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NATURE OF ANAEMIA IN RHEUMATOID ARTHRITIS

VII. STORAGE OF IRON IN RHEUMATOID DISEASE

BY

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Disturbance of iron metabolism is a prominent feature of the anaemia of rheumatoid arthritis. The plasma iron concentration is almost always reduced in the presence of active disease (Bruzzone and Massimello, 1940; Nilsson, 1948). Despite intensive investigation (Raymond, Bowie, and Dugan, 1965), the metabolic pathways of iron in rheumatoid disease and the relationship between the levels of plasma iron, the degree of anaemia, and the activity of the disease remain obscure.

The rapid clearance from the plasma of iron given intravenously (Roy, Alexander, and Duthie, 1955; Freireich, Ross, Bayles, Emerson, and Finch, 1957; Weinstein, 1959) may be due to an abnormal uptake by the reticulo-endothelial system. Gardner and Roy (1961) estimated the iron content of *post-mortem* material from rheumatoid and control subjects and showed that there was no increase in iron content in rheumatoid tissues as compared with controls. However, hyperplasia of the reticulo-endothelial system was observed and, in particular, the spleens of rheumatoid patients were significantly larger than those of controls. These results suggested that there was a greater absolute amount of iron in the reticulo-endothelial systems of the patients.

Muirden (1966), using electron microscopy, showed large quantities of ferritin in the cells of rheumatoid synovium. One explanation for this observation could be that iron may be diverted from the plasma and deposited in the inflamed synovial tissue.

Further evidence of increased iron deposition in rheumatoid arthritis, even in the presence of a low plasma iron, was provided by studies of the handling of endogenous iron released from erythrocytes after intravenous injection of nicotinic acid or aged autologous blood in patients with rheumatoid arthritis (Owen and Lawson, 1966). These studies showed that there was a smaller rise and a more rapid fall in plasma iron levels in rheumatoid patients compared with healthy control subjects. The authors suggested that these observations could be explained by an abnormally slow release of endogenous iron from the reticulo-endothelial system. On the assumption that iron might be stored in excessive amounts in the reticulo-endothelial system or inflamed tissue, it was decided to study the metabolism of iron in rheumatoid arthritis following administration of the iron-chelating agent desferrioxamine. A screening test for iron storage disease was suggested by Keberle (1964), using desferrioxamine B ("Desferal", Ciba), a tri-hydroxamic acid with a highly-specific ability to chelate trivalent iron.

The simple desferrioxamine test indicates that iron storage disease may be suspected if there is an increase in urinary iron excretion in excess of ten times the amount present in the urine before injecting the chelating agent (Unseld, 1964; Wöhler, 1964).

The simple desferrioxamine test does not allow for possible alterations in the excretion of the chelate, ferrioxamine, which has been shown to vary in different types of anaemia (Bannerman, Callender, and Williams, 1962). Also, the test does not permit calculation of chelation of iron *in vivo*. The more refined differential ferrioxamine test was devised by Fielding (1965) to overcome these defects. This procedure involves collection of urine for 6 hours before and after an intramuscular injection of 500 mg. desferrioxamine together with labelled ferrioxamine given in a dose of 50 mg./60 kg. body weight. The upper range of normal chelation *in vivo* is stated to be 500 μg./kg.

These tests were used in this study, but Fielding's differential desferrioxamine test was modified to avoid the use of radioactive isotopes. The urinary excretion pattern of ferrioxamine after an intramuscular injection of ferrioxamine (50 mg./60 kg. body weight) was measured in a series of patients and healthy subjects to confirm that the modification of the differential desferrioxamine test was satisfactory.

In addition, the pattern of iron excretion after daily intramuscular injection of desferrioxamine was

investigated. Moeschlin and Schnider (1964) found that a daily dose of 800 to 1,200 mg. desferrioxamine in divided doses gave an optimum excretion of iron.

Material and Methods

Clinical Material

The study was made on eight healthy control subjects (6 males and 2 females) and on twenty patients (12 males and 8 females) with classical or definite rheumatoid arthritis according to the diagnostic criteria of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959). The patients were admitted to the Rheumatic Diseases Unit, Northern General Hospital, Edinburgh, and during the study all received the same basic therapy of rest in bed, splintage, aspirin, and physiotherapy. All had clinically active arthritis (Table I) and the majority had an anaemia typical of that found in rheumatoid arthritis. Three patients had completed courses of ACTH and parenteral iron shortly before the studies were made. One of the three had a moderately raised total iron-binding capacity. Three patients had received parenteral iron alone.

TABLE I
CHARACTERISTICS OF SUBJECTS STUDIED

Group		Sex	Age (yrs)	Haemoglobin (g./100 ml.)	ESR (mm./1 hr)	Plasma Iron (μg./100 ml.)	Total Iron-Binding Capacity (μg./100 ml.)	Duration of Disease (yrs)
Controls ..	1	M	28	15·3	5	132	320	
	2	M	31	15·3	3	204	320	
	3	M	23	14·8	6	106	280	
	4	M	55	15·6	6	102	340	
	5	M	30	14·6	2	142	348	
	6	M	32	14·9	4	208	364	
	7	F	24	12·2	8	61	456	
	8	F	36	13·8	6	92	340	
Patients ..	1	M	61	14·1	24	60	388	2
	2	M	64	15·2	27	70	280	20
	*3	M	58	12·2	42	180	284	2
	4	M	62	11·6	96	44	372	20
	†5	M	37	12·5	46	40	164	7
	6	M	44	12·2	42	34	368	5
	7	M	45	10·9	61	50	184	5
	8	M	61	13·9	30	32	350	7/12
	9	M	58	12·2	52	60	—	6
	10	M	59	10·9	58	36	—	5
	11	M	63	11·7	20	16	—	1
	12	M	54	12·2	32	44	—	5
	*13	F	53	12·8	48	64	456	1½
	*14	F	42	13·9	28	106	256	3/12
	15	F	61	10·6	43	38	316	3/12
	†16	F	54	9·1	112	86	288	6/12
	17	F	42	10·3	41	40	364	8/12
	18	F	61	14·4	22	68	232	5/12
	19	F	59	9·7	38	50	264	3
	‡20	F	54	12·5	30	61	284	5

*After ACTH plus 2 g. intravenous iron
†After 3 g. intravenous iron
‡After 2 g. intravenous iron

Methods

The haemoglobin was measured against a cyanhaemoglobin standard (100 per cent. = 14·6 g./100 ml.) in an "EEL" haemoglobinometer. The erythrocyte sedimentation rate (ESR) was measured by the Westergren method modified by Dawson (1960). Plasma iron and total iron-binding capacity were measured by the methods of Ramsay (1957 a, b). All urine was collected in iron-free vessels. Ferrioxamine, the chelate of desferrioxamine, was measured as urinary iron. This method was shown to be satisfactory by measurement of the iron in a series of known dilutions of ferrioxamine in water.

Simple Desferrioxamine Test.—Urinary iron was measured in samples collected for 6 hours before and after the intramuscular injection of 500 mg. desferrioxamine.

Differential Ferrioxamine Test.—Urinary iron was measured in three 6-hour specimens collected (1) before injection, (2) after an intramuscular injection of 50 mg./60 kg. ferrioxamine, and (3) after an intramuscular injection of 50 mg./60 kg. ferrioxamine and 500 mg. desferrioxamine. Urine collections were made from 9.30 a.m. to 3.30 p.m., and an interval of 4 days was allowed between collections (2) and (3).

The amount of chelation *in vivo* was calculated according to the formula (Fielding, 1965):

$$Fv \text{ (}in\ vivo\text{ chelation)} = \frac{Fe - Fex}{Fex} \times 833\ \mu g./kg.$$

where Fex = ferrioxamine excretion after ferrioxamine injection

Fe = ferrioxamine excretion after injection of ferrioxamine and desferrioxamine.

TABLE II
EXCRETION OF IRON IN THE URINE BEFORE AND AFTER INJECTION OF 500 MG. DESFERRIOXAMINE

Group		Urinary Iron Excretion (0-6 hrs) (μg.)		
		Total before Injection of Desferrioxamine	Total after Injection of 500 mg. Desferrioxamine	Fold Increase after Injection of 500 mg. Desferrioxamine
Controls	1	156	332	2·1
	2	210	518	2·5
	3	125	548	4·4
	4	211	721	3·4
	5	198	356	1·8
	6	125	643	5·1
	7	32	248	7·8
	8	112	220	2·0
Patients	1	117	117	1·0
	2	99	213	2·2
	*3	78	394	5·1
	4	154	154	1·0
	†5	116	717	6·2
	6	272	340	1·3
	7	236	632	2·7
	8	222	236	1·1
	*13	132	132	1·0
	*14	45	45	1·0
	15	101	223	2·2
	†16	120	417	3·5
	17	51	194	3·8
	18	101	304	3·0
	19	140	202	1·4
	‡20	12	551	45·9

*After ACTH plus 2g. intravenous iron
†After 3 g. intravenous iron
‡After 2 g. intravenous iron

Pattern of Ferrioxamine Excretion.—Urinary iron was measured in three specimens collected 0-6, 6-24, and 24-28 hours after an intramuscular injection of 50 mg./60 kg. ferrioxamine. The collections were made throughout comparable times of the day in all patients and controls. The consistency of the excretion over the first 6-hour period in the three controls was checked by repeated estimations. Patient 3 was studied shortly after completing a course of ACTH plus 2 g. intravenous iron and again 6 weeks later without further iron or corticosteroid therapy.

Response to Prolonged Intramuscular Desferrioxamine.—The pattern of excretion of ferrioxamine was studied after the intramuscular injection of 1,000 mg. desferrioxamine per day for 16 to 32 days in two doses. Urinary iron was measured daily on 24-hour specimens for 2 to 7 days before starting injections and throughout the period of injections. Intermittent measurements of plasma iron and haemoglobin were also made in three of the four patients.

Results

Simple Desferrioxamine Test

The results of the test in eight controls and sixteen patients are shown in Table II. With the exception of one female (Patient 20), who had recently completed a course of 2 g. intravenous iron, none of the patients approached the 10-fold increase in excretion associated with iron storage disease. The range, after exclusion of the patient mentioned, was 1·0 to 6·2 fold, which was similar to that found in controls.

Differential Ferrioxamine Test

The results of the modified test in three controls and nine patients are shown in Table III. Patient 5 (male) and Patients 13 and 16 (female) gave results in excess of the upper range of normal of 500 μg./kg. These patients had recently had 2 to 3 g. of intravenous iron, which in Patient 13 was supplemented by corticotrophin. The test was repeated 6 weeks later in Patient 5, and although still above normal the chelation (F*v*) was reduced to about one-third of the original level. No chelation was demonstrated in four patients (Patients 1, 4, 15, 17).

Pattern of Ferrioxamine Excretion

The results in three controls and seven patients are shown in Table IV (overleaf). In the first 6 hours after injection the proportion of ferrioxamine excreted was significantly less than that in the control subjects. However, when the urinary excretion of ferrioxamine was measured over 48 hours, the total output differed little between the patients and controls. Only Patient 15 had a significantly lower total excretion than the controls. The results in Patient 3 showed a normal 0 to 6 hour pattern immediately after receiving intravenous iron and corticotrophin, but a reversion to the rheumatoid pattern 6 weeks later. The pattern of excretion of ferrioxamine was shown to be very consistent both in the healthy subjects and in the group of patients

TABLE III
RESULTS OF DIFFERENTIAL FERRIOXAMINE TEST

Group		Therapy	Urinary Iron Excretion (0-6 hrs) (μg.)			*Fv* (μg./kg.)
			Before Injection	After Injection of Ferrioxamine	After Injection of Ferrioxamine + Desferrioxamine	
Controls ..	1		108	1535	1720	108
	2		63	1488	1604	104
	3		282	1836	1909	39
Patients ..	1		117	704	536	0
	3	After ACTH + 2 g. intravenous iron	78	1328	1822	329
	4		154	521	353	0
	5	After 3 g. intravenous iron	116	346	1063	2683
		6 weeks later	236	802	1434	930
	8		222	617	853	498
	13	After ACTH + 2 g. intravenous iron	101	585	1108	900
	15		132	892	884	0
	16	After 3 g. intravenous iron	120	328	745	1670
	17		45	600	595	0

TABLE IV
EXCRETION OF FERRIOXAMINE

Group			Percentage Excretion of Ferrioxamine (50 mg./60 kg. body weight)			
			0-6 hrs	6-24 hrs	24-48 hrs	Total
Controls	1		32	15	0	47
	2		33	14	0	47
	3		27	6	11·5	44·5
Patients	2		12	21	16	49
	4		11	19	10	40
	6		14	23	15	52
	7		13	21	22	56
	15		4	13	10	27
	3	(*a*)	34			
		(*b*)	16	30		

(*a*) Immediately after treatment with corticotrophin and intravenous saccharated oxide of iron.
(*b*) The same patient 6 weeks later.

with rheumatoid arthritis. The excretion of ferrioxamine over the first 6 hours was measured on four occasions in Controls 1 and 2 and twice in Control 3. These results were also consistent within a narrow range, the mean percentage excretion being 28, 26, and 28 respectively. Only Patient 15 differed from the other subjects with rheumatoid arthritis in that, although the pattern of excretion was similar, the amount of ferrioxamine excreted was significantly less during the first two collection periods.

Response to Prolonged Intramuscular Desferrioxamine

The results of this study on Patients 9 to 12 are shown in the Figure. The urinary ferrioxamine excretion expressed as mg. iron per day was of the order of 0·5 mg. before injections were begun. This increased progressively to 2 to 3 mg. when desferrioxamine was given.

In all three patients (10, 11, 12) in whom measurements of plasma iron were made, the concentration of iron increased during the study period and, despite a tendency to fall at Week 4 in two patients, remained above the value at Week 0 (Table V).

TABLE V
PLASMA IRON (μg./100 ml.)

Week ..	..	0	1	2	3	4	5
Patient No.	10	36	32		80	76	56
	11	16	48	56	56	60	
	12	44	68	136	200	66	

A rise in haemoglobin (Table VI) was also observed in these three patients.

TABLE VI
HAEMOGLOBIN (g./100 ml.)

Week ..	..	0	1	2	3	4	5
Patient No.	10	10·9	11·4	12·7	11·0	11·0	12·2
	11	11·7	13·0	14·6		14·7	
	12	12·2	13·4	12·4	12·8	13·9	

Discussion

In this study, with the exception of four patients who had recently received 2 to 3 g. iron intravenously, neither the simple desferrioxamine test nor the differential ferrioxamine test demonstrated increased storage of iron in patients with rheumatoid arthritis. The pattern of urinary excretion of iron after prolonged daily intramuscular injection of desferrioxamine, however, suggested that there were considerable stores of iron in patients with this condition. In the four patients, mentioned above, who had been given parenteral iron therapy, chelation probably occurred while iron was still in a phase of redistribution. Evidence in favour of this was found in one patient in whom the differential ferrioxamine test was repeated 6 weeks after treatment had ceased. Chelation was still above the normal range but the increase was much less than at the first test. In another patient, in whom the differential ferrioxamine test was also made 6 weeks after cessation of treatment with intravenous iron, chelation was shown to be normal.

Previous reports (Unseld, 1964; Wöhler, 1964; Fielding, 1965) suggesting that the simple desferrioxamine and differential ferrioxamine tests are satisfactory means for demonstrating increased iron stores *in vivo* referred to studies of iron storage diseases, such as haemochromatosis, in which there is a high labile iron pool as well as increased iron stores. As there is, therefore, much iron in relatively soluble form in these diseases, the chelation with iron chelating agents is high. In rheumatoid arthritis, and particularly in active disease, the plasma iron is usually low and the labile iron pool is reduced. Response to a single dose of iron chelating agents is likely, therefore, to be limited, so that both these tests may fail to show increased iron stores in this disease. Also, studies of the pattern of ferrioxamine excretion over 48 hours demonstrated that normal subjects excrete about one half of the injected dose of ferrioxamine and that more than

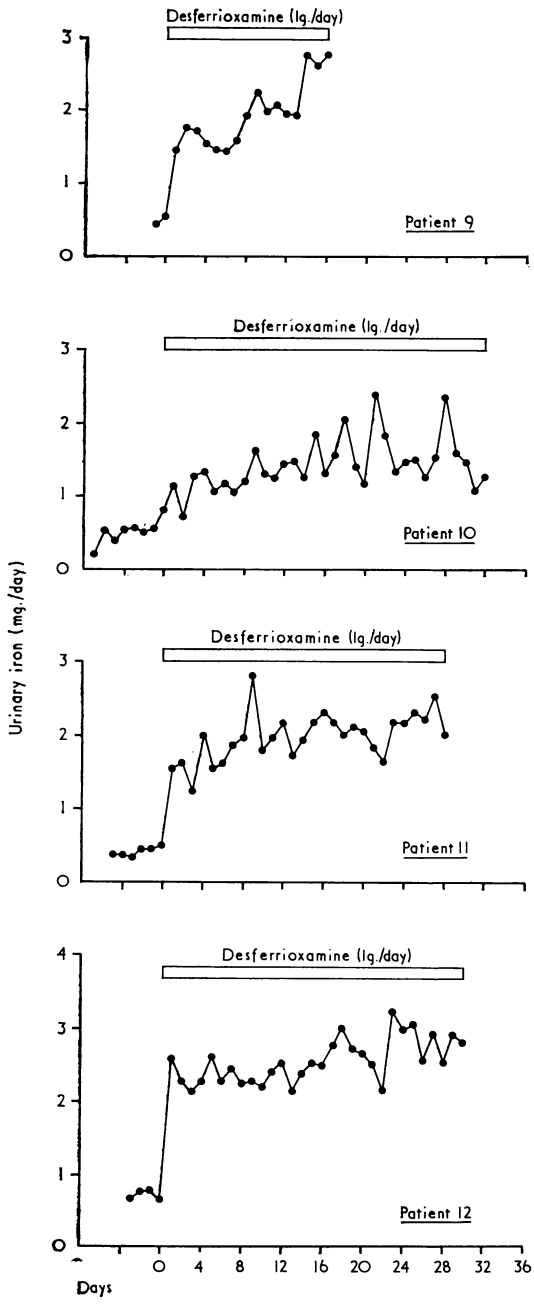

Figure.—Results in Patients 9 to 12.

half the total excretion occurred in the first 6 hours. Patients with rheumatoid arthritis, though excreting the same fraction of the total dose over 48 hours, showed delayed excretion, only a quarter of the dose being recovered in the first 6 hours. This difference in the excretion pattern of ferrioxamine made the simple desferrioxamine test unsatisfactory in these subjects.

The results of the prolonged desferrioxamine study showed an increasing urinary excretion of iron over a period as long as a month. Moeschlin and Schnider (1963) showed that, during daily administration of 1,200 mg. desferrioxamine in three "control patients", the daily urinary iron output increased from an initial level which rarely exceeded 0·5 mg. to 2·5-3·0 mg. on the second and third days, then slowly decreased to 1·0-2·0 mg. on the following days, but remaining above the basal level. However, if there were large iron stores deposited in a relatively insoluble form, as in haemochromatosis, the daily urinary excretion of iron increased progressively and was maintained at a high level for several weeks.

Schubert (1964) demonstrated that in iron-loaded animals the normal pattern of low and decreasing urinary iron excretion was consistent with most of the iron being present as freely circulating mononuclear compounds, and the pattern of continued high urinary iron excretion was consistent with iron being stored as insoluble polynuclear hydroxide in the proteins of ferritin and haemosiderin. The bulk of iron in store is not, therefore, immediately chelatable. He further suggested that the point at which the second pattern reverts to the first may indicate that the excess tissue deposits have been exhausted or the storage is of a particularly refractory type.

In this study with daily desferrioxamine, the initial excretions before injection of the chelating agent were within the normal range of 0·5 mg. per day, increasing to 2·0 to 3·0 mg. per day after desferrioxamine, and only one patient showed any tendency to revert to a normal pattern of excretion. This suggests that there are considerable stores of insoluble polynuclear iron present in patients with rheumatoid arthritis. The site of these stores is not established, but they may be in the reticulo-endothelial system (Gardner and Roy, 1961), the synovial tissue (Muirden, 1966), or both.

No exogenous iron was given to the patients during daily desferrioxamine study, but the plasma iron increased progressively and, although the level tended to fall after 4 weeks, it remained above the pre-treatment level. This increase in the plasma iron must have resulted from the mobilization of

iron from relatively insoluble stores. Moeschlin and Schnider (1964) made similar observations during treatment of patients with iron storage disease with desferrioxamine.

Together with the rise in plasma iron the haemoglobin levels also rose. Ferrioxamine iron can be used in haemoglobin synthesis (Bannerman, Callender, and Williams, 1962) and this observation was confirmed by Fielding (1965). It appears, therefore, that a factor in the anaemia of rheumatoid arthritis is that, although increased stores of iron are present, the iron is in such an insoluble form that it is not available for haemopoiesis. When, however, this form is converted to a more soluble form, haemoglobin synthesis occurs rapidly.

Summary

(1) Tests of iron storage disorder were carried out on eight controls and twenty patients with rheumatoid arthritis.

(2) The simple desferrioxamine test and the differential ferrioxamine test failed to demonstrate increased iron stores. Evidence of increased storage was only found immediately after courses of intravenous iron. The possible limitations of these tests as estimates of iron storage in rheumatoid arthritis are outlined.

(3) The pattern of ferrioxamine excretion in rheumatoid patients showed some delay compared with controls after 6 hours, but the excretions were normal after 48 hours.

(4) The pattern of urinary excretion of iron after prolonged intramuscular injections of desferrioxamine in rheumatoid patients suggested the presence of considerable iron stores.

(5) The results are discussed in the light of present knowledge of iron metabolism in rheumatoid arthritis.

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La nature de l'anémie dans l'arthrite rhumatismale VII. L'emmagasinage du fer dans la maladie rhumatismale

RÉSUMÉ

(1) On étudia les troubles de l'emmagasinage du fer chez vingt malades ayant une arthrite rhumatismale et chez huit témoins.

(2) Le simple examen de la desferrioxamine et l'examen différentiel de la ferrioxamine n'ont pas permis de monter une élévation de l'emmagasinage du fer. On montra que seules des injections intraveineuses de fer furent susceptibles de provoquer une augmentation de l'emmagasinage du fer. On indique que la valeur de ces tests pour l'estimation de l'emmagasinage du fer pourrait être limitée.

(3) La comparaison des résultats de l'excrétion de la ferrioxamine chez les rhumatisants accusa un retard, par rapport aux témoins, au bout de six heures, mais au bout de 48 heures le taux d'excrétion fut le même dans les deux groupes.

(4) Le tableau des chiffres d'excrétion urinaire du fer après un traitement prolongé par injections intramusculaires de desferrioxamine chez des malades atteints d'arthrite rhumatismale fait penser à l'existence d'une reserve considérable de fer.

(5) On discute ces résultats à la lumière des connaissances actuelles du métabolisme du fer dans l'arthrite rhumatismale.

La naturaleza de la anemia en la artritis reumatoide VII. El almacenamiento del hierro en la artritis reumatoide

SUMARIO

(1) Se estudiaron los disturbios del almacenamiento del hierro en veinte enfermos con artritis reumatoide y en ocho testigos.

(2) El simple test de la desferrioxamina y el test diferencial de la ferrioxamina no lograron a demostrar un aumento del depósito ferrico. Se comprobó que sólo inyecciones intravenosas de hierro fueron seguidas de un aumento inmediato de depósitos ferricos. Se indican las limitaciones de ests tests en la estimación del almacenamiento del hierro en la artritis reumatoide.

(3) La forma de excreción de la ferrioxamina en enfermos reumáticos mostró una cierta demora, en comparación con testigos al cabo de seis horas, pero la excreción se volvió normal a los 48 horas.

(4) La forma de la excreción urinaria de hierro después de un curso prolongado de inyecciones intramusculares de desferrioxamina en enfermos con artritis reumatoide sugiere la presencia de una reserva de hierro considerable.

(5) Se discuten estos resultados a la luz de los conocimientos actuales del metabolismo del hierro en la artritis reumatoide.