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Raised serum alkaline phosphatase in rheumatoid disease

An index of liver dysfunction?

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The concentration of serum alkaline phosphatase may be increased in patients with rheumatoid disease (Watson, 1940; Frank and Klemmayer, 1968). In normal serum this enzyme is derived mainly from the liver and skeleton, although other organs, including the intestine, contribute. The increase in rheumatoid patients has been attributed to osteoblastic activity (Frank and Klemmayer, 1968). However, we believe that an hepatic origin is more likely because a simultaneous rise in serum 5-nucleotidase (5-NT) occurred in our patients with increased alkaline phosphatase (Kendall, Cockel, Becker, and Hawkins, 1970). Serum 5-NT is increased in liver disease though normal in bone disorders (Dixon and Purdom, 1954). Hill and Sammons (1967) showed that simultaneous estimation of this is a useful way of detecting the origin of alkaline phosphatase; it is simpler and more objective than separating bone and liver alkaline phosphatase by starch gel electrophoresis. Histochemical localization of alkaline phosphatase and 5-NT has shown that the hepatic sites of these two enzymes are similar (Novikoff and Essner, 1960), which explains why they usually behave similarly as tests of liver function.

The clinical significance of a raised serum alkaline phosphatase in rheumatoid disease is unknown. We have therefore compared rheumatoid patients with a raised alkaline phosphatase with a control group of rheumatoid patients matched for age and sex in whom the alkaline phosphatase was normal. The investigation was designed to assess the type and severity of rheumatoid disease and to detect evidence of liver dysfunction or bone disease.

Patients and Method of Investigation

Ten women and five men aged 48-66 yrs (mean 57·3) with rheumatoid disease and a raised alkaline phosphatase (over 14 KA units) were reviewed clinically. Information was obtained about the duration of disease, drug therapy (past and present), previous history of jaundice, blood transfusions, and alcohol consumption. Full physical examination was performed and the following special points were noted: the extent and activity of disease, the presence of hepatomegaly, splenomegaly, enlarged lymph nodes, and rheumatoid nodules. The haemoglobin, ESR (Westergren), Waaler-Rose titre, prothrombin time, and the following biochemical values were estimated: glucose, creatinine, urea, sodium, potassium, alkaline phosphatase, bilirubin, albumin, globulin, calcium, glutamic-oxaloacetic transaminase, iron, uric acid, cholesterol, inorganic phosphate, and 5-nucheotidase. The bromsulphthalein test was performed on all cases (injecting 5 mg./kg. with samples taken at 5 and 45 minutes). Radiographs of bones and joints were examined with special reference to signs of metabolic bone disease and extent of bone destruction in relation to joints. Films were studied without knowing from which group the patient came. An arbitrary scoring system was used and the values added to obtain a group total.

The control group, evaluated in the same way, comprised fifteen patients with rheumatoid disease who had a serum alkaline phosphatase below 14 KA units and were matched for age (mean 56·3 yrs) and sex. When the results were collected in tabular form, many of the clinical points of similarity and difference were obvious. The numerical values from the haematological and biochemical investigations were analysed statistically using Student's 't' test.

Results

Analysis of the two groups of rheumatoid patients—those with and those without a raised alkaline phosphatase—showed that generally the type and duration of rheumatoid disease was similar. Thus, classifying them according to the revised American Rheumatism Association Classification (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) the former were grouped as one probable, six definite, and eight classical, and the latter as six definite and nine classical. Similarly, the mean duration of the disease in the first group was 11·4 yrs (range 12 mths to 22 yrs) and in the control group 11·9 yrs (range 18 mths to 24 yrs). The groups did not differ in drug history (apart from corticosteroids), incidence of jaundice, number of blood transfusions, and

alcoholic intake. Certain clinical findings showed no significant difference; their occurrence in the high alkaline phosphatase group and controls respectively was: rheumatoid nodules 4/6, hepatomegaly 3/5, and splenomegaly 1/1. Bone radiographs and the following laboratory tests were similar in both: haemoglobin concentration, prothrombin time (normal in all), glucose, creatinine, urea, sodium, potassium, calcium, bilirubin, glutamic-oxaloacetic transaminase, uric acid, cholesterol, inorganic phosphate, and bromsulphthalein retention.

The groups differed in two main ways; the details are shown in the Table.

(1) Those with a raised alkaline phosphatase had more active disease, a higher ESR, and a lower serum iron, and were more frequently found to have lymphadenopathy and a positive Waaler-Rose test; fewer were receiving corticosteroid therapy.

(2) The mean 5-NT value was significantly higher.

The serum albumin was lower and the serum globulin higher in the more active group, though the differences were not statistically significant.

As disease activity was associated with raised alkaline phosphatase, the effect of steroid therapy was investigated. Three patients with a high alkaline phosphatase were given steroids and followed biochemically. In all three the alkaline phosphatase was halved within 2 weeks and in one case the value fell to normal. An example is shown in Fig. 1. The coincident rise in serum albumin excludes a dilutional effect due to steroid-induced fluid retention. In each case there was also clinical improvement.

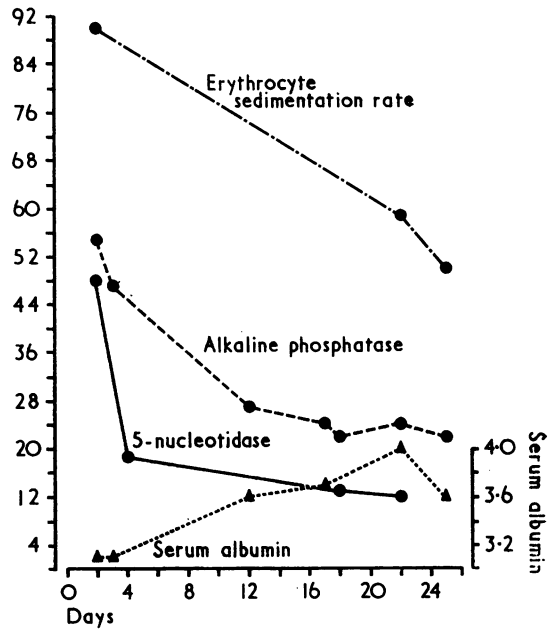

FIG. 1 *Effects of corticosteroid therapy on the erythrocyte sedimentation rate and tests of liver function in a patient with rheumatoid disease.*

Discussion

Raised alkaline phosphatase occurred particularly in patients in whom the disease was most active and severe. Thus it correlated with a high ESR and lower serum iron and patients more often had lymphadenopathy and a positive Waaler-Rose test. A few with a raised alkaline phosphatase were observed over many months and remission of disease activity was associated with return of alkaline phosphatase to normal values. Corticosteroid therapy produced

Table *Differences between the two groups each of fifteen Rheumatoid Patients*

Group		*High alkaline phosphatase* (15)	*Control* (15)
Corticosteroid therapy		5	10
Active disease		15	9
Lymphadenopathy		5	1
ESR (mean) (mm./1st hr)		81	53 †
Biochemical values (mean)	Alkaline phosphatase (KA units)	24	10
	Albumin (g./100 ml.)	3·37	3·77*
	Globulin (g./100 ml.)	3·58	3·16*
	Iron (µg./100 ml.)	27·9	40·7*
	5-nucleotidase (IU/litre)	16·9	4·8**
Waaler-Rose titre (1:32)		10/14	7/14

* $P > 0{\cdot}05$
** $0{\cdot}01 > P > 0{\cdot}002$
† $0{\cdot}02 > P > 0{\cdot}01$

clinical improvement with a simultaneous fall in alkaline phosphatase.

The significantly higher 5-NT in the high alkaline phosphatase group is strong evidence that the alkaline phosphatase is of hepatic origin, for Hill and Sammons (1967) showed that an elevated 5-NT is virtually specific for hepatic dysfunction. The parallel fall of 5-NT and alkaline phosphatase in response to corticosteroids (Fig. 1) and in spontaneous remissions supports a common origin. There were no clinical stigmata of liver disease and other tests of liver function, such as the bilirubin and serum glutamic oxaloacetic transaminase, were normal.

The alternative source of the raised alkaline phosphatase is osteoblastic activity, as suggested by Frank and Klemmayer (1968) who showed that the mean serum alkaline phosphatase was higher in rheumatoid patients than in a control group with degenerative arthritis. There is no evidence to support this hypothesis and we found that the serum calcium and phosphate and bone radiographs were similar in the two groups.

Recently hepatic dysfunction has been demonstrated in Felty's syndrome (Blendis, Ansell, Lloyd Jones, Hamilton, and Williams, 1970), but there is said to be remarkably little evidence of any hepatic abnormality, anatomical or functional, in classical rheumatoid disease (*Brit. med. J.*, 1970; Gardner, 1965). Nevertheless, in the past, abnormal serum proteins and flocculation tests, regarded as indicating liver dysfunction, have been reported (Lefkovits and Farrow, 1955), although such tests did not have the specificity of the 5-NT estimation. Sievers, Julkunen, Ruutsalo, and Hurri (1964) and Langness (1969) found abnormal BSP retention in 41 per cent. and 81 per cent. of patients in their respective series of cases of rheumatoid disease. Our results confirm the serum protein abnormalities, but we found few with increased BSP retention.

In addition to biochemical changes there is histological evidence of hepatic involvement in rheumatoid disease. Rosenberg, Baggenstoss, and Hersch (1944) reported changes in the liver in their *post mortem* series, although they were uncertain of their significance. Langness (1969) found minor non-specific abnormalities in one-third of 120 needle biopsies in rheumatoid patients, and we have seen a similar periportal infiltrate in some specimens (Fig. 2). In view of these non-specific findings, we did not feel justified in trying to obtain liver tissue as part of the present investigation.

The pathogenesis of the liver disturbance is obscure. There is no evidence to implicate hepatotoxic drugs, alcohol, or hepatitis, and the normal transaminases and normal hepatic architecture found on biopsy make hepatocellular damage unlikely. 5-NT has been found to be a valuable index of biliary stasis and in conjunction with a normal

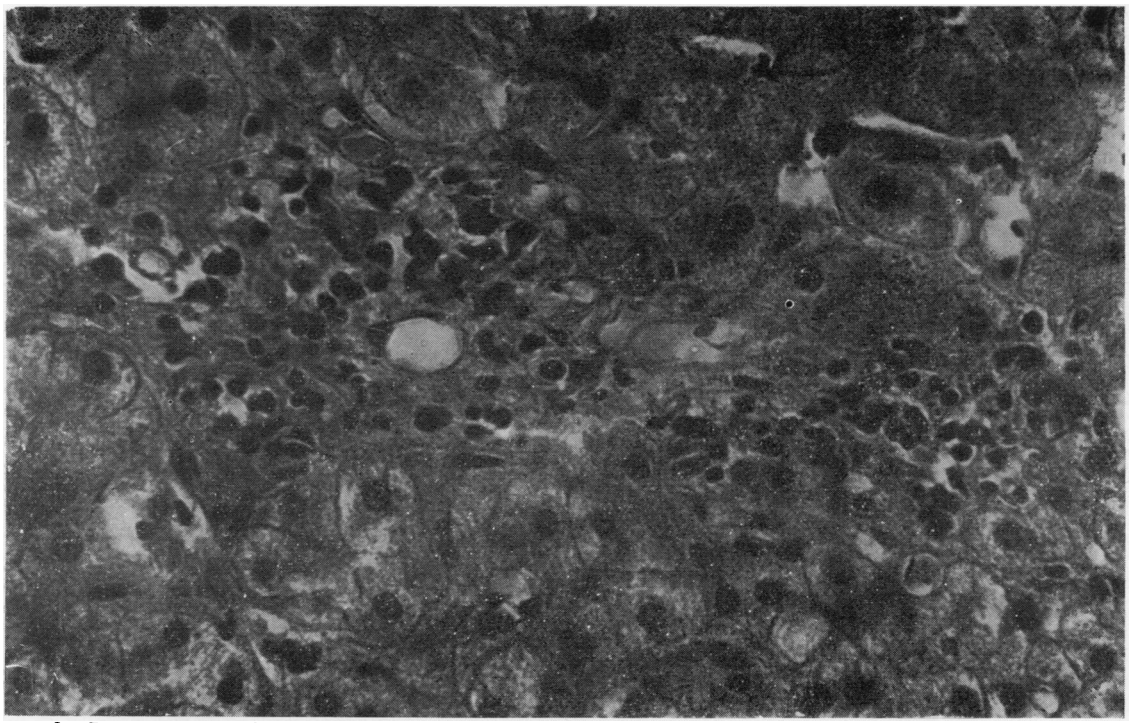

FIG. 2 *Biopsy specimen from liver of rheumatoid patient, showing periportal infiltrate of lymphocytes and plasma cells.* × 800.

serum bilirubin would suggest intrahepatic biliary obstruction (Hill and Sammons, 1967). Similar histological and biochemical abnormalities are frequently seen, for example, in some cases of Crohn's disease and ulcerative colitis (Eade, 1967), and are perhaps non-specific features of inflammatory disease. Amyloidosis may occur in rheumatoid disease, its frequency *post mortem* (7 to 20 per cent.) (Cruickshank, 1957; Gardner, 1962; Gedda, 1955) being higher than that recognized in life (5 to 10 per cent.) (Arapakis and Tribe, 1963). The organs involved by amyloid are most commonly the kidney and gastrointestinal tract; only rarely is the liver involved by secondary amyloidosis in rheumatoid disease.

Our observation of the raised 5-NT shows that the alkaline phosphatase is derived from the liver. The frequency with which the serum alkaline phosphatase is raised was shown in our previous series, when 26 of 100 consecutive rheumatoid admissions to hospital had values greater than 14 KA units/100 ml. (Kendall and others, 1970). Hepatic involvement is, therefore, not uncommon in rheumatoid disease and the liver must be added to the list of organs commonly affected by the rheumatoid process.

Summary

We have investigated the significance of a raised serum alkaline phosphatase in rheumatoid disease by comparing a group of 15 rheumatoid patients having a high alkaline phosphatase (> 14 KA units/100 ml.) with a matched control group of rheumatoid patients in whom the alkaline phosphatase was normal. A high alkaline phosphatase was associated (i) with activity of rheumatoid disease assessed clinically and by laboratory investigations and (ii) with a raised serum 5-nucleotidase, which is specific for liver disease. The hepatic changes are usually slight and may be a response to chronic inflammatory disease. However, evidence from the present study and from a review of the literature suggests that the liver is commonly involved by the rheumatoid process.

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