection may be transmitted by both hetero- and homosexual intercourse. Prostitutes and homosexuals with multiple sexual partners are frequently infected.

3. Mother-to-child transmission

Transmission *in utero* is possible, although it seems to occur rarely. Although no foetal infections have been discovered, HBsAg and the DNA of HBV have been found in cord blood. Probably only 5 to 10% of hepatitis B infections transmitted by mothers to their children are transmitted during pregnancy. Most of the infants are probably infected at birth, when they come in contact with the mother’s blood. Hepatitis B is also transmitted *after* birth by intimate contact between the neonate and the mother or other infected siblings. The probability of perinatal transmission from mother to child is highly correlated to the presence of HBeAg. Indeed 90% of the children born of HBeAg-positive women will become infected and half of these children will become chronic carriers while this risk is below 10% if the mother bears anti-HBe antibody.

HBV does not seem to be transmitted by breast-feeding, although HBsAg has been detected in breastmilk, while blood-borne contamination due to excoriation of the nipple is theoretically possible. In Africa, hepatitis B, extremely frequent in newborn babies and infants, is strongly perpetuated by foetal-maternal cycle.

4. Other routes of transmission

Although the three types of transmission outlined above account for the majority of infections, horizontal person-to-person transmission must not be discounted
as it might occur by objects of daily life (razors, tooth brushes, silverware, underclothes, bedding, etc.) that can be contaminated with HBV from saliva, sweat, tears, even urine. This is probably the predominant type of transmission in groups and institutions such as orphanages, day care centres, and institutes for the handicapped in which poor hygiene prevails.

Man seems to be the sole virus reservoir but the possibility that the disease can be transmitted by some biting insects, such as bedbugs, cannot be ruled out. Given the important clustering of infections within families between 1982 and 1985 in the Republic of Central Africa, the Centre national hospitalo-universitaire de Bangui (Bangui national teaching hospital centre) raised the possibility of insect-mediated transmission (Lesbordes et al., 1986).

A Gambian study among six month to five year old children revealed an association between the presence of HBcAg in the blood and cutaneous ulcerations caused by bedbugs found in the children’s beds. This could suggest that bedbugs might transmit HBV mechanically (Vall Mayans et al., 1990). HBV can probably be transmitted to infants and toddlers by cutaneous ulcerations and perhaps by saliva or bites.

1.3.3. Hepatitis D

Transmission in Northern Europe and the United States occurs primarily through blood. As a result, hepatitis D in those parts of the world affects primarily haemophiliacs and intravenous drug users, amongst whom it seems to be spreading quickly. Vertical transmission is possible. Sexual transmission is frequent and seems to be, together with blood transmission, the predominant route of transmission in Africa.

1.3.4. Hepatitis C

The transmission of hepatitis C is primarily parenteral, by transfusions of blood and blood products, or by the utilization of contaminated needles and syringes. Some studies have suggested that hepatitis C is transmissible by sexual intercourse, but not so easily as hepatitis B; others refute it. For the time being there is no proof that hepatitis may be transmitted vertically by a mother to her child. We still do not know all the details of how hepatitis C is transmitted. Indeed, some American studies of patients with hepatitis C found only in ten per cent of them a history of parenteral exposure. This means that other routes of transmission must exist.

1.3.5. Hepatitis E

Transmission of hepatitis E is basically faecal-oral. Epidemics and sporadic cases have been reported in connection with the contamination of drinking water with faecal material. Infection of members of a same family by person-to-person contact has also been reported.

1.4. Epidemiology

Before the time where serological tests were available, all cases of hepatitis were regarded as either infectious or as serum hepatitis. This differentiation cannot be accepted anymore, for we now know that the modes of transmission are shared by different types of hepatitis and neither clinical signs nor epidemiological peculiarities make it possible to identify the various types of viral hepatitis. Specific serological tests are required to make a distinction possible.

1.4.1. Hepatitis A

In Central Africa, 95% of Central African children come in contact with the virus before the age of twelve years. However, the disease is generally benign in this age group: only 4 to 16% of them will develop symptoms, whereas 75 to 95% of adults will develop jaundice.

A sero-epidemiological survey done in the course of 1985 in Northern Ubangui (Zaire) has shown that 94% of the people between ten and nineteen years of age had antibodies against hepatitis A virus (Werner, 1985). Similar results were reported from Rwanda.

In countries where good hygiene is the rule the population usually does not come into contact with the virus until adulthood, especially through the close contacts in student residences, military barracks, prisons, and summer camps. For residents of industrialized countries it often happens that they are exposed to the virus for the first time during a trip to a tropical area.

While hepatitis A tends to show a cyclic pattern in industrialized countries, with autumn peaks and epidemic waves every five to twenty years, such a distinct cyclic pattern has not been observed in Central Africa. Hepatitis A epidemics have often erupted among soldiers during military operations. A study of the health records of American missionaries living for a long time in Ethiopia and Sudan showed that the risk of contracting hepatitis in this group was 9% for the first year in the country; this means a 454 times greater risk than in the United States.

1.4.2. Hepatitis B

HBV is responsible for many cases of acute and chronic hepatitis. These cases are sporadic and man is the only reservoir for the virus. The spread of hepatitis B is ensured by the large reservoir of virus carriers.
The epidemiological patterns of hepatitis B in the tropical and industrialized countries are very different. The HBV-carrier rates in North America, Western Europe, and Australia are between 0.1 and 0.5%. They are 1 to 2% in Central and South America, 5 to 10% in the Mediterranean, the Soviet Union, South Africa, and Southeast Asia, 4.7 to 20.1% in China, depending on the province (16 provinces were studied by R. Palmer-Beasley, 1981) and 8 to 15% in the tropics, including Central Africa. WHO estimates that there are some 350 million HBV carriers in the world. The average age of initial contact with HBV is also much lower in Central Africa than in the industrialized world.

The prevalence of infection varies greatly from one place to another. Thus, 6.7% of 1,167 African blood donors screened in Kenya at Nairobi were found to be HBsAg carriers; 62% of the children between the ages of two and four years were carriers in one Gambian village and 27% in another. In Dar-es-Salaam (Linquist, 1973), HBsAg was detected in 44% of the hepatitis patients, 5.5% of the blood donors, and 2% of the investigated young women. The prevalence of HBsAg in Bangui, Central African Republic, was 15.5%. In a rural area of North Ubangi, Zaire, the rates of HBsAg carriers were as follows: 22% in the segment of the population aged 1 to 19 years, 21% in the 20 to 29 years group, and 15% in the over-30 years group. HBeAg was present respectively in 34%, 21%, and 0% of the HBsAg carriers.

1.4.3. Hepatitis D (Delta)

The prevalence of hepatitis D is particularly high in the Mediterranean people of southern Italy and the Middle East including Arabia. The highest prevalences have been reported in Kuwait and Saudi Arabia, where 40% of HBsAg carriers also carry anti-HDV antibody. Epidemics have been reported especially in isolated populations in developing countries, for example in the Amazonian basin. These hepatitis epidemics were fulminant, with extremely high case-fatality rates of 10 to 20%. In northern Europe and the United States HDV infections are found most frequently in certain risk groups, such as intravenous drug users and multiple transfusion recipients, but rarely in other individuals at risk, such as medical staff and homosexuals.

The following prevalences of anti-HDV antibodies have been found in HBsAg carriers in Africa: 80% in Senegal (Cronberg, 1984) and Kenya (Greenfield, 1986); 3.7% in Nigeria (Ayoola, 1988); and 37% in Cameroon (Ndumbe, 1991). The highest anti-HDV antibody prevalences in Cameroon were found in multiple transfusion recipients with Sickle cell anaemia (62%) and in prostitutes (26%). This suggests that blood and sexual intercourse are the two main sources of HDV transmission in Africa.

1.4.4. Hepatitis C

Hepatitis C virus (HCV) is probably responsible for more than 80% of post-transfusion Non-A, Non-B hepatitis. A Dutch study has shown that an anti-HCV-positive donor can be traced in three-fourths of post-transfusion hepatitis cases. The prevalence of HCV is particularly high among drug addicts (30 to 70%) in studies conducted in the United States and Europe, and among haemophiliacs. The serologically determined prevalences in blood donors in the United States and Europe range from 0.2 to 1.5%. It is 5.5% in Surinam. Hepatitis C infections are also found in Africa, where seroepidemiological studies of frozen plasma samples require confirmation (Tibbs, 1991). Still, the results are of great presumptive value. Manginetti and co-workers (1991) discovered a prevalence of 9.84% in Cameroon, but with great differences in the patterns found in the North and South and an increase in prevalence with increasing age. Tibbs (1991) found a prevalence of 6.5% in rural areas of Zaire; Ellis (1990) found a prevalence of 3.84% in the black inhabitants of a rural part of South Africa, and Courset (1980) found prevalences that varied greatly from one African country to the next: 2.9% in Senegal, 1.2% in Madagascar and 11% (the highest rate) in Burundi. The mean sero-prevalence among blood donors seems to be around 6%.

There are asymptomatic HCV carriers, but they are difficult to detect, given the absence of currently available specific markers.

1.4.5. Hepatitis E

Large epidemics of hepatitis E have been reported in India, the Soviet Union and South-East Asia. Sporadic cases appearing in cascades have also been reported in North Africa, Sudan, Somalia, the Ivory Coast and Mexico as well as among travellers returning from these countries. The epidemiological pattern of this infection is very similar to that of hepatitis A, but the virus is serologically different. People who have been infected with hepatitis A virus have no immunity to hepatitis E virus.

1.4.6. Other types of hepatitis

It is possible that other types of parenterally-transmitted Non-A, Non-B hepatitis (hepatitis F?) exist. Indeed, anti-HCV antibodies have not been found in a number of patients who contracted Non-A, Non-B hepatitis.
after blood transfusions. Some of these infections might actually be cases of hepatitis C escaping detection because the serotests are not sensitive enough. A giant cell form of hepatitis was described recently, perhaps caused by a new virus, hepatitis G? (Lancet, 1991).

1.5. Incubation periods

The incubation periods range from two to six weeks (four on average) for HAV and from four to thirty weeks (ten on average) for HBV. The incubation period for HDV in B + D co-infections is the same as for HBV. In the case of an HDV super infection of a chronic HBV carrier it is about five weeks. The incubation period for HCV is from one to five months (eight weeks on average) and that of HEV about six weeks.

1.6. Clinical symptoms and signs – Clinical forms

Although the hepatitis infections involve very different viruses, they have a similar clinical picture. Neither clinical symptoms nor biochemical liver tests allow to differentiate the various infections. Only serotests enable the identification of the specific virus involved.

Hepatitis can usually be subdivided into the following three phases:

a) a pre-icteric phase, which is characterized by general discomfort, muscle and joint pains, fatigue, and especially marked anorexia, often accompanied by nausea and aversion to cooking smells and tobacco smoke. There is often a slight abdominal pain, more especially in the right upper quadrant and moderate fever disappearing when the second phase takes over.

b) an icteric phase, which is preceded by darkening of the urine and worsening of the previous symptoms. In about half of the cases the liver is enlarged and tender upon palpation. The stools are pale and the patient becomes icteric. Still, an icteric phase does not necessarily develop in all patients.

c) a convalescent phase during which the symptoms and signs described above disappear gradually.

1.6.1. Signs evocative of a specific infection

Despite the common clinical picture shared by all hepatitis viruses, some signs may be evocative of a specific viral infection:

- HAV hepatitis by its oral route of contamination causes diarrhea in 60% of the children and 20% of the adults.
- One-third of hepatitis B cases are asymptomatic, another third show signs similar to a flu without jaundice, and the last third are icteric. Generalized lymphadenopathy is more common in hepatitis B than in hepatitis A infection.
- HDV co-infection with HBV or its superinfection in chronic hepatitis B are mainly responsible for the fulminant forms of hepatitis.
- The clinical manifestations of HCV infection are less severe as a rule than those of other forms of hepatitis. The number of cases without jaundice can be high, especially in children under the age of 2 years. As a rule amino-transferases (transaminases) are not as high during HCV infection as during hepatitis A or B infection and the disease seems less severe. On the other hand, hepatitis C tends more frequently to become chronic (50% of the cases), especially for infections caused by a transfusion.
- HEV produces forms of intermediate severity except in pregnant women; these intermittently severe cases of hepatitis are characterized by intense cholestasis. In pregnant women, however, especially during the third trimester, hepatitis E is more frequent and more serious. Fulminant hepatitis is seen in 10 to 30% of infected women, depending on the epidemic, some of which have led to high death rates (up to 40%).
- Extra-hepatic manifestations are seen in certain forms of the disease. These non-hepatic symptoms can be attributed to the virus itself, to deposits of immune complexes, or to an as yet unelucidated mechanism. These are neuromuscular, haematological (exceptional by aplasia), digestive and pancreatic, and renal manifestations (glomerulonephritis during hepatitis B, see p. 1154) and multiple joint pain.

- Fulminant hepatitis deserves special mention, because it can complicate all types of hepatitis, with a particularly high frequency for hepatitis B, hepatitis B + D, and hepatitis E during pregnancy. The risk is theoretically low in the case of hepatitis C, but given the latter’s frequency, it causes 20 to 30% of the fulminating cases of hepatitis. It is characterized by a depressed prothrombin rate, reaching 50% below the normal rate, a serious fall of factor V, hypovolaemia, acute renal failure, and hepatic encephalopathy which if it reaches the comatose stage, is fatal for 75 to 90% of the patients.

1.6.2. Biochemical signs

- The most characteristic sign is the increase of transaminases (Alanine amino-transferase, ALT and Aspartate amino-transferase, AST) from the pre-icteric phase on. The transaminase levels can reach 10 to 100 times the upper limit of the normal range without having any prognostic value.
- The serum bilirubin level rarely exceeds 200mg per litre and concerns primarily the conjugated form.
- Gamma-G transferase is slightly elevated (5-10 times the normal value).
- The alkaline phosphatase concentration rarely exceeds twice the normal level.

1.7. Aetiological diagnosis

The aetiological diagnosis relies on the serological findings.

1.7.1. Hepatitis A

Hepatitis A is diagnosed by using anti-HAV IgM radio-immuno-assay or enzyme-immuno-assay techniques. All patients are anti-HAV IgM positive at the onset of the clinical signs. The IgM antibodies usually disappear within three to six months. The hepatic enzymes return to normal levels in more than 85% of patients before or at the same time as the anti-HAV IgM disappear. The presence of anti-HAV IgM antibody without elevated transaminases means that the patient is in the convalescent stage of hepatitis A.

1.7.2. Hepatitis B

Hepatitis B is diagnosed by radioimmunological and ELISA tests looking for the HBs and HBe antigens and anti-HBs, anti-HBc and anti-HBe antibodies. Table I (below) shows how these serotests are interpreted.

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBeAg</th>
<th>Anti-HBs</th>
<th>Anti-HBe</th>
<th>anti-HBc IgM</th>
<th>anti-HBc IgG</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Incubation</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Infectious carrier</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Healthy carrier</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>Convalescence</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recovery without</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anti-HBs</td>
</tr>
</tbody>
</table>

1.7.3. Hepatitis C

A specific diagnosis cannot be made during the acute phase of the disease because unlike HBV, HCV's replication does not spawn a large number of viral particles. There are no specific proteins synthesized in excess and easily detectable. One must thus wait for an anti-HCV antibody to appear after one to three months, or even six months after the onset of the disease. These antibodies are detectable by ELISA serotests.

However the polymerase-chain-reaction (PCR) technique, although unfortunately complex, does enable one to detect HCV-RNA fragments in serum and tissues.

1.7.4. Hepatitis D

Screening for HDV infection by detecting its markers is useful only in the case of HBsAg carriers.
- In the case of HBV and HDV co-infections HD antigenaemia, which lasts only a few days, is rarely detectable. A diagnosis may be reached by revealing the presence of class IgM anti-HD antibodies (inconsistently followed by class IgG anti-HD antibodies). In practice, HBV-HDV co-infections are diagnosed by the co-existence of anti-HBe IgM antibody and anti-D antibody.
- HDV superinfections in chronic HBV carriers, which take the form of often severe, acute hepatitis, are diagnosed by the detection of class IgM anti-HDV antibody (testifying to a recent HDV infection) in the absence of class IgM anti-HBe antibody, to eliminate the possibility of a recent acute attack of hepatitis B infection.

1.8. Evolution

1.8.1. Hepatitis A

The very short viraemic period, which partly overlaps with the end of the preclinical phase, and the small number of liver cells attacked by the virus (to the order of 5% and without a direct cytopathic effect) explain why this infection does not become chronic
and why the cases are rarely severe. Elevated transaminase levels and cholestasis may persist for months, but are exceptional. Mortality for the most serious hospitalized cases is very low, of the order of 1 per thousand, and may be due to fulminant hepatitis or encephalic involvement.

1.8.2. Hepatitis B

It is particularly important to ascertain that HBsAg has disappeared after an apparent clinical cure and that the transaminase levels have returned to normal. Patients in whom HBsAg persists beyond six months (that is, who are anti-HBc positive but not anti-HBs positive) may:
- either be asymptomatic carriers, having normal transaminases
- or continue to present elevated transaminases. In this case, a liver biopsy must be performed systematically.

The biopsy will reveal the following:

a) In the case of chronic persistent hepatitis: inconsistent patchy necrosis, portal inflammation, intact lobular architecture, and slight fibrosis. In such patients, as a rule, neither cirrhosis nor extensive fibrosis appears. Monitoring is recommended every six months until the transaminase levels return to normal in order to detect the few patients in whom active chronic hepatitis may develop.

b) In the case of an active chronic hepatitis evolution (ACH) there will be a typical cellular necrosis, portal inflammation with extension into the lobule altering its structure, and frequently fibrosis. It is very important to diagnose ACH, as attempts to treat ACH with adenine arabinoside or alpha-interferon have led to the almost complete disappearance of the ACH’s activity in 25% of the patients. Otherwise, this condition will lead to cirrhosis.

There is a great deal of evidence to affirm that liver cell destruction in these patients triggers an interaction with the immune system controlled by or dependent on genetic factors (some histocompatibility groups). The histopathological lesions consist essentially in infiltration by T cells and plasmocytes. Various autoantibodies are often detected while other auto-immune diseases are frequently associated with ACH. Corticosteroids, effective in treating a certain number of immunological and auto-immune diseases are often beneficial if administered for a brief period before alpha-interferon is given.

The relationship between hepatitis B and hepatocellular carcinoma is discussed in detail in the chapter Malignancies (pp. 957-958 and 960-961) and in the section Cirrhosis hereafter (pp. 944 to 946).

1.8.3. Hepatitis D (Delta hepatitis)

The risk of this infection to become chronic will depend on the type of infection:
- Hepatitis B and D virus co-infections entail a low risk of becoming chronic, as hepatitis B infection usually disappears and HDV can no longer replicate;
- In contrast, when HDV superinfeccts a chronic HBV carrier, chronic B and D hepatitis occurs in more than 90% of the patients. These are usually very active infections that rapidly lead to cirrhosis. Alpha-interferon seems to have some efficacy in these cases.

1.8.4. Hepatitis C

After acute episodes, the transaminases can:
- either return completely to normal levels in 45% of the cases;
- or remain at a persistent elevated level in 30% of them;
- or fluctuate between elevated and normal blood levels in around 25% other cases. This last pattern is very typical of parenteral Non-A, Non-B hepatitis, which carries a high risk of becoming chronic and cirrhotic. Since chronic hepatitis C is often asymptomatic the diagnosis is often not made until the cirrhotic stage has been reached, if no systematic monitoring of the evolution is done.

Alpha-interferon is the only treatment which has some efficacy.

Chronic C hepatitis is the most frequent form of chronic viral hepatitis and a major cause of cirrhosis leading frequently to hepatocarcinoma.

1.8.5. Hepatitis E

The prognosis for hepatitis E is usually good except for those forms that arise during pregnancy. As in the cases of hepatitis A, hepatitis E infection does not seem to become chronic.

The clinical and epidemiological differences between the various types of viral hepatitis are summarized in Table 2 (next page).
### Table 2: Clinical and epidemiological differences among hepatitis A, B, C, D, and E

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Delta Hepatitis</th>
<th>Hepatitis C</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- faecal-oral</td>
<td>mainly</td>
<td>never</td>
<td>possible</td>
<td>never</td>
<td>mainly</td>
</tr>
<tr>
<td>- parenteral</td>
<td>rare</td>
<td>yes</td>
<td>yes*</td>
<td>yes**</td>
<td>unknown</td>
</tr>
<tr>
<td>- sexual intercourse</td>
<td>no</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- other</td>
<td>food or water</td>
<td>perinatal</td>
<td></td>
<td></td>
<td>food or water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bedbugs?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cutaneous</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>ulcerations?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incubation period</td>
<td>14-45 days</td>
<td>30-120 days</td>
<td>21-90 days</td>
<td>1-5 months</td>
<td>3-6 weeks</td>
</tr>
<tr>
<td></td>
<td>(mean: 7-8wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial phase</td>
<td>usually acute</td>
<td>usually</td>
<td>usually acute</td>
<td>insidious,</td>
<td>usually acute</td>
</tr>
<tr>
<td></td>
<td></td>
<td>insidious</td>
<td></td>
<td>often no</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>or aspecific</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>20%</td>
<td>30%</td>
<td>variable</td>
<td>symptoms</td>
<td>unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Sequelae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- carriers</td>
<td>no</td>
<td>5-10%</td>
<td>yes</td>
<td>about 50%</td>
<td>unknown</td>
</tr>
<tr>
<td>- chronic hepatitis</td>
<td>very rare</td>
<td>major cause</td>
<td>occasionally</td>
<td>major cause</td>
<td>no reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of chronic</td>
<td></td>
<td>of chronic</td>
<td>cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>viral hepatitis</td>
<td></td>
<td>viral hepatitis</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0.1-0.2%</td>
<td>0.5-2.0%</td>
<td>up to 30% in</td>
<td>1-2%</td>
<td>up to 40% in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chronic patients</td>
<td></td>
<td>some pregnant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>women;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2% for the</td>
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<td></td>
<td></td>
<td></td>
<td>population at</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>large</td>
</tr>
</tbody>
</table>

* less infectious through sexual contact than hepatitis B
** not impossible, but very low transmission rate

c) Hepatitis in neonates must be differentiated from cord infections and maternal-foetal blood incompatibility.
d) The parasitic diseases that must be taken into consideration include *P. falciparum* malaria, blackwater fever, hepatic amoebiasis, distomatosis, hepatic cysts, and mechanical obstruction of the biliary system by roundworms.
e) In addition, this point is especially important in some parts of Central Africa, one must never overlook the possibility of toxic hepatitis. Local remedies administered for a wide range of complaints can in many cases be toxic for liver cells and lead to true

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1.9. Differential diagnosis of the various kinds of hepatitis

Differential diagnosis of the various kinds of hepatitis includes the identification of other responsible agents.

- a) The other forms of *viral* hepatitis include yellow fever, Rift Valley fever, Zika fever, infectious mononucleosis, cytomegalovirus and herpes virus infections, to mention only a few of them.

- b) The *bacterial infections* that must be differentiated from viral hepatitis include leptospirosis, relapsing fevers, Q fever, bacterial septicaemia, salmonellosis, pneumonia, and pneumococcal infections.
toxic hepatitis. Experience has shown that most of the patients hospitalized for various complaints have previously been given local remedies that often add a toxic effect to the original underlying cause of the disorder.

It is often difficult to recognize the cause of the histopathological findings because a large number of pathogens and deficiencies can affect the liver. Abnormalities of the mesenchyme, the reticuloendothelial system and the portal system with its connective tissue can be caused by malaria, leishmaniasis, and helminths, with particular attention given to granulomas caused by schistosomiasis. The hepatocytes are also the target of many viruses causing acute and subacute necrosis. Malnutrition and haemodilution can produce major lesions. Finally, compression of the biliary tract and of the bile duct must also be invoked.

1.10. Treatment

In the absence of specific therapy one is confined to give symptomatic treatment. It is not necessary to impose extended bed rest, and hospitalization is rarely required. The diet should be high in calories and protein, but it is not vital to limit the consumption of fat. The fulminating forms demand to restore the electrolyte and acid-base balance in order to correct renal failure and also to deal with coagulation disorders.

If the encephalopathy reaches a comatose stage and if the factor V level is less than 20% of the normal level, an emergency liver transplantation can reduce the case fatality rate from 75 to 25%.

Prolonged administration of alpha-interferon to patients with chronic disease can often lower the transaminases and allow histological improvement. However, relapses are frequent. Other antiviral drugs are being tested.

1.11. Prevention

Prevention strategies depend on the route of contamination.

1.11.1. Hepatitis A

Since the main route of transmission of hepatitis A is the faecal-oral route, the most effective preventive measures are those that prevent the contamination of food and water and all other indirect contacts with faecal material from infected individuals.

A person infected with hepatitis A is most contagious in the period preceding the onset of clinical symptoms. Therefore it is essential to improve hygiene and sanitation to control hepatitis A's transmission. Strict isolation of patients is not necessary, but they should wash their hands carefully after passing stools. Health staff in contact with contaminated objects as bedpans, etc., must be careful to wash their hands thoroughly after touching such objects. Disinfecting the stools is not required if there is a good latrine system. As a rule, a person with hepatitis is considered to be infectious up to two weeks after the jaundice appeared.

Hepatitis A must be as a rule reported to health authorities. Experience has shown that many doctors and health workers fail to report cases of hepatitis, even in those countries where reporting is mandatory. Reporting is particularly unsatisfactory in Central Africa, where the overall organization of health care calls for the creation of epidemiological services. Indeed, surveillance is the key to success. As soon as a small epidemic breaks out it must also be drawn to the attention of the Public Health authorities so that a survey may be conducted to find and eliminate the source of contamination.

a. Passive immunity

By administering human immunoglobulins it is possible to prevent the development of clinical hepatitis after exposure to a source of contamination.

The length of the protection conferred by the immunoglobulins depends on the dose: a 0.06 ml/kg dose will provide an immunity for about 6 months. The recommended prophylactic dose after exposure to a source of contamination should be 0.01 to 0.02 ml/kg. It is very important to give immunoglobulins as soon as possible after contamination. Immunoglobulins injected two weeks after exposure provide practically no protection. The passive immunity conferred does not however, impair the development of an inapparent infection which would result in long-lasting immunity. Passive immunization is advised for people who have been in contact with patients with hepatitis A and also for travellers to areas with high risk of hepatitis A infection.

b. Active immunity

An inactivated vaccine against hepatitis A is currently available. It confers protective immunity for 99% of the individuals, four weeks after the first vaccination of a series of two injections one month apart. A booster is recommended 6 months or at most 12 months after the primary vaccination. This vaccine is recommended for all individuals who run the risk of contamination at work or during travels and lengthy stays in endemic countries.

1.11.2. Hepatitis E

For hepatitis E, the preventive measures are the same as for hepatitis A, as both infections are transmitted by the faecal-oral chain. Advances in molecular biology should ultimately lead to the development of a vaccine.
1.11.3. Hepatitis B

a. Prevention

People who come in contact with blood, as nurses, laboratory technicians, kidney dialysis attendants and dentists must be protected. The same hand washing rules must be observed for this formerly called serum hepatitis, as for hepatitis A.

The possibility of sexual transmission of hepatitis B calls for special attention. It should be underscored that sexual transmission has not reached the same proportions in rural Central Africa as in industrialized countries, where male homosexual practices involve large numbers of partners, high frequency and vehemence of sexual relations.

Precautions must be taken to prevent parenteral, sexual, and mother-to-child transmission.

b. Immunization

- Immunization by vaccination

Vaccination against hepatitis B makes it possible to avoid more than ten million new infections each year and more than two million deaths per year. Until recently, the only vaccine available contained inactivated HBsAg extracted from the plasma of chronic carriers. Today vaccines produced by genetic engineering are also available. Once the HBV genome was decoded it became possible to express the surface antigen (HBsAg) in micro-organisms.

The recommended vaccination schedule is three injections at one-month intervals, followed by a booster one year after the last dose.

It is recommended that children living in developing countries be vaccinated at birth, as this gives 90% protection. In developing countries with high levels of endemic hepatitis B it appears justified to vaccinate all neonates. Unfortunately, this is impossible for budgetary reasons, because an estimated 120 million doses would be needed each year to achieve this goal.

Vaccination is recommended for people exposed to hepatitis B infection, such as haemodialysis patients, medical and paramedical staff, kidney transplant patients, drug addicts, children in centres for the handicapped, homosexuals, and heterosexuals having many partners.

- Passive immunization

Passive immunization by hyperimmune serum from individuals with high anti-HBs antibody levels is advised at the same time as vaccination, for non-immune people who are exposed, for example, to hepatitis B after an injection with a contaminated needle or in children born to HBsAg-positive mothers. The immunoglobulins must be given within 48 hours after exposure. The recommended dose is 0.07 ml/kg.

High doses of anti-HBsAg immunoglobulins to neonates whose mothers are HBsAg-positive, lowers the risk of infection by 70-80%. When immunoglobulins are injected at the same time as the first dose of vaccine, the rate of protection may reach 94%.

Recipient of HBsAg-positive blood and the staff who handle it are at definite risk. By law all blood donations must be screened for HBsAg; carriers of the antigen cannot be accepted as blood donors.

1.11.4. Hepatitis C

Effective prevention of hepatitis C by using immunoglobulins is not clearly established. However, an injection of 0.06 ml of human immune globulin per kg/body weight could be offered if an individual is pricked accidentally by a needle that has been contaminated by the blood of a Non-A, Non-BHV-carrier.

The prevention of post-transfusion Non-A, Non-B hepatitis has already greatly benefited from the measures that have been taken over the past few years. Indeed studies have shown a correlation between the development of Non-A, Non-B hepatitis in blood recipients and the fact that anti-HBc antibodies and/or elevated transaminases are present in the blood donor. These two tests to screen blood donors eliminate more than 20% of those who carry anti-HCV antibodies.

Systematic screening for anti-HCV antibody will prevent most of the post-transfusion Non-A, Non-B hepatitis cases. Still, some cases of post-transfusion hepatitis arise after blood transfusion from donors who are not anti-HCV antibody carriers. This might point to a gap in our serological knowledge, or to the involvement of another virus.

2. Cirrhosis

Cirrhosis of the liver is an ultimate, irreversible stage of most chronic liver diseases.

The two major causes are viral hepatitis and alcohol abuse. The former is prevailing in Africa, the latter is the predominant cause in Europe. The other causes are haemochromatosis, primary biliary cirrhosis, and autoimmune cirrhosis; they are rather rare in Africa.

In addition, cirrhosis can be considered a pre-neoplastic state. The risk for a cirrhotic patient to develop a hepato-cellular carcinoma is 20-40%, regardless of the aetiology (J.P. Etienne, 1986) and is higher for men than for women.

In most cases cirrhosis develops after hepatocytic necrosis together with the disappearance of the supporting reticular network. Collagen deposits seem to be the earliest signs of the process. These deposits lead to intensive and extensive fibrosis distorting the
vascular bed. At the same time regenerative nodules appear. These are clumps of hepatocytes that have lost their normal vascular and biliary connections so that they are no longer organized in regular lines upsetting the liver's normal architecture. When these regenerative nodules appear they are the key to the diagnosis of cirrhosis, differentiating clearly this condition from liver fibrosis, for which it is often mistaken.

2.1. Classification

- On macroscopic examination: the liver has a nodular appearance, sometimes normal in size, sometimes shrunken (atrophic cirrhosis), or sometimes enlarged (hypertrophic cirrhosis). Areas of atrophy may alternate with areas of hypertrophy (atrophic-hypertrophic cirrhosis).

- By histopathology: tissue sections show that the normal liver architecture has been replaced by nodules of regenerating hepatocytes which are no longer orderly arranged. Depending on whether the nodules are smaller or larger than 3 mm the cirrhosis is called macro- or micro-nodular. These nodules are separated by fibrous septa which are either narrow and regular, suggesting a uniform, simultaneous process, or have a variable density (up to several centimeters in width).

Laënnec tried to classify cirrhosis on morphological grounds, (according to the size of the nodules and the extent of fibrosis), into micro- or macro-nodular, mixed and multilobular cirrhosis. Unfortunately, this classification was purely descriptive. Although in the past, each of these forms did evoke a specific aetiology, it was subsequently found that the same morphological type could cover a wide range of aetiologies, just as a given aetiology could lead to different morphological types. Moreover, it is not rare to see in the same patient the transition from one form to another during the progression of the disease, especially in the case of alcoholic cirrhosis.

In the tropics most cirrhoses are macronodular. Some histological abnormalities are characteristic for certain defined types of cirrhosis (Dive, 1993): steatosis and signs of alcoholic hepatitis in alcoholic cirrhosis; haemosiderin overload for haemochromatosis; abundant mononuclear inflammatory infiltration for postviral cirrhosis; and cholestasis with diminished numbers of small bile ducts for primary biliary cirrhosis.

2.2. Geographical distribution

Cirrhosis of the liver is distributed worldwide. As in Europe, the prevalence of cirrhosis in tropical Africa varies with the region. In Ghana, at the Korle Bu Teaching Hospital, 10% of the inpatients had cirrhosis.

The number of cirrhosis cases in Ghana was estimated at 4.5 per 100,000 population, in the island of Mauritius at 7.0 for men and 2.3 for women, or 4.7 per 100,000 population. The estimated rates in Egypt were 1.1 for men, 0.8 for women and 0.9 for 100,000 of the overall population, compared with respectively 11.1, 6.7 and 8.9 per 100,000 in Belgium and 36.7, 17.2 and 26.7 per 100,000 in France.

Most of the published data are based on postmortem examinations or liver biopsies: in Uganda 9.3% of histological findings in men and 3.3% in women showed signs of cirrhosis. In Egypt the number was 9.5%; in Mozambique 9.1% in men and 8.3% in women; in Zambia and Malawi the number was 9.6%, in Kenya 0.7%.

At the Butare Teaching Hospital, Rwanda, Nseniyumwa (1982) hospitalized 501 individuals over a two-year period for liver diseases, 67% of which proved to be cirrhoses. On 114 deaths due to liver disorders, he found cirrhosis to be involved in 64 (56%) of the cases.

During the fifties, in Zaire, on a series of 200 liver biopsies performed at the Kenge Hospital, in the Kwango district (Hugon, 1956), 14 cases of cirrhosis were diagnosed.

Janssens during the years 1937-1949 detected 23 cases of cirrhosis among 900 post-mortem examinations of deceased workers of the mines of Kilo in Upper Zaire; the prevalences were 3.4% for men and 1.6% for women; a series of 846 biopsies of children over the age of one revealed infantile cirrhosis in one little girl (Janssens, 1953).

Fifty-five (58.5%) of 94 cases of cirrhosis studied in Stanleyville (Kisangani) belonged to the postnecrotic variety and 36 (38.2%) to the portal variety in which the lobule is dismembered by fibrous bands connecting the portal spaces to the central lobular veins. In Europe this variety is more frequent in alcoholics, but cannot be opposed to the postnecrotic variety, as all cirrhoses progress towards necrosis.

2.3. Clinical manifestations

Cirrhosis of the liver results in the same structural and functional alterations regardless of the aetiology, as well in tropical Africa as in the Western world.

a) The main structural consequence of fibrosis is portal hypertension. Indeed, fibrosis causes many alterations in the vascular bed. Blood encounters increased resistance and is unable to flow at low pressure via the normal route, from the portal vein through the sinusoids and central veins to the suprahepatic veins. This leads
to portal hypertension, congestive splenomegaly and porta-caval venous anastomoses. These anastomoses are located in the rectum, the abdomen and, above all, in the gastro-oesophageal region, where they produce varices. These varices are a main cause of death, as when they burst, they cause digestive haemorrhages.

This portal hypertension also contributes to the development of ascites and oedema of the lower limbs.

Regenerative nodules are produced at the expense of normal parenchyma.

b) Cell necrosis involves gradual diminution of functional hepatocytes, leading necessarily to hepatocellular failure and numerous metabolic disorders. Protein metabolism disturbances will give rise to changes in plasma protein and clotting factors. Hypoalbuminaemia and the resulting drop in oncotic pressure, combined with the portal hypertension, will disturb the body’s fluid and electrolyte balance and contribute to ascites and oedema of the lower limbs. The diminished clotting factors are causing gastrointestinal haemorrhages. Metabolic disorders in the hepatocytes themselves lead to an accumulation of toxic end products such as ammonia and to disorders of a bilirubin breakdown with impaired bile excretion. Jaundice, poor uptake of liposoluble vitamins and hepatic encephalopathy are the main clinical expressions of these disorders.

The course of the disease can be roughly described in the following three clinical phases:

1) the first and usually longest phase is asymptomatic;
2) the second one is marked by asthenia and a change in the subject’s general condition; unfortunately, often the first consultation is sought at this stage, when a fine-needle biopsy (to be performed only in the absence of haemorrhagic disorders) may already show an established cirrhosis;
3) in the third phase appear complications of hepatic failure, portal hypertension, neoplastic degeneration (liver carcinoma) and infectious complications; peritonitis or septicaemia by common bacteria and tuberculosis occur particularly frequently in tropical Africa.

The length and progress of each of these phases depends on the activity of the disease process. Some cirrhoses are inactive and relatively stable, whereas others are active and progress rapidly.

2.4. Aetiology

The major aetiologies of cirrhosis found in the Western World are also encountered in Africa, with geographic variants and with large differences in prevalence.

Historically, in tropical Africa, in the search for an aetioloical link between chronic hepatitis and cirrhosis, malaria and parasitic infections were first taken into account. Attention for nutritional problems inevitably led to consider the possible connections between cirrhosis and nutrient deficiency. Advances in the diagnosis of the different viral hepatitis and the study of immunopathological mechanisms have now completely changed the views on the aetiologies of cirrhosis.

Liver carcinoma is estimated to complicate 40% of the postviral cirrhosis cases, 20-25% of the alcoholic cirrhosis cases, and more than 35% of haemochromatosis cases.

The infectious, parasitic, nutritional and toxic factors specific to tropical Africa probably play a significant role in the onset, the clinical symptoms and the course of cirrhosis.

2.4.1. Postviral cirrhosis

The correlation between viral hepatitis and cirrhosis is based on well-documented observations. The massive necrosis of the liver and repeated inflammatory attacks due to viral hepatitis are a favourable ground for the development of macronodular cirrhosis, formerly called postnecrotic cirrhosis. This is the most frequent type of cirrhosis in tropical Africa. Despite the liver's great regenerative abilities, it seldom restores itself fully, for the repair occurs around residual islets of cells, giving rise to irregular nodules of functional tissue. The connective tissue, squeezed by the necrotic patches, becomes the support for extensive fibrosis during the remission period and allows the more or less rapid development of postnecrotic cirrhosis. Active forms of cirrhosis may lead to serious complications, particularly jaundice and hepatic coma.

Although viral hepatitis has rightly been incriminated in the genesis of most of the postnecrotic cirrhosis, one must bear in mind that it is not the only aetiology in Central Africa. Many other factors such as aggressive chronic autoimmune hepatitis, toxic hepatitis, various types of medication, aflatoxins, a.o., can lead to the same consequences.

a. History

In an important thesis on the aetiology of serious jaundice in Africans, Bablet (1942) established the high frequency of viral hepatitis compared with other jaundice-causing diseases particularly yellow fever and leptospirosis. He also mentioned numerous cases of liver disease that matched the description of acute or chronic hepatitis and noted that some of the jaundice cases progressed gradually to cirrhosis.

A few years later, the personal observations of Bergeret and Roulet (1947) and their review of Bablet's cases, showed that not only the jaundice epidemics in
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French Equatorial Africa and the Belgian Congo were due to viral hepatitis, but that many cases of acute hepatitis also progressed slowly to cirrhosis. They suggested that the rearrangement of hepatic parenchyma after necrosis was generating cirrhosis, especially macronodular cirrhosis. Cases of chronic hepatitis progressing gradually to active cirrhosis were also described. They found that many macronodular cirrhoses were merely the terminal stages of progressive acute or chronic hepatitis, but held nutritional factors to be the most likely causal agents.

The discovery and isolation of an epidemic hepatitis virus by Pelissier and Lumaret in Ubangi in 1949 enabled Beheyt (1953) to attempt to determine the contributions of epidemic hepatitis and blood-borne hepatitis to the genesis of jaundice. Beheyt noticed the persistence of hepatic lesions and the eventual development of cirrhosis in patients who had apparently recovered from a viral hepatitis. He suggested the presumed role of an hepatitis virus in the pathogenesis of both cirrhosis and malignant hepatoma.

Studies carried out concurrently in Uganda, South Africa and the Dutch East Indies suggested that malnutrition was a major aetiological factor for the development of cirrhosis.

Blumberg's 1961 discovery of the Australia antigen was a decisive step forward for identifying the hepatitis viruses and to make epidemiological research feasible by using objective criteria. This triggered a large number of studies all over Africa, which all revealed a much higher prevalence of the HBs antigen and hepatitis B virus infections among African populations compared with temperate country populations. The early age at which African children are infected and the routes of transmission of the various hepatitis viruses, including injections and blood transfusions, were determined; even the hypothesis of mechanical transmission via blood-sucking arthropods was put forward. Rizzetto's discovery of hepatitis D virus in 1977 and Choo's discovery of hepatitis C virus in 1989 have since added to this wealth of information.

b. Biological and histological developments

Cirrhosis may develop after chronic hepatitis due to the hepatitis B, B+D and C viruses. Chronic hepatitis is defined biologically by the persistence of elevated amino-transferases (previously called transaminases) more than six months after acute viral hepatitis.

Elevated amino-transferases reflect the activity of the disease. In the absence of cirrhosis, the elevation of alanine amino-transferase ALT (formerly SGPT) is more marked than that of aspartate amino-transferase AST (formerly SGOT); the ratio is inverted if cirrhosis is present. Values that return to normal usually correspond to the absence of cirrhotic activity. However, the correlation between hepatic tissue activity and amino-transferase levels is not perfect. Liver biopsies are necessary if one is to consider alpha interferon therapy, which unfortunately is still very expensive. The earlier the diagnosis of cirrhosis is made, the greater the likelihood that the treatment will be active. A liver biopsy may show necrotic hepatocytes, inflammatory infiltration composed of mononucleate cells, and the existence of fibrosis, which is a sign of evolution towards cirrhosis.

Cirrhosis remains for a long time asymptomatic, except for major asthenia. Fairly inactive cirrhosis can be reactivated. This reactivation is characterized by the resumption of viral replication and by histological changes which go along with elevated amino-transferases. It can lead to liver cell failure which may be fatal. Finally, cirrhosis is leading to the development of liver cancer (carcinomas) in 40% of the patients.

c. Different types of post viral cirrhosis and their evolution

1) Hepatitis B virus cirrhosis

The number of such cases is thought to be about 60 million worldwide; this is higher than the number of alcoholic cirrhoses. According to recent studies, 46% of cirrhotic patients in Mali are HBsAg carriers, compared with 5% in the control group, (M. Gentilini, 1993). In Kenya, 27% of the cirrhotic patients carry HBsAg.

Cirrhosis, which follows active HBV chronic hepatitis, usually progresses in two phases:

a) The first phase is one of intense viral replication (DNA and DNA-polymerase are found in great quantities in the serum) and low biological activity (amino-transferases only slightly elevated) with little histological changes (liver biopsies demonstrate only weakly active chronic or persistent hepatitis). This dissociation is due to a weak immune response and a kind of tolerance of the cells infected by hepatitis B virus (HBV).

b) The second phase, which develops a few years later, is characterized by a stronger immune response, an increased hepatitis activity and a decline in viral replication. Amino-transferases are only slightly elevated, DNA is present in the serum in small amounts, but the tissue lesions (necrosis and inflammation) are important. At this stage fibrosis and, at worst, cirrhosis set in. Several episodes of exacerbation of chronic hepatitis occur before the hepatic cells in which the virus was replicating are eliminated. The hepatitis is then no longer active, but the colonized liver cells are eliminated by immune response, and cirrhosis develops. At this stage there is also an increased risk for the development of hepatic cell cancer.
2) Hepatitis D Virus cirrhosis

An HDV infection should be suspected in a chronic hepatitis patient who is positive for HBsAg. The diagnosis will depend on the presence of anti-D antibody in the serum. Infection with HDV usually inhibits the replication of HBV. Chronic HDV hepatitis is particularly severe and can quickly lead to cirrhosis. The risk of the development of carcinoma seems to be close to that for HBV cirrhosis.

3) Hepatitis C Virus cirrhosis

HCV virus is the most frequent cause of chronic viral hepatitis, and is the major cause of cirrhosis. An estimated 50% of acute HCV hepatitis becomes chronic and 20% of the latter turn into cirrhosis. The progress toward chronicity cannot be monitored by the usual seroretests, such as ELISA and even the second-generation RIBA (Recombinant Immunoblot Assay) which detect anti-HCV antibodies, because they cannot distinguish antibodies associated with persistent infection from antibodies produced by earlier exposure to the virus. In contrast, the Polymerase Chain Reaction (PCR) can detect HCV RNA in the serum. An increasing number of studies shows a strong association between the presence of anti-HCV and HCV RNA in serum or in the hepatocytes of patients with chronic hepatitis.

Anti-HCV is present in 90% of the chronic hepatitis cases previously called non-A, non-B, or transfusion, or cryptogenic hepatitis. These forms of chronic hepatitis are often asymptomatic and are only apparent by elevated amino-transferases (transaminases): therefore they are frequently not discovered until the stage of established cirrhosis has been reached. Unlike what happens in hepatitis B, the lesions seem to be due to the virus cytopathogenic action rather than to an immunological process. The risk of liver cancer is still poorly known, but is thought to be close to that for HBV.

The prevalence of HCV-induced cirrhosis is very high. In Spain Esteban (1989) found an anti-HCV antibody in 62% of transfusion patients with chronic hepatitis or cirrhosis whilst Bruix found an anti-HCV antibody in 77% of the cryptogenic cirrhoses and in 38% of the alcoholic cirrhoses cases he studied. In Italy Colombo (1989) found that 74% of patients with chronic hepatitis or cirrhosis were anti-HCV carriers whilst Caparasco (1991) found anti-HCV antibodies in 55% of cirrhotic patients, all aetiologies combined.

Turning to Africa, Coursaget (1990) found anti-HCV antibody in 51% of cirrhotic patients in Senegal.

4) HBV-HCV association

Markers for these two viruses are often found concurrently in cirrhosis. Bruix (1989) found anti-HCV in 25% of HBsAg carriers. Colombo (1989) reported that 19% of his patients with chronic non-A, non-B hepatitis were anti-HBc and anti-HCV carriers. Coursaget observed, pending confirmation by other tests, that 66% of the anti-HCV-positive cirrhotic patients in Senegal carry HBsAg.

5) Connection between cirrhosis and liver carcinoma

The connections are studied in the chapter Malignancies (p. 960). It should be reminded that recognized clinical or histological cirrhosis is preceding 90% of hepatic carcinoma (Bruix, 1989; Colombo, 1989; Etienne, 1986). Cirrhosis seems to be a vital contributing factor to cancer development.

The roles of HBV and HCV in this process are primordial:

a) HBV's DNA is incorporated in the genome of the tumoral hepatocytes of practically all liver carcinomas that are associated, even in the absence of serum markers of HBV, with either alcoholic cirrhosis (Břechot, 1992), or cirrhosis of another aetiology, such as primary biliary cirrhosis or haemochromatosis. Such viral sequences are only rarely found in carcinomas that develop on non-cirrhotic livers.

Hepatitis B virus might take place by various distinct but non-exclusive mechanisms which are probably to be found in the same patient. Hepatitis B virus is believed to induce the development of cirrhosis, as a pre-tumoral stage, but it may also play a direct role in the carcinogenic cell transformation (Břechot, 1992). Promoting factors such as hormones (given the strong male predominance) and perhaps alcohol, or chemical carcinogens such as aflatoxin B1 might also play a role.

b) It now appears proven that HCV, unlike HBV, is not incorporated in the hepatocyte's DNA. It induces active chronic hepatitis, then cirrhosis. However no direct carcinogenic role has been elucidated so far.

Nevertheless, 76% of patients having an alcoholic cirrhosis with hepatocarcinoma and 81.4% of patients having a cryptogenic cirrhosis with hepatocarcinoma are anti-HCV carriers (Bruix, 1989). The carrier rate is 75% for all the patients with liver carcinoma, either with or without cirrhosis. Coursaget (1990) found anti-HCV antibodies in 37% of liver cancer patients in Senegal. In South Africa and Mozambique 10% to 30% of liver cancer patients have been identified as anti-HCV positive.

Finally, it is not uncommon to find both anti-HCV antibody and hepatitis B markers simultaneously in the blood of patients with carcinoma of the liver. Fifty percent of the anti-HCV carriers in Bruix's study and 43.8% in Coursaget's study were HBsAg carriers. HBV and HCV may act as co-factors in the development of carcinoma of the liver.
2.4.2. Alcoholic cirrhosis

The role of alcohol in the pathogenesis of liver cirrhosis in inter-tropical Africa has long been underestimated. Several authors felt that sporadic drinking was unlikely to lead to cirrhosis. But, African populations – at least those who have remained outside the Islamic influence – often tend to be heavy consumers of a variety of alcoholic beverages.

The breakdown of alcohol yields an abundance of hepatotoxic metabolites such as acetaldehyde that affect the mitochondria and smooth endoplasmic reticulum in particular. In the beginning, modified oxydoreduction reactions lead to the accumulation of triglycerides, both ingested and synthesized from alcohol in the hepatocytes.

Such fat deposit or steatosis is observed following acute or chronic alcohol abuse, regardless of the subject’s nutritional status. It can be reversed totally when drinking is stopped.

Continued heavy drinking leads to much more severe lesions. The mitochondria swell and merge, the smooth endoplasmic reticulum dilates, Mallory hyalin bodies (as filaments or fibrils) appear and metabolic dysfunctions become obvious. The drop in lipoproteins enhances further the storage of intracellular fat deposits while diffuse cell necrosis soon develop. A granulocytic reaction around the degenerated or necrotic hepatocytes becomes the start of lipogranulomas. This reaction is the basis of the process leading to alcoholic hepatitis. As yet unelucidated factors stimulate a fibrogenesis starting from the lipogranulomas and the central veins: this fibrosis tends to disrupt the lobule into numerous small, dense nodules. This is the classical micronodular liver cirrhosis. Continued alcohol intake entails further inflammation, gradually increasing the nodules’ volume, leading eventually to macronodular cirrhosis.

In alcoholic cirrhosis, cutting out all alcohol before the onset of complications, regardless of the stage of the disease, will ensure a ten year survival of 60% of the patients. Only 30% will survive if drinking continues.

It seems that alcohol was well known in Africa before the Europeans arrived (Sankalé, 1974). Africans were drinking local beers or wines during feasts, although Islam served for a long time as an impediment for spreading their use. The slave trade, slavery and colonization (which led to the importation of often poor-quality spirits), followed by urbanization, changed the behaviour of the populations. Muslims began to increasingly neglect the Koran’s prohibitions, especially in towns. The alcohol-drinking habit shifted from a sporadic group practice to individual consumption.

There are two types of home brews in Africa:

a) First come the fermented drinks obtained by processing vegetable products. Grain malting yields beers with on average 4% alcohol by volume. Sorghum is the most widely used cereal, either alone or with eleusine, maize (corn), wheat, but also yams. Beers are also brewed from ripe banana juice. The number of local breweries is rising steadily. These beverages do not contain any methanol. Other common fermented beverages include the fermented juice of guavas, sugar cane, and coconuts and palm wine.

b) The distilled alcoholic beverages are obtained by distilling fermented liquids, such as alcohol obtained from rice, millet, maize (corn), yams, bananas, and palm juice. They have high alcohol contents (45 to 60% by volume) and may contain traces of methanol and other much more toxic alcohols than ethanol.

Large amounts of local cereal crops, which are already insufficient to meet local needs, are being diverted towards the many industrial breweries set up in the countries in addition to home brewing. It has been calculated that some tribes used 20% of their millet harvests for beer production and drank 13 to 15 litres of pure alcohol per capita per year, which is equivalent to the statistics for France.

The importance of imported alcoholic beverages is rising steadily; they include mostly wines, liqueurs, whisky and gin. A number of Third World countries are alarmed about this drastic increase in drinking in the past few years.

However, the impact of drinking on the health of the people is still difficult to assess by lack of systematic epidemiological studies.

In Dakar, where 90% of the population is Muslim, alcohol-related hospital admissions accounted for only 7.7% of the admissions in psychiatry, less than 1% in internal medicine and in only 5.5% of cirrhoses (Sankalé et al., 1974).

With recent advances in knowledge on hepatitis viruses, alcoholic cirrhosis does no longer appear to be a clinical entity due to a single cause, alcohol abuse, but also HCV, see p. 946.

2.4.3. Nutritional cirrhosis

For many years, the multiple dietary deficiencies, to which the African was submitted from childhood, were considered to play an important role in the development of cirrhosis. This opinion was backed by the findings of many animal experiments. Rats fed with imbalanced diets similar to those of the native populations developed cirrhosis identical in all respects to that seen in man. However, the same experiments conducted on primates did not reproduce the same effects.
Furthermore, children suffering from Protein-Energy Malnutrition (PEM) for more than 10 years have been shown to develop neither fibrosis nor cirrhosis, but rather a completely reversible steatosis. The nutritional explanation has hereby gradually lost most of its supporters although nutritional factors might facilitate the progression of viral infections towards cirrhosis. It is very likely that cirrhoses that were formerly labelled as being nutritional would currently be reclassified as viral, alcoholic, or mixed.

2.4.4. Primary biliary cirrhosis

It is the final stage of inflammation of the interlobular small bile ducts. It is complicated by extensive fibrosis around the portal area followed by the late development of regenerative nodules. The autoimmune mechanisms responsible for this disease are not fully understood.

In some other cases biliary cirrhosis develops when biliary retention occurs either by cholelithiasis, tumours of the head of the pancreas, or by other similar conditions. As diseases of the biliary tract are rather rare in Africa, the number of cases of biliary cirrhosis reported to date is extremely low.

2.4.5. Other aetiology

- The relationship between aflatoxins and hepatocarcinoma is studied in the chapter Malignancies (see p. 961). Recent investigations (Bréchot, 1992) have shown that this relationship could trigger a pinpointed mutation in a gene with anti-oncogenic effect. This P53 mutation is frequently detected in liver carcinoma of areas exposed to aflatoxin consumption. However it is not known whether this mutation itself causes cirrhosis.

- Veno-occlusive disease, which is very frequent in many countries, especially in the West Indies, where it is the cause of 30% of cirrhoses, has only been described in South Africa. It has been associated with the consumption of herbal teas or grains containing pyrrolyzidine alkaloids.

- Congenital and infantile cirrhosis, as described in India, also seem to be rare in Africa or are specific to some regions. They are due to an inherited tryptophan metabolism disorder.

- Numerous cases of hepatic siderosis leading to cirrhosis have been described. In South Africa the incidence of such siderosis, which is high even at a very young age, has been correlated with the consumption of some high-iron alcoholic beverages or excessive iron absorption in the intestines.

- Cirrhosis secondary to autoimmune hepatitis have not yet been explored in Central Africa.

- The role of antitrypsin deficiency as a cause of cirrhosis in Africa must still be determined.

- Syphilis no longer presents the importance that was attributed to it at the beginning of the century.

- Finally, metabolic disorders are rarely mentioned in conjunction with cirrhosis. Wilson's disease and haemo-chromatosis seldom take a place in the genesis of cirrhosis in Africa.

There is no doubt that fibrosis has often been mistaken for cirrhosis. Hepatic fibroses with portal hypertension, ascites, oedema of the lower limbs, and oesophageal varies are common in tropical Africa. Most of the cases are idiopathic (see 3 next p.). Some may be caused by parasites. Schistosoma mansoni (see page 1651) heads the list of parasites causing fibrosis of the liver in Central Africa. It is endemic in this region and its range is expanding steadily, reflecting among other things, the implementation of irrigation projects and conditions of poor hygiene and sanitation. Fibrosis develops as follows: if adult worms are present in the mesenteric veins, some of their eggs will be drained to accumulate in the portal system. The delayed hypersensitivity reactions and the action of the antigen-antibody immune complexes will do the rest: they cause a fibrosing granulomatous reaction of varying severity, depending on the number of eggs present in the portal spaces, and the eventual formation of interlobular septa. This process gives the impression of multilobular cirrhosis. The hepatic lobules and central veins remain well preserved and there are no signs of hepatocellular failure. True cirrhosis due to Schistosoma mansoni is rare.

2.5. Treatment

2.5.1. Treatment of the complications

a) Haemorrhages of the oesophageal varices are life-threatening. After the estimation of the blood loss, small transfusions of fresh blood containing coagulation factors often succeed to stop the bleeding. If not, vasopressin may be administered intravenously (20 units in a 5% dextrose solution infused over 20 minutes), unless the patient has myocardial ischaemia. Vasopressin will control the bleeding 80% of the time, but bleeding may recur. In well-equipped centres one may use a Sengstaken-Blakemore triple-tube for tamponade. If the haemorrhages are not controlled by this device, endoscopic sclerosis may be considered. Surgical decompression by anastomoses of the portal system has been performed in an attempt to lower the portal pressure in such patients, but it does not improve the survival of the cirrhotic patients.
b) Massive ascites is another serious complication. It may lead to pleural effusion at the right side and worsen renal failure or varicose bleeding. Restriction of salt and the administration of diuretics is an effective approach, at least for a while. Furosemide (Lasix®) is administered in daily doses of 40 to 120 mg, either alone or with a spiroloactone (Aldactone®). Massive needle aspiration of the liquid would lower the patient’s protein reserves and would also upset the electrolyte balance.

c) Hepatic encephalopathy: The treatment consists in lowering the blood ammonia concentration of the patient. As much protein as possible must be eliminated from the diet and constipation must be avoided. Ammonia uptake can also be diminished by administering lactulose and oral neomycin (0.5 to 1 gm every six hours).

2.5.2. Treatment of the cause

a) Alcoholic cirrhosis: Stopping alcohol consumption completely has a beneficial effect, whatever the stage of the cirrhosis’s development. Even after the first ascitic decompensation the ten-year survival rate is 50% when alcohol consumption is stopped, whereas it is 10% if the patient continues to drink.

b) Postviral cirrhosis: Alpha interferon seems to be the most effective of all the antiviral drugs used to date, although its results appear to be inconstant. Postviral cirrhoses should decrease with the introduction of effective hepatitis vaccines. Good vaccines are available for hepatitis B, but are insufficiently used (see Immunizations p. 743, and Malignancies p. 961). A hepatitis B+D vaccine has recently been developed. Research on a hepatitis C vaccine is pursued actively.

2.5.3. Liver transplants

Liver transplantation because of cirrhosis following viral hepatitis is controversial because of the possibility of relapses of the infection in the transplanted liver. Liver transplants require lengthy immunosuppressive treatment, are very costly and need a very well equipped surgical centre that has access to a network of organ donors.

3. Non-cirrhotic hepatic fibrosis

Fibrosis is often found in liver biopsies and post-mortem examinations in Africa. It can be defined as a marked increase of connective tissue around the small portal veins. Collagens (type I and III) are of the same type as the collagens of the normal connective tissue of the portal canals. This fibrosis is not observed among Black Africans who do not live in Africa. Therefore it appears to be an acquired rather than a hereditary disease.

The degree of fibrosis is usually not high enough to interfere with the normal portal circulation. However, it can lead to portal hypertension, to ascites, oedema of the legs, and oesophageal varicose veins. Signs of hepatocellular failure are absent. Aside from cases linked to schistosomiasis (see p. 1651), the cause of this type of fibrosis is unknown.

4. Cholelithiasis

The main studies on cholelithiasis in Bantu tribes have been conducted in the Republic of South Africa. Beyers (1927) found gallstones in only 4 out of the 18,000 people examined. Brebner (1934) set the prevalence at 0.7 per 1,000, versus 6 per 1,000 in whites. Lopes reviewed all of the post-mortem reports of Johannesburg’s General Hospital for 1936-1942 and found gallstones in 1.5% of the autopsied black males (17:1,099) and 5.7% of the black females (33:578). The rates for whites were 9.3% (111:1,182) and 19.7% (135:684), respectively. Most of the stones found in Bantu subjects were pigment (bilirubin) stones (68.8% of those in men, 54.3% of those in women), as opposed to mixed stones in whites (52.1% and 56.1%, respectively). Twenty-five percent of the stones were cholesterol stones in both ethnic groups.

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HÉPATITIS, CIRRHOSIS AND BILIARY DISEASES


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EXAMENS B
