INCIDENCE OF MACROCYTIC ANAEMIA IN RHEUMATOID ARTHRITIS

BY

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Moderate anaemia of a hypochromic normocytic type is common in patients suffering from rheumatoid arthritis. The presence of macrocytic anaemia in patients with rheumatoid arthritis, however, has been reported on only a few occasions. This association was regarded as coincidental by Short, Bauer, and Reynolds (1957), due to the presence of Hodgkin's disease (Varadi, 1960), or due to the use of anticonvulsant drugs (Chanarin, Laidlaw, Loughridge, and Mollin, 1960). Dixon (1961) described a case of rheumatoid arthritis with megaloblastic anaemia for which no other obvious cause was found.

In a study of the bone-marrow in 64 patients with rheumatoid arthritis, Richmond, Gardner, Roy, and Duthie (1956) found no consistent abnormality in cytology, apart from a moderate increase in plasma cells in about one-third of their cases. Reviewing the literature, these authors found that megaloblastosis had been reported in only one paper in 3 out of 21 cases (Marmont, 1948).

Two patients with long-standing rheumatoid arthritis who developed a macrocytic megaloblastic anaemia were described by Doig, Girdwood, Duthie, and Knox (1957). Both presented with most of the features of Addisonian pernicious anaemia, but the absorption of labelled vitamin B_{12} from the gut was normal. The gastric juice of each patient improved the absorption of labelled vitamin B_{12} when given to patients with Addisonian pernicious anaemia, indicating the presence of intrinsic factor.

This report describes the results of a survey of the records of patients attending the Rheumatic Diseases Unit at the Northern General Hospital, Edinburgh. The survey was designed to ascertain the incidence and characteristics of macrocytic anaemia associated with rheumatoid arthritis. The records of patients attending for conditions other than rheumatoid arthritis were used as controls.

Material and Methods

The records of 8,059 patients attending the unit during 1947 to 1961 have been reviewed. Of these, 2,544 suffered from rheumatoid arthritis. The composition of the two groups by age and sex is shown in Table I. In the control group approximately 44% were suffering from osteoarthrosis, 24% had symptoms due to intervertebral disk degeneration or non-articular forms of rheumatism, and the remainder suffered from a miscellaneous group of disorders with musculo-skeletal symptoms.

TABLE I.—*Composition of the Groups*

Group	Age in Years	Male	Female	Total	% of Group
Rheumatoid arthritis	0–39	148	264	412	16·2
	40–59	547	844	1,391	54·7
	60+	161	580	741	29·1
Controls	0–39	496	877	1,373	24·9
	40–59	757	1,606	2,363	42·8
	60+	453	1,326	1,779	32·3

Patients in whom a diagnosis of macrocytic anaemia had been made in the past were recalled for further examination. Patients no longer available because of default in attendance or death were included only where reasonable evidence of the presence of macrocytic anaemia was found in the case records.

The methods for measuring haemoglobin (Hb), red-cell count (R.B.C.), packed cell volume (P.C.V.), and erythrocyte sedimentation rate (E.S.R.) were those described by Richmond *et al.* (1956). Hb 100% was equivalent to 14.8 g. of Hb per 100 ml. of whole blood. Labelled vitamin B_{12} absorption, using either isotope ^{58}Co or ^{56}Co, was studied by the faecal recovery test of Heinle, Welch, Scharf, Meacham, and Prusoff (1952), or by the urinary excretion test of Schilling, Clatanoff, and Korst (1955). Folic acid absorption was measured by the method of Girdwood (1953, 1956). Gastric secretion was measured by the augmented histamine test (Kay, 1953).

Results

A total of 50 patients with macrocytic anaemia were discovered—15 among controls and 35 among patients with rheumatoid arthritis. The criteria used for the diagnosis of macrocytic anaemia are shown in Table II. The incidence of macrocytic anaemia in patients with rheumatoid arthritis was 1.38%, and in controls 0.27% (Table III).

TABLE II.—*Criteria for Diagnosis of Macrocytic Anaemia*

Criteria for Inclusion	Rheumatoid Arthritis	Controls
Megaloblastic marrow. Macrocytic blood picture	21	4
Macrocytic blood picture with response to vitamin B_{12}	12	9
Long-term therapy	2	2
Total	35	15

TABLE III.—*Incidence of Macrocytic Anaemia in the Groups*

Group	Total No. of Cases	No. with Macrocytic Anaemia	Percentage Incidence
Rheumatoid arthritis	2,544	35	1·38
Controls	5,515	15	0·27

Controls.—Of the 15 patients with macrocytic anaemia in the control group 14 suffered from Addisonian pernicious anaemia; in one case the anaemia was the result of a primary malabsorption syndrome with folic-acid deficiency.

Rheumatoid Arthritis.—Of the 35 cases in this group 27 were accepted as cases of Addisonian pernicious anaemia—in 11 the diagnosis was confirmed by the demonstration of malabsorption of vitamin B_{12}; in 10 achlorhydria and megaloblastic bone-marrow were present; and in 6 the diagnosis was based on the presence of macrocytic anaemia responding to the administration of vitamin B_{12}. One patient with malabsorption of vitamin B_{12} was shown to have diverticulosis of the jejunum. In this case the absorption of the vitamin was restored to normal by the administration of antibiotics.

Among the remaining seven patients with macrocytic anaemia absorption of vitamin B_{12} from the gut was

normal although the marrow was megaloblastic in each case. In all seven cases the absorption of folic acid was normal. In only one case could the administration of drugs have contributed to the development of anaemia. The main features of these seven patients and one additional case from another hospital (Case 8) are summarized in Table IV, and in view of the unusual characteristics of the anaemia their case histories are summarized.

Cases 1 and 2 have been described in a previous communication (Doig *et al.*, 1957), but are included in this series because of subsequent developments.

Case Reports

Case 1.—A woman aged 65 had had rheumatoid arthritis for 16 years associated with hypothyroidism. The bone marrow was megaloblastic, achlorhydria was demonstrated, serum vitamin B_{12} was low (50 $\mu\mu$g./ml.). Absorption of both vitamin B_{12} and folic acid was normal. Her gastric juice was shown to have intrinsic-factor activity. The administration of prednisolone led to correction of anaemia and reversion to normoblastic erythropoiesis. Withdrawal of the steroid was followed by relapse and the marrow again became megaloblastic. Correction was again achieved by prednisolone and maintained by administration of vitamin B_{12}. Two and a half years later reinvestigation revealed malabsorption of vitamin B_{12}.

Case 2.—A woman aged 66 had had rheumatoid arthritis for 26 years. A diagnosis of pernicious anaemia had been made nine years previously, but marrow biopsy had not been performed, nor had gastric secretion been investigated. Liver extract was given for four years, but was then stopped because the diagnosis was in doubt. At the time of investigation the marrow was megaloblastic, but absorption of both vitamin B_{12} and folic acid was normal. Intrinsic-factor activity was demonstrated in her gastric juice. Administration of prednisolone was followed by reversion to normal of the haematological indices, and this was maintained by vitamin B_{12}. Eighteen months later malabsorption of the vitamin had developed.

Case 3.—A woman aged 65 had had rheumatoid arthritis for three years. The marrow was known to have been normoblastic two years previous to admission. *Investigations:* Hb, 76%; R.B.C., 2,630,000/c.mm.; P.C.V., 33%; M.C.V., 125 cubic microns; M.C.H.C., 30%; E.S.R., 75 mm./1 hour. Bone-marrow—megaloblastic. Achlorhydria present. Gastric biopsy—gastric atrophy. Serum vitamin B_{12}, 180 $\mu\mu$g./ml. Faecal recovery after 0.5 μg. of 56Co vitamin B_{12}—31% (normal). Folic-acid absorption normal. Barium meal—small hiatus hernia. Administration of vitamin B_{12}, 100 μg. weekly, was followed by a return to normal of the blood picture and bone-marrow.

Case 4.—A woman aged 68 had had rheumatoid arthritis for 18 years. Five years previously the marrow was reported as possibly megaloblastic. Folic acid was given without improvement. One year before the present investigation a moderate degree of normochromic anaemia was recorded. *Investigations:* Hb, 59%; R.B.C., 1,940,000/c.mm; P.C.V., 25%; M.C.V., 129 cubic microns; M.C.H.C., 31%; E.S.R., 55 mm./1 hour. Marrow—increased proerythroblasts with some frank megaloblasts. Augmented histamine test—1.5 mEq of free acid in post-histamine hour. Serum vitamin B_{12}, 130 $\mu\mu$g./ml. Faecal recovery after 0.5 μg. of ^{58}Co vitamin B_{12}—1%. Folic acid absorption normal. Barium meal—hiatus hernia. Blood urea nitrogen—92 mg./100 ml. As there was evidence of gastro-intestinal bleeding the patient was transfused. Subsequent treatment with vitamin B_{12} was effective, although evidence of impaired renal function persisted.

Case 5.—A woman aged 66 had had rheumatoid arthritis for 15 years. Nine years previously she had had a severe degree of macrocytic anaemia which responded to injections of liver extract; but some degree of anaemia persisted in spite of apparently adequate doses of liver and vitamin B_{12}. Treatment was discontinued three years before admission. *Investigations:* Hb, 70%; R.B.C., 2,730,000/c.mm.; P.C.V., 32%; M.C.V., 117 cubic microns; M.C.H.C., 31%. Bone-marrow—hypoplastic, with occasional intermediate megaloblasts. Augmented histamine test—achlorhydria. Faecal recovery after 0.5 μg. of ^{58}Co vitamin B_{12}—54%. Barium meal normal. Absorption of folic acid normal. Treatment with vitamin B_{12} was followed by reversion to a normal blood picture.

Case 6.—A woman aged 62 had had rheumatoid arthritis for two years. On her first admission to hospital two years after the onset of symptoms Hb was 50% and the bone-marrow was megaloblastic. Signs of subacute degeneration of the cord were present. Vitamin B_{12} was effective. She was later admitted to hospital for further study. *Investigations:* Hb, 71%; R.B.C., 4,450,000/c.mm.; P.C.V., 32%; M.C.V., 81 cubic microns; M.C.H.C., 30%; E.S.R., 64 mm./1 hour. Bone-marrow—normoblastic. Faecal recovery after 0.5 μg. of ^{58}Co vitamin B_{12}—43.7%. Folic-acid absorption normal. Augmented histamine test—achlorhydria. Barium meal—small hiatus hernia. Eighteen months later malabsorption of vitamin B_{12} was demonstrated.

Case 7.—A man aged 42 had had rheumatoid arthritis for 12 years. He had been taking barbiturates for 10 years, and during the year prior to admission had taken 30–40 gr. (2–2.6 g.) cyclobarbitone daily. Haematuria had developed three weeks before admission. *Investigations:* Hb, 50%; R.B.C., 2,200,000/c.mm.; P.C.V., 23%; M.C.V., 104 cubic microns; M.C.H.C., 32%; E.S.R., 52 mm./1 hour. Marrow—megaloblastic. Faecal recovery after 0.5 μg. of ^{58}Co vitamin B_{12}—41%. Folic-acid absorption normal. Augmented histamine test—free acid present. Intravenous pyelogram—calculi present in both kidneys. Renal tubular acidosis was present. The response to vitamin B_{12} was excellent.

Details of a patient belonging to this group and attending another hospital have been made available to us.

Case 8.—A woman aged 49, with rheumatoid arthritis of 20 years' duration, was admitted for the investigation of jaundice and macrocytic anaemia. *Investigations:* Hb, 42%; R.B.C., 1,660,000/c.mm.; P.C.V., 17%; M.C.V., 102 cubic microns; M.C.H.C., 36%; E.S.R., 91 mm./1 hour. Marrow—megaloblastic. Serum vitamin B_{12}—136 $\mu\mu$g./ml. Augmented histamine test—5.4 mEq of hydrochloric acid in post-histamine hour. Faecal recovery after 0.5 μg. of ^{58}Co vitamin B_{12}—53.9 and 43.1%. Folic-acid absorption normal. Gastric biopsy—occasional parietal cells; abundant glands, serous in type.

TABLE IV

Case No.	Sex and Age	Duration of Arthritis (Years)	Marrow	Serum Vit. B_{12} Level ($\mu\mu$g. ml.)	Gastric Acidity (mEq Post-histamine hr.)	Labelled Vit. B_{12} Recovered in Stools (% of Oral Dose)	Folic-acid Absorption	Faecal Fat Excretion (g. Daily)	Barium Meal and Follow-through
1	F 65	16	Megaloblastic	50	Achlorhydria	47 48	Normal	3·5	Normal
2	F 66	26	,,	50	,,	50 55	,,	2·1	,,
3	F 65	3	,,	180	,,	31	,,	4·5	Hiatus hernia
4	F 68	18	,,	130	1·5	1	,,	—	,, ,,
5	F 66	15	,,	—	Achlorhydria	54	,,	—	Normal
6	F 62	2	,,	—	,,	43·7	,,	1·4	Hiatus hernia
7	M 42	12	,,	—	Free acid	41	,,	3·6	—
8	F 49	20	,,	136	5·4	53·9 43·1	,,	—	—

She was transfused with 2 pints (1,140 ml.) of packed cells and started on vitamin B_{12}; reticulocyte response, 26.5%. Hb had risen to 73% in two months.

Discussion

The results of this survey would indicate that the incidence of macrocytic anaemia among patients with rheumatoid arthritis is significantly higher than among patients of similar age and sex referred to hospital on account of other disorders giving rise to musculoskeletal symptoms.

The incidence of pernicious anaemia in the control group (0.25%) conformed closely to the incidence among the general population given by Tudhope and Wilson (1960) and Scott (1960).

The incidence of macrocytic anaemia among the patients with rheumatoid arthritis was 1.38%. Among 19 of the 35 patients in whom absorption of radioactive vitamin B_{12} was studied, 12 showed significant degrees of malabsorption. In one case this was shown to be due to jejunal diverticulosis and in two other patients partial gastrectomy and gastro-enterostomy may have been contributory causes.

In seven patients and in another outside the present series (Case 8), in all of whom the marrow was megaloblastic, absorption of vitamin B_{12} was normal or only slightly impaired. Absorption of folic acid was normal in all cases. In three of these eight cases free acid was present in the gastric juice. Excessive consumption of cyclobarbitone may have been a contributory cause in one instance In two patients (Cases 1 and 2) it was possible to obtain evidence for the presence of intrinsic factor in the gastric juice.

The response to prednisolone in these two patients is difficult to explain in the light of our present knowledge. Doig *et al.* (1957) reported similar responses in four patients with Addisonian pernicious anaemia, in two with coeliac disease, and in one who developed megaloblastic anaemia after partial gastrectomy. There was no significant alteration in serum-vitamin-B_{12} levels during steroid therapy. Other workers (Frost and Goldwein, 1958; Gordin, 1959; Kristensen and Friis, 1960) claim to have shown an increase in absorption of vitamin B_{12} in a proportion of cases with pernicious anaemia treated with steroids. Such an action would not explain the response in patients still absorbing the vitamin normally.

Taylor (1959) and Schwartz (1960) have shown that the sera of some patients with pernicious anaemia will inhibit the action of intrinsic factor in promoting the absorption of vitamin B_{12} from the gut. Taylor (1959) demonstrated that the inhibitory action can be markedly reduced following the administration of hydrocortisone to the donors of the serum. He suggested that the inhibiting factor in these sera might be an antibody to intrinsic factor and that it may have been suppressed or modified in some way in the donors by the administration of hydrocortisone. There is no direct evidence at present for the existence of such an antibody, but, if present, its action might explain certain characteristics of these patients who developed megaloblastic anaemia responsive to parenteral vitamin B_{12} while absorption of the vitamin from the gut appeared to be normal. Such an antibody might combine with a vitamin-B_{12}/intrinsic-factor complex during absorption. This might have the effect of preventing the utilization of vitamin B_{12} by the marrow. The administration of large doses by the parenteral route would overcome this barrier. The action of steroid hormones might be on the lines already suggested by Taylor (1959). It is of interest to note that three patients in this series (Cases 1, 2, and 6) subsequently developed malabsorption of vitamin B_{12}. It is possible that an antibody to intrinsic factor might ultimately damage the cells producing in it the gastric mucosa.

Summary

The incidence and characteristics of macrocytic anaemia among 2,544 patients with rheumatoid arthritis and 5,515 controls are reviewed.

The incidence in rheumatoid arthritis was 1.38% as compared with 0.27% in controls.

Normal absorption of vitamin B_{12} was demonstrated in 8 out of 20 cases of rheumatoid arthritis with megaloblastic marrows.

Intrinsic factor activity was demonstrated in the gastric juice of two patients with megaloblastosis who were absorbing vitamin B_{12} normally. Later both developed malabsorption of the vitamin.

All patients with macrocytic anaemia associated with rheumatoid arthritis responded to the administration of vitamin B_{12}, although less promptly than is usual in Addisonian pernicious anaemia.

The evidence for postulating the presence of an antibody to intrinsic factor which might prevent the utilization of vitamin B_{12} after absorption is discussed.

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