RHEUMATOID ARTHRITIS AND PERNICIOUS ANAEMIA

BY

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There are reports of an association between megaloblastic anaemia and rheumatoid arthritis. Partridge and Duthie (1963) found megaloblastic anaemia in 1.38 per cent. (35 cases) of 2,544 rheumatoid arthritis patients, as opposed to 0.27 per cent. (15 cases) of 5,515 controls. Of the 35 rheumatoid patients with megaloblastic anaemia, 27 were thought to have Addisonian pernicious anaemia, an incidence of 1.05 per cent. Gough, McCarthy, Read, Mollin, and Waters (1964) found two patients with megaloblastic anaemia among 46 rheumatoid patients selected at random. It is not clear from their paper whether one of these had pernicious anaemia, or whether the anaemia in both was due to folate deficiency. Deller, Urban, Ibbotson, Horwood, Milazzo, and Robson (1966) found one example of macrocytic anaemia due to folate deficiency among 41 rheumatoid patients.

The purpose of this study was two-fold: to determine the frequency of megaloblastic anaemia, vitamin B₁₂, and folic acid deficiency in rheumatoid arthritis, and to determine whether the auto-immune phenomena present in pernicious anaemia are also found in rheumatoid arthritis.

Patients Studied

92 patients (76 female and 16 male) suffering from definite rheumatoid arthritis according to the criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) were studied and were compared with a control group matched for age and sex. The mean age of the rheumatoid group was 57.7 years (range 19 to 85) and that of the control group 55 years. The mean duration from onset of the disease in the rheumatoid patients was 10 years (range 1 to 35). All patients were seen by one of us (M.E.C.); the rheumatoid patients were attending hospital with active disease, and were being treated with anti-rheumatic drugs, either singly or in combination. Most of the controls were healthy persons attending a varicose vein clinic, but a few were in hospital for miscellaneous conditions.

Methods

A sample of blood was obtained from all patients, and estimations were performed of serum vitamin B₁₂, using *Lactobacillus leichmannii*, and of serum folate using, *Lactobacillus casei*. Intrinsic factor antibodies were sought by an immunological method as described by Ardeaman and Chanarin (1963). Parietal cell antibodies were determined by an immunofluorescent technique.

Further investigations were carried out on all patients showing abnormal results, namely repetition of the original tests, followed by a Schilling test and gastric juice analysis with estimation of volume, pH, and intrinsic factor before and after histamine.

Results

Megaloblastic Anaemia

Nearly half the patients had anaemia of less than 12 g. per cent. and this was either due to iron deficiency or was the anaemia of chronic disease (Cartwright, 1966). Two of the 92 patients with rheumatoid arthritis had a megaloblastic anaemia. In one, this had been investigated before this study and was due to folate deficiency. The other patient, a woman of 71 years, was found to have pernicious anaemia. Her haemoglobin concentration was 15.0 g./100 ml.

Serum Vitamin B₁₂ Levels

Three patients with rheumatoid arthritis and one control had serum vitamin B₁₂ levels of less than 150 µµg./100 ml. (Table I). One of the three rheumatoid patients with a serum B₁₂ level of 45 µµg./

TABLE I
SERUM B₁₂ LEVELS (µµg./ml.)

Series	R.A.	Controls
Less than 150	3	1
150-200	7	4
More than 200	82	85
Total Cases	92	90

ml. had pernicious anaemia, but the other two, with levels of 115 and 140 $\mu\text{g.}/100$ ml. respectively, absorbed labelled vitamin B_{12} normally.

Schilling tests and gastric juice analysis were performed on the seven rheumatoid patients and four controls whose serum B_{12} levels were between 150 and 200 $\mu\text{g.}/100$ ml.; all but one had free acid in the gastric juice, all had normal intrinsic factor concentration, and all absorbed vitamin B_{12} normally. The patient with histamine-fast achlorhydria had adequate amounts of intrinsic factor present (34 units/ml.).

Serum Folate Levels

The mean serum folate level was not significantly different in the two groups (Table II): 5.3 $\text{m}\mu\text{g.}/\text{ml.}$ in the rheumatoid group as opposed to 5.7 $\text{m}\mu\text{g.}/\text{ml.}$ in the controls. However, there were more patients with levels between 2 and 5 $\text{m}\mu\text{g.}/\text{ml.}$ in the rheumatoid group than in the control group. This level is rather indeterminate from the diagnostic point of view.

TABLE II
SERUM FOLATE LEVELS ($\text{m}\mu\text{g.}/\text{ml.}$)

Series	R.A.	Controls
Less than 2	0	3
2-5	39	19
More than 5	53	70
Total Cases	92	92

Gastric Antibodies

Antibodies against intrinsic factor were absent (Table III). Parietal cell antibodies were present in seven out of 87 rheumatoid patients (8.0 per cent.) and in eight out of 92 controls (8.7 per cent.). Neither parietal cell nor intrinsic factor antibodies were found in the one patient with pernicious anaemia.

Discussion

The finding of two patients with megaloblastic anaemia among 92 rheumatoid patients whose mean age is 57.7 years is insufficient evidence for an association of these disorders. We have seen four

TABLE III
GASTRIC ANTIBODIES

Series	R.A.		Controls	
	No. Tested	Positive	No. Tested	Positive
Parietal cell	87	7 8 per cent.	92	8 8.7 per cent.
Intrinsic factor	86	0	91	0

more patients with both diseases since closing the admission to this study, but the numbers still remain small.

Similarly, the data of Partridge and Duthie (1963) do not provide conclusive evidence of an increased incidence of megaloblastic anaemia in rheumatoid arthritis. The expected frequency of pernicious anaemia in the 40 to 69-year age group is 16 per 1,000 (Mosbech, 1952). This does not allow for the higher incidence in any population with a female predominance. The frequency in Partridge and Duthie's series above the age of 40 was 13 per 1,000.

An association between pernicious anaemia and rheumatoid arthritis is not supported by the incidence of parietal cell antibodies in the patients with rheumatoid arthritis. The percentage of rheumatoid patients with parietal cell antibodies in six studies including our own varies from 4.7 to 16.3 per cent. (Table IV) and this is the expected range of these antibodies in women of the age groups in these studies (Doniach and Roitt, 1964). In conditions with which there is a known association with pernicious anaemia, notably thyroid disease, Addison's disease, and hypoparathyroidism, the incidence of parietal cell antibodies is of the order of 20 per cent. or more (Blizzard, Chee, and Davis, 1966).

Summary

The incidence of anaemia, parietal-cell and intrinsic factor antibodies, serum vitamin B_{12} , and folate levels were observed in 92 patients with rheumatoid arthritis and a matched control group. There were no significant differences between the two groups.

TABLE IV
PARIETAL CELL ANTIBODIES IN RHEUMATOID ARTHRITIS

Authors	Date	No. with Antibodies	No. Tested	Percentage with Antibodies
Bernhardt, Burkett, Fields, and Killian	1965	2	27	7.3
Doniach and Roitt	1964	—	—	—
Goudie and Buchanan	1967	34	223	11.0
Irvine, Davies, Teitelbaum, Delamore, and Wynn Williams ..	1965	3	64	10.8
Present study	1967	7	87	4.7
te Velde, Abels, Hoedemaeker, Arends, and Nieweg	1964	13	80	8.0
				16.3

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La polyarthrite rhumatoïde et l'anémie pernicieuse

RÉSUMÉ

On étudia chez 92 patients atteints de polyarthrite rhumatoïde et dans un groupe de témoins comparables la fréquence de l'anémie, les anticorps contre la cellule pariétale et contre le facteur intrinsèque, la vitamine B₁₂ dans le sérum et le taux du folate. On ne trouva pas de différences significatives entre les deux groupes.

La poliartritis reumatoide y la anemia perniciosa

SUMARIO

En 92 enfermos con poliartritis reumatoide y en un grupo de testigos comparables se investigaron la frecuencia de la anemia, los anticuerpos contra la célula parietal y contra el factor intrínseco, la vitamina B₁₂ sérica y las cifras de folato. No hubo diferencias significativas entre estos dos grupos.