Progress in Medical Aspects of Liver Disease

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SUMMARY

Recent advances in the medical aspects of liver disease are reviewed, especially in the areas of viral hepatitis, chronic aggressive hepatitis and cirrhosis.


It is hardly possible to review adequately the many developments in liver disease in recent years and I intend to confine myself to a few specific areas which seem to be of particular importance.

VIRAL HEPATITIS

Good evidence for the viral aetiology of this disease is accumulating and we have also obtained a better understanding of 'infectious' hepatitis and 'serum' hepatitis. This is largely due to the work at the Willowbrook School where two infectious agents have been identified: the short incubation agent (30 - 38 days) MS-1 and the long incubation agent (41 - 108 days) MS-2. This important study not only clearly defines the two types of infective agents but also shows that they each have immunological identity, i.e. infection with one strain does not confer immunity to the other. It was also shown that hepatitis can be spread by contact, and that the MS-2 type, i.e. serum hepatitis, while usually transmitted through the skin with contaminated material on needles, etc., and although not highly infectious by contact, is communicable and infective by mouth. The existence of two types of orally transmissible hepatitis also explains why some patients get second attacks of hepatitis.

Linked with this important information has been the explosion of interest in the Australia antigen or better termed Hepatitis Associated Antigen (HAA).

In 1965, Blumberg and his colleagues were working in Philadelphia on the development of antibodies against human serum lipoproteins and found that there was a precipitin which reacted with an antigen in a single serum which came from an Australian Aborigine. A relationship was recognized between HAA and leukaemia, Down's syndrome, lepromatous leprosy and hepatitis. The last association proved to be the significant one. Reports on the incidence of HAA vary from 95% in post-transfusion hepatitis and 47% in infectious hepatitis to 13% or 0% respectively. The variable results are dependent upon differing techniques and methods of sampling. Early frequent blood samples give the highest number of positive results. It is of interest that in a subsequent Willowbrook study HAA was found only in patients with MS-2 infection.

Its relationship to chronic liver disease has also given conflicting results. Wright and his co-workers from Yale found the antigen persisting for months or years in 7 of 14 cases of unresolved hepatitis, 4 of 15 cases of subacute hepatic necrosis progressing to posthepatitic cirrhosis, and 6 of 24 cases of chronic active hepatitis. In London, Fox and his colleagues could not detect HAA in 32 patients with active chronic hepatitis. As new data become available similar striking differences are being found.

Hepatitis has developed in patients receiving HAA-positive blood but it is noteworthy that HAA-positive post-transfusion hepatitis has followed transfusion with HAA-negative blood. More recently the incidence of hepatitis after the administration of HAA-positive blood has been reported as 70%, while only 4 cases were seen in 69 patients who received HAA-negative blood.

There is still no direct evidence that HAA is an infectious agent. It seems unlikely that it represents the virus particles of hepatitis virus, but it is probably closely related to the causative agent.

Clinically there has been an increased awareness of the syndromes which may follow on viral hepatitis. It is common for patients to experience mild chronic ill-health for some months after an attack of viral hepatitis, and it is important to recognize that the great majority of these patients make a complete recovery. It is not uncommon for the serum globulin levels to remain elevated for some time, and for the patient to have a persistent mild unconjugated hyperbilirubinaemia. These have no adverse prognostic significance, and the latter may well represent mild increased haemolysis, or a temporary defect in bilirubin transport across the liver cell membrane. Indeed, Conrad has recently emphasized the occurrence of increased haemolysis in patients with viral hepatitis. Three of his patients had a persistent reticulocytosis and an elevated unconjugated bilirubin in the plasma for more than a year after recovery, while in 68 patients there was a significant decrease in the packed cell volume in the second or third week of the illness. He also noted an increase in circulating reticulocytes in these patients during the third and fourth week.

In recent years, a group of patients has been clearly recognized who have persistently or intermittently elevated serum transaminase levels after viral hepatitis. The term 'transaminitis' has been used and these abnormalities may persist for up to 3 years after the original illness. Becker et al. have studied 20 patients followed up for 2 - 14 years after viral hepatitis. Some of the patients had lost weight and a few had had mild recurrent abdominal pains. Eight had enlarged livers, but there was no other
evidence of chronic liver disease. During the first year of the illness, laboratory tests were of no value in differentiating these patients with persistent hepatitis ('transaminits') from those with chronic aggressive ('active') hepatitis. The transaminase levels were considerably elevated, but after the second year fluctuated at a lower level. Throughout the course alkaline phosphatase and bilirubin levels were not diagnostically helpful, being either normal or slightly elevated. Globulin levels during the first year were variable. HAA was negative in 14 sera tested.

The characteristic portal tract lymphocytic infiltration with preserved architecture and mild piecemeal necrosis were found histologically. Serial biopsies in 12 patients showed no evidence of progression to chronic aggressive hepatitis. At a follow-up examination on an average of 6 years from the onset, 16 of the 20 patients were well and without clinical evidence of liver disease, and in 3 patients transaminase levels were still mildly elevated. Ten patients received corticosteroids for either prolonged jaundice or persistently elevated transaminase levels. However, there was no difference in the course between the treated and untreated patients. Chronic persistent hepatitis is a relatively benign entity that must be distinguished from chronic aggressive hepatitis. Although there is no adequate long-term follow-up, present evidence suggests that the prognosis is good in persistent hepatitis. The liver biopsy is critical in distinguishing it from chronic aggressive hepatitis.

**CHRONIC AGGRESSIVE HEPATITIS**

Chronic aggressive hepatitis (active chronic hepatitis) is a well-recognized syndrome, the aetiology of which remains unknown. While there is evidence for an immunological, possibly autoimmune pathogenesis for this disease, there is no proof of what Popper has called 'autoagression'. Chronic aggressive hepatitis affects subjects of both sexes and of all ages but is characteristically seen in young women. There is intermittent jaundice, hepatosplenomegaly and eventual liver failure. Gamma-globulin levels tend to be very high and the transaminase levels are often elevated. Other systems are often involved, e.g. thyroiditis, ulcerative colitis, renal tubular acidosis, arthritis and arteritis may all occur. Smooth-muscle antibody is characteristically present in the plasma, but may be present in other forms of liver disease.

A great deal of interest in the role of the immune system in liver disease has been stimulated by the recognition of chronic aggressive hepatitis, and has led to studies of other circulating antibodies, notably antimitochondrial antibodies in primary biliary cirrhosis, anti serum immunoglobulins and delayed hypersensitivity in liver disease, and has resulted in immunosuppressive therapy being assessed in the treatment of chronic aggressive hepatitis in particular. Sherlock has recently published an excellent review of this important aspect of liver disease.

The detection of the LE cells in some patients with chronic aggressive hepatitis raised the possibility of an aetiological association with systemic lupus erythematosus. While this has not been established there is an increasing awareness of liver lesions in systemic lupus erythematosus.

**CIRRHOSIS**

There has been a better understanding of the aetiology of portal hypertension and of the greatly increased lymphatic flow and of the alteration of bile flow in cirrhosis. Jaundice in cirrhosis is usually cholestatic and in most cases there is no extrahepatic obstructive cause. It is probably due to a defect in the liver cells themselves as in cholestatic hepatitis. There is an alteration of organelles around the bile canaliculus which is dilated, while its microvilli are altered. This morphological picture is thought to be an expression of the interference with secretion of bile salts, which results in a disturbance of micelle formation with consequent defective formation of bile. It was previously believed that the changes in the cholangioles were secondary to the liver cell pathology. It is interesting that in the absence of jaundice, bile flow may be increased in cirrhosis presumably as a result of increased intrasinusoidal pressure.

Our understanding of the pathogenesis of cirrhosis has laid much greater emphasis on the role of the necrosis rather than on fatty change. Indeed, while there is little doubt that alcohol abuse leads to cirrhosis and almost always causes fatty change, there is no evidence that fatty change itself results in cirrhosis. Necrosis is the link to cirrhosis and Popper has described the different forms of necrosis which are its possible precursors: necrosis produced by known exogenous factors such as alcohol, anoxic necrosis, cholestatic necrosis and piecemeal necrosis. Necrosis is diagnosed histologically but the biochemical derangements must significantly precede the microscopical changes. There is no certainty as to where the process begins but the early conception of mitochondrial damage remains a possibility. Peroxidative changes may also be important either through involvement of phospholipids particularly in membranes or as a result of the formation of free radicals.

There have been advances in our understanding of collagen metabolism and of the pathogenesis of fibrosis. Formerly the consequences of collapse after parenchymal destruction received emphasis but it is now realized that new fibre formation plays a vital role. This represents a balance between stimulation of fibroblasts, maturation and deposition of fibres and catabolism of fibres, the whole process probably being stimulated by hepatocellular injury. Damage to liver cells as a result of fibrosis may in turn stimulate more fibrosis and may prove to be a more important mechanism in the development of cirrhosis than any immunological one.

A better understanding of the pathogenesis of the complications of cirrhosis has resulted in improvement in therapy of ascites and encephalopathy. Renal failure (hepatorenal syndrome) in cirrhosis has become one of the common causes of death. It is characterized by azotaemic oliguria and urine with a low sodium content and high osmolality. These kidneys may function normally if transplanted and the dysfunction does not seem to result from changes in systemic blood volume or cardiac...
output" but seems to be due to circulatory changes within the kidneys, possibly with vasoconstriction. The pathogenesis of this syndrome may not be the same in all patients and in some plasma expansion may be effective treatment.

**OTHER DEVELOPMENTS**

The demonstration that a number of pharmacological agents are capable of inducing microsomal enzymes is of great potential therapeutic importance. This knowledge has been used clinically to lower unconjugated hyperbilirubinaemia by giving phenobarbitone. More recently, dicophane has been used for the same reason in a boy aged 17 years. This compound has still to be proved to be safe from the toxic point of view and indeed convincing demonstration of the induction of glucuronyltransferase has not been achieved in the case of either drug. Of interest also has been the demonstration that ethanol can be metabolized by a microsomal oxidizing system, but the importance of this in ethanol metabolism remains to be established. Induction of enzymes may play a role in determining the toxicity of some compounds. Carbon tetrachloride is much less lethal in rats previously fed a low-protein diet and this effect is reversed by pretreating them with phenobarbitone or DDT.

This is because the toxicity of CCl₄ is dependent upon its being metabolized by the microsomal hydroxylation enzymes and a low-protein diet reduces the activity of the enzyme system to a third or less than normal in 4 days. These drug metabolizing enzymes are usually thought of as 'detoxicating' enzymes and indeed often do act in that way. It is clear that in some instances the reverse may occur.

Further studies by Arias and his colleagues on the two hepatic cytoplasmic protein fractions Y and Z have shown that it is very likely that these proteins are important in the uptake of bilirubin and bromsulphthalein by the liver cell. These substances are preferentially bound to the Y and Z proteins within the cell. The same workers have produced evidence to suggest that a lack of Y protein may play a role in Gilbert's syndrome and neonatal jaundice. These proteins may prove to be of fundamental importance in the transport of many substances across the liver cell membrane and within its cytoplasm.

Major advances made in bilirubin and bile salt metabolism have been reviewed recently.

The study of alpha-feto-protein has been very rewarding. In primary liver cell carcinoma it is present in 30% of Caucasians and in 60-70% of non-Caucasians.

Five patients with cirrhosis and primary hepateoma had HAA in the plasma and two of these had alpha-feto-protein in the plasma as well. It is possible that viral hepatitis is potentially precancerous as suggested by Steiner and others some time ago.

The treatment of acute liver failure by exchange transfusion, pig-liver perfusion and cross-circulation has been closely studied in a number of centres, particularly in Cape Town. While these procedures may improve the patient from the neurological standpoint there is no clear evidence that they prolong life. There is a better understanding of the many complications of fulminant hepatitis and a greater realization of the importance of liver cell regeneration in prognosis.

Liver disease has become the fourth or fifth most frequent cause of death in the USA and is very common in South Africa. Recent advances in liver disease have not, on the whole, led to more rational treatment—which is, indeed, conspicuously lacking. The identification and culture of the hepatitis virus and a clear understanding of the causes of cryptogenic cirrhosis and primary liver cancer remain three of the most important unanswered questions in this field.

**REFERENCES**