ORAL AND INTRAVENOUS IRON THERAPY IN THE ANAEMIA OF RHEUMATOID ARTHRITIS

BY

D. N. ROSS

For many years it has been realized that anaemia is a frequent feature of the rheumatoid syndrome, and the recent Empire Rheumatism Council Survey (Davidson and others, 1950) gives statistical support to this. Previous work of our own has shown that, although the haemoglobin is low, the red-cell count is but little reduced, so that the anaemia is of the normocytic, hypochromic type and does not take the usual microcytic form of iron-deficiency anaemia.

In spite of textbook assurances that the " simple " anaemia found in rheumatoid arthritis will respond satisfactorily to ordinary iron therapy, in the course of our duties at various rheumatic clinics during the past 9 years, we have found that this anaemia is stubbornly resistant to iron therapy by mouth in doses which are effective in idiopathic hypochromic anaemia.

A report from the U.S.A. of the apparently successful use of folic acid in the treatment of this refractory anaemia (Stephens and others, 1947), and the recent introduction of an iron preparation suitable for intravenous injection (Nissim, 1947), provided us with new agents in our efforts to find an effective haematinic, and we used them in the following preliminary investigation.

First Test Series

Some 500 cases of rheumatoid arthritis were examined, and 200 with unequivocal anaemia were selected for therapeutic trial. These test cases were divided into four groups of fifty each, and were treated as follows:

Group I.—No specific anti-anaemic therapy.
Group II.—Given 15 gr. (1·0 g.) ferrous sulphate daily in the form of haematinic " plastules ".
Group III.—Given 15 gr. (1·0 g.) ferrous sulphate plus 15 mg. folic acid daily.
Group IV.—Given no iron therapy by mouth, but 800 mg. (40 ml.) of an iron compound intravenously in divided doses over the test period.

Since most of the hospital cases are available for a month only, the test period was set at 25 days—which should be sufficient to produce an increase in haemoglobin of 25 per cent. in the usual " simple " anaemia. Before and after the test period each patient had a blood count: the haemoglobin estimations were performed by the alkaline haematin method, using the Gibson-Harrison standard in a photo-electric colorimeter; and the E.S.R. readings were made by the " Spa Hospital "

method (Collins and others, 1939). These results, summarized in Table I, show that there is no significant difference between Groups II, III, and IV, and indicate the refractory nature of the anaemia.

TABLE I
RESPONSE TO ONE MONTH'S IRON THERAPY

Test Group	No. of Cases	Average Haemoglobin %		Average Increase %
		Before treatment	After treatment	
I (Control). No iron therapy	50	73·68	73·90	0·22
II Ferrous sulphate orally	50	73·88	78·20	4·32
III Ferrous sulphate+folic acid	50	72·24	77·44	5·20
IV Intravenous iron therapy	50	69·74	75·96	6·22

Second Test Series

With further experience, we learned that a " lag " often occurs before the intravenous iron produces its maximum effect, so we decided to treat another group of fifty cases and to observe the improvement, if any, occurring over a three-month test period. We gave a larger total dose of iron than in the first trial, but did not exceed 200 mg. (10 ml.) at a time. Our usual scheme comprises eight injections: the first four of 50 mg., 100 mg., 150 mg. and 200 mg. (2·5, 5·0, 7·5, 10·0 ml.), and four subsequent ones of 200 mg. (10 ml.), given twice weekly, making a total of 1·3 g. (65 ml.).

In over 1,000 injections, only one severe reaction occurred, and this took the paroxysmal form described by Ramsey (1950). A few mild reactions occurred in the form of colicky pain in the lumbar region lasting for about 10 to 30 seconds, but in no case did haemoglobinuria result.

For comparison, a similar group was treated with oral iron throughout the test period, and the comparative results appear in Table II.

TABLE II
RESPONSE TO THREE MONTHS' IRON THERAPY

Therapy	No. of Cases	Average Haemoglobin %		Average Increase %
		Before treatment	After treatment	
Oral iron	50	71·0	79·0	8
Intravenous iron	50	69·0	84·0	15

Discussion

The results in Table II show the statistically significant superiority of the administration of iron by the intravenous route, and are comparable with the findings in

a similar trial made in Edinburgh by Sinclair and Duthie (1949). These investigators describe sixteen cases which gave a good response (a mean rise in haemoglobin of 20·4 per cent.) and seven which responded poorly (a mean rise of only 3·9 per cent.): if their two groups were added, the mean increase in haemoglobin for the 23 cases would be 15·4 per cent.—in comparison with a mean increase of 15·0 per cent. for our group of fifty cases.

It has been shown previously (Ross, 1942) that the response to oral iron varies inversely with the erythrocyte sedimentation rate, and Sinclair and Duthie note that their best results with intravenous iron occurred in cases with a low, falling E.S.R., and that poor results were found in cases with a high (rapid) E.S.R. Although our findings (Table III) tend to support this, so few of our cases had a low sedimentation rate that a definite conclusion cannot be drawn. However, Tötterman (1949) in a detailed study of iron metabolism in " infectious anaemia " found that the response to intravenous iron was poor while the primary disease process remained in a highly active state, as shown by the persistently high E.S.R.

TABLE III
INFLUENCE OF SEDIMENTATION RATE ON THE RESPONSE TO IRON THERAPY

Therapy	Sedimentation Rate	No. of Cases	Mean Haemoglobin Increase %
Oral iron	Slight or moderate increase	16	10·3
	Marked increase (over 35 per cent.)	34	7·2
Intravenous iron ..	Slight or moderate increase	19	18·0
	Marked increase (over 35 per cent.)	31	12·6

In our series, the 31 cases with a high E.S.R. gave a much better response than the seven similar cases in the Edinburgh group; and, apart from the statistical difference, we would suggest that our practice of giving the injections only twice weekly, thereby taking a month to give the total amount of iron, is more effective than the daily-injection technique, which completes the course in six days. We have found, too, that where a patient has only one " good " vein, it remains patent longer if there is an interval of several days between injections, and thus allows the course to be completed without interruption.

From a theoretical aspect, the superiority of iron therapy by the intravenous route is shown more plainly in Table IV (opposite), which gives the approximate figures for utilization of the available iron in the two main test groups. These results cast some light on the aetiology of the anaemia, which we may consider briefly:

There is no extravascular blood loss or haemorrhage, and no intravascular loss

by haemolysis, so that the anaemia comes within the dyshaemopoietic group—that is to say, there is inefficient blood production.

The causes of the anaemias in this group include deficiencies in food intake, digestion, absorption, storage, endocrine function and utilization, and, although each item may play some part in the " rheumatoid anaemia ", our experimental evidence implicates chiefly absorption and utilization.

TABLE IV

UTILIZATION OF IRON

Therapy	Total Amount	Actual Fe. Content (g.)	Mean Haemoglobin Increase		Utilization %
			%	g. %	
Oral iron	84 g.	28·0	8·0	1·25	0·76
Intravenous iron ..	65 ml.	1·3	15·0	2·34	30·60

Mean whole blood volume 5 litres.
1·0 g. haemoglobin contains 3·4 mg. Fe.

It would appear, firstly, that iron is very poorly absorbed from the intestine and, secondly, that when this difficulty is avoided by giving iron directly into the veins the utilization is still rather poor. The latter fact may be due to a low level of iron in the basic stores of the body, following longstanding defective absorption. The restoration to a normal level of this " storage-depot " iron takes precedence over the synthesis of haemoglobin—which may account for the " lag " in the response to iron therapy.

As a result of these trials, we now feel able to do much more to correct the anaemia complicating rheumatoid arthritis; this correction also appreciably improves the general health and well-being of the patient. We are continuing our investigations, and the tendency is to give a still greater total dose of Iviron, but we do not feel that the individual dose should exceed 200 mg. (10 ml.) since beyond that point the likelihood of reaction increases.

It is noticeable that, once again, a simple investigation has provided a side-result of perhaps greater significance than the end-result aimed at; and we hope that our evidence, suggesting that iron absorption from the gut is defective, may pave the way for a more detailed study of intestinal absorption in this peculiarly complex rheumatoid syndrome.

Summary

A preliminary trial showed that neither oral iron, oral iron with supplementary folic acid, nor intravenous iron medication, had any appreciable effect on the anaemia of rheumatoid arthritis over a test period of one month.

A similar trial on two groups of fifty cases, over a test period of three months, showed the marked superiority (statistically significant) of iron by the intravenous route; and the results, expressed as a utilization percentage of the available iron, suggest that there is defective absorption of the oral preparation.

We are indebted to the physicians of the Royal Bath Hospital, Harrogate, for access to the cases; to Professor Hartfall and Dr. Yeoman for referring suitable cases from the Rheumatism Clinic at Leeds General Infirmary; and to Dr. G. Norman Myers, Director of Rheumatism Research of the University of Leeds, for his interest and encouragement.

The intravenous iron preparation used in the above experiment was "Iviron", for a generous supply of which we are much indebted to Messrs. British Schering Ltd.

References

Collins, D. H., Gibson, H. J., Race, J., and Salt, H. B. (1939). *Annals of the Rheumatic Diseases*, **1**, 333.

Davidson, L. S. P., Chairman of Committee (1950). *Brit. med. J.*, **1**, 799. Report of the Scientific Advisory Committee of the Empire Rheumatism Council. This is also to appear in full as a special Supplement to this Journal, ed. E. Lewis-Faning (1950).

Nissim, J. A. (1947). *Lancet*, **2**, 49.

Ramsey, A. S. (1950). *Brit. med. J.*, **1**, 1109.

Ross, D. N. (1942). "Observations on Rheumatoid Arthritis with Special Reference to the Anaemic Factor"—lodged in the library of the University of Glasgow.

Sinclair, R. J. G., and Duthie, J. J. R. (1949). *Lancet*, **2**, 646.

Stephens, C. A. L., Borden, A. L., Holbrook, W. P., and Hill, D. F. (1947). *Ann. int. Med.*, **27**, 420.

Tötterman, L. E. (1949). *Acta med. scand.*, Suppl. 230.

Traitement de l'Anémie de l'Arthrite Rhumatismale par le Fer par Voies Buccale et Intraveineuse

Résumé

Des essais préliminaires ont montré que le fer introduit par voie buccale—avec ou sans l'acide folique—et par voie intraveineuse ne produisait aucun effet appréciable sur l'anémie de l'arthrite rhumatismale pendant une période d'un mois.

Des essais similaires pendant une période de trois mois sur deux groupes de cinquante cas ont montré la supériorité marquée (statistiquement manifeste) du fer par voie intraveineuse. Les résultats, exprimés en pourcentage d'utilisation du fer disponible, font penser à un défaut d'absorption de la préparation buccale.

Tratamiento de la Anemia de la Artritis Reumatoide por el Hierro Oral e Intravenoso

Resumen

Ensayos preliminares han mostrado que hierro introducido por vía oral—con o sin ácido fólico—y por vía intravenosa no producía efecto apreciable sobre la anemia de la artritis reumatoide durante un período de un mes.

Ensayos similares durante un período de tres meses sobre dos grupos de cincuenta casos han comprobado la superioridad marcada (estadisticamente acentuada) del hierro por vía intravenosa. Los resultados, expresados en percentage de utilización del hierro disponible, sugieren un defecto de absorpción de la preparación oral.