Rheumatoid Arthritis and Liver Involvement

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Over the years the complex relationships that may exist between joint diseases and disorders of the liver have been subjects of considerable interest. In this analysis we have reviewed the literature relating to types and frequency of liver involvement in rheumatoid arthritis as well as new information gained from studies of the immunological mechanisms involved.

CLINICAL EVIDENCE OF LIVER INVOLVEMENT
This is often considered to be uncommon in uncomplicated rheumatoid arthritis (RA) and is mentioned rarely in early reports. In a recent prospective survey, however, Webb et al. (1975) found enlargement of the liver on clinical examination in 10.6 per cent of 216 patients. Assessment of liver size in this way may be unreliable and a more convincing finding is that of Tiger et al. (1976) who, on hepatic scintiscanning of a prospective series of 32 patients, found hepatomegaly in 7. Other clinical signs of liver disease are usually lacking, and jaundice is rare. Palmar erythema (liver palms) is a frequent finding in RA and is not necessarily associated with hepatic abnormalities (McAvoy et al., 1969). If clinical liver disease does develop in a patient with RA, the most likely explanation will be toxicity from one of the many drugs used in its therapy or from a concurrent liver disease of another aetiology.

ABNORMALITIES IN LIVER FUNCTION TESTS
The indirect tests of liver function based on serum proteins — thymol turbidity, cephalin flocculation, colloid gold, etc., now mainly of historic interest — have commonly been found to be abnormal in rheumatoid arthritis, but are usually due to changes in serum proteins consequent on RA and not to liver disease. The finding of a false positive latex agglutination test for HBsAg in RA (Burrell et al., 1972) or the detection of rheumatoid factor in primary liver disease (Atwater and Jacox, 1963) are similarly non-specific. Abnormalities in various excretion tests using bilirubin, azorubin, and hippuric acid are also reported (Rawls et al., 1939). BSP excretion tests using the standard 5 mg/kg dose are abnormal in up to 30 per cent of patients (Webb et al., 1975; Darby, 1953; Leekovits and Farrow, 1955).
In some patients there is a positive correlation between BSP retention and disease activity.

Serum transaminases are usually normal, suggesting that significant hepatocellular necrosis is rare in RA (Webb et al., 1975; Barr et al., 1958; Nettelbladt, 1960). However, another enzyme marker of hepatocellular damage, the serum ornithine carboxamidotransferase, has been reported to be elevated in 14 to 22 per cent of RA patients, although in one study such elevations were considered to be attributable to gold or phenylbutazone therapy (Nettelbladt, 1960; Malmqvist and Reichard, 1962).

Numerous reports record an elevation in alkaline phosphatase (AP) in up to 50 per cent of RA patients (Webb et al., 1975; Leekovits and Farrow, 1955; Cockel et al., 1971). In some instances the elevation appeared to have been related to the activity of the disease and has subsequently fallen with corticosteroid therapy (Kendall et al., 1970). Similar elevations have been reported in rheumatic fever (Katsu et al., 1965). The finding of an elevated 5'-nucleotidase in such cases has suggested that the AP is of hepatic origin, but 5'-nucleotidase is also produced by synovial cells and may be found in synovial fluid at concentrations higher than those in serum (Kendall et al., 1971; Farr et al., 1973). However, the occasional finding of elevated gamma glutamyl transpeptidase and leucine aminopeptidase would suggest that at least in those cases the AP is of hepatic origin. In a prospective series of 100 rheumatoid patients attending our own out-patient department, a serum alkaline phosphatase greater than 90 i.u./litre, and occasionally greater than 250 i.u./litre, was found in 45 per cent (Sullivan et al., 1978b). In two-thirds of the patients with a raised AP the elevation was attributable to the liver isoenzyme and 58 per cent of these had concomitant elevations in gamma glutamyl transpeptidase. In all, 18 per cent of the patients had an elevated AP of liver origin together with a raised gamma glutamyl transpeptidase. In general, serum enzyme changes do not correlate well with hepatic histological abnormalities but show a better correlation with the activity of the rheumatic process or the presence of the sicca complex.

With regard to serum autoantibodies suggestive of liver disease, Whaley et al. (1970) in screening of rheumatoid sera found antimitochondrial antibodies in 7 of 1,068 patients. Of the 7 patients, 3 had additional biochemical evidence of liver disease with mild elevations in aspartate aminotransferase (AST), and 2 had hepatomegaly. The final diagnosis made in these patients was not given, although it would seem, from clinical criteria quoted, to have been primary biliary cirrhosis.

HEPATIC HISTOLOGICAL CHANGES IN UNCOMPLICATED RHEUMATOID ARTHRITIS

In most studies the ability to distinguish between changes due possibly to drug therapy and those relating to a specific 'rheumatoid liver' could not be made. Of the several hundred RA patients who have had liver biopsies during life or whose
liver was examined at postmortem, histological alterations have been recognised in 25 to 50 per cent (Webb et al., 1975; Leekovits and Farrow, 1955; Baggenstoss and Rosenberg, 1943; Movitt and Davis, 1953; Meyer-Leddin, 1960; Taubner, 1963; Schafer, 1962; Kokot et al., 1967; Dietrichson et al., 1976). The commonest abnormalities have been those of fatty liver or mononuclear cell infiltration in the portal tracts. Similar cell infiltration in the parenchyma occurs less frequently. Amyloid deposition is not often specifically looked for but probably occurs in 7 to 14 per cent (Fingerman and Andrus, 1943; Lender and Wolf, 1972), although it has been suggested that the frequency is no greater than in an age-matched control population (Ozdemir et al., 1971). The hepatic histological abnormalities in RA do not correlate well with the biochemical abnormalities or with the severity of the arthritis.

LIVER ABNORMALITIES IN JUVENILE RHEUMATOID ARTHRITIS, FELTY'S AND SJÖGREN'S SYNDROME
Hepatic abnormalities have also been observed in juvenile rheumatoid arthritis (Still's disease) and in 'complicated' adult rheumatoid arthritis (Felty's syndrome and those with the sicca complex). In Still's disease, altered hepatic function may arise by three distinct mechanisms. It may be a primary manifestation of the disease and as such is more common in the systemic form of the disease than in the polyarticular and pauciarticular forms. The patient is often ill with fever, liver and spleen are enlarged, and jaundice may also be present (Schlesinger, 1949; Schaller et al., 1970; Kornreich et al., 1971). Serum transaminases are elevated and BSP excretion is impaired. Histological descriptions are scarce but portal lymphocytic and plasma cell infiltrates with some Kupffer cell hyperplasia have been reported (Schaller et al., 1970; Kornreich et al., 1971). Hepatocellular necrosis is unusual. The clinical and biochemical changes regress with improvement in the disease. Such hepatic abnormalities may be indistinguishable from those induced by salicylate toxicity. Hepatocellular necrosis may be more prominent in salicylate induced 'hepatitis', but only by measurement of serum salicylate levels and by ascertaining the effect of a reduction in salicylate dosage may it be possible to distinguish between a salicylate-induced lesion and one related to the rheumatic diseases. Finally, the hepatitis may be unrelated, and serology testing for hepatitis A and B viruses, cytomegalovirus, herpes virus, and Epstein-Barr virus may indicate the aetiology.

In Felty's syndrome, hepatic abnormalities are said to be more common than in uncomplicated adult RA. Alkaline phosphatase and, less commonly, transaminases may be elevated and increased BSP retention is reported (Blendis et al., 1970). The most frequent morphological changes are similar to those of uncomplicated rheumatoid arthritis, with sinusoidal and portal mononuclear cell infiltrates and, occasionally, fibrosis of the portal tracts. Nodular regenerative hyper-
plasia and, rarely, cirrhosis may also occur and cause portal hypertension (Ritland, 1973; Blendis et al., 1974).

Keratoconjunctivitis sicca together with xerostomia (sicca complex) is found frequently in patients with autoimmune varieties of liver disease, such as active chronic hepatitis and primary biliary cirrhosis (Golding et al., 1973). In patients with sicca complex and arthritis (Sjögren’s syndrome) as part of primary rheumatoid disease, liver abnormalities appear to be particularly common. Up to 20 per cent have clinical hepatomegaly (Vanselow et al., 1963; Bloch et al., 1965). Abnormal BSP retention has also been noted. Elevated alkaline phosphatase and gamma glutamyl transpeptidase levels are particularly common, as are abnormalities in liver alkaline phosphatase isoenzyme (Webb et al., 1975; Sullivan et al., 1978b). Antimitochondrial antibody was found by Whaley et al. (1970) in the serum of three of 71 patients with sicca complex without arthritis and in one of 50 patients with Sjögren’s syndrome and RA.

More recently, Ellman et al. (1974) reported the development of antimitochondrial antibody negative primary biliary cirrhosis in a 60-year-old black female who had suffered from arthritis for 18 years and who also had Sjögren’s syndrome and autoimmune thyroiditis.

HEPATOTOXICITY CONSEQUENTIAL ON ANTIRHEUMATIC DRUG THERAPY

Many of the drugs used in the treatment of rheumatoid arthritis are potentially hepatotoxic. Gold therapy is a well-recognised cause of hepatocellular necrosis and cholestasis (Hartfall and Garland, 1936; Wiontzek and Schmidt, 1969). The cholestasis may occasionally be so prolonged as to suggest extrahepatic biliary tract obstruction. Salicylate hepatotoxicity has been documented more recently. Elevations in serum transaminases and, less frequently, alkaline phosphatase have been noted in salicylate treated patients with adult and juvenile RA (Rich and Johnson, 1973), as well as in systemic lupus erythematosus (Seaman et al., 1974), rheumatic fever (Iancu, 1972), traumatic fractures and spinal disc disease (Drivsholm and Madsen, 1961). Statistical relationships between elevated transaminases and the serum salicylate concentration are described.

Excessive serum salicylate levels in some individuals may be associated with a mild, usually anicteric, hepatitic illness. The usual threshold for hepatic damage has been a serum salicylate level of approximately 25 mg/dl, although lower levels have been incriminated. In most cases the transaminases rapidly fall with discontinuation or reduction in dosage. However, prolonged elevations have been described in a patient with juvenile rheumatoid arthritis and sickle cell disease (Athreya et al., 1973). Liver biopsy may show patchy parenchymal necrosis with lobular and portal mononuclear cell infiltrates and occasionally the histological picture may mimic active chronic hepatitis. Eosinophilia has been
described, suggesting an ‘allergic’ aetiology, but it is more likely that salicylates have a direct hepatotoxic effect.

Phenylbutazone may also cause jaundice with either hepatitic or cholestatic features. Toxic doses have varied from 1.5 to 32 g and duration of therapy from 3 to 40 days. Usually, the daily dose has been in excess of the recommended maximum of 400 mg (Mauer, 1953). Liver biopsy has shown hepatocellular damage with portal inflammation and in one patient the development of fever, rash, lymphadenopathy, hepatosplenomegaly (sarcoid-like hepatic granulomas); a positive skin test for phenylbutazone suggested a hypersensitivity reaction (Goldstein, 1963).

Corticosteroids may induce a fatty liver and azathioprine may cause hepatic necrosis and cholestasis, albeit rarely, in man (Starzl et al., 1965; Sparberg et al., 1969). Fibrous obliteration of the central veins was attributed to azathioprine in one patient (Marubbio and Danielson, 1975).

The other drugs used in the treatment of RA are less frequently associated with hepatic abnormalities. The propionic acid derivatives naproxen, ibuprofen, and ketoprofen are remarkably free of adverse hepatic effects, particularly considering the marked hepatotoxic properties of one of their precursors, ibufenac (Thompson et al., 1964). Indeed, ibuprofen has only rarely been identified as the cause of transaminase elevations. Likewise, indomethacin is also an uncommon cause of raised hepatic enzymes although a fatal case of ‘toxic’ hepatitis (Kelsey and Scharyj, 1967) and a case of hepatitis with hyperbiliverdinaemia (Fenech et al., 1967) have been attributed to it. Penicillamine appears to spare the liver.

POSSIBLE IMMUNOLOGICAL MECHANISMS IN THE AETIOLOGY OF THE LIVER LESIONS

Panayi (1976) has recently demonstrated induction of antibody mediated lymphocyte cytotoxicity to Chang human liver cells in 31 per cent of RA patients when normal human leucocytes are preincubated with RA sera. Why lymphocyte cytotoxicity to hepatocytes should have developed in these patients is obscure. It would seem much more likely, considering that one of the commonest biochemical abnormalities in liver function in RA is an elevation in alkaline phosphatase and that one of the most frequent histological abnormalities is mononuclear infiltration of the portal tracts, that the bile ducts are the main site of damage. This is particularly true for those patients whose RA is complicated by keratoconjunctivitis sicca. The sicca complex is believed to result from cell-mediated immune destruction of the salivary and lachrymal glands; cellular sensitisation to salivary antigens can be shown in patients with RA as well as in those with primary autoimmune liver disease and the sicca complex (Sullivan et al., 1978a; McFarlane et al., 1976).

Recently we have demonstrated that the salivary and biliary ducts share antigenic determinants (McFarlane et al., 1976; Sullivan et al., 1978c; Wojcicka,
1978) and that patients with RA and sicca complex show sensitisation to salivary antigens (Sullivan et al., 1978a) similar to that which can be demonstrated in the auto-immune liver diseases (McFarlane et al., 1976). It appears then that some unknown factor (or factors) initiates an immune response directed at shared antigenic determinants in salivary-lachrymal ducts and the biliary system. The salivary and lachrymal damage is manifest as xerostomia and xerophthalmia while the bile duct damage is indicated by abnormalities in liver alkaline phosphatase. Clinically, the bile duct lesion in RA is usually mild and asymptomatic although one might expect to observe a primary biliary cirrhosis-like picture if the lesion were to progress. Perhaps the patient of Ellman et al. (1974) represented such a sequence of events.

CONCLUSION
Until the aetiology of RA itself is elucidated, one can only speculate on the possible aetiology of the liver abnormalities that may occur. In some cases these may not be directly related to RA but to the various drugs used in its treatment, and prospective studies of patients started before institution of drug therapy are needed. If RA is the result in some way of a bacterial or viral infection, it is possible that the liver may also be directly involved by the same infection. Alternatively, if RA is a disease of autoimmunity or altered immune response, then similar processes may also affect the liver. The recent finding of shared antigenic determinants in salivary and bile ducts and the finding of cellular immunity against salivary antigens in the sicca complex suggest an immunological basis for liver involvement, at least in those cases of RA in which Sjögren’s syndrome forms part of the condition.

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