tion between the presence of a cutaneous response and the histology of the tumour.

It is suggested that the reactions obtained are true immunological reactions, and that they are due to the presence of specific cancer antigens in the tumours concerned.

We would like to thank Mr. Harold Edwards and Mr. J. G. Murray for their help and advice in the carrying out of this work and in the preparation of this paper. We are also grateful to the members of the surgical staff of King's College Hospital for their co-operation in this study. The work was carried out during the tenure of whole-time grants from the British Empire Cancer Campaign.

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# Folic-acid Deficiency in Rheumatoid Arthritis

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Megaloblastic anaemia (other than pernicious anaemia) associated with rheumatoid arthritis has been reported in two patients by Doig *et al.* (1957) and in a further six patients by Partridge and Duthie (1963). The cause of the megaloblastic anaemia in these patients was uncertain, but it was suggested that it might be due to failure to utilize vitamin $B_{12}$ absorbed from the diet (Partridge and Duthie, 1963).

During the past two years we have studied four patients with rheumatoid arthritis who suffered from megaloblastic anaemia other than pernicious anaemia. In each instance the cause of megaloblastic anaemia was folic-acid deficiency. The purpose of this paper is to report the findings in these patients and the results of a subsequent survey of the incidence of folic-acid deficiency in a randomly selected group of patients with rheumatoid arthritis. In the course of this survey two further patients with megaloblastic anaemia were discovered and details of these are also given. A summary of these observations was reported at a Scientific Meeting of the Royal College of Physicians of London on 30 November 1962 (Gough *et al.*, 1962) and in a letter (Mollin *et al.*, 1963).

## Patients Studied

*Patients with Megaloblastic Anaemia.*—Six patients with megaloblastic anaemia were studied: four of these were admitted to the Hammersmith Hospital and two were found among the survey group of 46 patients with rheumatoid arthritis who were selected at random from the diagnostic index of the Records Department at the Bristol Royal Infirmary. These two patients were admitted to the Department of Medicine, Bristol Royal Infirmary, for further investigation.

*The Survey.*—Forty-six patients were studied in the survey. They attended the Department of Medicine at the Bristol Royal Infirmary for a day. An assessment was made of the duration of the disease, and the functional disability of the patients was graded as "mild," "moderate," or "severe." Details of the drugs used in treatment were noted, and if a patient was found to be taking barbiturates or anticonvulsant drugs he was excluded from the survey. A careful dietary history was taken and the haemoglobin, haematocrit, white-cell count, and E.S.R. were measured and a blood film was examined. Serum was taken for serum folate and vitamin $B_{12}$ assays, and the urinary excretion of formimino-glutamic acid was estimated. Similar studies were made on 57 control subjects who were all healthy non-medical employees of the United Bristol Hospitals.

## Methods

1. *Haematological methods* were those described by Dacie (1956).

2. *Urinary Formimino-glutamic Acid.*—Patients were given an oral loading dose of 15 g. of histidine and urinary Figlu was detected by conventional voltage electrophoresis on cellulose acetate strips (Kohn *et al.*, 1961). The method is not strictly quantitative, but a rough grading of the Figlu "spot" was made as +, ++, or +++, where the +++ spot was equivalent to a urinary Figlu concentration of more than 500 $\mu$g./ml.

3. *Serum-folate levels* were measured by microbiological assay with *Lactobacillus casei* ATCC 7469 (Waters and Mollin, 1961) (normal range 5.9–21 m$\mu$g./ml.). Patients with megaloblastic anaemia due to folic-acid deficiency have serum-folate levels less than 4 m$\mu$g./ml. (Waters and Mollin, 1961).

4. *Serum-vitamin-$B_{12}$ levels* were measured by microbiological assay using *Lactobacillus leichmanii* (Spray, 1955) (normal range 140–900 $\mu\mu$g./ml.). Patients with pernicious anaemia have serum-vitamin-$B_{12}$ concentrations of less than 100 $\mu\mu$g/ml. (Mollin, 1960 ; Matthews, 1962).

5. *Dietary History.*—Detailed dietary histories were obtained by the hospital dietitian. An assessment was made of the average daily intake of folic acid, vitamin $B_{12}$, ascorbic acid, iron, protein, and total calories, using the values quoted by McCance and Widdowson (1960). The figures quoted are for the uncooked dietary content.

(It must be stressed that the calculated "folic-acid" content of the diet is an arbitrary figure, and serves only as an index for comparison of the dietary "folic-acid" intake of different groups of patients. The figures obtained by this method do

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not necessarily indicate the available folate in the diet—firstly, because they are based on microbiological assay methods that do not protect the labile folates in natural material (Dawbarn *et al.*, 1958 ; Romine, 1960), and, secondly, because it is uncertain how much of the microbiologically active folates in the diet are available to man. Furthermore, cooking leads to considerable but variable loss of dietary folate activity.)

6. *Folic-acid absorption* was assessed by measuring the serum-folic-acid level by microbiological assay with *Streptococcus faecalis* after a standard oral test dose of folic acid (Chanarin *et al.*, 1958). The tests were usually carried out after the patients had been treated with folic acid for some weeks.

7. *Absorption of $^{58}$Co-labelled Vitamin $B_{12}$.*—This was assessed by measuring the urinary excretion of radioactivity after an oral test dose of 1 μg. of $^{58}$Co-vitamin-$B_{12}$ (Schilling, 1954). A parenteral "flushing" injection of 1,000 μg. of non-radioactive vitamin $B_{12}$ was given at the same time as the test dose. In our hands patients with pernicious anaemia excrete less than 5% of an oral test dose of 1 μg., and usually less than 2.5% ; normal subjects excrete more than 10%.

8. *Jejunal Biopsy.*—Intestinal specimens were obtained using the Crosby capsule with the Bristol modified head (Read *et al.*, 1962). After fixation they were examined under a dissecting microscope and photographed. Histological sections were subsequently prepared by conventional techniques.

9. *Fat Balance.*—Patients were given a diet containing 100 g. of fat, and after a three-day equilibration stools were collected for five days.

10. *Augmented histamine test meal* was carried out as described by Kay (1953).

## Results in Patients with Megaloblastic Anaemia and Rheumatoid Arthritis

The haematological and gastro-enterological features of the six patients are summarized in Tables I and II. The haematological responses to treatment are given in Table III.

All suffered from a mild or moderately severe megaloblastic anaemia. In five patients (Cases 1, 2, 4, 5, and 6) this appeared to be due to uncomplicated folic-acid deficiency. In these patients the serum-folate levels were subnormal, and Figlu excretion was increased above normal, and the serum levels of vitamin $B_{12}$ were well within the normal range. All of these patients responded to treatment with folic acid (Table III). The other patient (Case 3) also suffered from folic-acid deficiency, but her serum-vitamin-$B_{12}$ level, although outside the range found in patients with megaloblastic anaemia due to uncomplicated vitamin-$B_{12}$ deficiency, was subnormal. While vitamin-$B_{12}$ deficiency may have been a contributing cause of the megaloblastic anaemia in this patient, treatment with vitamin $B_{12}$ after folic-acid therapy produced no further improvement in her condition.

TABLE I.—*Haematological Details of Patients with Megaloblastic Anaemia Associated with Rheumatoid Arthritis*

| Case No. | Age and Sex | Duration of Disease (Years) | Hb (g./100 ml.) | M.C.V. (μ³) | Retic. (%) | Marrow | Serum Folate (mμg./ml.) | Serum Vitamin $B_{12}$ (μμg./ml.) | Figlu |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 38 F | 10 | 8·0 | 108 | 1·0 | Megaloblastic | 2·5 | 300 | + |
| 2 | 55 M | 9 | 8·5 | 111 | 1·2 | ,, | 2·6 | 450 | + |
| 3 | 53 F | 5 | 9·6 | 105 | 0·5 | ,, | 3·2 | 130 | ± |
| 4 | 42 M | 10 | 10·0 | 106 | 1·0 | ,, | 2·5 | 215 | + |
| 5 | 70 F | 10 | 10·4 | 102 | 0·6 | ,, | 2·9 | 420 | +++ |
| 6 | 52 F | 1 | 10·1 | 110 | 1·5 | ,, | 1·7 | 355 | +++ |

TABLE II.—*Gastro-intestinal Function in Patients with Megaloblastic Anaemia Associated with Rheumatoid Arthritis*

| Case No. | Augmented Histamine Test | Schilling Test (1 μg. $^{58}$Co-Vitamin $B_{12}$) | | Folic-acid Absorption Peak Serum Concentration (mμg./ml.) | Fat Balance (g./Day Excreted) | Barium Meal | Jejunal Biopsy | Liver-function Tests |
|---|---|---|---|---|---|---|---|---|
| | | Done Alone | Done with I.F. | | | | | |
| 1 | Free acid | 10·5 | — | 60 | 2·0 | Normal | Normal | Normal |
| 2 | ,, ,, | 22·0 | — | 47 | — | ,, | — | ,, |
| 3 | Achlorhydria | 4·5 | 15·0 | 52 | 1·7 | ,, | Normal | ,, |
| 4 | Free acid | 15·6 | — | 63 | 2·5 | ,, | ,, | ,, |
| 5 | ,, ,, | 8·6 | — | 94 | 1·8 | ,, | ,, | ,, |
| 6 | ,, ,, | 5·2 | — | 140 | 3·2 | ,, | ,, | ,, |

TABLE III.—*Haematological Response to Treatment in Patients with Megaloblastic Anaemia Associated with Rheumatoid Arthritis*

| Case No. | Reticulocyte Response | | | Haemoglobin Increase (g./100 ml.) | | | Barium Meal 5th Day | Treatment |
|---|---|---|---|---|---|---|---|---|
| | Initial (%) | Peak (%) | Day | Initial | 14th Day | 30th Day | | |
| 1 | 1·0 | 7·0 | 11 | 8·0 | 9·8 | 12·2 | Normal | Hospital diet and 15 days on 15 mg. F.A. daily |
| 2 | 1·0 | 6·0 | 7 | 8·5 | 10·5 | 13·5 | ,, | 5 mg. F.A. daily |
| 3 | 2·0 | 3·5 | — | 9·6 | 10·8 | 11·2 | ,, | Hospital diet 15 days ; then 15 mg. F.A. daily |
| 4 | 1·5 | 3·0 | 8 | 10·3 | 10·6 | 11·5 | ,, | 5 mg. F.A. daily |
| 5 | 0·6 | 5·0 | 9 | 10·4 | 11·4 | 11·3 | ,, | 200 μg. F.A. daily ; diet contained |
| 6 | 1·5 | 9·0 | 12 | 10·1 | 10·5 | 12·0 | ,, | 15 mg. F.A. daily and no significant vitamin $B_{12}$ |

The cause of folic-acid deficiency in these patients is uncertain. The results of folic-acid-absorption tests were normal in all of them, and none suffered from the intestinal malabsorption syndrome or liver disease (Table II). None of the patients was receiving butazolidine or barbiturates at the time they became anaemic.

The dietary intake of folic acid and ascorbic acid in these patients was compared with that found in the average British diet (calculated from the National Food Survey, 1960) and in patients with megaloblastic anaemia due to nutritional deficiency of folic acid (Gough *et al.*, 1963). The calculated folate intake of the average British diet was 110 μg./day before cooking, while that of patients with the nutritional deficiency was less than 30 μg./day. The folate intake of the patients with megaloblastic anaemia and rheumatoid arthritis was not as low as in patients with nutritional megaloblastic anaemia but lower than in the average diet.

The cause of the subnormal serum-vitamin-$B_{12}$ level in Case 3 appeared to be defective absorption of vitamin $B_{12}$ (Table II). The results of the radioactive vitamin-$B_{12}$ absorption test were at the upper limit of the range found in patients with Addisonian pernicious anaemia. Absorption was not improved by the administration of carbachol, but rose to within the normal range when the dose was given with intrinsic factor concentrate. The absorption of radioactive vitamin $B_{12}$ was borderline in one other patient (Case 6) and less than normal (10%) in a third patient (Case 5).

## Results in Survey Patients

### Haemoglobin Concentration

Fig. 1 compares the haemoglobin concentrations in the controls and the patients with rheumatoid arthritis. In the normal controls the levels ranged from 13 to 17.2 g./100 ml., with a mean of 15 g./100 ml. The levels in the patients were significantly lower ($t=5.18$ ; $P<0.001$), ranging from 4.4 to 15.6 g./100 ml., with a mean of 13 g./ml. All the control subjects had levels above 13 g./100 ml., but 30% of the patients had levels below this figure. Two patients with low levels—10.4 and 7.5 g./100 ml.—were admitted to hospital and were shown

to have megaloblastic anaemia. These patients have been described fully in the first part of this paper (Cases 5 and 6).

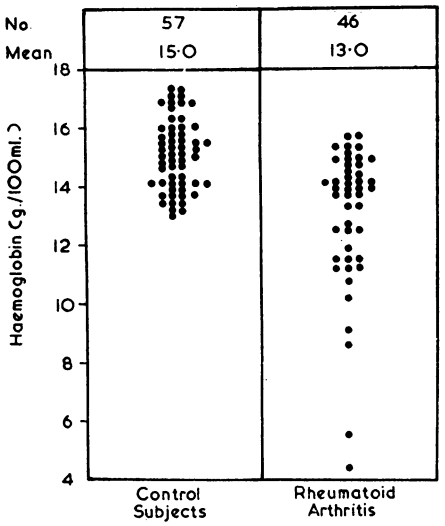


FIG. 1. — Haemoglobin levels of 57 control subjects and 46 patients with rheumatoid arthritis.

## Serum-vitamin-$B_{12}$ level

The levels of the patients ranged from 120 to 810 $\mu\mu$g./ml., with a mean of 353 $\mu\mu$g./ml. Only one patient had a level below the normal range of 140–900 $\mu\mu$g./ml. This patient's serum-vitamin-$B_{12}$ level was 120 $\mu\mu$g./ml., haemoglobin 102% (15.1 g./100 ml), serum folate 5 m$\mu$g./ml., and the Figlu excretion test was negative.

## Serum-folate levels

Fig. 2 compares the serum-folate levels of the controls and the patients. The levels were significantly lower in the patients compared with the controls ($t=7.06$ ; $P<0.001$). Thirty (65%) of the patients had subnormal levels—that is, less than 6 m$\mu$g./ml.—and 15 (33%) had levels of 4 m$\mu$g./ml., or less, and were therefore within the range found in patients with megaloblastic anaemia due to folic-acid deficiency (Waters and Mollin, 1961).

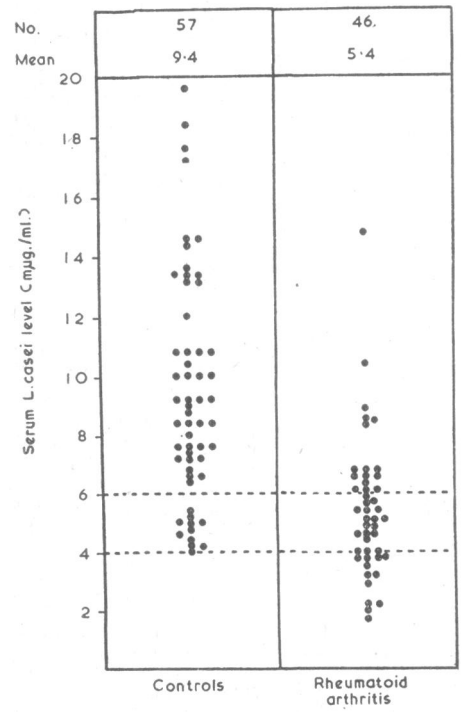


FIG. 2. — Serum-folate levels (*L. casei* assay) in control subjects and patients with rheumatoid arthritis. The horizontal dotted lines represent (1) the *lower* limit of the normal range (6 m$\mu$g./ml.) and (2) the level below which folic-acid deficiency is known to cause megaloblastic anaemia (4 m$\mu$g./ml.)

In contrast, only 11 (19%) of the control subjects have levels less than 6 m$\mu$g./ml., and none of these was below 4 m$\mu$g./ml.

There was no close correlation between the serum-folate levels and the haemoglobin concentration (Fig. 3). Some patients with low serum-folate levels were not anaemic. However, 12 of the 16 patients with haemoglobin concentrations less than 13 g./100 ml. had subnormal serum-folate levels. Two of these patients had obvious megaloblastic anaemia and eight had iron-deficiency anaemia.

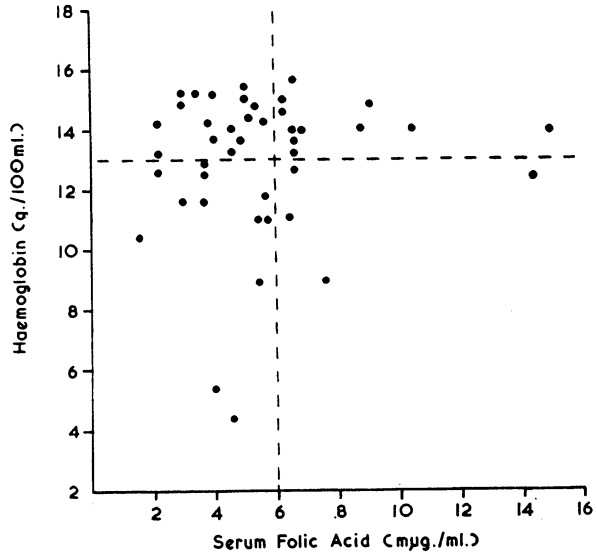


FIG. 3.—Relationship between haemoglobin level and serum-folate levels in patients with rheumatoid arthritis. Although some patients with low serum-folate levels were not anaemic, most patients with haemoglobin levels below 13 g./100 ml. had subnormal serum-folate levels.

## Urinary Excretion of Figlu

None of the controls excreted abnormal amounts of Figlu in the urine after a loading dose of histidine. Of the 30 patients with subnormal serum-folate levels, 22 (73%) excreted excessive amounts of Figlu in the urine. Fig. 4 compares the results of the Figlu test with the serum-folic-acid levels. Although some patients with low serum-folate levels did not excrete Figlu in the urine, all except three patients with increased urinary

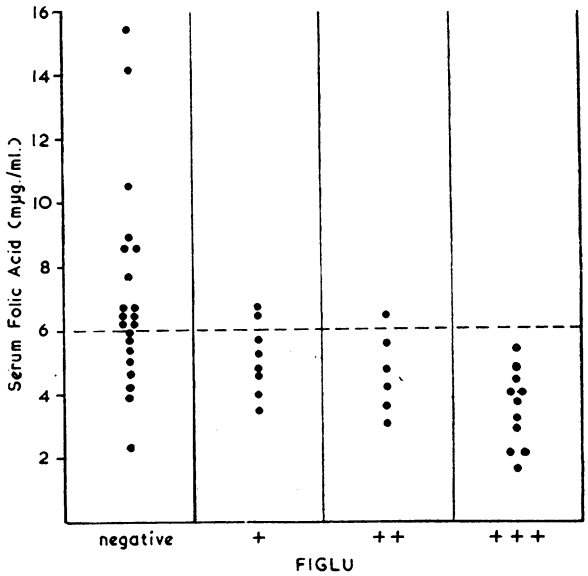


FIG. 4.—Relationship between serum-folate level and the urinary excretion of Figlu. Some patients with subnormal serum-folate levels did not excrete Figlu, but almost all patients with increased urinary excretion (+, ++, and +++) had low serum-folate levels.

excretion of Figlu had subnormal serum-folic-acid levels. All of the patients with + + + Figlu excretion had subnormal serum-folic-acid levels; two of these were the patients with megaloblastic anaemia.

## Dietary History

*Average Daily Intake of Folic Acid.*—Fig. 5 compares the daily folic-acid intake of the patients and controls on the basis of age. We have calculated that the average British diet quoted by the National Food Survey (1960) contains 100 μg./day. Only one of the patients and one of the controls were apparently taking this amount. Four patients and two controls were taking diets containing less than 30 μg., the level below which nutritional folic-acid deficiency is accompanied by megaloblastic anaemia (Gough *et al.*, 1963). However, there was no significant difference between the folic-acid intake of the patients and controls in any age-group.

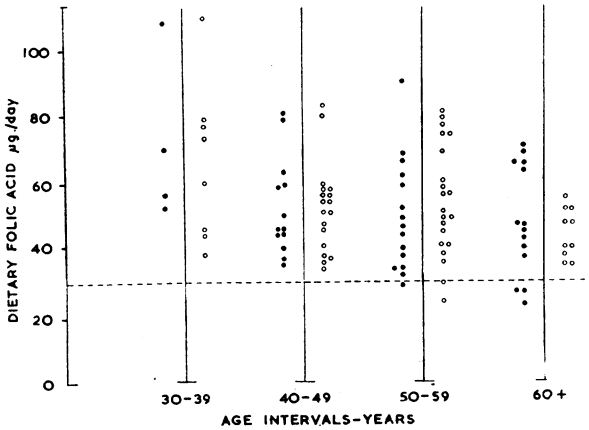


FIG. 5.—Mean daily intake of folic acid, as assessed by dietary history (●=patients, O=controls). The dotted line, drawn at 30 μg./day, represents the intake of folic acid below which nutritional folic-acid deficiency is severe enough to cause megaloblastic anaemia (Gough *et al.*, 1963).

*Average Daily Intake of Ascorbic Acid.*—The ascorbic-acid content of the diet taken by the patients was significantly lower than that taken by the control subjects. Fig. 6 compares the intake of the two groups on the basis of age. The dotted line represents the recommended minimum daily intake—that is, 20 mg./day (B.M.A., 1950). Twenty-eight (61%) of the

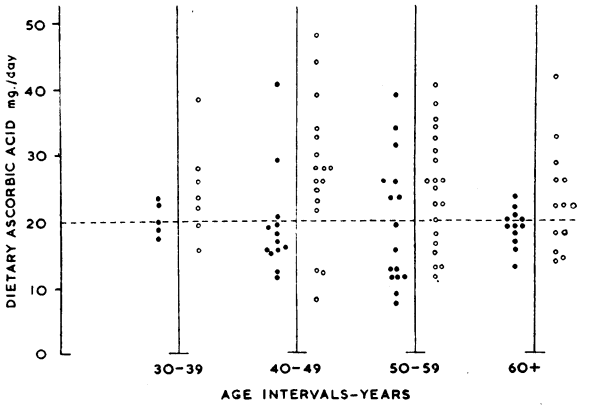


FIG. 6.—Mean daily intake of ascorbic acid (●=patients, O=controls). The dotted line represents the recommended daily intake (B.M.A., 1950).

patients, compared with 15 (26%) of the controls, were taking less than the recommended level. Only in the subjects below the age of 50 was there a statistically significant reduction in intake. At all age levels the difference in ascorbic-acid intake between the patients and the controls could be attributed to the lower consumption by the patients of both fresh fruit and vegetables. Financial considerations and infrequent shopping excursions due to decreased mobility seemed to be the responsible factors.

*Iron, Protein, and Total Calories.*—Although the patients tended to take smaller amounts of iron, protein, and total calories, the difference between the two groups was not significant.

## Clinical Features

*Duration and Severity of the Arthritis.*—There was no relation between our assessment of the severity of the arthritis and evidence of folic-acid deficiency. Similarly, elevation of the E.S.R. as an index of activity of the disease was not related to evidence of folic-acid deficiency; neither was the duration of the disease.

*Associated Clinical Features of the Disease.*—Two clinical features were noted to be associated with evidence of severe folic-acid deficiency. Gross splenomegaly was noted in four patients, three of whom had serum-folate levels below 4 mμg./ml. and strongly positive (+ + +) Figlu excretion tests. Two of these patients also had megaloblastic anaemia. The other clinical finding which was associated with evidence of severe folic-acid deficiency was oedema of the legs and severe hypoproteinaemia. This was observed in two male patients, but was not accompanied by anaemia.

*Drug Treatment of the Disease.*—Difficulty was experienced in assessing the possible relationship between the administration of drugs and evidence of folic-acid deficiency because many patients were treated with several drugs, often simultaneously, and for varying periods of time. However, no correlation was apparent between any one drug or combination of drugs and folic-acid deficiency. Only three patients were not taking drugs. Two of these had mild arthritis and the third moderately severe arthritis. Two of these patients had low serum-folate levels and both excreted excess Figlu. Eleven patients were taking aspirin only; of these, six had low serum-folate levels and seven excreted excess Figlu. It was particularly difficult to assess the effect of treatment with corticosteroids, since these drugs were invariably used in combination with other drugs. Ten patients were taking steroids in combination with aspirin only. Eight had low serum-folate levels and seven excreted excess Figlu. None of the patients was taking barbiturate drugs.

## Discussion

Girdwood (1953) reported that some patients with rheumatoid arthritis retained a greater percentage of injected folic acid than control subjects and suggested that this might indicate the presence of folic-acid deficiency. Our results presented in this paper demonstrate that folic-acid deficiency is common in patients with rheumatoid arthritis and that this deficiency may be the cause of megaloblastic anaemia in some patients. The incidence of folic-acid deficiency was greater in the more anaemic patients in the present survey (Fig. 3), and in the two most anaemic patients the anaemia was mainly due to folic-acid deficiency. However, the importance of folic-acid deficiency as a factor causing anaemia in patients with rheumatoid arthritis is uncertain. This problem can be satisfactorily settled only by a clinical trial of the effect of treatment with folic acid on patients with rheumatoid arthritis. Our experience so far suggests that folic-acid deficiency is not a major factor responsible for the anaemia of rheumatoid arthritis. However, folic-acid deficiency may well contribute to the lack of well-being in these patients, and may also lead to glossitis and the complaint of a sore tongue. Furthermore, such patients are more likely to be severely affected by the administration of drugs such as barbiturates, which may interfere with the utiliza-

tion of folic acid. Thus the patient reported by Chanarin *et al.* (1960) who suffered from megaloblastic anaemia induced by phenobarbitone also suffered from rheumatoid arthritis, and barbiturates precipitated megaloblastic anaemia in one of the patients with rheumatoid arthritis reported by Partridge and Duthie (1963).

The cause of folic-acid deficiency in these patients is uncertain. The patients with megaloblastic anaemia absorbed normal amounts of folic acid from an oral test dose and they had no other evidence of intestinal malabsorption or cirrhosis of the liver. Dietary deficiency of folic acid can give rise to folic-acid deficiency (Herbert, 1962 ; Gough *et al.*, 1963), but the dietary intake of folic acid in most of the patients in the present study was significantly greater than in patients with nutritional megaloblastic anaemia. Furthermore, the dietary intake of folic acid in the patients with rheumatoid arthritis did not differ significantly from that of the controls. The dietary intake of ascorbic acid was significantly lower in the patients with rheumatoid arthritis than in the controls. Whether this played a part in increasing the incidence of folic-acid deficiency in these patients is uncertain.

The part played by drugs in the pathogenesis of folic-acid deficiency associated with rheumatoid arthritis is difficult to assess. Barbiturates and anticonvulsants may precipitate folic-acid deficiency, leading to megaloblastic anaemia, but patients taking these drugs were excluded from the survey. Butazolidine has also been reported to produce megaloblastic anaemia (Robson and Lawrence, 1959), and patients taking this drug were also excluded from the present series. The part played by the various combinations of analgesics and steroids is uncertain. The administration of steroids may affect the utilization of vitamin $B_{12}$ and folic acid, for such treatment has induced haematological remissions in some patients with megaloblastic anaemia (Doig *et al.*, 1957), but we could find no correlation between the ingestion of any one drug or combination of drugs and evidence of folic-acid deficiency.

It has been shown that folic-acid deficiency may result from an increased demand for the vitamin (Chanarin *et al.*, 1958). Cellular proliferation in the joints in rheumatoid arthritis might lead to an increased demand for folic acid, as might also the increased metabolic rate associated with salicylate therapy. The haemopoietic demand for folic acid may also be increased by alimentary blood loss, which often accompanies the administration of salicylates (Scott *et al.*, 1961), or by increased haemolysis. However, red-cell-survival studies with $^{51}Cr$-labelled autotransfused red cells suggest that haemolysis plays only a minor part in the anaemia of rheumatoid arthritis (Lewis and Porter, 1960 ; Biechl *et al.*, 1962). The combination of a borderline dietary intake and an increased demand for the vitamin may well be the cause of folic-acid deficiency in these patients.

The precise incidence of megaloblastic anaemia due to folic-acid deficiency in patients with rheumatoid arthritis is uncertain. Partridge and Duthie (1963) showed that megaloblastic anaemia is commoner in patients with rheumatoid arthritis than in a control group of similar age distribution. In approximately three-quarters of their patients megaloblastic anaemia was thought to be due to Addisonian pernicious anaemia, but the evidence for such a diagnosis in some of their patients was by no means conclusive. However, it has also been our experience that *severe* megaloblastic anaemia in patients with rheumatoid arthritis is usually due to pernicious anaemia. Partridge and Duthie (1963) were uncertain of the cause of megaloblastic anaemia in their patients with rheumatoid arthritis who were not thought to be suffering from Addisonian pernicious anaemia. They suggested that failure of utilization of vitamin $B_{12}$ absorbed from the alimentary tract may have been responsible.

However, as Forshaw (1963) and Mollin *et al.* (1963) have pointed out, the megaloblastic anaemia in these patients could well have been due to folic-acid deficiency. Although two of Partridge and Duthie's patients (Cases 1 and 2) had very low serum-vitamin-$B_{12}$ levels, the significance of these two results is difficult to assess, since the sera were apparently assayed with *L. leichmanii* without the addition of cyanide during the extraction procedure (Doig *et al.*, 1957), which may result in false low levels (Spray, 1955). Furthermore, the serum-vitamin-$B_{12}$ level may be depressed by folic-acid deficiency and rise when the folic-acid deficiency has been corrected (Mollin *et al.*, 1962 ; Forshaw, 1963). The subnormal vitamin-$B_{12}$ absorption and depressed secretion of HCl seen in their Cases 3 and 4, and the subsequent loss of ability to absorb vitamin $B_{12}$ found in Cases 1 and 2, might simply be the result of associated atrophic gastritis. In this connexion it is of interest that the absorption of radioactive vitamin $B_{12}$ and the secretion of HCl were depressed in three of the patients with megaloblastic anaemia reported in this paper. The depression of vitamin-$B_{12}$ absorption was not as severe as in pernicious anaemia but was more typical of the findings in atrophic gastritis (Whiteside, Mollin, Coghill, and Anderson—to be published).

In conclusion these results suggest that the nutritional state of patients with rheumatoid arthritis is unsatisfactory. This may result from the combined effects of inadequate dietary intake, increased requirement, and the disease process itself. In this paper we have been primarily concerned with deficiency of folic acid, but it is likely that there may also be deficiencies of other B group vitamins in these patients, and in this connexion it is of interest that Bett (1962) also found abnormalities of pyridoxine metabolism in patients with rheumatoid arthritis.

The deficiency of folic acid in these patients could readily be relieved by the administration of 100–200 $\mu$g. of folic acid daily, and such treatment would seem justified, particularly if the patients were taking barbiturates. However, patients with rheumatoid arthritis are particularly liable to develop Addisonian pernicious anaemia, and the indiscriminate use of folic acid might be dangerous. The administration of small doses of 100–200 $\mu$g. of folic acid daily is unlikely to precipitate severe subacute combined degeneration in the way that large doses may do (Will *et al.*, 1959). Such treatment—that is, large doses of the acid—might tend to mask the haematological features of vitamin-$B_{12}$ deficiency, so that a patient might ultimately present with neurological complications rather than anaemia. Folic acid should therefore be given only to patients who are under medical supervision or in whom malabsorption of vitamin $B_{12}$ has been excluded.

## Summary

Details are present of six patients with rheumatoid arthritis and megaloblastic anaemia. In each case folic-acid deficiency was shown to be the primary cause, although intestinal absorption of vitamin $B_{12}$ was also depressed in three patients.

A survey of 46 patients with rheumatoid arthritis was then conducted to determine the incidence of folic-acid deficiency, and compared with a series of 57 normal controls.

There was a significant increase in the incidence of anaemia and of biochemical evidence of folic-acid deficiency in the patients with rheumatoid arthritis.

Reasons for the association of megaloblastic anaemia in patients with rheumatoid arthritis are reviewed.

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# Meclozine and Foetal Malformations: A Prospective Study

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Meclozine is an antihistamine with a marked anti-nausea and anti-sickness effect. It is contained in three proprietary preparations marketed in Great Britain: "ancolan" (25 mg. meclozine), "ancoloxin" (25 mg. meclozine with 50 mg. pyridoxine), and "sea-legs" (12.5 mg. meclozine). The first two of these preparations are widely used for the treatment of pregnancy sickness; the third is used chiefly for travel sickness.

In December 1962, almost exactly one year after the first reports of the teratogenicity of thalidomide, attention was called to the possibility that meclozine might be causing foetal malformations (*British Medical Journal*, 1962). The Swedish National Board of Health withdrew the drug from public sale in Sweden and warned doctors not to prescribe it for women in the early months of pregnancy. The evidence which had led them to this decision was not at that time generally available. Almost simultaneously, Watson (1962) published a preliminary report from the Epidemic Observation Unit of the College of General Practitioners in which he referred to "mounting evidence against the safety of ancoloxin in pregnancy."

## Methods

Three groups of pregnancies have been studied, using slightly different techniques. All three were studied prospectively. A few mothers came into more than one group. When these duplicates are excluded we have records of 219 infants born to mothers for whom meclozine was prescribed in the first 12 weeks of pregnancy. In every case the preparation prescribed was ancoloxin.

### Series 1

Early in 1962 a circular letter was sent to all general practitioners practising obstetrics in the Liverpool area, requesting information about pregnant women for whom ancoloxin had been prescribed. The replies included the names of 44 women for whom the drug had been prescribed in the first 12 weeks of pregnancy. For this group the date of the last menstrual period is known, and it has therefore been possible to determine accurately the stage of pregnancy at which the drug was prescribed. It is possible that in this group some of the mothers may not have taken the prescription to the chemist, or may have obtained the tablets but not taken them. However, these prescriptions were issued in 1961 (except for five in January 1962), before the teratogenic effect of thalidomide was known, and it is therefore probable that the majority of these women took the drug. Later, in 1962, after these women had had their babies, the presence of malformations was determined as in Series 2 (below).

### Series 2 and 3

These two series were based on copies of prescriptions kindly provided by the Liverpool Pricing Bureau. All prescriptions for ancoloxin issued in Liverpool in the four-months period November 1961 to February 1962 were used. In several instances prescriptions were issued to the same person on more than one occasion; in these cases only the earliest known prescription is considered. Steps were taken to determine which of the patients to whom the prescriptions were issued had given birth to children after the appropriate time interval. In these series it is certain that the tablets were issued to the patients, although it is possible that in some instances they may not have been taken. In these two series the date of the last menstrual period is known only if the infant was abnormal, when the information is available from the Congenital Abnormalities Register (see below). In calculating the stage of pregnancy at the time of the prescription a 40-weeks gestation period has been assumed in the case of normal infants. Some of the births will, in fact, have been premature, and in these cases the drug will have been prescribed *earlier* in pregnancy than estimated. This factor and the assumption of a 40-weeks gestation mean that some mothers of *normal* babies who took meclozine in the first 12 weeks of pregnancy have been estimated to have taken it

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