Immunological Liver Disease

ALAN E. READ, MD, FRCP, Professor of Medicine, University of Bristol

The past twenty years have seen the recognition of the fact that certain diseases of the liver represent the complete or partial effects of immunological damage to that organ. The considerable evidence supporting this thesis will not be reviewed here, as this article is concerned with the clinical features of these diseases, in particular the diagnostic difficulties and where they occur. Table 1 shows the major varieties of these types of liver disease, but they are not in

| Table 1. ‘Immunological’ liver disease |
|--------------------------------------|
| 1. Chronic active hepatitis          |
| 2. Primary biliary cirrhosis         |
| 3. Multiple endocrine syndrome       |
| 4. Drug-induced liver disease        |
| 5. Liver disease in collagen disease |
| 6. ? Cryptogenic cirrhosis           |

water-tight compartments and part of the confusion surrounding this aspect of liver disease centres on the existence of many mixed forms in what may be a continuous spectrum of chronic liver disease (Poulson and Christofferson, 1969).

CHRONIC ACTIVE HEPATITIS

The major features of chronic active hepatitis are well known (Waldenström, 1950; Read et al., 1963). The predilection for the young female and the evidence of multi-organ disease are also recognised, but it is worth remembering that the male and the elderly are not exempt and that, on occasions, the disease may present as a non-hepatic problem with a condition such as ulcerative colitis. There is also confusion with some cases of lupus erythematosus (SLE) in which liver function tests and, indeed, liver structure may be abnormal. The introduction of tests such as the smooth muscle antibody reaction (SMA) has been of help in distinguishing between the two diseases (Johnson et al., 1965), though liver biopsy is also extremely valuable.
Some of the less well-recognised complications of this disease are worth noting because they make the original disease more difficult to diagnose. Pulmonary arteriovenous shunting with clubbing or pulmonary hypertension (Cohen and Mendelow, 1965), and fibrosing alveolitis (Turner-Warwick, 1968) with arterial desaturation are unusual but dramatic findings. They are important because of the sinister prognosis they carry. Renal damage with renal tubular acidosis may produce hypokalaemia, nitrogen retention, and renal calcification, while renal disease may progress to produce hypertension, an otherwise rare complication in cirrhosis. The finding of LE cells is, of course, not required to complete the diagnosis of the disease. The incidence of positive LE cell tests is probably of the order of 30 per cent and varies with the diligence of the search and the phase of the disease. There is some evidence to suggest that the LE cell phenomenon is related only to the activity and severity of the disease and that its finding is therefore of limited value (Soloway et al., 1972).

Among the peculiar complications of chronic active hepatitis I have seen are polymyositis and bilateral optic neuritis, both fortunately responding well to corticosteroids. The patient with bilateral optic neuritis rapidly became blind on stopping corticosteroids and, in her, the diagnosis of chronic active hepatitis had already been made. If the ocular disorder—incidentally, also recorded in SLE—had been the first manifestation of the disease, I think its significance would have been less easily appreciated.

It is nowadays correct, when faced with a patient with chronic active hepatitis, to consider aetiological causes other than immunological disorders. Thus, drug therapy, which could be immunological, particularly with

| TABLE 2. Differential diagnosis of chronic active hepatitis |
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| **(a) Liver cell jaundice**                               |
| Chronic persistent hepatitis                              |
| Alcoholic and drug hepatitis                              |
| Wilson's disease                                          |
| **(b) Obstructive jaundice**                              |
| (i) Cirrhosis with cholestasis either primary or due to gallstones or hepatoma |
| (ii) Primary biliary cirrhosis                            |

laxative preparations containing oxyphenisatin (Reynolds et al., 1970a; Willing and Hecker, 1970) or aldomet, may produce a reversible disorder of this type, whereas the immunological disorder and that associated with chronic
Australia antigenaemia are usually irreversible, though in the latter example progression of the disease is often slow.

Portal hypertension with the production of oesophageal varices is, in my experience, a particularly sinister association and there is no doubt that, despite their possible youthfulness, patients with this disorder tolerate surgery poorly. It is perhaps fortunate that portal hypertension to the point of bleeding oesophageal varices is comparatively rare. The differential diagnosis of chronic active hepatitis is shown in Table 2. In general, most of the hepatic disorders associated with chronic jaundice can cause confusion, and chronic hepatitis due to drugs, alcohol and that accompanying Wilson’s disease (particularly important in the age group usually affected) must not be forgotten. Primary biliary cirrhosis and cirrhosis associated with cholestasis can usually be differentiated by the liver function tests and histology, though radiology of the bile duct system may also be required.

**PRIMARY BILIARY CIRRHOSIS**

In its typical form, this disorder should present no great diagnostic difficulty. Evidence of chronic obstructive jaundice with a patent extrahepatic biliary system, best displayed by endoscopic retrograde cholangio-pancreatography (ERCP), and a positive mitochondrial antibody test are most helpful.

So often, however, the diagnosis is not considered until a laparotomy has been performed and no cause found for extrahepatic biliary obstruction. So often, too, the appropriate tests at surgery, namely a cholangiogram, a wedge biopsy looking for granulomata and examination of the serum for mitochondrial antibodies, have been delayed. The difficulty with the classical case is intensified when the picture is atypical and Zeegen et al. (1969) showed that the disease may not be diagnosed until portal hypertension has occurred, which in any case is usually a late feature when nodular regeneration has occurred. Other cases may be entirely symptomless and discovered by accident with elevation of the serum alkaline phosphatase on biochemical screening, or with a positive mitochondrial antibody test or, perhaps, because of pruritus in pregnancy.

It is also striking that, though considered to have an immunological basis, primary biliary cirrhosis is rarely accompanied by other disease processes that cannot be attributed to the main hepatic lesion. There are some exceptions to this, and one should not forget the association first noted by Reynolds et al. (1970b) of primary biliary cirrhosis with hereditary telangiectasia and scleroderma, and the relationship with renal tubular acidosis and Sjögren’s syndrome (Golding et al., 1971). The significance of this odd trio is unknown, but at least one of these diseases (scleroderma) is generally accepted as having a
possible immunological basis, though Osler’s disease carries no such implications. One fascinating case of proven primary biliary cirrhosis is worth a short description. During the course of protracted jaundice and pruritus a man with primary biliary cirrhosis and no signs of intrinsic heart disease had two attacks of acute left ventricular failure and needed continuous therapy with digitalis and diuretics to prevent heart failure. At autopsy following terminal renal failure we were able to demonstrate classical endomyocardial fibrosis of the left ventricle in addition to primary biliary cirrhosis. This disease is virtually confined to the tropics and is rare in Caucasians even if they have been domiciled in tropical regions. Work by Shaper et al. (1968) tends to suggest an immunological cause for this cardiac disease, though there have been many other suggested causes. I have since heard of other patients with cardiological complications such as pericarditis and myocarditis that have been presumed to have an immunological aetiology.

**MULTIPLE ENDOCRINE SYNDROME**
The multiple endocrine syndrome is rare, but in its fully expressed form it consists of adreno-cortical failure, hypoparathyroidism, gastric atrophy, and thyroid failure. There is a special likelihood, too, of development of mucocutaneous candidasis. Though this used to be thought of as a manifestation of the hypoparathyroidism, there is in fact good evidence to show a primary deficiency of T-cell responsiveness (Holt et al., 1972) and improvement of the candidasis by the infusion of normal lymphocytes. The hepatic disorder (Craig et al., 1955)—usually chronic hepatitis—is rarely obvious clinically and in most cases has been found incidentally at autopsy or on liver biopsy. We have two examples of this disorder in our unit in a brother and sister, and secondary findings in the latter patient are primary amenorrhoea (presumably immunological, as there are antibodies to ovarian tissues) and alopecia. Specific treatment for the liver disease has not been required in either patient, though they are on corticosteroids for their adreno-cortical failure, and presumably the end result will be hepatic cirrhosis.

**DRUG-INDUCED LIVER DISEASE**
The subject of drug disease and the liver is a vast one. Some of the disorders obviously represent the effects of immunological damage, but perhaps there has been a tendency to over-emphasise this aspect of the aetiology. Features such as eosinophilia, generalised multi-organ involvement, etc., are likely to suggest an allergic aetiology, but on some occasions (notably with chlorpromazine) a rechallenge or continuation of drug therapy may produce no further effects. Also, the limitation of a generalised immunological disorder to
one organ when it occurs is difficult to explain. Other varieties of hypersensitivity may explain these phenomena.

There is no doubt that the problem of drug jaundice related to the anaesthetic halothane (and, less often, fluothane) has evoked a great deal of mistrust between the hepatologists and the anaesthetists, as some of the latter deny that halothane ever causes jaundice, and note that perhaps only two or three genuine cases (often, incidentally, anaesthetists) exist. Certainly much of the difficulty with proof lies with the rather negative results of the National Halothane Survey, though figures have become more positive in associations shown by the Fulminant Hepatitis Survey, and in the UK there are about 200 documented examples of so-called halothane hepatitis, of which nearly 25 per cent have been fatal. The difficulties of differentiation from hepatitis have been solved only for HAA-positive cases, though the evidence of positive mitochondrial antibodies and lymphocyte transformation studies may be helpful and suggestive of an immunological process; the results of these tests have again been challenged by various workers. The tragedy of halothane hepatitis is that, though such a reaction is rare following halothane, its use for many simple operations such as squint correction does lend itself to the production of the occasional tragedy. In my opinion it should be reserved for major operations that are less likely to be followed by further administrations.

Liver Disease in Autoimmune Disorders

The collagen diseases that are also held by many to have an autoimmune basis are also occasionally accompanied by hepatic damage of a presumed similar cause. Both polyarteritis nodosa and SLE may be accompanied by liver damage, but it is rather variable and non-specific in each case. More evidence of a regular component of liver disease either with portal infiltration with lymphocytes, hepatic fibrosis, chronic active hepatitis or cirrhosis is a feature of rheumatoid disease (Blendis et al., 1970), scleroderma (Morris et al., 1972) and Sjögren’s syndrome (Whaley et al., 1970). The association of primary biliary cirrhosis with scleroderma and hereditary telangiectasia has already been noted. The presence of liver disease is usually associated with abnormal liver function tests, though it should be noted that these are not infrequently ‘positive’ in patients with collagen disease with normal hepatic structure, while portal hypertension with bleeding from varices may be the end result of liver disease. The importance of this association lies in the rather better prognosis related to the generally less severe and progressive nature of the liver lesion in such patients, while the association with systemic sclerosis produces a higher incidence of associated systemic hypertension than is usually seen in cirrhosis of other causes, at least in the UK.
CRYPTOGENIC CIRRHOSIS

I should not leave this subject without at least brief reference to cryptogenic cirrhosis. Whether this disease is immunological in type is unknown, but such a cause would undoubtedly fit it. There is a higher incidence of non-specific organ antibodies than there should be, though this may represent effect rather than cause, but the silent long-term nature of the disease and, in particular, the valuable detector of liver disease that a positive anti-mitochondrial antibody test presents has been shown to make such an association a possibility.

In conclusion, the pattern of immunological liver disease is an ever-broadening one, sufficient in its clinical repertoire to mislead, mystify, and yet fascinate the attendant clinician.

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