ANAEMIA OF RHEUMATOID ARTHRITIS*

BY

M. R. JEFFREY

From the Rheumatism Research of the South West and Oxford Regions, Royal National Hospital for Rheumatic Diseases, Bath

(RECEIVED FOR PUBLICATION JANUARY 1, 1952)

It has long been recognized that anaemia is a common feature of rheumatoid arthritis. Garrod (1876) who introduced the term " rheumatoid arthritis ", noted the association. Much more recently, the report of the Scientific Advisory Committee of the Empire Rheumatism Council (1950) has provided evidence of a frequent and important relationship.

Although this anaemia is usually not very severe, it is frequently refractory to all forms of treatment. The introduction of iron preparations suitable for intravenous injection has considerably reduced, but by no means abolished, the problem of cases refractory to treatment (Sinclair and Duthie, 1950; Ross, 1950).

Very little attention has been paid to the causes and nature of this anaemia. Apart from one monograph by Nilsson (1948), no comprehensive investigation has been attempted. We therefore felt it worth while to examine this anaemia in some detail; the results obtained are presented below.

Results

Peripheral Blood.—The first step was to study the morphological characters of the anaemia and the cellular composition of the red bone marrow. The anaemia was found to be essentially normocytic and hypochromic. Red cell size, as shown by the mean corpuscular volume (M.C.V.) was normal in 48 of the 65 cases studied; the values in the other cases were distributed equally above and below the normal range and were almost certainly due to inaccuracies in the red cell count rather than to the rheumatoid arthritis.

On the other hand, the haemoglobin concentration in the red cell was almost invariably diminished; only five out of 136 cases examined gave a normal value for mean corpuscular haemoglobin concentration (M.C.H.C.).

It is interesting to compare the relative importance of reduction in the number of circulating red cells and of reduction of the haemoglobin concentration in the red cells in producing anaemia. In our cases, the average red cell count was about 15 per cent. below the normal average value in both sexes. The average reduction of M.C.H.C. below the normal mean was also about 15 per cent. It appears therefore that reduction in the number of circulating red cells may be more important in producing anaemia than has been generally recognized.

By dividing the cases into clinical groups according to the activity of their rheumatoid disease, it was evident that the lowest average values for red cell counts, haemoglobin, and M.C.H.C. were found in the cases with very active disease (see Table, opposite). The M.C.V. on the other hand, showed no consistent change in the various activity groups.

The cases were also divided into groups according to their age and the duration of their disease; neither of these factors, however, appeared to have a significant effect upon the degree of anaemia.

Evidence of Undue Haemolysis.—In about fifteen cases we sought evidence of undue haemolysis by estimating plasma bilirubin, faecal urobilinogen, and reticulocytes; all

* Paper read to the Heberden Society on December 7, 1951.

TABLE

Sex	Male			Female		
Activity Group	1	2	3	1	2	3
R.B.C. (mill:/c.mm.)	4·70	4·50	3·70	4·52	4·07	3·93
Hb (g./100 ml.)	13·2	12·1	10·9	11·3	10·8	9·6
M.C.H.C. (per cent.)	29·9	29·7	28·8	29·2	28·9	28·0

Notes. (*i*) Activity Group 1=slightly active, 2=moderately active, 3=very active disease.
(*ii*) All figures represent mean values.
(*iii*) Differences between the means given by activity Groups 1 and 3 are statistically significant in all cases except the male values for M.C.H.C.

these tests gave normal results. The red cell fragility was also tested in a few cases; the only abnormality found was an increased resistance to haemolysis in some cases, a not infrequent phenomenon in any variety of hypochromic anaemia. We concluded, therefore, that undue haemolysis was not of material importance in this anaemia.

Red Bone Marrow.—Haemopoiesis in the red bone marrow was studied in sixteen cases by examination of stained smears of marrow juice withdrawn by sternal puncture. No regular major change was found, though there were one or two points of interest. The myeloid series was almost entirely normal; we observed neither the " hypocellularity " found by Merlo and Tortori-Donati (1945), nor the " global granuloblastic hyperplasia " described by Luchesi and others (1946): the most our cases achieved was a slight increase of metamyelocytes. As regards the red cell series, only one female case showed well-marked normoblastic hyperplasia. This woman improved considerably during her stay in hospital, her arthritis becoming much less active and her haemoglobin rising from 50 to 85 per cent., here the hyperplasia was apparently spontaneous, the result of a natural remission in the rheumatoid disease. The other cases showed essentially normal proportions of normoblasts, though, in view of the fact that all the patients were distinctly anaemic, the marrows showed less evidence of activity than might have been expected. The majority of the normoblasts had a polychrome cytoplasm; few had acquired a normal haemoglobin content even at a late stage of nuclear maturation. Our findings agree, therefore, with those of Nilsson (1948, p. 99), who observed disturbance of haemoglobin formation in the normoblasts. It is of interest too that about half of our cases showed a relative diminution of the more mature normoblasts and that these cases had red cell counts in the peripheral blood which were distinctly below the counts of the cases with normal proportions of primitive red cells. There is a suggestion, therefore, that disturbance of normoblast production may play a part in producing this anaemia.

Another minor point of interest concerns the megakaryocytes. Normally, about two-thirds of these cells show clear evidence of platelet production, platelets being budded off from the edge of the cell. The proportion is markedly decreased in idiopathic thrombocytopenic purpura, which is ascribed by Dameshek and Miller (1946) to " hypersplenism ". Four of our cases showed a decreased proportion of actively budding megakaryocytes, and it is conceivable that these four cases were also examples of mild " hypersplenism ". The reports that occasional cases of rheumatoid arthritis improve considerably after splenectomy (Bach and Jacobs, 1951) raise the question whether there is any correlation between the marrow cytology and the result of the operation, and whether in fact it may be possible to select cases suitable for the operation by examination of marrow smears.

Blood, Plasma, and Corpuscle Volumes.—The suggestion of Robinson (1943), that dilution of the blood by an increased volume of plasma might produce apparent anaemia in rheumatoid arthritis, was investigated by estimating the plasma volumes of fifty cases, using the Evans blue method of Gregersen (1944). The detailed figures will be published elsewhere;

it may, however, be said that the results did not support the idea of haemodilution. In fact, volume changes fitted in with those defined by Gibson and Evans (1939) in a variety of types of anaemia, namely, a reduction in the total mass of circulating red cells and in the whole blood volume with a normal plasma volume.

Iron Metabolism.—Cartwright and others (1946) have shown that the concentration of iron in the plasma is reduced during infection or experimental inflammation. Nilsson (1948, p. 62) found a similar reduction in cases of rheumatoid arthritis, and our observations agree with his. The plasma iron was below normal in 156 of the 200 cases which we examined. Women exhibited low values rather more frequently than men and the average value for the women was considerably lower. There was a tendency for the cases suffering from the most active rheumatoid disease to exhibit the lowest plasma iron values. In very active cases, and in those who were markedly anaemic, lowering was invariable.

We did not observe any consistent change in the plasma iron as a result of cortisone or ACTH therapy when these substances were given for relatively short periods, not exceeding 3 weeks.

The plasma iron is, of course, raised by intravenous iron therapy and quite frequently remains raised above its initial value for a period of weeks or months, even in cases who show no material increase in haemoglobin. From the cases so far observed, it appears that the degree or duration of this persistent rise in plasma iron (as distinct from the very large and transitory increase immediately following injection) bears little relation to any increase which may occur in the haemoglobin value. The plasma iron does, however, become normal after therapy only in those whose haemoglobin level becomes normal.

There is good evidence, therefore, that iron metabolism is altered in rheumatoid arthritis. From the clinical point of view, cases who become anaemic may be divided into three categories:

(*a*) Those who respond rapidly and completely to iron by mouth; this is a small group with the characteristics of ordinary iron deficiency anaemia, in whom the occurrence of anaemia and rheumatoid arthritis may well be coincidental.

(*b*) Those whose anaemia is entirely refractory to all haematinics; this probably represents the real anaemia of " rheumatoid arthritis " about whose origins our knowledge is fragmentary.

(*c*) Those whose anaemia is refractory to iron by mouth but responds completely, or to a material extent, to intravenous iron.

There are three obvious explanations for the occurrence of this third group (*c*). The intestinal absorption of iron might be greatly impaired; the mechanism for transporting iron from the intestine to the tissues might be inefficient; the absorbed iron might be rapidly removed from the blood stream by some non-haemopoietic tissue and thus prevented from taking part in blood formation.

(*i*) *Iron Absorption.*—To try and assess the efficiency of intestinal absorption, we investigated the changes in plasma iron in twenty cases after a single test dose of iron by mouth. The subjects were given 9 gr. ferrous sulphate, the largest dose commonly employed therapeutically, together with 250 mg. ascorbic acid to preserve the iron in the reduced form and to minimize the effects of a possibly altered gastric secretion.

The amount of the maximal increase in the plasma iron after this test dose varied greatly among the cases; they can, however, be divided roughly into three groups, of which the two extremes are of interest.

(*a*) In three women, a very large increase in plasma iron followed the test dose, the concentration rising from a markedly low level in the region of 30 μg. to about 400 μg./100 ml. These women were subsequently given ferrous sulphate therapeutically by mouth and all responded well, their haemoglobin values rising to normal within 6 weeks. This first group, then, showed excellent absorption and undoubtedly suffered from simple iron deficiency anaemia.

(*b*) At the other extreme were eight cases in whom only a very small increase in plasma iron concentration followed the test dose, an increase insufficient to raise the initially low plasma iron value into the normal range. There was no evidence of the general tendency for anaemia to increase iron absorption, but rather a suggestion that this function was impaired.

The failure of the plasma iron to rise does not, of course, prove that the absorptive function of the intestine is at fault, for there are at least three other possible explanations: that the iron was not available to the intestine for absorption, that the tablets had not dissolved, or that the iron had formed some not readily ionized compound. Against these possibilities are the facts that in all cases the stools were blackened by the test dose of iron, and that, as the patients had fasted overnight before the test, the upper small intestine should have been free of any food which might have reduced the availability of the metal. In these circumstances, ascorbic acid is very effective in preserving iron in the reduced state available for absorption (Moore and others, 1939). It therefore seems unlikely that conditions within the intestine played a large part in reducing iron absorption.

(*ii*) *Iron-Transporting Protein.*—A second possible explanation of the failure of the plasma iron to rise after the test dose is that, though absorption from the intestine occurred normally, the transporting mechanism in the plasma was unable to carry the metal. Iron is carried in the blood stream by a specific protein, a β globulin. Rath and Finch (1949) developed a method for the photometric estimation of this protein in terms of its iron-carrying capacity, based on the fact that the iron-protein complex possessed a characteristic pinkish colour. Using this method, we investigated fifty cases of rheumatoid arthritis, of various degrees of anaemia and severity, and found no essential abnormality. The average values were almost identical with those of Rath and Finch's normal subjects and, though the range in the rheumatoid cases was slightly greater than normal, in no case was there a reduction present which could have interfered with the transport of absorbed iron. Thus the transport mechanism is intact in rheumatoid arthritis.

(*iii*) *Abnormal Removal of Iron from the Plasma.*—A third possible explanation of the failure of the plasma iron to rise after the test dose is that the absorbed iron was very rapidly removed from the blood stream. There is evidence that, in the presence of inflammation, iron given intravenously is unusually rapidly removed from the blood stream, and Nilsson (1948, p. 141) has shown that this holds true in rheumatoid arthritis. Nevertheless, the rate of removal in Nilsson's cases was not very greatly increased, nor has it been found to be so in the few cases which we have so far studied. It is difficult to believe that in our cases the removal mechanism was adequate, or was sensitively enough adjusted, to prevent a rise of more than 35 μg. in the plasma iron concentration in the face of normal absorption—as in fact happened in six of the twenty cases studied.

It seems, therefore, that there is at least a strong possibility that impaired absorption accounts for the superiority of intravenous over oral iron therapy in some cases of rheumatoid arthritis. It is worthy of note that therapeutically iron is usually given by mouth in circumstances which would tend still further to reduce absorption, for the dose is often less than the present test dose and is given after food without ascorbic acid.

The present investigations shed no light on the possible role of impaired absorption in producing anaemia in rheumatoid arthritis. In the day-to-day absorption of iron from food, quantities are involved of the order of 1 mg., and alterations in gastric secretion and intestinal contents may well be important. This is, therefore, a separate problem from that of the absorption of therapeutic doses, and it is one on which we hope to begin work shortly.

Summary

(1) The anaemia of rheumatoid arthritis is normocytic and hypochromic, its severity running roughly parallel with the degree of disease activity.

(2) The anaemia is not haemolytic.

(3) The sternal marrow is not grossly abnormal but gives some evidence of disturbed haemoglobin formation and normoblast production.

(4) The plasma volume is normal; in the more anaemic cases, whole blood and corpuscle volumes are reduced.

(5) The plasma iron is usually reduced, but the iron transport mechanism of the plasma is unimpaired.

(6) Part of the anaemia is often due to iron deficiency; impaired intestinal absorption and other factors are probably usually responsible for the failure of oral iron therapy.

I am indebted to Dr. G. D. Kersley for his advice and encouragement, and for permission to study patients under his care; to Dr. H. J. Gibson for the results of routine pathological investigations; to Dr. G. Herdan for statistical help; to the sisters and nursing staff of the Unit for invaluable co-operation; and to Miss M. K. Dingle for secretarial assistance.

References

Bach, F., and Jacobs, J. H. (1951). *Annals of the Rheumatic Diseases*, **10**, 320.
Cartwright, G. E., Lauritsen, M. A., Jones, P. J., Merrill, I. M., and Wintrobe, M. M. (1946). *J. clin. Invest.*, **25**, 65.
Dameshek, W., and Miller, E. B. (1946). *Blood*, **1**, 27.
Empire Rheumatism Council, Report of Scientific Advisory Committee (1950). *Brit. med. J.*, **1**, 799; and (1950). *Annals of the Rheumatic Diseases*, **9**, Suppl.
Garrod, A. B. (1876). "A Treatise on Gout and Rheumatic Gout." 3rd ed., p. 501. Longmans, Green, London.
Gibson, J. G., Harris, A. W., and Swigert, V. W. (1939). *J. clin. Invest.*, **18**, 621.
Gregersen, M. I. (1944). *J. Lab. clin. Med.*, **29**, 1266.
Lucchesi, M., Lucchesi, O., and da Silva, M. P. (1946). *Rev. argent. Reum.*, **10**, 294.
Merlo, P., and Tortori-Donati, B. (1945). *Rass. Fisiopat. clin. terapeut.* (Suppl. 2), **17**, 37.
Moore, C. V., Arrowsmith, W. R., Welch, J., and Minnich, V. (1939). *J. clin. Invest.*, **18**, 553.
Nilsson, F. (1948). *Acta med. scand.*, Suppl. 210.
Rath, C. E., and Finch, C. A. (1949). *J. clin. Invest.*, **28**, 79.
Robinson, G. L. (1943). *Annals of the Rheumatic Diseases*, **3**, 207.
Ross, D. N. (1950). *Ibid.*, **9**, 358.
Sinclair, R. J. G., and Duthie, J. J. R. (1950). *Brit. med. J.*, **2**, 1257.

Anémie de l'arthrit rheumatismale

Résumé

(1) L'anémie de l'arthrite rhumatismale est normocytique et hypochromique, et sa gravité est à peu près proportionnelle à celle de l'activité morbide.
(2) Cette anémie n'est pas hémolytique.
(3) La moelle sternale, sans être franchement anormale, présente quelques indications de la formation defectueuse de l'hémoglobine et des normoblastes.
(4) Le volume du plasma est normal; dans les cas d'anémie plus prononcée le volume sanguin total et corpusculaire se trouvent diminués.
(5) Le fer plasmatique est généralement diminué, mais le mécanisme du transport de fer par le plasma n'est pas affecté.
(6) L'anémie est souvent due partiellement au manque de fer; les échecs de la thérapie martiale par voie buccale sont généralement dus à un défaut de l'absorption intestinale ou à d'autres facteurs.

La anemia de la artritis reumatoide

Sumario

(1) La anemia de la artritis reumatoide es normocítica e hipocrómica, y su gravedad corresponde aproximadamente a la de la actividad morbosa.
(2) Esta anemia no es hemolítica.
(3) La médula esternal no es muy anormal pero presenta algunas indicaciones de perturbación de la formación hemoglobínica y normoblástica.

(4) El volumen del plasma es normal; en los casos muy anémicos el volumen total y corpuscular están reducidos.

(5) El hierro plasmático está generalmente reducido pero el mecanismo plasmático de transporte del hierro no está afectado.

(6) En parte, la anemia es a menudo ferripriva; un defecto en la absorción intestinal y otros factores constituyen probablemente la causa de los fracasos de la ferriterapia por via oral.