

# Malabsorption in rheumatoid disease

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Rheumatoid disease is a systemic disorder involving many organs. Though abdominal symptoms are common, possibly due in many cases to drugs, little is known of the structure and function of the bowel in this disease. Gastrointestinal disturbances occur in other collagen disorders (O'Neill, 1961) and may cause impaired absorption (Toivonen, Pitkänen, and Siurala, 1964; Scudamore, Green, Hoffman, Rosevear, and Tauxe, 1968). Small intestinal abnormalities in rheumatoid patients could play a part in causing the nutritional disturbances and weight loss which are common when the disease is active. Moreover an association between joint and bowel disease is well established, since arthropathy is an occasional complication of Crohn's disease and ulcerative colitis (Ansell and Wigley, 1964; Bowen and Kirsner, 1965) and in Whipple's disease there is a specific malabsorption syndrome. We have, therefore, studied a series of patients with rheumatoid disease to assess the degree of nutritional disturbance and the evidence for malabsorption.

## Material and methods

### PATIENTS

28 patients were studied during a stay in hospital. They were assessed clinically, radiologically, and serologically, and according to the revised ARA criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959), sixteen had classical, ten definite, and two probable rheumatoid arthritis. The results of xylose tests performed on seven patients before this study have also been included.

### ABSORPTION STUDIES

The xylose test was performed by giving 5 g. d-xylose in 300 ml. water and collecting the urine for an initial 2-hour and further 3-hour period. Results for the 2 hours and the total 5 hours are compared with similar results obtained after a 5 g. intravenous dose (Kendall, 1970). An excretion of less than 1.3 g. in 5 hours is accepted as abnormal. The 2-hour result, which is a better guide to intestinal absorption, should be over 0.7 g. (Sammons, Morgan, Frazer, Montgomery, Philip, and Phillips, 1967). Xylose excretion decreases with age because of impairment of renal function, making it difficult to compare

groups of patients of different ages (Kendall, 1970). The results have therefore been corrected for age by expressing them as the percentage of the mean value for each decade. This is designated the decade mean fraction (DMF).

Faecal fats were estimated on a 72-hour specimen (Van den Kamer, Huinink, and Weyers, 1949). The patients were placed on a 100 g. fat diet 2 days before the stool collection was started. More than 5 g. stool fat per day is abnormal (Raffensperger, D'Agostino, Manfredo, Ramirez, Brooks, and O'Neill, 1967). Intestinal absorption of vitamin B<sub>12</sub> was studied in two patients, using the method of Schilling (1953) in which 0.5 mg. vitamin B<sub>12</sub> was given together with one capsule of concentrated hog intrinsic factor (IF) after an overnight fast and the urine collected for 24 hours. The remaining eleven patients were studied using the Dicapac modification of the technique and only results with IF have been plotted. Normal subjects excrete more than 10 per cent. of the dose.

### OTHER LABORATORY INVESTIGATIONS

Biochemical and haematological estimations were performed in the routine laboratory by standard methods in order to assess the degree and extent of deficits within the patients. Bromsulphthalein (BSP) retention was measured at 5, 25, and 45 min. after an intravenous dose of 5 mg./kg. Normal subjects retain less than 5 per cent. at 45 min.

Jejunal biopsies were obtained using a Crosby capsule and were examined by standard histological and, in four cases, electron microscopical techniques.

## Results

### A. NUTRITIONAL SURVEY

#### *Serum albumin* (Fig. 1)

Nine (32 per cent.) of 28 results were below 3.5 g./100 ml. and the mean value was 3.6 g./100 ml.

#### *Serum folate* (Fig. 1)

Fourteen (74 per cent.) of nineteen results were below 4 ng./ml. and three (16 per cent.) were below 2 ng./ml. The mean value was 2.9 ng./ml.

#### *Serum cholesterol and serum vitamin B<sub>12</sub>* (Fig. 1)

All were within the normal range.

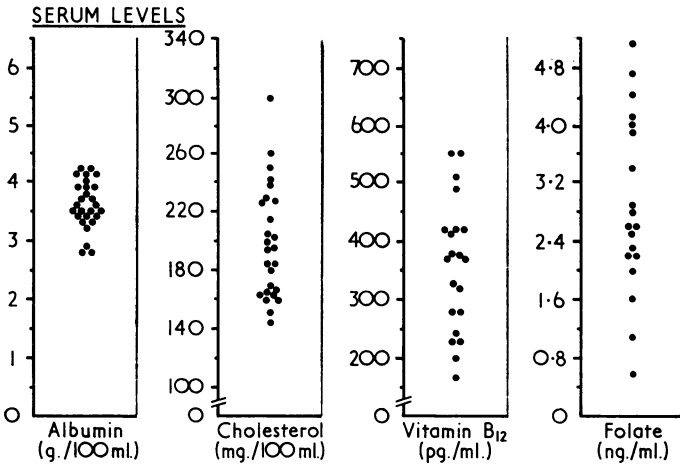


FIG. 1 Scattergrams showing serum levels of albumin, cholesterol, vitamin B<sub>12</sub>, and folate in 28 patients with rheumatoid disease.

**Haemoglobin**

Of the 28 patients, fourteen had a haemoglobin below 12 g./100 ml.

**Serum calcium**

Seven patients had a level less than 9 mg./100 ml.

**Serum iron**

23 had a level less than 60 µg./100 ml., but the iron-binding capacity (IBC) was not raised in any and was less than 250 µg./100 ml. in two-thirds; a feature of many chronic inflammatory disorders.

There was no correlation between the serum albumin and the IBC.

5-hour less than 1.3 g. in four (11.4 per cent.) When these results were corrected for age and expressed as decade mean fractions the 2-hour excretion was low in eight cases (22.8 per cent.) and the 5-hour in two (5.7 per cent.). After intravenous xylose, the excretion was low in five (15.6 per cent.) and four (12.5 per cent.) respectively. Seven of the eight patients with low 2-hour excretions also had intravenous studies, so that an oral/intravenous fraction could be calculated. This was less than 40 per cent. in four patients, indicating intestinal malabsorption (Kendall and Nutter, 1970), whereas in the remaining three subjects, low xylose excretion was due to impaired renal function.

**B. ABSORPTION STUDIES**

**(1) Xylose absorption (Fig. 2)**

After a 5 g. oral dose the 2-hour excretion was less than 0.7 mg. in seven patients (20 per cent.) and the

**(2) Faecal fat (Fig. 3, overleaf)**

Of fifteen patients studied, six excreted more than 5g./24 hrs and three more than 7 g./24 hrs.

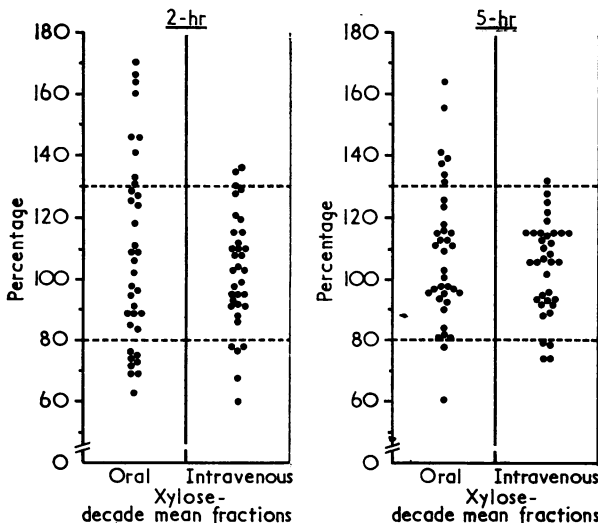


FIG. 2 Scattergrams of urinary excretion of xylose after oral and intravenous loads expressed as decade mean fractions. Dotted lines indicate normal range.

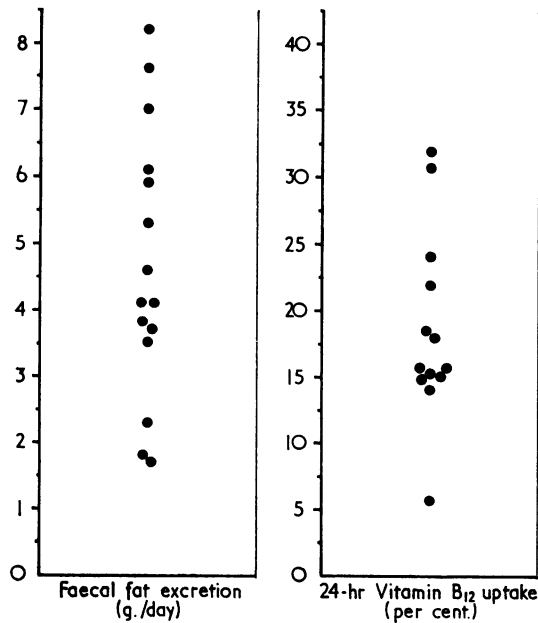


FIG. 3 Scattergram of faecal fat excretion and vitamin B<sub>12</sub> absorption.

### (3) Vitamin B<sub>12</sub> absorption (Fig. 3)

Thirteen patients were studied in the presence of intrinsic factor and only one excreted less than 15 per cent. in 24 hrs. Eleven were studied without additional intrinsic factor and none of these malabsorbed the vitamin, indicating adequate gastric secretion of intrinsic factor.

Drug therapy may influence intestinal absorption (Kendall, Nutter, and Hawkins, 1971). The effects of treatment on the tests of absorption in this study

are difficult to evaluate since many patients were taking more than one preparation. Abnormal absorption tests could not be correlated with any of the individual drugs used (Table).

### C. INTESTINAL HISTOLOGY

Thirteen patients had a biopsy of the fourth part of the duodenum or first loop of the jejunum. Using the dissecting microscope, finger-like villi with leaf forms were seen on the surface of all biopsies. Three patients showed 'fusion' of some villi to form short ridges. These appearances may be found in any patient who undergoes jejunal biopsy for abdominal symptoms in this country and cannot be considered abnormal.

The surface epithelium was histologically normal in all patients. Three patients had a slight increase in lymphocytes and plasma cells in the lamina propria associated with minor distortion of the villi. Two of these three subjects had clusters of haemosiderin-containing macrophages in the lamina propria of the villous tips, suggesting old haemorrhage. There was no correlation between these minor histological changes and the finding of ridges on dissecting microscopy.

Electron microscopy was performed on the biopsies of four subjects and confirmed that the epithelial cells were normal. No other abnormalities were noted.

### D. LIVER FUNCTION (Fig. 4, opposite)

Serum alkaline phosphatase was raised in 25 per cent. and 5-nucleotidase was raised in 17 per cent. An abnormal BSP retention at 45 mins occurred in 40 per cent. However, only one patient had a raised SGOT and two a raised SGPT.

Table Mean values and standard deviations for xylose absorption (as decade mean fraction), faecal fat excretion, and serum folate related to drug therapy

Drug therapy	No. of cases	Xylose 2-hr oral (g.)	No. of cases	Faecal fat (g./24 hrs)	No. of cases	Folic acid (ng./ml.)
Salicylates	16	105.8 (30.61)	4	5.01 (2.01)	7	3.34 (2.02)
Indomethacin	12	99.9 (26.55)	6	5.28 (2.05)	8	3.04 (2.33)
Steroids	16	105.2 (38.71)	5	5.13	5	2.64 (1.97)
Phenylbutazone	4	106.5 (26.83)			3	2.13 (0.71)
Gold	3	124.3 (22.01)				
None	3	143.7 (46.69)				

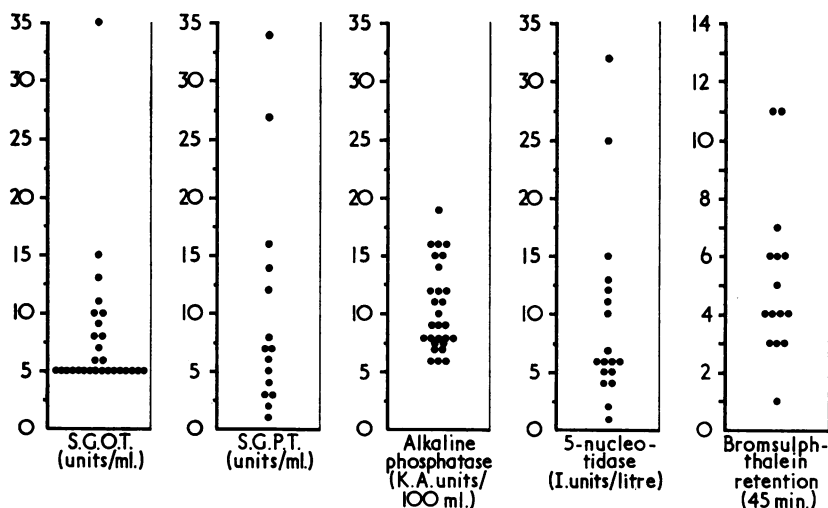


FIG. 4 Scattergram of liver function tests. Normal values for SGOT and SGPT 0-20 units; alkaline phosphatase and 5-nucleotidase 3-13 units; Bromsulphthalein retention less than 5 per cent. at 45 min.

### Discussion

The results indicate that a proportion of rheumatoid patients have evidence of malabsorption of xylose and fat, although small bowel morphology is normal. Vitamin B<sub>12</sub> absorption was impaired in only one case and all serum levels were normal; similar findings have been reported by Pitcher, Lindsay, and Hill (1970).

A low xylose excretion in rheumatoid disease was reported by Gamble, Abbruzzese, Gray, and Bayles, (1969). This study confirms that xylose tolerance is frequently impaired. However, the low intravenous results show that this is due to renal dysfunction in half of the cases. The remainder appear to have true xylose malabsorption which cannot be explained by intestinal mucosal disease. Malabsorption is best detected at the 2-hour collection (Sammons and others, 1967) and six of our patients who showed impaired absorption at 2 hours would not have been detected at a single 5-hour collection. There is no evidence of bacterial overgrowth or rapid intestinal transit. Drugs are known to cause malabsorption (Faloon, 1970), and indomethacin, which is widely used in the treatment of rheumatoid disease, has been shown to increase the rate of gastric emptying and to impair xylose absorption (Kendall and others, 1971). Our patients were frequently taking a number of drugs, one or more of which may have impaired absorption. We were unable to demonstrate a correlation between any one preparation and malabsorption, but the effects of combinations of drugs could not be assessed in such a small series.

The finding of steatorrhoea, albeit mild, in six out of fifteen patients was surprising. In addition to the causes of malabsorption already mentioned, the possibilities of hepatic disease, pancreatic disease,

and malnutrition remain. Evidence of liver dysfunction was found in our patients (Fig. 4) but was unlikely to have been sufficient to cause steatorrhoea. Pancreatic function has been studied in a few cases and is usually normal (Pettersson, Wegelius, and Skrifvars, 1970). Many rheumatic patients are malnourished, and since malnutrition and starvation can cause malabsorption (Herskovic, 1969) this factor may be important. The absence of structural abnormalities in the jejunal mucosa is in agreement with the findings of Pettersson and others (1970). We failed to find evidence of villous atrophy (Toivonen and others, 1964), amyloid (Pettersson and others, 1970), or vasculitis as described in rectal biopsies (Schneider and Dobbins, 1968). Electron microscopy of the jejunal mucosa also failed to show any abnormalities and, in particular, there was no evidence of bacillary bodies, which further suggests that there is no close relationship between seropositive rheumatoid disease and Whipple's disease.

This study shows once again that some patients with rheumatoid disease have laboratory evidence of malnutrition. Although it is tempting to attribute at least some of this deficiency to malabsorption, it must be emphasized that the incidence of malnutrition assessed by biochemical and haematological parameters exceeds that of malabsorption. Thus, it is likely that other factors, such as decreased dietary intake and excessive consumption of these substances by the inflammatory process, are more important. Moreover, a proportion of the abnormal absorption tests may be due to factors such as impaired renal function and drug therapy.

### Summary

Malabsorption has been detected in a small group of rheumatoid patients. 40 per cent. had mild

steatorrhea. A low xylose excretion occurred in 23 per cent. which was due to renal impairment in half the cases. Vitamin B<sub>12</sub> absorption and small bowel histology were usually normal. The cause of the malabsorption remains uncertain.

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