Absorption of vitamin B₁₂ in rheumatoid arthritis

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Since auto-immunity may possibly be a common denominator in pernicious anaemia, thyroid dysfunction, and the rheumatic diseases, the suggested increased incidence of pernicious anaemia in rheumatoid arthritis (Partridge and Duthie, 1963) is of considerable interest. Their figure of 1.4 per cent., which was five times higher than in their patients with other musculoskeletal disorders, was based on a retrospective study of the case notes of some 8,000 patients. However, the diagnosis of pernicious anaemia was often presumptive, as many patients had not had a marrow examination or had not been shown to be achlorhydric or to have a malabsorption of vitamin B₁₂. In those cases in which vitamin B₁₂ malabsorption had been demonstrated, the effect of intrinsic factor had not been assessed. Further retrospective studies of the incidence of pernicious anaemia in rheumatoid arthritis are likely to produce similar incomplete data. It is widely accepted, however, that the incidence of latent pernicious anaemia is considerably higher than that of the overt disease (Witts, 1960), and it would therefore be expected that a population with a high incidence of pernicious anaemia would also show a high incidence of latent malabsorption of vitamin B₁₂. Couchman, Bieder, Wigley, and Glenday (1968) reported malabsorption of vitamin B₁₂ in fifteen out of 52 cases of rheumatoid arthritis, but based their assessment largely on the result of a single Schilling test without further and confirmatory investigations. In the study reported here, vitamin B₁₂ absorption was measured in 100 patients with rheumatoid arthritis with a full investigation of all those who had an abnormal Schilling test result, to confirm and to define their malabsorption of the vitamin.

Patients and methods

100 unselected but consecutive patients with definite or classical rheumatoid arthritis were studied, of whom 66

were women. All had been admitted to the Oxford Regional Rheumatic Diseases Research Centre, Stoke Mandeville Hospital, for medical or surgical reasons. No patient with a history of gastrointestinal disorder or operation was included, an exception being made in six patients with symptoms of peptic ulceration. Only one patient gave a family history of pernicious anaemia. Sjögren's syndrome, sometimes associated with poor gastric secretion (Buchanan, Cox, Harden, Glen, Anderson, and Gray, 1966), was found in another patient, but her symptoms were mild.

86 per cent. of the patients were over the age of 40 years. Since the incidence of any complication increases with the duration of the primary disease, it should be noted that in 77 per cent. the duration of the rheumatoid arthritis was 5 years or more and in 53 per cent. 10 years or more (Table I).

Table I *Age and duration of disease*

<i>Age (yrs)</i>	<i>No. of cases</i>	<i>Duration of disease (yrs)</i>	<i>No. of cases</i>
Under 30	3	Less than 5	23
31 to 40	11	5 to 9	24
41 to 50	25	10 to 14	25
51 to 60	23	15 to 19	13
61 to 70	28	20 to 29	11
Over 70	10	30 and over	4

The absorption of ⁵⁷Co-labelled vitamin B₁₂ was measured by the urinary excretion method (Schilling, 1953), normal renal function being established by a creatinine clearance and blood urea estimations. In any patient with an abnormal Schilling test, the test was repeated in case the abnormality arose from incomplete urine collection. Where the results were again abnormal, the hepatic uptake of ⁵⁷Co-B₁₂ (Glass, Boyd, Gellin, and Stephanson, 1954) was measured using a shielded but uncollimated Burndepht scintillation counter. Approximate quantitation of the uptake was measured by counting the administered material immediately after ingestion with the counter over the epigastrium. The effect of intrinsic factor of vitamin B₁₂ absorption was also assessed by the Schilling method.

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Results

Of the 100 patients investigated, 92 showed completely normal absorption of vitamin B₁₂ with an excretion of 12 per cent. or more of the dose in a 24-hour urine collection.

Of the remaining eight, five had repeatedly abnormal Schilling tests of between 4 and 8 per cent., but in each case hepatic uptake was normal, ranging from 42 to 62 per cent. of the dose (Table II).

Table II *Patients with repeatedly abnormal Schilling tests not suffering from pernicious anaemia*

Patient no.	Schilling (per cent.)		Hepatic uptake of ⁵⁷ CoB ₁₂	Histamine test meal
	Part I	Part II*		
1	6	4	42	Normal
2	7	8	44	Normal
3	7	7	48	Normal
4	4	4	62	Normal
5	7	8	42	Normal

*plus intrinsic factor

The normal hepatic uptake in these five patients was in contrast to their low urinary excretion of the labelled vitamin B₁₂ but this did not appear to be due to any obvious defect in the renal function (Table III).

Table III *Renal function in patients with repeatedly abnormal Schilling tests and normal hepatic uptake of ⁵⁷CoB₁₂*

Patient no.	Blood urea	Creatinine clearance
1	29	108
2	22	99
3	26	116
4	30	101
5	41	90

The remaining three patients were all females (Table IV) with histamine-fast achlorhydria. Low

Schilling tests, well within the pernicious anaemia range, were confirmed in two of the three patients by a low hepatic uptake; one patient died of pneumonia before this test could be performed.

(1) In the first patient a diagnosis of overt pernicious anaemia was based on megaloblastic marrow with a low serum vitamin B₁₂, a low Schilling test which improved with intrinsic factor, and the haemoglobin level responding to vitamin B₁₂. Both gastric parietal cell and intrinsic factor antibodies were present.

(2) The second patient had a low Schilling test, confirmed by a low hepatic uptake. The Schilling test returned to normal with intrinsic factor. There were no antibodies to intrinsic factor, although gastric parietal cell antibodies were demonstrable. Since the serum vitamin B₁₂ was normal, this would appear to be a latent case of pernicious anaemia.

(3) The third patient had a low Schilling test on two occasions, confirmed by a low hepatic uptake. Serum vitamin B₁₂ levels were between 120 and 130 pg./ml. The response to intrinsic factor was poor, however, suggesting the possibility of a malabsorption syndrome. Gastric biopsy showed mild atrophic gastritis, and d-xylose and faecal fat tests were normal, as were barium meal and follow-through x rays. On balance, this would appear to be another case of latent pernicious anaemia.

Discussion

The results of this study show that, of the 100 patients investigated, three showed malabsorption of vitamin B₁₂ with results that lay well within the range expected in pernicious anaemia. In the remaining 97 patients, vitamin B₁₂ absorption was entirely normal, with no patients showing results in the intermediate range—seen in patients with malabsorption syndrome or in those who had had partial gastrectomies or had a strong family history of pernicious anaemia. There was thus no suggestion of a sizeable group of patients in whom the vitamin

Table IV *Clinical particulars of three patients with a possible diagnosis of overt or latent pernicious anaemia*

Patient no.	1	2	3
Age (yrs)	59	74	57
Hb (g. per cent.)	9.1	12.4	10.9
Schilling (per cent.)	2	2	2; 2
Schilling + intrinsic factor (per cent.)	7	16	4
Hepatic uptake ⁵⁷ CoB ₁₂	18	18	2
Histamine test meal	Achlorhydria	Achlorhydria	Achlorhydria
Serum vitamin B ₁₂ (pg./ml.)	28	265	120
Sternal marrow	Megaloblastic		
Barium test meal	Normal	Normal	Normal
Hb response vitamin to B ₁₂ (g. per cent.)	9 to 13	None	None
Parietal cell antibody	+	+	—
Intrinsic factor antibody	++	—	—

B₁₂ absorption had become subnormal though not yet within the pernicious anaemia range. This is in contrast to the expected high incidence of individuals with some degree of malabsorption of vitamin B₁₂ which might be expected in a population with a high incidence of overt pernicious anaemia.

Of the three patients with confirmed malabsorption of vitamin B₁₂, one was an overt case of pernicious anaemia. The reported incidence of pernicious anaemia in south-east England is 0.85 per 1,000 (Scott, 1960). However, most patients with the disease are over 40 years of age and many authors report a predominance of women patients, so that the incidence in a predominantly female population, the majority of whom were over 40 years of age, could be expected to be several times higher than this. Mosbech (1952) reported that the incidence of this disease in Denmark in persons over age 40 varied between 1.7 per 1,000 (males: 50–59 years) and 4.4 per 1,000 (females: 70–79 years). Our finding of only a single case in 100 patients with rheumatoid arthritis does not therefore lend significant support to the view that pernicious anaemia is more common in patients with this disease. Our observations are also supported by those of Carter, Ardeman, Winocour, Perry, and Chanarin (1968), who found only one patient with pernicious anaemia among 92 rheumatoid arthritics screened by serum vitamin B₁₂ measurements and tests for intrinsic factor and parietal cell antibody. They also reported that the incidence of gastric parietal cell antibody in their patients did not differ significantly from that expected in patients of similar age and sex.

In considering the incidence of latent pernicious anaemia in this series (those patients with definite malabsorption of vitamin B₁₂ associated with histamine-fast achlorhydria but without overt megaloblastic change), comparison of our figures with other series presents some difficulties. McIntyre, Hahn, Conley, and Glass (1959) found only one malabsorber in 97 normal subjects, but only twenty of these were over 40 years of age. Witts (1960), basing his estimates on reported percentages of normal persons who have achlorhydria and the

percentage of achlorhydrics showing malabsorption of vitamin B₁₂, has suggested that about 5 per cent. of the population over the age of 40 years might be expected to show some degree of malabsorption of the vitamin. The percentage in a largely female population might well be higher still, and, on this basis, the present study certainly does not suggest any increase in latent malabsorption of vitamin B₁₂ in rheumatoid arthritis.

Finally, it may be considered doubtful whether the overall incidence of megaloblastic anaemia of any type is increased in rheumatoid arthritis. In the series of Partridge and Duthie (1963), the incidence of megaloblastic anaemia was 13.8 per 1,000, and it seems likely that their patients included a considerable number suffering from megaloblastic anaemia due to folic acid deficiency, a condition which is not uncommon in patients with rheumatoid arthritis (Gough, McCarthy, Read, Mollin, and Waters, 1964). Scott (1960) reported an incidence of pernicious anaemia in the Edinburgh region of two per 1,000, and Davis and Brown (1953) reported that in Glasgow the disease was three times as common among their female patients as in males. The expected incidence of pernicious anaemia alone in an elderly, predominantly female, Scottish population might thus be almost the same as the overall incidence of megaloblastic anaemia due to both vitamin B₁₂ and folic acid deficiency as reported by Partridge and Duthie in their rheumatoid arthritis patients.

Summary

Of 100 patients with rheumatoid arthritis, impaired absorption of vitamin B₁₂ was found in only three cases. A previous report has suggested that the incidence of pernicious anaemia in rheumatoid arthritis is five times higher than in patients with other musculoskeletal disorders. The results of the present study do not support this suggestion.

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