
NATURE OF ANAEMIA IN RHEUMATOID ARTHRITIS

I. METABOLISM OF IRON

BY

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(RECEIVED FOR PUBLICATION NOVEMBER 1, 1954)

Anaemia of moderate severity is commonly present in patients suffering from rheumatoid arthritis. The degree of anaemia bears a close relationship to the activity of the disease. No completely satisfactory explanation of its presence has ever been advanced. In the past it has been ascribed to "toxic" depression of marrow function, iron deficiency, or a combination of these factors. Iron by mouth was usually prescribed, but results were seldom satisfactory. The characteristics of the anaemia have been studied in detail by a number of investigators in recent years, but a review of their reports reveals no general agreement as to underlying causes.

Nilsson (1948) stated that the anaemia was of a hypochromic and normocytic type. He considered that the red cells were of abnormal shape in that the mean corpuscular volume (MCV) was within normal limits, but the mean corpuscular diameter was decreased. Inadequate haemoglobinization was apparent from a reduction in the mean corpuscular haemoglobin concentration (MCHC). Jeffrey (1952, 1953a) found that the MCV was within the normal range in 74 of 100 cases examined (74 per cent.), whereas the MCHC was less than 30 per cent. (normal range 32-36 per cent.) in 97 of 136 cases (71 per cent.). Ross (1950) confirmed that the anaemia was of hypochromic, normocytic type.

Nilsson (1948) and Jeffrey (1952) examined myelograms from twelve and sixteen patients respectively. No consistent abnormality was reported, but in many instances the haemoglobinization of normoblasts was impaired and the production of immature normoblasts increased.

Cartwright and Wintrobe (1952) reported that free erythrocyte protoporphyrin was increased in ten or fifteen cases of anaemia in rheumatoid arthritis. That this increase was probably independent of changes in free erythrocyte coproporphyrin content was later shown by Krammer and others (1954). These findings were interpreted as being indications of retarded erythropoiesis. In the patients studied by Jeffrey (1953b) the free erythrocyte protoporphyrin varied widely from case to case.

A moderate increase in reticulocytes was noted by Nilsson (1948) in a number of female patients, but he found no evidence of increased haemolysis. Jeffrey (1952, 1953a) measured serum bilirubin, faecal urobilinogen, the number of reticulocytes, and the fragility of red cells in saline. He concluded that haemolysis was not a significant factor in the causation of this anaemia.

Robinson (1943) reported that the anaemia was largely produced by an increase in plasma volume. Jeffrey (1953a) did not consider that changes in plasma volume were of significance. Recently, however, Dixon (1954) has confirmed that a moderate increase in plasma volume occurs in rheumatoid arthritis. Nevertheless, it seems unlikely that mere dilution of the red cell mass could account for hypochromia or the severe degrees of anaemia sometimes encountered.

Nilsson (1948) found that in patients in an active phase of rheumatoid disease, marked hypochromic anaemia was relatively common. The relationship between the severity of the anaemia and activity of the arthritis was confirmed by Jeffrey (1952, 1953a), but the degree of hypochromia (as estimated by the MCHC) was commensurate with activity of disease only in female patients.

Abnormalities of the metabolism of iron in rheumatoid arthritis were recognized before the morphological characteristics of the anaemia had been fully described. Bruzzone and Massimello (1940) and Heilmeyer and others (1941) observed that the serum iron level was below normal. This observation has been repeatedly confirmed, and Nilsson (1948) found that hypoferraemia was most marked in patients with severe degrees of anaemia and active arthritis. Jeffrey (1953a) correlated low levels of plasma iron and hypochromia. He reported that the total iron-binding capacity of the plasma was not significantly abnormal—a finding in contrast to the increase in binding capacity found in anaemia directly due to deficiency of iron.

Despite the hypochromic character of the anaemia in rheumatoid arthritis, the response to the administration of iron has been reported as variable. Collins (1935) noted improvement in only five of twelve patients given adequate doses of oral iron. Nilsson (1948) considered that improvement of the anaemia was more directly
related to the onset of natural remission than to the administration of iron by mouth. The introduction of a preparation of saccharated oxide of iron suitable for intravenous administration was followed by reports of its use in rheumatoid arthritis. Sinclair and Duthie (1949) observed a good response to intravenous iron in sixteen of 23 anaemic patients who had shown no benefit from oral iron. Of the sixteen patients responding adequately, thirteen maintained a satisfactory haemoglobin level for periods ranging from 7 to 23 months. Good haematological response was reported in a further 22 of 28 patients, all of whom had failed to respond to oral iron (Sinclair and Duthie, 1950). Ross (1950) and Jeffrey (1952, 1953a, 1953b) confirmed the value of intravenous iron in cases where the anaemia had failed to improve on adequate doses of iron by mouth.

The failure of the majority of cases to respond to oral iron might be explained on the assumption that absorption from the gut is inadequate in rheumatoid arthritis. Nilsson (1948), using 0-5 g. iron lactate as a test dose, considered that absorption was impaired to some extent, especially in patients with active disease and increased erythrocyte sedimentation rate (E.S.R.). Jeffrey (1953a) reported good absorption from the gut following after a dose of 0-6 g. ferrous sulphate in six patients; three showed exceptionally low resting values of plasma iron (30-36 μg. per cent.) and a very large rise in plasma iron following the test dose. In the other three a moderate increase in plasma iron was noted. In eight cases the rise in plasma iron after the same test dose was slight and taken as presumptive evidence of impaired absorption. Sinclair and Duthie (1950) found absorption to be normal in seven anaemic patients. None responded to oral iron, but six responded satisfactorily to intravenous iron. The test dose in these cases was 1-2 g. ferrous sulphate.

From these studies it seems improbable that the superiority of intravenous iron in the treatment of the anaemia of rheumatoid arthritis can be ascribed to impairment of absorption from the gut. In a small percentage of cases frank iron-deficiency anaemia is present and response to oral or intravenous iron is satisfactory. Sinclair and Duthie (1949) observed that in the presence of a persistently high E.S.R. a satisfactory response to intravenous iron was much less frequent. Jeffrey (1953b) considered that a good response was predictable when one or more of the following features were present: low E.S.R., microcytosis, gross hypochromia, and raised total iron-binding capacity. It should be noted that these conditions occur in simple iron-deficiency anaemia and are not characteristic of the anaemia of rheumatoid arthritis.

Little information is available regarding the immediate fate of saccharated oxide of iron after its intravenous injection in human subjects, although Cappell (1930) described in detail its distribution in animal tissues. He observed that after injection the iron was rapidly removed from circulation and could be demonstrated in leucocytes and in the cells of the reticuloendothelial system. "These cells appeared to act upon the iron"; in about 72 hours "a soluble iron compound" could be demonstrated in the plasma and this increased in amount during the following weeks. The "soluble iron" was deposited largely in the lymphatic glands and in the parenchyma cells of the liver and kidney. In the mouse, the liver, spleen, and lymphatic glands appeared to be the most important sites of iron storage. The liver parenchyma contained the greatest amount in animals killed in the later stages of the experiment. A similar distribution of iron in human subjects given large doses intravenously has been reported by Kuhns and others (1950). From the foregoing review of the literature it would appear that the fundamental cause of anaemia in rheumatoid arthritis remains unknown and that the role of iron in the correction of this anaemia is still unexplained. In a proportion of cases which have failed to respond to adequate doses of iron taken by mouth, improvement occurs after the administration of large doses of intravenous iron. This suggests an increase in the demand for iron which cannot be met by absorption from the gut. In these circumstances it was felt that further studies of the characteristics of the anaemia and of the metabolism of iron in rheumatoid arthritis was well worth while. The object of the present communication is to present the results of the first stage of this investigation.

Material and Methods

These studies were conducted on patients suffering from rheumatoid arthritis attending the Rheumatic Unit, Northern General Hospital, Edinburgh. The majority were in-patients. Control material was obtained from members of the staff and from blood donors at the Blood Transfusion Unit, Edinburgh Royal Infirmary.

The preparation of saccharated oxide of iron (S.O.I.) used throughout these experiments was "Iviron", a colloidal solution* containing 20 mg. elemental iron per ml.

Iron.—Samples of blood were collected in iron-free centrifuge tubes, sodium oxalate (1 mg./ml.) being used as an anticoagulant when plasma was required. The method for the measurement of plasma and serum iron was essentially that described by Ramsay (1953). This method has been found to give values about 15 per cent. higher than other methods reported in the literature. Two modifications of the method were made. In order to decrease the error introduced by slight haemolysis of the blood sample, sodium sulphite (0·5 ml./0·1M) was used as the reducing agent in place of hydroxylamine (Ramsay, 1954). The final solution was centrifuged in place of the filtration recommended in the original method. This eliminated the error introduced by extraction of iron from the filter paper.

It was found that iron in the saccharated oxide is not measured by the above method unless heating of the solution is prolonged to 90 min. Identical results have been obtained by this method and by the "total iron"
method of Ramsay (1950), when solutions of S.O.I. were used. As a small percentage of the iron in S.O.I. reacts with 2-2'-dipyridyl even after heating for 5 minutes, it has been found impossible to estimate β'-globulin bound iron in the presence of S.O.I. All values stated represent the total iron content of plasma.

The method as modified for the measurement of S.O.I. was used in determination of iron in urine. Although no iron could be detected in a 24-hour sample of urine, either from normal subjects or from patients suffering from rheumatoid arthritis, recoveries of added ferrous sulphate and of S.O.I. were quantitative.

Iron-Binding Capacity.—This was estimated by the method of Rath and Finch (1949).

Plasma Protein Fractions.—Plasma proteins were precipitated by appropriate concentrations of Na₂SO₃ (Howe, 1921) and the protein estimated by the method of Lowry and others (1951). Bovine fibrinogen was used as the standard. The method was checked periodically by nitrogen determinations using the micro-Kjeldahl technique.

Iron Absorption.—Ferrous sulphate 1-2 g. was given at 10 a.m. Blood was withdrawn for measurement of serum iron at 10 a.m., 12 noon, 2 p.m., and 4 p.m. The subjects were on normal diet.

Bilirubin.—Bilirubin was measured by the method of Haslwood and King (1937), a recrystallized sample of bilirubin being used as the standard.

Bromsulphophthalein Retention Test.—The method of Mateer and others (1943) was used. The amount of dye retained 30 and 45 minutes after administration was measured.

Results

Chemical and Physical Properties of Saccharated Oxide of Iron.—Since a proprietary preparation of saccharated oxide of iron was to be used in these studies, it was considered important to examine its chemical and physical properties in detail.

“IViron” is a stable colloidal solution of a complex of iron and a non-reducing carbohydrate residue to which the iron is very firmly bound. Boiling with N-HCl or N-NaOH releases the iron and the solution then reduces Benedict’s reagent. Iron may also be liberated, but more slowly, by incubation of S.O.I. at 37° C. with the following reagents: hydroxylamine 0·3 per cent.; sodium sulphite 0·2 M; cysteine 0·2 M; hydroquinone 0·3 per cent.; ascorbic acid 0·002 per cent.; sodium hydrox sulphite 0·025 per cent.; plasma. Although both sodium hydroxyl sulphite and hydroxylamine liberated more iron from the S.O.I. complex than did sodium sulphite, they are unsuitable for routine estimation for reasons already discussed.

S.O.I. diluted 1 : 1 with saline dialyses only slowly through Visking cellulose tubing, but when subjected to ultrafiltration using Gradacol membranes of known porosity it is possible to show that the solution is non-homogeneous. With pore diameters of 6, 23, and 58 Mₜ, 7, 40, and 95 per cent. respectively of the iron could be recovered in the filtrates. When S.O.I. was diluted in plasma (1 : 400) no iron could be detected in the ultrafiltrate. A possible explanation of this would be the adsorption of iron on protein. To examine this possibility, plasma containing S.O.I. was subjected to paper electrophoresis under conditions described by Kerr and Ramsay (1954). Over the pH range 7·1-8·6 S.O.I. was found to be preferentially adsorbed on to the filter paper and only the β'-globulin bound iron could be detected in the protein fractions by the method given by Kerr and Ramsay (1954). The quantity of this iron was probably increased by small amounts of iron liberated by slow hydrolysis of S.O.I. during the 18 hours required for separation of the proteins.

S.O.I., even in the presence of protein, is easily adsorbed from solution by cellulose, alumina, and certain ion exchange resins. As a method of determining the association, if any, of S.O.I. and protein, the plasma protein fractions were precipitated with (NH₄)₂SO₄, Na₂SO₃, or cold ethanol (Cohn and others, 1946). From these experiments, using plasma to which S.O.I. had been added to give an iron concentration of 4-6 mg./100 ml., it appeared that S.O.I. was firmly bound by the fibrinogen fraction and only loosely bound by the globulin and albumin fractions. The fibrinogen-S.O.I. complex was not dissociated by washing with saline or by reprecipitation, and chemical analysis showed that 1 μg. iron combined with approximately 50 μg. fibrinogen. In both plasma and serum the albumin and globulin complexes were found to be much less stable, and analysis suggested a ratio of 1 : 1,000 rather similar to that of iron in the β'-globulin fraction.

Using plasma and serum in which the concentration of S.O.I. was reduced to 1 mg. Fe/100 ml. no stable protein-S.O.I. complex was found.

Plasma Iron Levels in Normal Subjects and in Patients suffering from Rheumatoid Arthritis.—In 35 healthy males the mean level of plasma iron was 181 μg./100 ml. with a standard deviation of 25 μg. In 21 male patients suffering from rheumatoid arthritis, the mean value was 113 μg./100 ml., the standard deviation being 30 μg. The corresponding figures for 35 healthy females and 46 female patients were 135 ± 21 μg./100 ml. and 100 ± 26 μg./100 ml. respectively.
Fig. 1 shows the distribution of the plasma iron values in both sexes, healthy and diseased; the values in the patients are lower than those in controls. The difference of the means is 68 and the standard error 7.7919 in the case of the male groups and 35 and 7.0495 respectively in the case of the female groups. Thus both differences are highly significant.

The total iron-binding capacity of the β'-globulin fraction was determined in 42 patients. No significant difference from the values quoted by Rath and Finch (1949) for normal individuals was found (Table I).

Iron Absorption.—The results appear in Table II (opposite). Serum iron levels before administration of the test dose ranged from 45-125 μg./100 ml. in the rheumatoid group (mean 87 μg./100 ml.). In the normal subjects, none of whom was anaemic, the range was from 90-207 μg./100 ml. (mean 158 μg./100 ml.). After the administration of 1.2 g. ferrous sulphate the rise in serum iron ranged from 42-202 μg./100 ml. (mean 102 μg./100 ml.) in the rheumatoid group, and from 72-185 μg./100 ml. (mean 110 μg./100 ml.) in normal subjects. In one case of rheumatoid arthritis and in one normal subject no rise of serum iron occurred.

Distribution of Iron between Plasma and Serum after the Intravenous Injection of S.O.I.—After the injection of 10 ml. of the solution of S.O.I., the distribution of iron between serum and plasma was studied in three normal individuals and eight rheumatoid patients. Examples of the results of these experiments are shown in Fig. 2 (opposite).

The concentration of iron was greater in plasma than in serum in all instances where the iron level exceeded 1,000 μg./100 ml. It was possible to show by precipitation that this additional iron was associated with the fibrinogen. The level of fibrinogen in the plasma did not appear to bear any relationship to the quantity of iron adsorbed, both normal subjects and patients with marked elevation of fibrinogen giving similar results. It would appear that below the apparently critical level of 1,000 μg. Fe/100 ml. S.O.I. does not combine with fibrinogen.

Iron concentrations were determined at daily intervals after a single injection of 10 ml. S.O.I. The mean result for seven normal subjects and

### Table 1

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<th>Sex</th>
<th>Rheumatoid Arthritis</th>
<th>Controls*</th>
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<td>Female</td>
<td>298 ± 27</td>
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* Figures quoted from Rath and Finch (1949), the standard deviation being calculated from the data in Table II of that paper.
NATURE OF ANAEMIA IN RHEUMATOID ARTHRITIS.

TABLE II
ABSORPTION OF IRON (AS FERROUS SULPHATE) IN CASES OF RHEUMATOID ARTHRITIS AND CONTROLS
(Test Dose 1.2 g. Ferrous Sulphate)

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<th>Before Test Dose</th>
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</table>

Fig. 2.—Typical curves showing distribution of iron between plasma and serum after injection of 10 ml. saccharated oxide of iron in a control and a patient suffering from rheumatoid arthritis.

Seventeen patients suffering from rheumatoid arthritis are given in Fig. 3 (overleaf). In rheumatoid patients the injected iron has been cleared from the plasma within 24 hours. In normal subjects clearance was not complete until 72 hours had elapsed. In three patients in the rheumatoid group the plasma iron concentration 24 hours after injection remained above their pre-injection level.

To ascertain whether similar results would be obtained in anaemia of different origin, observations were made in one case of pernicious anaemia, one case of iron deficiency anaemia, and one case of idiopathic steatorrhoea with normoblastic anaemia (Table III, overleaf). In all three patients plasma iron measured at 24 hours was still well above the pre-injection level, corresponding to the pattern obtained in controls.

Urinary Excretion of Iron after Injection of S.O.I.—To exclude the possibility that the more rapid clearance of S.O.I. from the plasma of patients suffering from rheumatoid arthritis might be due to an increase in the urinary excretion, urine was collected at hourly intervals after the injection of 10 ml. S.O.I. and the iron content measured.
Fig. 3.—Average plasma iron concentration in seven controls and seventeen patients suffering from rheumatoid arthritis after intravenous injection of 10 ml. saccharated oxide of iron. Each ▲ indicates the mean of seventeen observations and the standard deviation at a given time; each × indicates the mean of seven observations and the standard deviation at a given time.

Table III
PLASMA IRON CONCENTRATION AFTER INJECTION OF 10 ml. S.O.I. IN PATIENTS WITH OTHER FORMS OF ANAEMIA

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Plasma Iron (µg./100 ml.)</th>
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<tr>
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<td>Pre-Injection</td>
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<tr>
<td>Pernicious Anaemia</td>
<td>141</td>
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<tr>
<td>Iron-deficiency Anaemia</td>
<td>46</td>
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<tr>
<td>Idiopathic Steatorrhoea</td>
<td>60</td>
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Table IV shows that the maximum excretion of iron occurred during the first 2 hours after injection, corresponding to the highest concentrations of iron in the plasma.

Table IV
EXCRETION OF IRON MEASURED AT HOURLY INTERVALS AFTER INTRAVENOUS INJECTION OF 10 ml. S.O.I. IN THREE CASES OF RHEUMATOID ARTHRITIS

<table>
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<th>Time after Injection (hrs)</th>
<th>Total Iron (µg.)</th>
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<tr>
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<td>Case A</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>1,083</td>
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<td>532</td>
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Urine was collected for 6 hours after injection in seven normal subjects and sixteen patients. The mean value for iron excreted by the normal group was 6,114 ± 1,280 µg., and that for the patients was only 3,219 ± 1,301 µg.

It seemed possible that, as the saccharated oxide of iron preparation had been found to be non-homogeneous, the excreted fraction might be of lower molecular size. From the method of analysis it was known that the iron excreted was still in the saccharated form, maximum colour being developed only when heating was continued for 90 minutes. When S.O.I. was added to urine in suitable concentration and the solution dialysed overnight against distilled water at 0° C., it was found that 5-10 per cent. of the iron passed through the membrane. If, however, urine excreted during the first few hours after injection of S.O.I. was treated in a similar fashion, 30-40 per cent. of the iron was in the dialysate. This would indicate a preferential excretion of the smaller particles of S.O.I.

Iron-Binding Capacity of Plasma after Injection of S.O.I.—It is obvious that S.O.I. could not saturate the metal-combining β'-globulin fraction, but that iron liberated by hydrolysis of the saccharated compound can combine with this protein. The binding capacity of plasma was determined in normal individuals and in patients suffering from rheumatoid arthritis at intervals after injection of S.O.I. From the data presented in Fig. 4, it is obvious that a slow hydrolysis of S.O.I. occurs in the body with subsequent saturation of the β'-globulin with iron. The amount of iron required to saturate the β'-globulin is very small (approx. 16 mg.) in comparison with the iron injected as S.O.I. (200 mg.).

Effect of a Single Injection of S.O.I. on Plasma Bilirubin.—An investigation of the plasma bilirubin levels was undertaken in seven normal subjects and nine patients suffering from rheumatoid arth-
The nature of anaemia in rheumatoid arthritis. I.

Fig. 5.—Percentage change in concentration of plasma bilirubin in seventeen rheumatoid patients and seven controls after intravenous injection of 10 ml. saccharated oxide of iron.

Rheumatoid arthritis. Only in the normal group was any change noted (Fig. 5). After a delay of 1-3 days there was a rise in the bilirubin concentration, which did not, however, exceed normal limits (1 mg./100 ml.). The concentration fell to the pre-injection level in 9 days.

As these results suggested transient impairment of liver function, the B.S.P. retention test was performed before injection of S.O.I., 3 days after injection (when the maximum change in bilirubin concentration was found), and 7 days after injection when the bilirubin concentration had returned to pre-injection value.

Table V records changes in the B.S.P. retention test which occurred in four normal subjects in whom

| TABLE V | PERCENTAGE OF BROMSULPHOPHTHALEIN RETAINED AFTER INJECTION OF 10 ml. SACCHARATED OXIDE OF IRON |
|------------------|-----------------------------------|------------------|-------------------|-------------------|
| Diagnosis        | Before Injection                  | 3 days after Injection | 7 days after Injection |
|                  | Bilirubin (mg. %) | Per cent. Retention of Bromsulphophthalein | Bilirubin (mg. %) | Per cent. Retention of Bromsulphophthalein | Bilirubin (mg. %) | Per cent. Retention of Bromsulphophthalein |
| Control          | 0.39 | 0.5 | 0.64 | 1.1 | 0.30 | 0.2 |
|                  | 0.55 | 1.3 | 0.90 | 2.2 | 0.52 | 0.7 |
|                  | 0.53 | 1.2 | 0.88 | 4.1 | 0.49 | 1.0 |
|                  | 0.46 | 0.4 | 0.73 | 0.6 | 0.44 | 0.0 |
| Rheumatoid Arthritis | 0.41 | 2.0 | 0.46 | 1.5 | — | — |
|                  | 0.52 | 0.5 | 0.48 | 0.2 | — | — |
|                  | 0.36 | 1.3 | 0.40 | 1.4 | — | — |
|                  | 0.44 | 5.2 | 0.40 | 6.0 | — | — |

Retention values calculated 30 minutes after injection of bromsulphophthalein. No retention at 45 minutes was found in any case.
there was a rise in plasma bilirubin following injection of S.O.I. In four cases of rheumatoid arthritis no such rise in plasma bilirubin or change in B.S.P. retention occurred.

Discussion

Measurements of the plasma iron concentration in patients suffering from rheumatoid arthritis confirmed the presence of subnormal values, more marked in females than in males, although these levels were considerably above those found in true iron deficiency (Smith, 1952). Investigation of iron absorption from the gut revealed little evidence of impairment when the results were compared with those in normal controls given the same dose by mouth. This is in contrast to the diminished absorption reported by Cartwright and others (1946) in patients suffering from anaemia complicating infection, although these workers believe that rapid removal of iron from the plasma may partly explain the minimal rise which followed the test dose.

Before going on to study the fate of S.O.I. after injection by the intravenous route it was considered essential to define in as much detail as possible the physical and chemical properties of S.O.I. It was found that, to measure the iron content of solutions of this preparation by the method used, heating had to be prolonged to 90 minutes. Many recent reports of levels of iron in the plasma after intravenous injection of S.O.I. are of no significance because only variable fractions of the iron were measured (Cameron and others, 1951).

It has also been shown that the solution used is non-homogeneous and that the iron-carbohydrate complex is of varying molecular size. By in vitro experiments it was possible to show that S.O.I. in concentrations of 4 to 6 mg. Fe/100 ml. was firmly bound by fibrinogen, and combined only loosely with albumin and globulin. When the concentration of S.O.I. in plasma was reduced to 1 mg. Fe/100 ml. no linkage with protein took place. This observation was confirmed when the distribution between plasma and serum iron was studied in vivo after the injection of 10 ml. S.O.I. From this it is obvious that, when iron levels are measured immediately after the injection of S.O.I., plasma, not serum, must be used. The possible significance of the combination of S.O.I. with fibrinogen is not apparent at the present time.

By measurement of the iron-binding capacity at intervals after injection it was shown that it slowly fell to zero during the following 6 hours, in both normal subjects and rheumatoid patients, indicating a slow hydrolysis of the S.O.I. The combination of rapid removal and slow hydrolysis provides an explanation for the absence of toxic effects, which are believed to be due to the presence of free ionic iron (Cartwright and Wintrobe, 1949).

Daily measurement of plasma iron after a single injection of 10 ml. S.O.I. showed that in the majority of patients with rheumatoid arthritis the iron was cleared within 24 hours, whereas in normals clearance was rarely complete before 72 hours. This could not be explained by increased excretion in the urine. Rheumatoid patients were found to excrete a smaller proportion of the dose given than normal controls. Similar observations regarding the rapid clearance of non-colloidal preparations of iron from the plasma in patients with rheumatoid arthritis have been recorded by Nilsson (1948) using 10 mg. iron as iron and ammonium citrate, and by Cartwright and others (1946) using iron ascorbate, (0·5 mg./lb. body-weight) in patients with anaemia complicating infections.

In view of the transfer of iron from the cells of the reticulo-endothelial system to the liver parenchyma noted by Cappell, plasma bilirubin was measured at intervals following injection. In normal subjects a small but fairly consistent rise was noted on the third or fourth day. Values returned to previous levels within 7 to 8 days. No such change was found in rheumatoid patients. Investigation of the excretory function of the liver by the bromsulphophthalein test suggested transient impairment in normal subjects, which was not evident in the rheumatoid group. Mills and Dragstedt (1936) found that there was abnormal retention of bromsulphophthalein in animals after injection of indian ink and saccharated oxide of iron. It is clear that a much more detailed study of liver function after administration of iron by the intravenous route in normal subjects and patients suffering from rheumatoid arthritis will be necessary before the significance of the differences found can be assessed, but these preliminary observations provide some additional evidence of abnormal metabolism of iron in this disease. It has been suggested by Cartwright and Wintrobe (1952) that, in the anaemia of infection, an increased demand for iron by the cells of the reticulo-endothelial system may account for the hypoferraemia and the rapid clearance of iron from the blood. They state, however, that nothing is known of the function iron may fulfil in these circumstances. The apparent derangement of iron metabolism in rheumatoid arthritis conforms to a similar pattern, although there is no evidence that infection plays a significant part in this disease. The common factor would appear to be extensive tissue damage. The relationship between anaemia
and abnormal metabolism of iron is by no means clear. The characteristics of the anaemia in rheumatoid arthritis differ significantly from those of true iron deficiency anaemia. The red cells are of normal size, the iron-binding capacity of the plasma is normal, and, although plasma iron levels are subnormal, it would appear unlikely that the reduction in both haemoglobin concentration and red cell count are explained solely by deviation of iron from the marrow. The authors have obtained unequivocal evidence (to be reported in a later communication) that the survival of normal red cells transfused to patients with active rheumatoid arthritis is substantially reduced. This would suggest that reduction in the survival time of the patient’s own red cells may be of importance. In these circumstances the improvement in anaemia which follows the administration of large doses of S.O.I. intravenously may depend to some extent at least on actions other than an increase in the amount of iron available to the marrow. Cappell’s observation that, in animals given saccharated oxide of iron, the metal is slowly transferred from the cells of the reticulo-endothelial system to those of the liver parenchyma may be of some significance in this connection. The haematological response to intravenous iron in patients with rheumatoid arthritis may not attain its maximum for 2-3 months; there is no correlation between plasma iron levels and improvement in the anaemia, and the amount of S.O.I. required to produce a response is often far in excess of that calculated to restore the haemoglobin concentration to normal. These preliminary studies have not revealed the cause of anaemia in rheumatoid arthritis, but the presence of marked abnormality in the metabolism of iron in this disease has been confirmed. The mode of action of iron complexes given intravenously is not clear, but it is felt that a more complete knowledge of their initial distribution and ultimate localization is of great interest.

Summary

(1) Previous work on the nature of anaemia in rheumatoid arthritis and the metabolism of iron in this disease has been reviewed.

(2) The existence of significant degrees of hypoferaemia in the presence of normal iron-binding capacity has been confirmed.

(3) No evidence of impaired absorption of iron from the gut has been obtained.

(4) The physical and chemical properties of a commercial preparation of saccharated oxide of iron have been examined.

(5) The rate of removal of iron from the plasma after intravenous injection of the saccharated oxide is more rapid in patients with rheumatoid arthritis than in healthy individuals. The more rapid clearance from the blood is not accounted for by excretion in the urine.

(6) Evidence of transient impairment of liver function in normal individuals after a single injection of saccharated oxide of iron has been obtained. No signs of interference with liver function have been found in patients with rheumatoid arthritis.

(7) The relationship between the derangement of iron metabolism and the occurrence of anaemia in rheumatoid arthritis is not clear, nor has any adequate explanation been found for the improvement in anaemia which follows the administration of saccharated oxide of iron in some cases.

We wish gratefully to acknowledge the help given us by Dr. R. A. Cumming, Blood Transfusion Service, Edinburgh Royal Infirmary, who supplied samples of blood for control observations from donors attending his unit.

During the period when this work was done the Rheumatic Unit was in receipt of grants from the Nuffield Foundation, the Medical Research Council, and Boots Pure Drug Company. One of us (W.R.M.A.) was the holder of the Hastilow Research Scholarship in Rheumatism, awarded by the University of Edinburgh.

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Nature de l'anémie dans l'arthrite rhumatismale

RÉSUMÉ

1. On passe en revue les travaux antérieurs sur la nature de l'anémie dans l'arthrite rhumatismale et le métabolisme du fer dans cette maladie.

2. On confirme l'existence d'une carence significative du fer sanguin en présence d'une capacité normale de fixation de cet élément.

3. On n'a pas trouvé de preuves de l'altération de l'absorption intestinale de fer.

4. On a étudié les propriétés physiques et chimiques d'une préparation commerciale d'oxyde saccharé de fer.

5. Le taux d'élimination du fer sanguin après l'injection intraveineuse de son oxyde saccharé est plus grand chez les rhumatisants arthritiques que chez les sujets normaux. L'excrétion urinaire de fer ne rend pas compte de son élimination sanguine plus rapide.

6. On a trouvé des signes d'altération passagère de la fonction hépatique après une seule injection d'oxyde saccharé de fer chez des sujets normaux. Chez les rhumatisants arthritiques on n'a pas observé de signes d'atteinte de la fonction hépatique.

7. Le rapport entre le métabolisme ferrique dérangé et l'apparition de l'anémie dans l'arthrite rhumatismale n'est pas clair; on ne peut pas, non plus, expliquer d'une manière satisfaisante pourquoi, dans un certain nombre des cas, l'anémie s'améliore après l'administration d'oxyde saccharé de fer.

La naturaleza de la anemia en la artritis reumatoide

SUMARIO

1. Se pasa en revista los trabajos anteriores sobre la naturaleza de la anemia en la artritis reumatoide y sobre el metabolismo del hierro en esta enfermedad.

2. Se confirma la existencia de una hipoférémia de grado apreciable en presencia de una capacidad normal para fijar el hierro.

3. No encontraronse indicios de deterioro de la absorción intestinal de hierro.

4. Las propiedades físicas y químicas de una preparación comercial de óxido sacarado de hierro fueron estudiadas.

5. La pérdida de hierro sanguíneo después de la inyección endovenosa de óxido sacarado es más rápida en enfermos con artritis reumatoide que en sujetos normales. La excreción urinaria de hierro no da cuenta de su eliminación sanguínea más rápida.

6. Encontraronse indicios de deterioro temporal de la función hepática en sujetos normales después de una sola inyección de óxido sacarado de hierro; no se observaron signos de tal deterioro en enfermos con artritis reumatoide.

7. La relación entre el disturbio del metabolismo férice y la ocurrencia de la anemia en la artritis reumatoide no parece clara; tampoco se puede hallar una explicación adecuada para la mejoria de la anemia en un número de casos después de la administración de óxido sacarado de hierro.
Nature of Anaemia in Rheumatoid Arthritis: I. Metabolism of Iron


Ann Rheum Dis 1955 14: 63-72
doi: 10.1136/ard.14.1.63

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