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Liver disease in rheumatoid arthritis and Sjøgren's syndrome

Prospective study using biochemical and serological markers of hepatic dysfunction

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Webb, J., Whaley, K., MacSween, R. N. M., Nuki, G., Carson Dick, W., and Buchanan, W. W. (1975). *Annals of the Rheumatic Diseases*, **34**, 70. **Liver disease in rheumatoid arthritis and Sjøgren's syndrome. Prospective study using biochemical and serological markers of hepatic dysfunction.** The prevalence and the inter-relationships of biochemical and immunological tests of liver function have been studied in a prospective study of 216 patients with rheumatoid arthritis (RA), 32 patients with Sjøgren's syndrome, and 27 patients with the sicca syndrome, and these results have been compared with those obtained in 289 patients with osteoarthrosis or with a form of seronegative polyarthropathy.

In general the prevalence of abnormalities in serum alkaline phosphatase, bromsulphthalein excretion, smooth muscle antibody, and mitochondrial antibody in the former three groups was higher than in patients with osteoarthrosis. Patients with Sjøgren's syndrome with RA had a higher prevalence of abnormalities of bromsulphthalein excretion, salivary duct antibody antinuclear factor, and splenomegaly than patients with RA alone, and had a higher prevalence of rheumatoid factor antinuclear factor and salivary duct antibody than patients with the sicca syndrome. Patients with RA had a higher prevalence of rheumatoid factor than those with the sicca syndrome.

Patients with a positive smooth muscle or mitochondrial antibody were found to have a higher prevalence of hepatomegaly and splenomegaly, of abnormal liver function tests, of other autoantibodies, and of histological abnormalities of liver than those in whom these tests were negative.

Abnormal biochemical tests of liver function have been reported in a variable but surprisingly large proportion of patients with rheumatoid arthritis (RA) (Kalbak, 1951; Lövgren, 1953; Movitt and Davis, 1953; Lefkovits and Farrow, 1955; Darby, 1956; Nettelbladt, 1962; Shäfer, 1962; Castenfors, Hultman, and Lövgren, 1964; Sievers, Julkunen, Ruutsalo, and Hurri, 1964; Langness and Muller, 1965; Langness, 1969; Forgacs, Feher, Genti, Kertesz, and Safrany, 1971; Rau and Kühn, 1972; Kierat, 1973) and with juvenile rheumatoid arthritis (Good, Venters, Page, and Good, 1961; Schaller, Beckwith, and Wedgewood, 1970). While many such tests reflect nonspecific alternations in serum proteins, a remarkable proportion of the rheumatoid patients studied have had abnormal bromsulphthalein excretion tests, often correlating with duration and severity of the disease. In several studies (Nettelbladt, 1960; Malmqvist and Reichard, 1962; Kokot, Nowak, Zielinski, Zmudzinski, Grzybek, and Aleksandrowicz, 1967) levels of serum enzymes that reflect hepatocellular integrity have been found to be normal, as have the serum alkaline phosphatase levels, but in one study the mean levels in RA were higher than in osteoarthrosis (Frank and Klemmayer, 1968).

Overall, evidence for hepatic dysfunction in RA is therefore inconclusive, especially as the reported abnormalities of liver function have shown no correlation with the minor histological abnormalities

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found in the livers of such patients (Laine, Holopainen, and Koskinen, 1955; Roy, Wigzell, Demers, Sinclair, Duthie, Atherden, and Marrian, 1955; Hollingsworth, 1958). Recently, interest in hepatocellular involvement in RA has been revived by Kendall and co-workers (Kendall, Cockel, Becker, and Hawkins, 1970a, b; Cockel, Kendall, Becker, and Hawkins, 1971; Kendall, Farr, Bold, and Hawkins, 1971) who reported that some 26% of such patients had raised serum alkaline phosphatase levels which correlated with a rise in serum 5-nucleotidase.

Hepatomegaly and abnormal biochemical liver function tests have been found in up to 25% of Sjøgren's syndrome patients (Denko and Bergenstal, 1960; Vanselow, Dodson, Angell, and Duff, 1963; Bertram and Halberg, 1965; Bloch, Buchanan, Wohl, and Bunim, 1965; Zawadski and Edwards, 1970). There were 3 cases of primary biliary cirrhosis and 2 of chronic active hepatitis among eighty Sjøgren's syndrome patients reported by Shearn (1971), and a high proportion of patients with these liver diseases have been found to have the sicca syndrome (Golding, Bown, Mason, and Taylor, 1970). The frequency of mitochondrial antibody, a marker for primary biliary cirrhosis (Goudie, MacSween, and Goldberg, 1966; Walker, Doniach, and Doniach, 1970; Klatskin and Kantor, 1972), has been observed to be higher in patients having the sicca syndrome and Sjøgren's syndrome with RA, than in patients having RA alone, and this was considered to represent evidence that subclinical 'autoimmune' hepatocellular damage occurs in such patients (Whaley, Goudie, Williamson, Nuki, Dick, and Buchanan, 1970; Whaley, Webb, McAvoy, Hughes, Lee, MacSween, and Buchanan, 1973a).

The present study was aimed at evaluating, in a prospective fashion, the frequency of two serological markers of hepatic disease, mitochondrial antibody and smooth muscle antibody, and the frequency of abnormal laboratory tests of hepatic function, in a series of patients having RA alone, Sjøgren's syndrome with RA, the sicca syndrome, and a variety of other arthritides.

Materials and methods

PATIENTS STUDIED (Table I)

The disease groups studied and their numbers, ages, and sex are shown in Table I. The patients with RA alone, Sjøgren's syndrome with RA, and the sicca syndrome comprised a prospectively studied consecutive series of patients seen at the Centre for Rheumatic Diseases during a 2-year study period. Patients in other disease groups were included as they attended the clinic, or by recalling old patients.

RA was diagnosed using the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958), and Sjøgren's syndrome by our own previously described criteria (Whaley, Williamson, Chisholm, Webb, Mason, and Buchanan, 1973b).

At the initial clinical examination, patients were examined for hepatosplenomegaly and other stigmata of liver disease. The articular index (Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieveson, and Buchanan, 1968) was performed as an index of the clinical severity of the joint disease.

Patients with juvenile rheumatoid arthritis and with other intercurrent illnesses were not included in the study, and some patients originally included were later excluded from analysis when either Paget's disease of bone, or amyloidosis was subsequently diagnosed.

GENERAL CLINICAL LABORATORY INVESTIGATIONS

These included haemoglobin concentration, erythrocyte sedimentation rate (Westergren), serum alkaline phosphatase, bilirubin, glutamic-oxaloacetic and pyruvic transaminases, total proteins, albumin and globulin concentrations.

SPECIAL TESTS OF LIVER FUNCTION

A standard bromsulphthalein (BSP) excretion test was performed in the following manner: 5 mg BSP/kg body weight were injected intravenously and blood was taken from the opposite arm after 5 minutes and again at 45 minutes. The percentage of dye remaining in each of these samples was assayed. A test was said to be abnormal when over 5% of the dye remained at 45 minutes.

Table I *Number of patients and sex in groups studied, with their mean ages*

Disease	*No. in group*	*No. of females*	*Age (yrs) (Mean ± SD)*
Rheumatoid arthritis	216	182	54·2 ± 13·2
Sjøgren's syndrome + rheumatoid arthritis	32	30	55·9 ± 13·6
Sicca syndrome	27	26	66·5 ± 10·2
Osteoarthrosis	170	143	61·9 ± 9·9
Ankylosing spondylitis	18	3	45·7 ± 15·9
Reiter's disease	21	0	34·9 ± 10·8
Psoriatic arthritis	46	33	46·3 ± 14·8
Gout	20	1	53·8 ± 13·0
Pyrophosphate crystal arthritis (pseudogout)	14	8	67·4 ± 8·3
Total	564	426	—

In each of 32 patients found to have raised serum alkaline phosphatase levels a further fresh and unfrozen serum sample was examined for isoenzyme patterns of alkaline phosphatase using polyacrylamide gel electrophoresis (Connell and Dinwoodie, 1970).

Percutaneous liver biopsies were performed in a limited number (18) of patients only where it was considered clinically indicated because of abnormalities of hepatic function, with the patients's informed consent; paraffin sections were embedded routinely, stained by haematoxylin and eosin, Masson's trichrome, Gordon and Sweet's reticulin, and Perls's reaction for iron.

AUTOANTIBODY TESTS

Rheumatoid factor was detected by screening sera at a 1/20 dilution using the Hyland RA latex agglutination test, and positive sera were titrated in doubling dilution using the R_3 Titration Test (Denver Laboratories). Sera were regarded as positive when they produced agglutination at a dilution of 1/32.

Antinuclear factor was detected by indirect immunofluorescence using rat liver as substrate (Beck, 1961). Sera were screened at a dilution of 1 in 16 and positive sera were tested by serial fourfold dilutions until an end point was reached. The morphological patterns of nuclear fluorescence were noted.

Salivary duct antibody was detected by indirect immunofluorescence using undiluted sera (MacSween, Goudie, Anderson, Armstrong, Murray, Mason, Jasani, Boyle, Buchanan, and Williamson, 1967). Mitochondrial antibody reacts with the mitochondria of the salivary duct epithelial cells, producing a pattern of fluorescence which is indistinguishable from salivary duct antibody. We have therefore assumed that sera containing mitochondrial antibody do not contain salivary duct antibody. Mitochondrial antibody was detected by indirect immunofluorescence using rat kidney as substrate, sera being screened at a dilution of 1 in 16. Positive sera were tested at serial fourfold dilutions until an end point was reached (Goudie and others, 1966). Smooth muscle antibody was detected by indirect immunofluorescence using rat gastric mucosa as substrate at a serum dilution of 1 in 16 (Johnson, Holborow, and Glynn, 1965; Whitehouse and Holborow, 1971).

Results

The results and their statistical evaluation are shown in the accompanying tables, and only the salient features will be commented upon.

GENERAL PARAMETERS

The numbers and sex of the patients in the various disease groups studied, and their mean ages, are shown in Table I.

The mean values for disease duration, articular index, haemoglobin, erythrocyte sedimentation rate, serum albumin and globulin in patients having RA, Sjøgren's syndrome with RA, and the sicca syndrome are shown in Table II. It is worth noting that there were less marked alterations in these parameters in patients with the sicca syndrome, which suggests that such patients in this study had less severe systemic disease than those reported in other studies (Bloch and others, 1965).

Table II *Means of several parameters studied in patients with RA, Sjøgren's syndrome with RA, and the sicca syndrome*

	RA	*Sjøgren's syndrome + RA*	*Sicca syndrome*
Disease duration (yrs)	10·5 ± 9·8	13·9 ± 10·5	—
Articular index	19·8 ± 14·1	21·9 ± 11·3	—
Haemoglobin (g/dl)	12·1 ± 2·0	11·3 ± 1·75	13·4 ± 1·6
ESR (mm/h)	53·5 ± 33·6	67·0 ± 32·8	28·0 ± 28·9
Serum albumin (g/l)	36·0 ± 5·8	36·0 ± 4·7	41·0 ± 6·1
Serum globulin (g/l)	37·0 ± 7·3	39·0 ± 9·3	35·0 ± 9·5

Results expressed as mean ±1SD.

HEPATIC FUNCTION AND SERUM AUTOANTIBODIES (Table III)

In Table III are shown the mean values in all disease groups for the liver function tests and serum autoantibodies, as well as the numbers and percentages with abnormal or positive tests, and numbers with observed hepatomegaly or splenomegaly. Most of the abnormalities found were in patients having RA, Sjøgren's syndrome with RA, and the sicca syndrome. In particular, the highest frequencies of raised serum alkaline phosphatase levels and abnormal BSP tests were found in these 3 patient groups, which also contained twelve of the thirteen mitochondrial antibody–positive patients, 73 of 76 with salivary duct antibody, and 21 of 23 with smooth muscle antibody (19 of the latter being in patients with RA alone).

There were fewer abnormal results and lower mean levels of serum alkaline phosphatase and bromsulphthalein in the seronegative arthropathies than in the 3 principal groups (Sjøgren's syndrome with RA, the sicca syndrome, and RA alone).

COMPARISONS OF PREVALENCE OF ABNORMAL TESTS IN DIFFERENT DISEASES (Table IV)

Table IV shows the statistical analysis (using χ^2 test with Yates's correction for continuity) of differences in prevalence of abnormal findings in all test parameters, between the four groups of patients, *i.e.* with RA alone, with Sjøgren's syndrome including RA, with the sicca syndrome, and with osteoarthrosis. The prevalence of raised serum alkaline phosphatase levels, abnormal BSP tests, hepatomegaly, splenomegaly, and serum autoantibodies was with two exceptions greater in patients having RA, Sjøgren's syndrome with RA, and the sicca syndrome, than in patients with osteoarthrosis. The two exceptions were the normal prevalence of smooth muscle antibody in patients with RA with

Table III *Means, together with numbers and percentages of abnormal or positive results, of the various liver function tests, serum autoantibodies, and hepatosplenomegaly, in all disease groups*

Disease (No. in group)	*Bilirubin*	*SAP*	*SGOT*	*SGPT*	*BSP retention*	*Rheumatoid factor†*	*Antinuclear factor†*	*Salivary duct antibody*	*Smooth muscle antibody*	*Mito-chondrial antibody*	*Hepato-megaly*	*Spleno-megaly*
RA (216)	0·33 ± 0·23*	14·3 ± 12·3 39 (18·1)	16·1 ± 12·9 4 (1·9)	13·0 ± 11·7 1 (0·5)	4·02 ± 2·11 12 (5·6)	332 165 (76·4)	153 74 (34·4)	53 60 (27·7)	19 (8·8)	7 (3·2)	23 (10·6)	12 (5·6)
Sjøgren's syndrome + RA (32)	0·37 ± 0·13	16·3 ± 24·5 8 (25·0)	19·3 ± 12·8 2 (6·3)	13·9 ± 6·27 0	5·11 ± 4·37 6 (18·8)	344 25 (78·1)	202 17 (53·1)	17 1 (59·4)	1 (3·1)	2 (6·3)	5 (15·6)	5 (15·6)
Sicca syndrome (27)	0·51 ± 0·19	19·0 ± 27·7 7 (25·9)	23·0 ± 15·5 3 (11·1)	19·7 ± 14·0 1 (3·7)	5·57 ± 7·78 4 (14·8)	197 14 (51·9)	191 6 (22·2)	6 6 (22·2)	1 (3·7)	3 (11·1)	3 (11·1)	1 (3·7)
Osteoarthrosis	0·43 ± 0·22	10·8 ± 3·29 11 (6·5)	15·9 ± 6·14 0	14·7 ± 5·39 0	3·85 ± 0·62 1 (0·4)	(32; 128) 2 (1·2)	(11 × 16; 4 × 32; 1 × 128) 16 (9·4)	3 (1·8)	1 (0·6)	1 (0·6)	1 (0·6)	0
Ankylosing spondylitis (18)	0·31 ± 0·13	12·5 ± 3·68 3 (16·7)	18·6 ± 8·91 0	14·5 ± 4·09 0	2·9 ± 1·08 0	(64; 286) 2 (11·1)	(16) 1 (5·6)	0	0	0	1 (5·6)	1 (5·6)
Reiter's disease (21)	0·34 ± 0·15	11·4 ± 2·91 2 (9·5)	13·1 ± 17·8 2 (9·5)	15·9 ± 10·58 1 (4·8)	3·2 ± 0·96 0	(4 × 16) 4 (19·1)	(3 × 16) 3 (14·3)	0	0	0	0	0
Psoriatic arthritis (46)	0·41 ± 0·25	12·0 ± 5·52 6 (13·0)	13·7 ± 4·63 0	13·2 ± 4·12 0	3·9 ± 2·26 4 (8·7)	(6 × 16; 1 × 128) 7 (15·2)	(3 × 16) 3 (6·5)	0	1 (2·2)	0	1 (2·2)	0
Gout (20)	0·62 ± 0·38	10·3 ± 3·09 1 5	21·7 ± 8·6 0	20·1 ± 5·09 0	3·9 ± 1·19 1 5	0	(2 × 16) 2 (10)	0	0	0	1 (5·0)	0
Pyrophosphate crystal arthritis (14)	0·50 ± 0·23	13·4 ± 3·84 1 (7·1)	13·2 ± 7·1 0	10·2 ± 3·56 0	3·7 ± 1·44 0	(16) 1 (7·1)	(16) 1 (7·1)	0	0	0	2 (14·2)	1 (7·1)
Normal values	1·2 mg/100 ml	5–15 King Armstrong units/ml	13–42 Reitman-Frankel units/ml	11–55 Reitman-Frankel units/ml	5% retention at 45 min	Reciprocal of R3 titre	Reciprocal titre	—	—	—	—	—

* For all parameters; the mean ± standard deviation, followed by number with abnormal or positive results (% in brackets);
† where only a small number are positive, the numbers at each reciprocal titre are indicated.
SAP = Serum alkaline phosphatase; BSP = bromsulphthalein.
Conversion: Traditional Units to SI Units—Bilirubin: 1 mg/100 ml ≃ 17·1 μmol/l.

Table IV *Comparison of prevalence of abnormal results for parameters studied between patients having RA, Sjøgren's syndrome with RA, sicca syndrome, and osteoarthrosis. Units as in Table III*

Comparisons	*SAP*	*BSP*	*Rheumatoid factor*	*Antinuclear factor*	*Salivary duct antibody*	*Smooth muscle antibody*	*Mitochondrial antibody*	*Hepatomegaly*	*Splenomegaly*
RA *v.* SS + RA	0·88 NS	7·21 0·01	0·05 NS	4·27 0·05	12·82 0·001	1·21 NS	0·12 NS	0·69 NS	4·43 0·05
RA *v.* sicca	0·97 NS	3·35 NS	6·23 0·025	1·57 NS	0·37 NS	0·82 NS	3·77 NS	0·01 NS	0·16 NS
RA *v.* OA	11·32 0·005	7·21 0·01	219·2 0·005	32·85 0·005	47·13 0·001	13·05 0·005	3·30 NS	16·51 0·005	9·75 0·005
SS + RA *v.* sicca	0·01 NS	0·16 NS	4·51 0·05	5·88 0·025	8·28 0·005	0·02 NS	0·45 NS	0·25 NS	2·28 NS
SS + RA *v.* OA	10·85 0·005	26·55 0·005	137·7 0·005	37·65 0·005	92·10 0·001	1·77 NS	5·90 0·025	21·13 0·005	27·24 0·005
Sicca *v.* OA	10·62 0·005	19·06 0·005	80·18 0·005	3·85 0·05	22·37 0·001	2·25 NS	12·97 0·005	12·97 0·005	6·33 0·025

χ^2 test with Yates's correction for continuity. SS = Sjøgren's syndrome; Sicca = sicca syndrome; OA = osteoarthritis; SAP = serum alkaline phosphatase; BSP = bromsulphthalein test.

Sjøgren's syndrome and in patients with the sicca syndrome. Mitochondrial antibody was significantly more prevalent in Sjøgren's syndrome with RA and in the sicca syndrome than in osteoarthrotic patients but there were no significant differences from patients with RA alone.

Patients having Sjøgren's syndrome with RA had a higher prevalence of abnormal BSP tests than those with RA alone, and the former patients also had a higher prevalence of antinuclear and salivary duct antibodies than patients with RA or with the sicca syndrome.

COMPARISONS BETWEEN PATIENTS WITH AND WITHOUT MITOCHONDRIAL AND SMOOTH MUSCLE ANTIBODIES (Table V)

The 3 patient groups (RA, Sjøgren's syndrome with RA, and the sicca syndrome) were analysed with regard to the prevalence of all other abnormal test results according to whether they were mitochondrial antibody positive or negative, and smooth muscle antibody positive or negative (Table V). The prevalence of raised serum alkaline phosphatase and glutamic oxaloacetic transaminase levels, abnormal BSP tests, hepatomegaly, and splenomegaly was significantly greater in mitochondrial antibody-positive patients. Patients with smooth muscle antibody were found to have a greater prevalence of abnormalities of all liver function tests, of rheumatoid factor, of mitochondrial antibody, and of hepatomegaly, than those who were smooth muscle antibody negative. The latter patients also had a lower prevalence of antinuclear and salivary duct antibodies than patients with smooth muscle antibody.

SERUM ALKALINE PHOSPHATASE AND BSP TESTS; COMPARISONS AND CORRELATIONS WITH OTHER PARAMETERS STUDIED (Tables VI, VII)

In Table VI the serum alkaline phosphatase levels and BSP excretion values found in osteoarthrotic patients were compared with levels found in patients having RA, Sjøgren's syndrome with RA, and the sicca syndrome (Student's 't' test for unpaired variables). With the exception of BSP levels in RA, the mean levels of serum alkaline phosphatase and BSP excretion were higher in these 3 groups than in osteoarthrotic patients, although the mean levels were outside the normal range only in patients having Sjøgren's syndrome with RA and in the sicca syndrome.

Serum alkaline phosphatase levels and BSP excretion (Table VII) were further examined in patients having RA, Sjøgren's syndrome with RA, and the sicca syndrome for correlations with each other and with a number of other parameters which often reflect disease activity (disease duration; articular index; haemoglobin; ESR; serum albumin; serum globulin). Higher serum alkaline phosphatase levels were found to correlate with higher articular indices, ESR, and serum globulin levels in RA. The obverse was found in patients with the sicca syndrome, in whom there were correlations between higher BSP values and higher serum alkaline phosphatase levels; and higher serum albumin and lower serum globulin levels; and higher BSP values with lower ESR. Higher BSP values were found to correlate with longer disease duration, higher ESR, and higher serum alkaline

Table V *Comparison of prevalence of abnormal results for parameters studied (grouping all patients with RA, Sjøgren's syndrome with RA, and sicca syndrome) in those with and without mitochondrial antibody, and those with and without smooth muscle antibody. Units as in Table III*

Groups	*No. in groups*	*SAP*	*SGOT*	*SGPT*	*BSP*	*Rheumatoid factor*	*Antinuclear factor*	*Salivary duct antibody*	*Smooth muscle antibody*	*Mitochondrial antibody*	*Hepatomegaly*	*Splenomegaly*
With mitochondrial antibody:												
(1) RA	7	3	1	0	3	6	2	*	2	—	2	1
(2) Sjøgren's syndrome + RA	2	1	0	0	2	2	0	*	0	—	1	1
(3) Sicca syndrome	3	2	2	1	3	2	0	*	0	—	2	1
Total in above groups 1 + 2 + 3 with mitochondrial antibody	12	6	3	1	8	10	2	*	2	—	5	3
Total in above groups 1 + 2 + 3 without mitochondrial antibody	263	48	6	1	14	194	95	73	19	—	26	15
Statistical differences between those with and without mitochondrial antobody	$\chi^2 =$ $P \leqslant$	16·97 0·005	12·22 0·005	2·06 NS	50·63 0·005	0·14 NS	2·85 0·1	*	0·42 NS	—	10·72 0·005	4·18 0·05
Total in above groups 1 + 2 + 3 with smooth muscle antibody	21	9	3	2	4	18	4	3	—	2	5	2
Total in above groups 1 + 2 + 3 without smooth muscle antibody	254	45	6	0	18	186	93	73	—	10	26	16
Statistical differences between those with and without smooth muscle antibody	$\chi^2 =$ $P \leqslant$	62·53 0·005	5·35 0·025	96·99 0·005	23·19 0·005	9·94 0·005	34·47 0·005	28·13 0·005	—	6·16 0·025	23·44 0·005	0·13 NS

χ^2 test with Yate's correction for continuity.
* Salivary duct antibody is not separately demonstrable in the presence of a positive antimitochondrial antibody fluorescence.

Table VI *Comparisons of BSP excretion values and serum alkaline phosphatase levels in osteoarthrotic patients and in patients with RA, Sjøgren's syndrome with RA, and sicca syndrome*

Osteoarthritis v.	*RA*	*Sjøgren's syndrome + RA*	*Sicca syndrome*
BSP excretion test	t = 0·4535 NS	t = 2·9512 P ⩽ 0·005	t = 2·6846 P ⩽ 0·005
Serum alkaline phosphatase	t = 4·4482 P ⩽ 0·001	t = 1·7905 P ⩽ 0·05	t = 1·7447 P ⩽ 0·05

Student's 't' test for unpaired variables.

phosphatase levels in patients with RA, and with higher serum alkaline phosphatase levels in Sjøgren's syndrome with RA. It can readily be seen that, despite their statistical significance, all of these correlations have very poor coefficients of determination (or 'strength') due to their very low '*r*' values, and are thus of questionable practical significance.

SERUM ISOENZYME OF ALKALINE PHOSPHATASE (Table VIII)

Sera were obtained from 32 patients with raised serum alkaline phosphatase levels for isoenzyme examination. At the time of isoenzyme examination the serum alkaline phosphatase levels were normal

Table VII *Correlations between serum alkaline phosphatase levels and BSP retention values, and other parameters studied, in patients having RA, Sjøgren's syndrome with RA, and sicca syndrome*

	Disease with correlation	*Correlation coefficient 'r'*	*Student's 't' test*	*Significance P*
Serum alkaline phosphatase compared with				
Articular index	RA	0·1464	2·1397	0·025
Erythrocyte sedimentation rate	RA	0·1603	2·3640	0·01
Serum albumin	Sicca	0·3819	1·9818	0·05
Serum globulin	RA	0·1594	2·3282	0·025
	Sicca	0·2704	1·3467	0·1
BSP retention test compared with				
Disease duration	RA	0·1554	2·2899	0·025
Erythrocyte sedimentation rate	RA	0·1160	1·6966	0·05
	Sicca	0·5378	2·9921	0·005
Serum albumin	Sicca	0·4597	2·4827	0·025
Serum globulin	Sicca	0·5995	2·5924	0·001
Serum alkaline phosphatase	RA	0·2552	3·8339	0·001
	RA + SS	0·4276	2·5476	0·01

Student's test of the linear correlation coefficient, significant results only shown. SS = Sjøgren's syndrome; Sicca = sicca syndrome.

Table VIII *Results of serum alkaline phosphatase isoenzymes: patterns found with their diagnoses*

Serum alkaline phosphatase isoenzymes	*Numbers* * †	*Diagnoses and numbers*
Principal isoenzymes		
(1) Bone	8	Paget's disease of bone + osteoarthritis (7) Still's disease aged 14 years (1)
(2) Bone + liver	1 (1)	Primary biliary cirrhosis + sicca syndrome + Paget's disease of bone + osteoarthritis
(3) Liver	3 (1)	RA (3)
(4) Liver + origin	4 (1)	RA (3) together with primary biliary cirrhosis in one (1)
(5) Origin	2	RA (1)
Other bands	2	RA (2)

* Plus normal SAP in 10 RA and 2 having Sjøgren's syndrome with RA not shown here.
† Numbers with mitochondrial antibody in brackets.

in twelve (10 having rheumatoid arthritis, and 2 Sjøgren's syndrome with RA). The distribution of the four principal isoenzymes usually found in pathological sera in the other twenty patients' sera, with their diagnoses, are shown in Table IX (no serum had intestinal isoenzyme). Two patients with normal principal isoenzymes had an unusual band of activity running faster than origin but slower than kidney or intestinal isoenzymes. None of the patients with Paget's disease of bone or Still's disease were included in other data analysis, and neither was the patient with Paget's disease of bone with sicca syndrome and primary biliary cirrhosis. This latter patient had both liver and bone isoenzyme in serum.

LIVER BIOPSY RESULTS (Table IX)

Adequate liver biopsy material was obtained from fourteen patients, five of whom were positive for M-antibody. The findings in these biopsies are summarized in Table IX. In those three patients in whom the histological features were those of primary biliary cirrhosis, the diagnosis had been suspected on the clinical and biochemical findings.

Discussion

Abnormal serum alkaline phosphatase levels and BSP excretion tests were found more frequently in RA, Sjøgren's syndrome with RA, and the sicca syndrome than in patients with osteoarthrosis, and the mean values for these tests were higher in the former 3 patient groups than in the latter patients. This is in agreement with most other studies (Lefkovits and Farrow, 1955; Darby, 1956; Nettelbladt, 1962; Schäfer, 1962; Castensfors and others, 1964; Sievers and others, 1964; Langness and Muller, 1965; Langness, 1969; Forgacs and others, 1971; Rau and Kühn, 1972; Kierat, 1973), many of which noted a correlation with parameters reflecting activity and severity of RA and disease duration. Improvement in abnormal liver function tests in patients with RA has also been noted with remission (Todd, 1935) and after corticosteroid therapy (Kalbak, 1951; Pettersson, Wegelius, and Skrifvars, 1970; Kierat, 1973). Kendall and his colleagues (Kendall and others, 1970a, b; Cockel and others, 1971) found raised serum alkaline phosphatase levels in 26% of rheumatoid arthritics, and noted a relationship between serum alkaline phosphatase and 5-nucleotide levels. They suggested that their findings reflected hepatic involvement in this systemic disease process, and supported this by observing the return to normal of these abnormalities after corticosteroid induced remission of the disease. Because there was no correlation between the very high synovial fluid 5-nucleotidase levels and corresponding serum levels, It was considered unlikely that the former contributed to the latter (Kendall and others, 1971). These same authors found that raised serum alkaline phosphatase levels correlated with rheumatoid disease activity, high ESR, low serum albumin, high serum globulin, and low serum iron concentrations. Similarly, correlations for both raised serum alkaline phosphatase levels and abnormal BSP tests with indices of disease severity were found in the present study. However, the correlation coefficients were extremely low, which suggests that they have little practical significance and further suggests that variables other than the ones studied are involved. Unfortunately, we are not able to compare our findings with those of the above-mentioned authors who did not publish the figures for the correlations they found.

Although it is generally agreed that the juxta-articular demineralization and erosions which occur in RA do not contribute to serum alkaline phosphatase levels (Lehman, Kream, and Brogna, 1964), it is still sometimes argued that the higher mean levels of this enzyme in patients with RA compared with controls may result from excessive osteoblastic activity (Frank and Klemmayer, 1968). Certainly this may account for raised serum alkaline phosphatase levels during youth (Clark and Beck, 1950), and for this reason we excluded patients with juvenile

Table IX *Liver biopsy findings*

Group	*Histological findings*	
M-antibody positive (no. = 5)	Primary biliary cirrhosis	3 (RA 2, SS 1)
	Mild chronic inflammatory cell infiltrate in portal tracts	1 RA
	Mild portal tract fibrosis	1 SS
M-antibody negative (no. = 9)	Normal	4 (RA 2, SS 2)
	Portal tract fibrosis with mild chronic inflammatory cell infiltrate	1 *
	Mild fatty infiltration	2 all RA
	Mild portal tract fibrosis	1
	Amyloidosis (excluded from other data analysis)	1

* Previously diagnosed clinically as having chronic active hepatitis: on prednisolone 15 mg/day for 12 months before biopsy.

rheumatoid arthritis from the study. Minimal rises of serum alkaline phosphatase levels have also been reported in some normal persons over 60 years of age (Klaassen, 1966), but in view of their negligible magnitude we doubt the relevance of this in the present context.

BSP excretion may be altered in the presence of low serum albumin concentrations (Grausz and Schmid, 1971), but in this study we have failed to find a correlation between these two parameters in patients having RA, with or without Sjøgren's syndrome, while a correlation between impaired BSP excretion and higher serum albumin concentrations was found in patients with the sicca syndrome; findings which might suggest that the low serum albumin concentrations which are found in these diseases are unlikely to be due to hepatocellular dysfunction. It is known that the albumin fractional catabolic rate is increased in RA (Ballantyne, Fleck, and Dick, 1971), suggesting that enhanced degradation of albumin may be more important than reduced synthesis.

Another factor possibly relevant to the occurrence of abnormal liver function tests in these diseases is the ingestion of anti-inflammatory drugs. Most patients with RA ingest large quantities of such drugs during their lifetime, many of which are known to be hepatotoxic; even therapeutic doses of salicylates may produce raised serum transaminase and alkaline phosphatase levels (Russell, Sturge, and Smith, 1971). In previous studies anti-inflammatory drugs have been incriminated (Forgacs and others, 1971), and exonerated (Kierat, 1973), as causes of abnormal liver function tests. As we did not take drug therapy into account, it is possible that this may account for some of the abnormal liver function tests found. However, this does not explain two facts. First, the mean levels of these tests in patients with seronegative inflammatory arthropathies were normal, although most of them took similar quantities of the same anti-inflammatory drugs. Secondly, an increased prevalence of abnormal liver function tests was found in patients with the sicca syndrome, who do not take anti-inflammatory drugs.

Amyloidosis is another well-known complication of chronic RA which could conceivably affect the results of this study. This was not specifically excluded in the present study except on clinical grounds. Patients already known to have this complication were not studied and one patient found to have amyloidosis on biopsy was excluded from the analysis. It is possible that other unbiopsied patients had this complication. The reported frequency of this complication in RA ranges from none (Rau and Kühn, 1972) to 2·4% (Dilsen, 1969), or even to 19% (Brandt, Cathcart, and Cohen, 1968), of rheumatoid patients. One recent study suggests that there is no increase in the prevalence of overt amyloidosis in RA patients (Ozdemir, Wright, and Calkins, 1971).

That the raised alkaline phosphatase levels represented an increase due to liver enzyme was suggested by coexistent rises in the serum 5-nucleotidase levels in seven patients so examined (date not known), and was confirmed by the alkaline phosphatase isoenzyme studies. It is of interest to note that raised alkaline phosphatase levels had reverted to normal in twelve of 32 patients who had second serum samples taken for isoenzyme studies. This suggests that the rise of serum alkaline phosphatase levels represents another variable, fluctuating during the course of RA. Unfortunately, disease activity was not assessed at the time the second sample was taken in the present study.

Histological evidence of liver disease occurring in RA has been reported. Early autopsy studies confirmed the presence of secondary amyloidosis in RA (Fingerman and Andrus, 1943), and these workers suggested that amyloidosis was the only specific and significant hepatic lesion found in RA. Other changes such as fatty infiltration are nonspecific and usually mild in degree, and 'serious hepatitis' proved to be artefactual (Baggenstoss and Rosenberg, 1941; Rosenberg, Baggenstoss, and Hench, 1944). Since then there have been a number of liver biopsy studies in RA.

Apart from amyloidosis, and occasional cases of cirrhosis, which have proved difficult to classify (Lövgren, 1953; Schäfer, 1962; Blendis, Ansell, Jones, Hamilton, and Williams, 1970; Losada, Prat, and Fernandez, 1972), these studies have revealed only minor changes including variable fatty change, some Kupffer cell hyperplasia, and mild mononuclear cell infiltration of the portal tracts (Lövgren, 1953; Movitt and Davis, 1953; Lefkovits and Farrow, 1955; Schäfer, 1962; Taubner, 1963; Langness and Müller, 1965; Kokot and others, 1967; Langness, 1969; Forgacs and others, 1971; Rau and Kühn, 1972). These changes were present in between 10 and 40% of cases but showed no correlation with abnormal liver function tests and were generally considered 'nonsignificant' as they were not characteristic of any specific pathological process. Similar findings have been reported in juvenile rheumatoid arthritis (Portis, 1938; Schaller and others, 1970).

Another 'specific' liver lesion which occurs in RA is necrotizing arteritis, but this has only been seen in the presence of widespread RA (Ball, 1954; Sinclair and Cruikshank, 1956; Clinicopathological Conference, 1966; Karten, 1969).

Mitochondrial antibody (M-antibody) is a selective serological marker for primary biliary cirrhosis, occurring in up to 98% of such patients in some series (Doniach, 1970; Klatskin and Kantor, 1972). It may also occur in 11–24% of patients with

chronic active hepatitis, and 6–26% of patients with cryptogenic cirrhosis. It has also been found in 1·5% of patients with RA and in a slightly greater proportion of patients with other connective tissue diseases (Doniach, 1970; Klatskin and Kantor, 1972).

In a previous study from this centre (Whaley and others, 1970) M-antibody was found to occur more frequently in the sera of patients with the sicca syndrome (6%) and with RA with Sjøgren's syndrome (1·5%) than in patients with RA alone (0·97%). Walker and others (1970) examined a group of 35 patients without overt clinical liver disease, but in whom M-antibody had been shown. These patients suffered primarily from collagenoses or organ-specific autoimmune conditions. In ten patients there was biochemical evidence of liver abnormalities, and in each of eight in whom a liver biopsy was obtained definite histological abnormalities were present. In the present study we have shown that the prevalence of hepatomegaly and splenomegaly, raised serum alkaline phosphatase, SGOT, and abnormal BSP tests, was greater in mitochondrial antibody–positive patients. In the patients in whom liver biopsy was performed, histological abnormalities were present in all five who were M-antibody positive, whereas four of the nine M-antibody negative patients had normal biopsies, and in three (fatty infiltration 2, amyloidosis 1) the histological abnormalities could not be regarded as indicating primary hepatic dysfunction. Klatskin and Kantor (1972) did not find M-antibody in any of their patients with RA or other collagen diseases who did not have evidence of associated liver disease. Similary in the present series the demonstration of smooth muscle antibody was found to be associated with a higher prevalence of abnormalities of all liver function tests.

Screening for these two antibodies should provide a useful indication of underlying or associated liver disease in RA and other collagenoses.

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