INTRAVENOUS IRON IN RHEUMATOID ARTHRITIS: POSSIBLE PROGNOSTIC FACTORS

BY

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The anaemia which often accompanies rheumatoid arthritis is usually improved by intravenous iron therapy. Some patients, however, derive no benefit, and, in view of the not infrequent technical difficulty of intravenous injections in these cases, it would be useful if they could be easily recognized. Useless and perhaps awkward therapy could thus be avoided and blood transfusion given at once if, for example, orthopaedic procedures were imminent.

To try to discover factors of possible prognostic value, the results of a variety of observations upon patients who received intravenous iron have been assembled, but no satisfactory test has emerged.

Material and Methods

Only data from anemic cases of uncomplicated rheumatoid arthritis are included. Cases receiving treatment other than simple analgesics and physiotherapy were excluded. The effect of treatment was gauged from the haemoglobin value three months after treatment; figures of 14 and 12.5 g. per 100 ml. were taken as the lower limit of normality for men and women respectively, and an increase of 1.5 g. or more per 100 ml. was regarded as "material improvement." The dose given was one and a half times the amount calculated to raise the haemoglobin to 100% (14.8 g.), on the basis that 100 mg. of iron raises the level by 4%. Injections were given thrice weekly.

The following techniques were used:

Red-cell count: the top and bottom rows of each side of an improved Neubauer chamber were counted—that is, four rows of five large squares.

Haemoglobin: alkaline haematin, comparing photometrically with Gibson and Harrison's artificial standard.

Haematocrit: Wintrobe's tubes, spun to constant volume at 1,500 g (about 3,200 r.p.m.).

Sedimentation rate: Westergren method.

Plasma iron: Kitzes, Elvehjem, and Schuette (1944).

Free erythrocyte protoporphyrin: Grinstein and Watson (1943), comparing the fluorescence of the final extract in 5% HCl with that of a standard safranin solution (100 mg. per litre). This standard had previously been compared with pure protoporphyrin.

Iron-binding capacity of the serum: Rath and Finch (1949).

Serum proteins: biuret method for total protein and albumin after precipitation of globulin by half-saturated ammonium sulphate.

Comment upon Results

The effects of intravenous iron upon haemoglobin levels are shown in Table I. Roughly one-quarter of the patients derived no material benefit, and a return to normal levels was more frequent in the women than in the men.

TABLE I.—Effects of Intravenous Iron on Haemoglobin Levels

	No. of Cases	Haemoglobin Three Months after Treatment		
		Normal	Improved	Unchanged
Men ..	14	1	9	4
Women ..	36	14	13	9

In Table II the cases are grouped according to the effect of treatment, the results of various investigations being summarized for each group. It is obvious that with every investigation some overlap between the groups occurred and no single characteristic infallibly distinguished potential failures or successes.

As noted by previous workers, a good response to intravenous iron was more likely when the disease was relatively inactive, and was unlikely if very severe disease with much constitutional disturbance was present. Nine out of 15 "successes" had sedimentation rates below 30 mm. in one hour, and no patient with a sedimentation rate below this figure failed to achieve normal levels; conversely, in only one "failure" was the rate below 45 mm. A high rate did not, however, necessarily preclude a good result, for patients with relatively slight constitutional disturbance usually responded well, whatever the laboratory findings. In fact, the amount of subcutaneous fat was as good a guide to the result of treatment as any other.

None of the indices, mean corpuscular volume, mean corpuscular haemoglobin, or mean corpuscular haemoglobin concentration regularly distinguished failures or successes, though in each case the mean values were lowest in the group whose haemoglobin became normal. The haemoglobin levels of the four cases showing microcytosis all returned to normal, as did the levels of the six cases having grossly diminished mean corpuscular haemoglobin (<21 μ g.).

Plasma iron and the degree of saturation of the iron-binding protein were of no prognostic value. A raised total iron-binding capacity was found in nine women, all of whom achieved final haemoglobin values above 12 g. per 100 ml.; normal or reduced iron-binding capacity showed no significant correlation with the result of therapy. To try to assess the rate of removal of injected iron from the blood stream, plasma iron was estimated half an hour and three hours after a dose of 50 mg. intravenously. At both times there was a suggestion that the "failures" removed the metal more quickly, but the differences were slight and overlap was considerable. Only the three-hour figures appear in Table II.

Serum albumin and globulin gave no prognostic guidance. Estimation of free erythrocyte protoporphyrin was also use-

TABLE II

Investigation	Haemoglobin Unchanged			Haemoglobin Improved			Haemoglobin Normal		
	Mean	Range	Cases	Mean	Range	Cases	Mean	Range	Cases
Disease activity:									
Slight			2			6			10
Marked			11			16			5
Sedimentation rate (mm./1 hr.)	67	30-125	13	68	15-110	22	39	11-108	15*
M.C.V. (μ^3)	89.5	79.5-102	11	92	83-100	11	78.5	64.5-92.5	9
M.C.H. (μ g.)	26.0	21.6-30.4	11	25.1	23.2-27.8	11	20.8	14.6-26.2	9†
M.C.H.C. (%)	28.9	26.0-31.7	13	27.5	25.7-29.8	17	25.7	22.4-29.5	14
Plasma iron (μ g./100 ml.)	33	12-82	13	36	7-91	21	31	7-66	14
T.I.B.C. (μ g./100 ml.)	320	185-415	7	362	255-475	13	448	335-570	10‡
Saturation of iron-binding protein (%)	9	4-16	7	9	3-17	13	7	2-11	10
3-hr. plasma iron rise (μ g./100 ml.)	149	30-205	5	251	110-355	8	195	165-240	6
Serum albumin (g./100 ml.)	4.5	4.0-5.4	5	4.4	3.6-5.6	13	4.5	3.8-5.2	8
" globulin	3.0	2.1-3.7	7	3.3	1.9-4.9	12	2.4	1.8-2.7	8
Free erythrocyte protoporphyrin (μ g./100 ml.)	16, 32, 37, 50, 52, 130, 304		5	28, 34, 39, 41, 42, 47, 48, 50, 80		9	20, 32, 162, 166, 1,100		5

* 9 were <30 mm./1 hr. † 6 were <21.5 μ g. ‡ 6 were >430 μ g./100 ml.

less, normal and raised values occurring in all groups. The raised values always became normal after iron therapy, however, even in the absence of a material rise in haemoglobin level.

Conclusions

In 50 cases of rheumatoid arthritis, failure of their anaemia to respond to intravenous iron could not be predicted from the results of any of the investigations examined.

Return of the haemoglobin to normality occurred regularly when one or more of the following were present: sedimentation rate below 30 mm. in one hour, microcytosis, gross hypochromasia, and raised total iron-binding capacity of the serum.

The haemoglobin, however, returned to normal or improved greatly in many cases which showed none of the above criteria.

It appears that intravenous iron is always worth trying in the anaemia of rheumatoid arthritis, except when severe constitutional disturbance or the imminence of surgery makes preferable the rapid rise in haemoglobin which follows blood transfusion.

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ACTINOMYCOTIC PYAEMIA

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Human infection with filamentous organisms of the group *Actinomyces* is an uncommon but well-recognized condition. In most cases the anaerobic species *Actinomyces israeli* is the causal organism, and infection with it usually results in localized lesions in the neck or abdomen (Cope, 1938), although on rare occasions generalized pyaemic spread occurs with multiple abscesses throughout the body (Israël, 1878; Harbitz and Grondahl, 1911; Shrewsbury, 1928). In a much smaller number of cases infection is due to aerobic filamentous organisms, most commonly *Nocardia asteroides*, which usually cause pulmonary lesions and are often associated with systemic spread (Biggart, 1934; Benbow *et al.*, 1944; Kirby and McNaught, 1946). The relative frequency of infection with the different organisms is difficult to determine, since few detailed bacteriological studies are reported and diagnosis has often been based upon the appearance of a filamentous organism in a stained film or on the presence of "granules" in pus.

Systemic spread was equally fatal in both types of infection until the use of antibiotics in treatment, and precise bacteriological diagnosis was therefore not important. Since the behaviour of the two species

towards antibiotics is different, cultural identification of the organism has become imperative, particularly in view of the possibility of complete recovery even after prolonged illness and in the presence of pyaemic dissemination as in the following case.

Case Report

The patient, a 50-year-old director, first noticed vague malaise, with loss of appetite and weight, in March, 1950. In August he had a mild fever for several days, which subsided without treatment. In October he developed left-sided chest pain, and on admission to hospital two weeks later was pyrexial and ill, but, apart from some loss of weight, there were no abnormal physical signs. A chest x-ray film showed some loss of translucency at the left costo-phrenic angle. A blood examination showed: red cells, 4,100,000 per c.mm.; Hb, 84% (12 g. per 100 ml.); white cells, 6,400 per c.mm.; blood urea, 36 mg. per 100 ml.; erythrocyte sedimentation rate (E.S.R.), 24 mm. per hour (Wintrobe). The pyrexia subsided without treatment after a week in hospital and the patient was discharged.

He remained unwell and continued to lose weight. In April, 1951, he had a further attack of chest pain, which improved after several days' treatment with penicillin. On May 24 he suddenly developed a fluctuant painful swelling in the left arm, and at about this time developed several painful whitlows. The swelling in the arm was aspirated, but the contents were sterile on culture; it continued to discharge for about two months. A chest x-ray film showed no change since October, 1950. On July 5 a painful swelling appeared in the left calf, and smaller swellings occurred on his feet and left arm before readmission to hospital on July 26. He was then febrile, ill, and wasted, and had lost 3 stone (19 kg.) in weight. There was a productive cough, with abundant purulent sputum; numerous rales and crepitations were audible at both lung bases. The liver and spleen were not palpable, and the abdomen appeared normal. The cardiovascular system was normal. A very tender, fluctuant swelling (5 by 2 by 2 cm.) was present in the left gastrocnemius; and a smaller nodule (about 2 by 1 by 1 cm.) was felt in the muscles of the left forearm. There were two flat greyish lesions about 0.2 cm. diameter in the skin at the margin of the nail bed on the left hand, and larger bluish grey lesions in the skin over the right tibia, on the medial surface of the right foot, and on the right heel. These lesions consisted of a central zone of necrotic skin (the largest was 2 by 1 cm.) surrounded by a thin, slightly raised red area and a wider diffuse zone of induration tender to touch.

A blood count showed: red cells, 4,200,000 per c.mm.; Hb, 88% (12.2 g. per 100 ml.); white cells, 7,400 per c.mm. (89.3% polymorphonuclear leucocytes). The E.S.R. was 129 mm. per hour (Westergren), and the chest x-ray film now showed diffuse miliary shadowing throughout both lung fields. The urine was normal. Aspiration of the calf abscess produced about 0.5 ml. of thick blood-stained material, containing numerous pus cells, and a Gram-positive filamentous branching organism with many smaller Gram-negative bacilli. Similar filamentous organisms were seen in the pus from all the superficial lesions, and were also present in the sputum, which contained yellowish granules. Exploration of the calf showed a thick-walled abscess cavity, containing about 40 ml. of viscous blood-stained pus in which were numerous yellow granules, which showed typical "ray fungus" on microscopical examination. The patient was first treated with intramuscular streptomycin, 2 g. a day, since infection with *N. asteroides* seemed probable. He remained pyrexial, several new lesions appeared in the extremities, and after one week 2 mega units of penicillin daily were given together with the streptomycin. The latter was replaced after 14 days' treatment by "sulphatriad," 3 g. daily, in view of the isolation of *A. israeli* from the pus and sputum, and the penicillin was increased to 4 mega units daily.