Occasional survey

Clinical associations between arthritis and liver disease

PETER R. MILLS and ROGER D. STURROCK

From the Gastroenterology Unit, Royal Infirmary and Centre for Rheumatic Diseases, Baird Street Hospital, Glasgow, Scotland

The purpose of this paper is to review clinical associations between diseases of the liver and joints. Since the publication of an excellent review of arthropathy and liver disease by Whelton1 in 1970 there has been an increasing awareness of the systemic manifestations of many primary liver or joint diseases. Recognition of the pattern of systemic involvement of a disease may be of considerable assistance in making a firm diagnosis and may help elucidate the cause of these diseases where so little understanding of the basic pathophysiology exists. In addition, a review of the more common examples of liver disease induced by antirheumatic drugs will be included.

The first observation of a possible link between arthritis and liver disease was the recognition of an ameliorating effect of jaundice in patients with rheumatoid arthritis reported by Still2 in 1897 and Wishart3 in 1903. Philip Hench at the Mayo Clinic in the 1930s confirmed that 31 out of 45 patients with rheumatic conditions obtained complete (71%) or incomplete (29%) remission from joint symptoms for a mean of 19.5 weeks following the spontaneous onset of jaundice.4 The remission was dependent on the degree of jaundice, requiring serum bilirubin of concentration greater than 8 mg/100 ml (137 μmol/l) rather than the cause, as viral hepatitis or obstructive jaundice seemed equally effective. Attempts to reproduce this phenomenon artificially by intravenous infusion of bile salts, human bile, liver extracts, or highly jaundiced blood were all initially unsuccessful.5 However, an infusion of a combination of bilirubin and dehydrocholic acid was then reported to give prolonged pain relief and reduction in joint swelling to 10 patients with rheumatoid arthritis.6 Infusion of chenodeoxycholic acid alone was, much later, also shown to produce mild transient relief of pain in 6 out of 10 rheumatoid arthritis patients.7 Interest in the therapeutic response obtained continued, with deliberate induction of viral hepatitis resulting in temporary remission of symptoms in most rheumatoid arthritis patients, the improvement in several cases preceding the development of jaundice.8,9

The search for 'Nature's' active agent in this response which could be induced by jaundice, but probably also by pregnancy,10 finally culminated in the hypothesis that corticosteroid hormone metabolism was deranged in these conditions. The first dramatic responses to corticosteroid therapy in rheumatoid arthritis were then reported.11 However, while the rate of hepatic cortisol conjugation has subsequently been demonstrated to be reduced in patients with acute and chronic liver disease, this in turn results in diminished ACTH release, and a steady state is re-established in which cortisol synthesis is reduced and plasma levels remain normal.12 Further exploration of the mechanism underlying the beneficial effect of acute hepatic dysfunction on chronic arthritis therefore continues.

In an ingenious study Pinals13 demonstrated that in rats the hepatotoxin dimethylnitrosamine may rapidly produce a severe but transient necrotising hepatitis without causing jaundice, as the rat liver can handle large bilirubin loads. If dimethylnitrosamine was given to the rat on the fourth day after an injection of Freund's adjuvant, which would normally produce adjuvant arthritis within a few weeks, then partial suppression of the subsequent development of arthritis resulted. Injection of necrotic rat liver extracts, but not normal rat liver, also produced the same effect, suggesting that some anti-inflammatory material was being released from necrotic liver and inhibiting the development of adjuvant arthritis. Acute hepatic injury rather than jaundice itself therefore appears to be all that is necessary to obtain the required effect in adjuvant disease. The mechanism thus still remains unsolved and must surely be a
rewarding area for further experimentation. The possible immnosuppressive effect of acute liver injury has not yet been invoked as the cause of rapid remission of arthritis symptoms.

The review will be divided into the following sections:

(A) Primary diseases of the liver in which joints may become involved.

- Primary biliary cirrhosis.
- Chronic active hepatitis.
- Acute virus hepatitis.
- Haemochromatosis.
- Wilson’s disease.

(B) Primary diseases of joints in which the liver may become involved.

- Rheumatoid arthritis/Sjögren’s syndrome.
- Felty’s syndrome.
- Juvenile chronic arthritis.
- Adult Still’s disease.
- Systemic lupus erythematosus.
- Systemic sclerosis.
- Polymyalgia rheumatica.
- Polyarteritis nodosa.

(C) Anti rheumatic drug-induced liver disease.

(A) Primary diseases of the liver in which joints may become involved

**Primary biliary cirrhosis**

Primary biliary cirrhosis (PBC) is an uncommon form of chronic liver disease, of unknown aetiology, which predominantly affects middle-aged women. The disease usually presents with pruritus followed by slowly progressive jaundice but is clearly a multisystem disorder, the majority of patients having associated sicca syndrome, renal tubular acidosis, and pancreatic hyposcretion.14-16

Rheumatoid arthritis has been described in 5-9.7% of PBC patients.17-19 Rheumatoid factor was present in 73 (64%) out of 114 patients, but in low titre, being <1/64 in 72% of the positive cases.18 A radiological study of hands in 13 PBC patients showed that 12 had distal small joint erosions which were largely asymptomatic.20 However, in a larger series with more extensive radiological screening the prevalence of joint erosions was 13 (31%) out of 42 patients, 8 of whom had a positive rheumatoid factor but only 4 suffered from symptomatic arthritis.21 Circulating immune complexes were detected by C1q binding assay in 31 (62%) of 50 PBC patients, 17 of whom had arthritis.22 This took the form of a seropositive inflammatory polyarthritis in 12 of 18 patients with C1q binding >20%, whereas a milder seronegative arthritis associated with scleroderma and Raynaud’s phenomenon was found in 5 of 13 patients with C1q binding <20%, suggesting that circulating immune complexes may be involved in the development of inflammatory polyarthritis in PBC patients.

The sicca complex of dry eyes and mouth was found in 72% of patients with PBC, 42% with chronic active hepatitis, and 38% with cryptogenic cirrhosis, although less than 5% had accompanying arthritis completing Sjögren’s syndrome.23 If investigated with a battery of tests, including Schirmer’s test, rose Bengal ocular staining, parotid gland scintigraphy, salivary gland scintigraphy, and lip biopsy, then all of 14 PBC patients had 2 or more abnormal tests indicating features of the sicca complex.14

Scleroderma was first described in association with PBC in 1964,24 since when there have been several confirmatory reports.19-25 Later the association of the whole CRST syndrome of calcinosis cutis, Raynaud’s phenomenon, sclerodactyly, and telangiectasia was noted.26 In a detailed study of 83 PBC patients (17%) were found to have scleroderma, which was usually confined to mild cutaneous changes and loss of oesophageal peristalsis.27 However, one patient had extensive progressive systemic sclerosis which resulted in death from cardiopulmonary failure. Of the 14 patients with scleroderma 10 had Raynaud’s phenomena, 7 had telangiectasia of hands and face, and only 2 had calcinosis. The complete CRST syndrome has been noted in 2.4-5.4% of series of PBC patients.17-18-27

Hypercholesterolaemia is a common biochemical finding in PBC patients and may be associated with the formation of symptomless periarticular bone cysts, especially of the small bones of the hands.28 In addition hypercholesterolaemia may cause a transient, flitting polyarthritis such as is found in patients with familial hyperbetalipoproteinaemia.29 Hypercholesterolaemic arthropathy has been described in a patient with PBC as a transient flitting polyarthritis, often initiated by unusual exercise, with joint effusion and erythema of the overlying skin.30 Cholestyramine is recommended in the long-term management.

Polymyalgia rheumatica has been noted in 3 patients thought to have PBC who responded well to corticosteroids.31 However, 2 of these patients did not have a liver biopsy, the diagnosis of PBC resting on elevation of serum alkaline phosphatase and IgM and a positive mitochondrial antibody. With some justification it has been argued that the diagnosis of PBC was not adequately confirmed.32

The association of cirrhosis with digital clubbing is well established, especially in PBC and chronic active hepatitis.1 Hypertrophic osteoarthropathy was considered to be a very rare accompanying feature of chronic liver disease until the description of 20 cases
by Epstein et al.33 in 1979, 10 of which had PBC. Subsequently prospective radiological surveys of the skeleton have revealed that 35% and 38% of PBC patients have periosteal new bone formation.21 34 The distribution of periostitis between these 2 series differed, for in the former the lower tibia and fibula and in the latter the first metacarpal were the most frequently affected sites. Many of these patients have no symptoms, though marked tenderness over the distal leg bones, when present, may be a reliable sign of underlying periostitis. Periostitis is found less commonly in other forms of chronic liver disease.21 34 The reason for the development of periosteal new bone formation in chronic liver disease remains unknown. No difference could be established between patients with liver disease with and without periostitis in relation to cardiac index, degree of right to left pulmonary arteriovenous shunting, presence of oesophageal varices or surgical portacaval shunts, arterial Po2, blood levels of growth hormone, parathyroid hormone, and vitamin A, and urinary excretion of oestrogen.33

CHRONIC ACTIVE HEPATITIS
Chronic hepatitis is defined as chronic liver disease existing for longer than 6 months and is divided pathologically into 2 categories, chronic persistent and chronic active hepatitis. Chronic active hepatitis may have several causes, including hepatitis B virus infection, drugs, Wilson’s disease and alpha-one antitrypsin deficiency, and even excess alcohol may cause similar changes. However, this discussion will be limited to chronic active hepatitis of unknown cause, predominantly affecting young women and constituting the largest subgroup found in Britain. This disease is postulated to have an immunological basis, and multisystem organ involvement is common.35 Joint symptoms are common in chronic active hepatitis but take the form of arthralgia and stiffness more often than true inflammatory arthritis.1 The arthralgia may be of acute onset, transient or recurring, migrating from joint to joint, particularly involving large joints such as knees, ankles, wrists, and elbows and tending to reflect disease activity of the liver. Occasionally joint symptoms may precede the onset of liver disease. The arthralgia is often accompanied by swelling and erythema of the periarticular structures, but joint effusion is uncommon. These changes resolve without causing joint deformity. Occasional patients with all the features of rheumatoid arthritis are seen. Joint symptoms were described in 11–28% of patients with chronic active hepatitis in the 4 largest series.1 13 36 37 Rheumatoid factor and antinuclear factor were present in 95% and 84% of patients with arthralgia and were slightly less commonly found at 73% and 64% in patients without arthralgia.1 In 13 patients with arthralgia who had radiological studies one had changes of rheumatoid arthritis, one showed early osteoarthritis of both elbows, and 2 showed erosion of the ulnar styloid together with erosion of a phalangeal head in one patient.1 No radiological abnormality was seen in the remaining 9 patients.

A striking case of painless seronegative destructive arthritis of small joints of the hands and feet has been described in association with chronic active hepatitis.39 The patient developed marked swelling and warmth of the involved joints, and radiology showed erosions and periosteal new bone formation. The arthritis resolved spontaneously after 10 months, leaving the joints clinically appearing normal. Synovial biopsy showed moderate villous villification and a striking abundance of surface fibrinoid material resembling a rheumatoid nodule. Immunofluorescent studies revealed IgG and C3 complement in the surface fibrinoid, suggesting the possibility of immune complex deposition.

VIRAL HEPATITIS
Arthritis has been associated with the prodromal stages of several viral illnesses, including rubella, mumps, and arboviruses.39 The earliest description of arthritis occurring in viral hepatitis was given by Robert Graves, an Irish physician, in 1843, and a review of the substantial literature summarising our clinical knowledge was published by Fernandez and McCarty in 1971.40 Acute viral hepatitis is often associated with a serum-sickness-like illness characterised by arthralgia, frank arthritis, skin rash, angioneurotic oedema, and occasionally haematuria and proteinuria.41 These clinical features usually precede the onset of jaundice but, as 80% of patients with viral hepatitis are anicteric,42 may be the sole indicators of the illness, thus causing difficulty in establishing the correct diagnosis unless serum transaminase values are checked. The arthritis is usually mild, transient, and leaves no residual joint deformity. In occasional patients, however, the presentation may be more severe and prolonged, imitating the clinical picture of rheumatoid arthritis. The pattern of joint involvement is variable but usually symmetrical, affecting peripheral joints, especially the proximal interphalangeal joints, but large joints and the spine may also be involved. Joint swelling and morning stiffness are both recorded.

Joint symptoms are reported to have occurred in 118 (36%) of 324 patients at some stage during the course of viral hepatitis.43 In contrast to an earlier study,44 in which all 18 patients had virus B hepatitis, there was no difference in the incidence of joint symptoms between HBsAg positive and negative
patients. However, 38% of the HBsAg positive patients suffered joint symptoms for more than 2 weeks compared with 15% of those in whom the antigen was not detected. The frequency of joint symptoms in the HBsAg negative group increased with age from an incidence of only 18% in children to 45% in adults over 30 years.

The remarkable similarity of this syndrome to serum sickness suggests that immune complexes might play a role in its pathogenesis. There is strong evidence that the hepatitis B virus may produce complement-binding immune complexes, which are detected only during the period of activity of the joint disease, whether in association with acute viral hepatitis or chronic active hepatitis.44–46 During the acute phase of joint disease both total serum haemolytic complement (CH 50) and C4 were severely depressed.44 Cryoprecipitates extracted from serum contained IgG, IgM, and IgA, complement components C3, C4, and C5, HBsAg and hepatitis B surface antibody (anti-HBs) in high concentration in comparison with serum alone and could activate both the classical and alternate complement pathways in vitro.45 These immune complexes disappear with the resolution of joint symptoms. However, direct virus infection of synovial cells has also been suggested because of the finding of virus-like particles deep in synovial cells in cases of HBsAg positive associated arthritis.47

HAEMOCHROMATOSIS AND WILSON’S DISEASE

The joint symptoms associated with these 2 rare inherited disorders of iron and copper metabolism respectively have been the subject of a recent comprehensive review by Dr E. B. D. Hamilton48 and have also been well covered in a standard textbook.49 This short account is therefore limited to recent additions to the literature.

In haemochromatosis a further warning is given that chronic arthropathy may be the only initial symptom of the disease.50 In 3 patients, 2 of whom presented with arthritis in the hands and one with pain in both shoulders, there were no other abnormal physical signs and liver function tests were normal. The finding of high serum iron levels suggested the correct diagnosis, which was confirmed by observing excess quantities of iron in liver biopsy specimens. Phlebotomy had no effect on the joint symptoms, but the importance of recognising and treating iron overload before the development of overt haemochromatosis is stressed.

In a review of arthropathy in Wilson’s disease Golding and Walshe found symptoms or signs relating to the locomotor system in 24 (75%) of 32 consecutive hospital admissions of patients with Wilson’s disease.51 The most common symptoms were pain and stiffness in the knees (9 patients) and spine (16 patients) associated with premature osteoarthrosis. Joint hypermobility was found in 9 patients in the absence of any features of Marfan’s syndrome or homocystinuria. Five patients had suffered attacks of acute polyarthritis resembling acute rheumatoid arthritis which were thought to be related to penicillamine therapy. No clinical, biochemical, or radiological evidence of osteomalacia or rickets was observed. A radiological survey revealed generalised loss of bone density (21 cases), premature osteoarthrosis (8 cases—mean age 28 years), spinal osteochondritis (5 cases) and a tendency to narrowing of intervertebral joint spaces and squaring of vertebral bodies.

Recurrent polyarthritis has been reported in a child with Wilson’s disease before starting penicillamine therapy.52 Technetium scintigraphy of joints was described in 25 patients with Wilson’s disease, 11 of whom had joint pains.53 Evidence of synovitis was reported to have been found in 22 joints of 10 patients and postinflammatory articular degeneration in 15 joints of 8 patients. Unfortunately these findings showed little correlation with the presence or absence of joint symptoms.

(B) Primary diseases of joints in which the liver may become involved

RHEUMATOID ARTHRITIS/SJÖGREN’S SYNDROME

Rheumatoid arthritis and Sjögren’s syndrome will be considered together. Rheumatoid arthritis is a common chronic, predominantly articular, condition which has many systemic manifestations. The question of liver involvement has been examined by many clinicians, and the evidence for and against will be presented.

The clinical evidence for liver disease in rheumatoid arthritis is limited. Hepatomegaly was reported in 23 (10·6%) of 216 patients with rheumatoid arthritis, 5 (15·6%) of 32 patients with Sjögren’s syndrome, and only one (0·6%) of 170 patients with osteoarthrosis.54 Liver scintigraphy has been used to assess liver size, when 7 (22%) out of 32 rheumatoid arthritis patients were shown to have hepatomegaly.55 Other clinical signs of chronic liver disease are usually lacking.

Abnormal biochemical tests of liver function have been reported in a large proportion of patients. The concept of a ‘rheumatoid liver’ was based on the finding that 26% of rheumatoid arthritis patients had raised serum alkaline phosphatase levels, which were confirmed to be of hepatic origin by correlation with elevated serum 5-nucleotidase concentrations.56–58
These results have been confirmed with serum alkaline phosphatase levels being elevated in 18%, 35%, and 51% of 3 large series of rheumatoid arthritis patients, suggesting the isoenzyme being of liver origin in the majority of cases. In 100 rheumatoid arthritis patients serum alkaline phosphatase was elevated in 47% of patients with features of the sicca complex but in only 19% of those with normal salivary and lacrimal gland function. Dynamic tests of hepatic function, in particular the bromsulphthalein (BSP) excretion test were abnormal in 5-6% of rheumatoid arthritis patients and 18-8% of Sjögren’s syndrome patients. Serum bilirubin and the transaminases are, in contrast, almost invariably normal.

Serum autoantibody tests may be useful markers for autoimmune liver disease. Mitochondrial antibody was found in 6 (0.9%) of 997 rheumatoid arthritis patients, 1 (1.5%) of 71 Sjögren’s syndrome patients, and 3 (6%) of 50 patients with the sicca syndrome. The prevalence of mitochondrial antibody in 0.5% of a healthy population was probably only significantly exceeded by the sicca syndrome patients, a condition which is known often to accompany chronic liver disease.

A review of liver biopsy findings in rheumatoid arthritis does not reveal any consistent structural abnormality, the majority of reports demonstrating only minor nonspecific changes. For example, in an unselected series of 117 patients with rheumatoid arthritis liver histology was normal in 35%, showed nonspecific reactive hepatitis in 43%, and fatty change in 22%. However, when liver biopsy was carried out in 31 rheumatoid arthritis patients who had clinical and/or biochemical evidence of hepatic dysfunction, 4 (13%) had definable chronic liver disease, 23 (74%) nonspecific reactive changes, and only 4 were normal. The liver disease discovered included one example each of primary biliary cirrhosis, chronic active hepatitis, alcoholic cirrhosis, and amyloidosis. The only useful marker for the presence of liver disease in this study was the finding of a positive mitochondrial antibody. Amyloid deposition is not often specifically sought but probably occurs in 15–21% of rheumatoid arthritis cases, though the frequency and distribution may be identical with an age- and sex-matched control population. The only ‘specific’ histological lesions seen in the liver in rheumatoid arthritis are necrotising arteritis, which may accompany extensive visceral disease and nodular regenerative hyperplasia, which has only once been described in uncomplicated rheumatoid arthritis, but appears in association with Felty’s syndrome.

Therefore occasional hepatic enlargement, elevation of serum alkaline phosphatase, and impaired BSP excretion and nonspecific reactive histological changes in the liver all appear to be merely a feature of the systemic disease process in rheumatoid arthritis. The biochemical abnormalities have been shown to correlate with rheumatoid disease activity, high ESR, low serum albumin, and high serum globulin and seem to be improved by successful anti-inflammatory drug therapy. Nonspecific reactive hepatitis may represent either the residuum of previous inflammatory intrahepatic disease or a response to a variety of extrahepatic disease processes including infections, gastrointestinal tract disorders, collagen diseases, or drug reactions. In effect these nonspecific changes represent ‘wear and tear’ from a very large number of possible causes, and it is not surprising that it should be a common feature in a disease such as rheumatoid arthritis, which is associated with generalised systemic manifestations. Patients with rheumatoid arthritis are treated with many potentially hepatotoxic therapeutic agents, but no relationship between alteration in hepatic function and any single drug or combination of drugs has been identified. Arguments against a drug effect are the lower prevalence of hepatic abnormalities seen in patients with seronegative arthritis who take similar quantities of the same anti-inflammatory drugs as the rheumatoid arthritis patients, and the apparent improvement in biochemical abnormalities, and occasionally in liver histological changes, in patients whose disease activity was reduced by drug therapy, irrespective of the drug used.

Recent developments of interest in the immunological field are the demonstration of IgG antibodies in the sera of 31% of rheumatoid arthritis patients which, when preincubated with normal human lymphocytes, caused antibody-dependent lymphocyte cytotoxicity of human Chang liver cells. Also patients with rheumatoid arthritis and the sicca complex have been demonstrated to have lymphocyte sensitisation to salivary antigens which may cross-react with antigenic determinants present in the normal human biliary tract. Further studies are required to determine whether cellular immune responses to biliary antigens are to be found in patients with rheumatoid arthritis.

**Felty’s Syndrome**

Felty’s syndrome is considered separately because of its association with nodular regenerative hyperplasia of the liver, portal hypertension, and haemorrhage from oesophageal varices.

Felty’s syndrome is defined as rheumatoid arthritis in association with splenomegaly and neutropenia. Abnormal liver function tests were found in 8 out of 12 consecutive patients with this syndrome, 5 of whom had histological changes in the liver consisting...
of pronounced sinusoidal lymphocytic infiltration, Kupffer cell prominence, and periportal fibrosis and one of whom had macronodular cirrhosis in addition.79 Nodular regenerative hyperplasia was then described in 5 patients with Felty’s syndrome, one of whom had died from haemorrhage from oesophageal varices.73 This is a rare lesion of the liver, as examination of 51 necropsies on patients with rheumatoid arthritis revealed no other cases.73 Nodular regenerative hyperplasia of the liver, as originally described by Steiner80 in 1959, is a difficult histological diagnosis to make and may be missed in a small needle biopsy. The surface of the liver may appear normal, finely granular, or nodular. Histologically there is diffuse nodulation of the liver, the size of the nodules usually ranging from 0.1 to 0.2 cm but occasionally reaching as large as 2-0 cm. The nodules are not outlined by true fibrosis but by condensed reticulin fibres giving a negative stain for collagen with Mallory’s trichrome, and there is reversed lobulation, so that the hepatic vein radicle is found in the periphery of the nodule within compressed columns of hepatocytes.81

The interest in nodular regenerative hyperplasia of the liver is the association with the development of portal hypertension. Of 26 cases of nodular regenerative hyperplasia so far reported 12 had Felty’s syndrome and one uncomplicated rheumatoid arthritis.81 Five of these rheumatoid patients developed massive haemorrhage from oesophageal varices, which was fatal in 3 cases. Portal hypertension in this condition probably has 2 causes: first, an increase in splenic and hence portal blood flow, and secondly, an increase in post sinusoidal venous resistance probably caused by compression and distortion of intrahepatic venous radicles.81 The importance of being aware of nodular regenerative hyperplasia in Felty’s syndrome is that after variceal haemorrhage the optimal surgical treatment should be splenectomy, with consideration given to a stunt procedure in addition only if the patient is fit.

**Juvenile Chronic Arthritis**

Since the original description of chronic joint disease in children by Still82 in 1897 there has been confusion over terminology and definitions, which has been partly resolved recently.82 At a conference in 1977 the term chosen was juvenile chronic arthritis, which included subgroups consisting of juvenile ankylosing spondylitis, seropositive juvenile rheumatoid arthritis, seronegative chronic arthritis (the main subgroup, still known as juvenile rheumatoid arthritis in the USA), psoriatic arthritis, and arthropathies associated with inflammatory bowel disease.82 This discussion will be limited to that group of patients with seronegative chronic arthritis whose clinical presentation at onset may be classified into 3 groups: systemic illness, polyarthritis, and pauciarticular disease (≤4 joints involved).83

The systemic disease presentation of seronegative juvenile chronic arthritis was found in 32 (26%) of 124 patients.83 These patients all had high intermittent fever of greater than 2 weeks’ duration; 30 had the typical evanescent pale red macular skin rash, 29 (91%) had hepatosplenomegaly and/or generalised lymphadenopathy, 12 had pleuritis, 10 pericarditis, 29 showed a peripheral blood leucocytosis, and all had seronegative polyarthritis. Six of these 32 patients had evidence of mild hepatic dysfunction together with massive hepatomegaly, 5 of whom have been reported in detail.84 Liver function tests showed increased serum SGOT (mean 115 IU/l) in 4, increased serum bilirubin (mean 1·6 mg/100 ml = 27 μmol/l) in 3, and impaired BSP excretion (mean 9·5% retention at 45 minutes) in 3. Liver biopsy in 4 patients showed similar mild changes, including periportal lymphocyte infiltrates and Kupffer cell hyperplasia. The massive hepatomegaly was therefore not associated with any great distortion of hepatic architecture or cell necrosis and normally regressed with remission of other systemic disease manifestations.

Acute hepatic dysfunction, probably due to intercurrent viral hepatitis, has been described in 7 children with juvenile chronic arthritis.85,86 All the children had a striking clinical remission from joint symptoms, fever, and skin rash during the period of hepatic dysfunction. The remissions were transient in four (<1 month) but lasted 2 months, 7 months, and 5 years in the remaining 3 children. These observations were similar to those of Hench in adult rheumatoid arthritis.5

**Adult Still’s Disease**

In 1971 it was first recognised that adults may present with an illness similar to seronegative juvenile chronic arthritis with systemic manifestations.87 This symptom complex is currently known as adult Still’s disease, and 58 cases have been reviewed.88 Adult Still’s disease has the same clinical features as juvenile chronic arthritis, including intermittent fever, skin rash, seronegative polyarthritis, lymphadenopathy, splenomegaly, pleuritis, and pericarditis.88 Hepatic abnormalities were reported in 3 out of 10 cases, consisting of mild hepatomegaly or modest abnormalities of liver function tests.89 These hepatic abnormalities could not be attributed to drug therapy, as they returned to normal shortly after the patients started anti-inflammatory therapy and reappeared with relapse of the disease. All 3 patients showed periportal infiltration with inflammatory cells on liver biopsy. Overall, 19 (33%) of the 58 cases of adult Still’s disease had hepatic abnormalities.88
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More disturbing preliminary reports have been published concerning acute hepatic failure in adult Still's disease, which was life-threatening in 2 cases\(^9\) and fatal in one other.\(^8\) However, both of the 2 surviving patients were taking high doses of aspirin, and one indomethacin in addition, so drug-induced hepatotoxicity was also a possible explanation.

**Systemic Lupus Erythematosus**

Hepatomegaly has been found in 23–39% of patients with systemic lupus erythematosus (SLE),\(^9\)\(^1\)\(^-\)\(^9\) though clinically significant liver disease had not been thought to be common.\(^4\) Most hepatic interest in SLE had centred around the increased sensitivity to aspirin hepatotoxicity,\(^\text{95}\) the unconfirmed high chronic carrier rate for HBsAg as a possible reflection of impaired immunological competence,\(^\text{96}\)\(^\text{97}\) and the rare complication of arteritis causing hepatic infarction and spontaneous rupture of the liver.\(^\text{98}\)\(^\text{99}\)

Cirrhosis had been reported in 3 (2%) of 138 patients\(^\text{91}\) and hepatic insufficiency was the cause of death in 4 (3%) out of 135 SLE patients.\(^\text{92}\) Systematic studies of hepatic histology in SLE are found in 2 papers.\(^\text{92}\)\(^\text{102}\) Of 19 patients who had hepatomegaly or abnormal liver function tests 6 showed normal or insignificant changes in liver histology; 11 showed minor alterations including fatty change, portal tract fibrosis, and mild to moderate cellular infiltration; and 2 had chronic active hepatitis which had progressed to cirrhosis.\(^\text{92}\) Of 18 unselected SLE patients 5 had normal liver histology and 13 showed the same minor changes described above.\(^\text{100}\)

In 1980 Runyon et al. reported on a retrospective review of the spectrum of liver disease in 206 SLE patients.\(^\text{101}\) Clinical changes were as follows: hepatomegaly (39%), splenomegaly (6%), and jaundice (24%), and 43 (21%) of the patients were defined as having liver disease on the basis of abnormal liver histology or the repeated 2-fold or greater increase in 2 or more liver function tests. All patients were HBsAg negative, and aspirin was being taken more frequently by patients without liver disease. Liver histology was available in 33 patients and included the following findings: steatosis (12 cases), cirrhosis (4), chronic active hepatitis (4), primary biliary cirrhosis (1), hepatic granulomas (3), chronic persistent hepatitis (2), haemochromatosis (1), centrilobular necrosis (3), microabscesses (2), cholestasis (1), and nonspecific reactive changes (1). Therefore 9 (4.4%) of the SLE patients had serious chronic liver disease and 3 had died from hepatic failure at the time of review. Three possible conclusions can be drawn: that SLE and the chronic liver disease were coincidental, that chronic liver disease is a manifestation of SLE, or that chronic active hepatitis may be associated with systemic manifestations suggesting a diagnosis of SLE. The latter conclusion seems most satisfactory, as 20% of chronic active hepatitis patients may have features which would fulfil the American Rheumatism Association's criteria for the diagnosis of SLE.\(^\text{102}\) Patients with chronic active hepatitis and features of SLE should probably be considered as having both diseases, so that the liver lesion will be treated appropriately while careful vigilance is maintained for other life-threatening manifestations of SLE.

**Systemic Sclerosis**

Liver disease appears to be uncommon in systemic sclerosis, with only 8 (1.1%) instances of hepatic involvement reported in a review of 727 patients.\(^\text{103}\) Moreover, in a retrospective review of necropsy findings in systemic sclerosis hepatomegaly and cirrhosis were both more common in a matched control group.\(^\text{103}\)

However, in a prospective assessment of the extent of visceral involvement in systemic sclerosis 16 (52%) of 31 patients were shown to have abnormal liver function tests or lengthened prothrombin times.\(^\text{104}\) There is an association between systemic sclerosis and primary biliary cirrhosis, in particular when all the features of the CRST syndrome are present.\(^\text{25}\)\(^\text{26}\)

Portal hypertension, leading to haemorrhage from oesophageal varices, has been described in 4 patients, 3 of whom had cirrhosis.\(^\text{105}\) Extrahepatic biliary disease has been recorded in systemic sclerosis consisting of fibrosis of the gall-bladder\(^\text{106}\) and hepatic duct obstruction caused by ulceration associated with vasculitis.\(^\text{107}\)

**PolyMyalgia RheumatIca**

Serum alkaline phosphatase of hepatic origin is elevated in 20–62% of patients with polymyalgia rheumatica,\(^\text{106}\)–\(^\text{110}\) when it parallels disease activity together with the erythrocyte sedimentation rate and returns to normal with steroid treatment.\(^\text{108}\) Serum transaminases and BSP excretion may also be mildly abnormal, but jaundice is unusual.\(^\text{111}\) A limited number of reports of liver histology have appeared, but the features described include: normal liver (2 cases), mild fatty change (2),\(^\text{111}\) hepatic necrosis (1),\(^\text{112}\) chronic persistent hepatitis (1),\(^\text{113}\) and hepatic granulomas (2).\(^\text{114}\)\(^\text{115}\) An association with primary biliary cirrhosis has also been recorded.\(^\text{31}\)

An initial report of a high prevalence of serum anti-HBs in polymyalgia rheumatica\(^\text{116}\) has not been subsequently confirmed.\(^\text{117}\)\(^\text{118}\) The prevalence of serum HBsAg and anti-HBs did not differ from matched control populations.

**Polyarteritis Nodosa**

Polyarteritis nodosa is a multisystem disease that affects almost all organs in the body. It is included in
this review because arthralgia or arthritis are dominant features of the disease and because of the association with the hepatitis B virus and accompanying liver disease.

Abnormalities in liver function tests are common in polyarteritis and the presentation may often misleadingly suggest the diagnosis of primary liver disease. Since the initial description in 1970 by Gocke et al., the association between the hepatitis B virus and polyarteritis has become firmly established. Serum HBsAg has been found in 45–71% of cases of polyarteritis recently described, but a slightly lower frequency is the general UK experience. It is clear that exposure to the hepatitis B virus may produce 2 distinct connective tissue syndromes. Transient polyarthritis may precede the onset of acute virus hepatitis as has already been described. However, a subacute or chronic illness featuring arthralgia/arthritides, mononeuritis multiplex, fever, renal disease, hypertension, and central nervous system disease may also occur, and this illness does not differ in clinical presentation or target organ involvement from polyarteritis not associated with the hepatitis B virus. The only differences noted between HBsAg positive polyarteritis and those without evidence of hepatitis B virus infection are that the former are more frequently associated with liver involvement, usually have a good response to corticosteroid therapy, and may have a better prognosis. However, the relationship between HBsAg positive polyarteritis and liver disease is very variable. In a series of 27 cases of HBsAg positive polyarteritis 8 had acute hepatitis, 10 chronic hepatitis, 3 cirrhosis, and in 6 there was no hepatic abnormality.

Other hepatic abnormalities which may occur in polyarteritis are the formation of multiple hepatic artery aneurysms and hepatic infarction due to arteritis. Polyarteritis nodosa is by definition associated with the formation of nodular aneurysms in medium-sized arteries, so that renal or hepatic arteriography may be the simplest way to achieve a clear diagnosis of polyarteritis. Liver biopsy carries a risk of aneurysm puncture and haemorrhage and is therefore best avoided. Polyarteritis is the commonest single cause of hepatic infarction which may lead to jaundice or intraperitoneal haemorrhage.

(C) Antirheumatic drug-induced liver disease

The range of antirheumatic drugs currently in use is extensive, but fortunately hepatotoxicity is a rare occurrence. Despite a succession of elegant hypotheses the mode of action of these antirheumatic drugs remains unknown, and any hepatotoxicity is usually not predictable or dose-related. However, in view of the frequency of hepatic involvement in the rheumatic diseases and the danger of missing a drug toxicity reaction it was considered important briefly to review accumulated experience of those antirheumatic drugs in which hepatotoxicity has been recorded.

The following major antirheumatic drugs will be reviewed:


Third-line drugs. (i) Azathioprine.

Aspirin. This was first recognised to cause abnormalities of liver function in patients with acute rheumatic fever in 1956. Since then aspirin has been frequently reported to produce elevation of serum transaminases in patients with rheumatoid arthritis, systemic lupus erythematosus, juvenile chronic arthritis, and Reiter's syndrome but not apparently in normal individuals.

In a prospective study aspirin given in sufficient dose to produce a serum salicylate level of 25–30 mg/100 ml (1.81–2.17 mmol/l) caused an increase in serum transaminases in 4 of 20 rheumatoid arthritis patients and 7 of 16 systemic lupus erythematosus patients after 2 weeks of therapy. Serum transaminases were elevated considerably higher in the patients with systemic lupus erythematosus but returned to normal in all patients when therapy was stopped. These enzyme abnormalities are rarely associated with symptoms of liver disease, hepatomegaly, alteration in serum bilirubin or prothrombin time, or evidence of severe hepatic dysfunction. While enzyme abnormalities are more common on high-dose aspirin, when serum salicylate levels exceed 25 mg/100 ml (1.81 mmol/l), they also occur with lower-dose therapy. Liver biopsy reveals a nonspecific hepatitis with mild focal hepatocyte changes including necrosis, ballooning of cells, and lobular infiltrates with mononuclear cells. These abnormalities are all rapidly reversible after stopping therapy, and there are no firmly documented examples of fatality or progression to chronic liver disease.

More recently there have been 3 reports of aspirin hepatotoxicity associated with short-lasting encephalopathy in 5 children. These children were given high-dose aspirin and developed high serum transaminases, occasional slight elevation of serum bilirubin and prolongation of prothrombin time, altered level of consciousness, and electroencephalographic (EEG) changes of a metabolic encephalopathy, all of which rapidly improved when...
aspirin was stopped. However, the evidence for acute hepatic failure is limited as the EEG changes are nonspecific, and hypoprothrombinaemia may be induced by salicylic acid alone. Acute salicylate poisoning with associated mild hepatitis is an alternative explanation for these clinical changes.

**Diflunisal.** A single example of reversible mild cholestatic jaundice has been reported with this drug.139

**Indomethacin.** There is little evidence of hepatotoxicity of indomethacin in the literature despite its wide usage. A 12-year-old boy developed fulminant and fatal hepatitis while on indomethacin 100 mg daily, which he had taken for 6 months. Biliverdinaemia, biliverdinuria, and a toxic hepatitis appeared after taking 75 mg indomethacin daily for 3 weeks. The patient presented with a greenish hue to his body, and his urine was green. Recovery ensued, but it remained possible that he had a partial defect in biliverdin reductase which had been made symptomatic by indomethacin hepatitis.

**Sulindac.** Three reports of a toxic hepatitis due to sulindac therapy exist. The 3 patients survived, but 2 had a severe hepatitis which came on soon after starting sulindac. In the third case mild hepatitis was confirmed on rechallenge.

**Ibuprofen.** A closely allied compound, ibufenac, which is a precursor of ibuprofen, was associated with severe hepatotoxicity and has been withdrawn. Ibuprofen appears to be a markedly safer drug with no hepatotoxicity recorded in one series. However, there have been 3 isolated examples of hepatotoxicity, in 2 cases reversible hepatitis and in the third massive and fatal fatty change associated with bilateral pleural effusions.

**Naproxen.** Three examples of transient toxic hepatitis causing jaundice are reported with naproxen. All patients developed jaundice within one to 6 weeks of starting therapy. None were rechallenged, and only one had a liver biopsy. Fennoprofen. A single case of a jaundiced illness with high serum transaminases followed the use of fenoprofen for 7 weeks. The toxic hepatitis was mild and settled quickly. No liver biopsy was obtained and no challenge carried out. Ketoprofen. No record of clinical hepatotoxicity has been found.

**Phenylbutazone.** This is a toxic agent and has been recognised to cause toxic hepatitis, with several fatalities, and the formation of hepatic granulomas. In a series of 800 patients receiving phenylbutazone 2 developed a toxic hepatitis, given an incidence of 0-25%. The first detailed report on phenylbutazone hepatotoxicity described 5 patients in whom jaundice appeared 6–40 days after the start of therapy. There have subsequently been many reports of toxic hepatitis, including 8 fatalities. Hepatic granulomas have been recorded in 11 patients in association with phenylbutazone therapy, the illness being accompanied by fever, pruritus, jaundice, and occasionally eosinophilia.

**Gold.** So-called ‘gold hepatitis’ has disappeared as a clinical problem since the introduction of disposable syringes. However, gold therapy has now been reported to cause intrahepatic cholestasis in 5 patients. The jaundice was marked and accompanied by eosinophilia in 2 cases. Cholestasis is an early feature of gold toxicity, appearing after a mean of only 110 mg of gold had been given. All patients recovered, although jaundice lasted 2 months in one case.

**Penicillamine.** In a series of 99 rheumatoid arthritis patients receiving penicillamine therapy 6 developed elevation of serum transaminases and 2 had evidence of toxic hepatitis on liver biopsy. These abnormalities reverted to normal in 5 patients when penicillamine was stopped. Penicillamine has been reported to cause fatal cholestatic jaundice in association with renal failure and 2 examples of reversible toxic hepatitis.

**Azathioprine.** Azathioprine was found to cause marked jaundice in 2 patients with no change in serum alkaline phosphatase and either normal or slightly elevated serum transaminases. Liver biopsy in one case showed evidence of cholestasis but no necrosis. The other patient was challenged on 2 occasions with azathioprine and repeatedly showed hypersensitivity reactions, even to a very low dose of 5 mg. It was postulated that azathioprine might interfere with bilirubin excretion rather than cause hepatic damage.

**Conclusion**

It is apparent that joint symptoms are frequent and important markers of the systemic nature of many liver diseases. In particular, the occurrence of joint symptoms in patients with haemochromatosis, chronic active hepatitis, or virus hepatitis may be of considerable diagnostic value. Conversely, there is little evidence of serious hepatic disease in patients with rheumatic conditions where minor changes predominate and tend to reflect systemic disease activity. Awareness of the significance of these minor hepatic abnormalities will often prevent unnecessary investigation and the occasional unwarranted operation. However, if patients with rheumatic conditions have persistent signs of hepatic dysfunction or a positive mitochondrial antibody, liver biopsy will reveal a variety of subclinical liver diseases. As yet there is little evidence that treatment of underlying liver disease prevents the progression of the associated joint changes.
Considerable overlap between hepatic and rheumatic diseases may occur, as exemplified by the occasional difficulty in distinguishing between systemic lupus erythematosus and chronic active hepatitis. In such circumstances it would seem advisable to manage the patients as though they had both conditions. The association between the hepatitis B virus and polyarteritis nodosa is so far the only established example of a chronic rheumatic disorder which may be caused by a viral infection but offers some hope that in the future a viral aetiology may be found to underlie more common disorders such as rheumatoid arthritis.\(^1\)

Antirheumatic drugs, with the exception of phenylbutazone, have a low level of reported hepatotoxicity and probably account for few of the minor hepatic abnormalities seen in the rheumatic diseases. However, with an increasing number of new agents becoming available, vigilance in this field must be maintained.

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Occasional survey: Clinical associations between arthritis and liver disease


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P R Mills and R D Sturrock

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