**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 B$_{12}$, 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 B$_{12}$, using *Lactobacillus leichmannii*, and of serum folate using, *Lactobacillus casei*. Intrinsic factor antibodies were sought by an immunological method as described by Ardemar 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 B$_{12}$ Levels**

Three patients with rheumatoid arthritis and one control had serum vitamin B$_{12}$ levels of less than 150 μg./100 ml. (Table I). One of the three rheumatoid patients with a serum B$_{12}$ level of 45 μg./

**Table I**

<table>
<thead>
<tr>
<th>Series</th>
<th>R.A.</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 150</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>150-200</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>More than 200</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Total Cases</td>
<td>92</td>
<td>90</td>
</tr>
</tbody>
</table>

**Discussion**

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.
ml. had pernicious anaemia, but the other two, with levels of 115 and 140 μg./100 ml. respectively, absorbed labelled vitamin B₁₂ normally.

Schilling tests and gastric juice analysis were performed on the seven rheumatoid patients and four controls whose serum B₁₂ levels were between 150 and 200μg./100 ml.; all but one had free acid in the gastric juice, all had normal intrinsic factor concentration, and all absorbed vitamin B₁₂ 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 μg./ml. in the rheumatoid group as opposed to 5.7 μg./ml. in the controls. However, there were more patients with levels between 2 and 5 μg./ml. in the rheumatoid group than in the control group. This level is rather indeterminate from the diagnostic point of view.

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 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 B₁₂, 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.

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**Table III**

**GASTRIC ANTIBODIES**

<table>
<thead>
<tr>
<th>Series</th>
<th>R.A.</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal cell</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Intrinsic factor</td>
<td>86</td>
<td>91</td>
</tr>
</tbody>
</table>

**Table IV**

**PARIENTAL CELL ANTIBODIES IN RHEUMATOID ARTHRITIS**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Date</th>
<th>No. with Antibodies</th>
<th>No. Tested</th>
<th>Percentage with Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernhardt, Burkett, Fields, and Killian</td>
<td>1965</td>
<td>2</td>
<td>27</td>
<td>7.3</td>
</tr>
<tr>
<td>Doniach and Roitt</td>
<td>1964</td>
<td>—</td>
<td>—</td>
<td>11.0</td>
</tr>
<tr>
<td>Goudie and Buchanan</td>
<td>1967</td>
<td>34</td>
<td>223</td>
<td>10.8</td>
</tr>
<tr>
<td>Irvine, Davies, Teitelbaum, Delamore, and Wynn Williams</td>
<td>1965</td>
<td>3</td>
<td>64</td>
<td>4.7</td>
</tr>
<tr>
<td>Present study</td>
<td>1967</td>
<td>7</td>
<td>87</td>
<td>8.0</td>
</tr>
<tr>
<td>te Velde, Aela, Hoedemaeker, Arends, and Nieweg</td>
<td>1964</td>
<td>13</td>
<td>80</td>
<td>16.3</td>
</tr>
</tbody>
</table>
We should like to thank the physicians of St. Mary's Hospital who allowed us to study their patients, and we are also indebted to Dr. A. St. John Dixon and to Dr. E. B. D. Hamilton for access to some of their patients. The work was supported by a grant from the St. Mary's Hospital Endowment Fund, which we gratefully acknowledge.

REFERENCES


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.
Rheumatoid arthritis and pernicious anaemia.

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