CLINICAL INVESTIGATIONS ON A NEW INTRAMUSCULAR HAEMATINIC

BY

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According to Brown and Moore (1956) there are three clear indications for parenteral iron therapy: (1) hypochromic anaemia in patients unable to tolerate or unwilling to take adequate doses of iron orally; (2) hypochromic anaemia in patients unable to absorb adequate amounts of orally administered iron; and (3) hypochromic anaemia in patients who need their haemoglobin bringing rapidly to normal but for whom transfusions are undesirable or unsuitable.

After the appearance of saccharated oxide of iron (Nissim, 1947) and a preparation containing a special ferridextrin complex in colloidal form (Agner *et al.*, 1948; Andersson, 1950) the intravenous method of therapy was that most commonly used; of the two preparations, the latter can also be injected intramuscularly (Andersson and Bergström, 1956).

The intramuscular method of administration has, however, been increasingly applied since Fletcher and London (1954) produced their iron-dextran complex; this preparation, whose clinical properties, after intramuscular injection, were studied by Baird and Podmore (1954) and others, has been found to give very good therapeutic results. Certain side-effects after the use of solutions containing this complex have, however, been reported (Karlefors and Nordén, 1958; and others). It has also been found that, when given to laboratory animals in high total amount for a prolonged period of time, the iron-dextran complex produces sarcoma at the site of injection (Richmond, 1959, 1960; Haddow and Horning, 1960).

A new iron preparation, "jectofer," intended for intramuscular injection, has recently been presented by Lindvall and Andersson (1961). The present paper describes clinical studies on its therapeutic effect and on the side-effects it produces. The previously mentioned iron-dextran preparation, "imferon," was used for purposes of comparison.

Properties of Jectofer

The iron in this preparation is present in the form of a sterile solution of an iron-sorbitol–citric-acid complex with dextrin as a stabilizer. The solution contains 50 mg. Fe/ml. and has a *p*H of 7.5. It is stable in serum; it does not cause haemolysis and does not affect the clotting mechanism. Absorption after intramuscular injection takes place rapidly—two-thirds of a dose injected into a rabbit is absorbed within three hours and 80–85% after 12 hours. Absorption is followed by a rapid rise in the iron concentration of serum. A small transferrin. About 30% of the dose of iron given is excreted with the urine (Fig. 1) (Lindvall and Andersson, 1961). It has no antigenic properties; LD50 for the mice is about 35 mg./kg. body weight (Svärd, 1961). This value may seem low in comparison with other parenteral iron preparations, but the margin between the clinical dose of about 1.5 mg./kg. and a toxic one is nevertheless fully adequate.

Administration.—The preparations here called iron-sorbitol and iron-dextran respectively were injected deeply into the gluteal region in a dose corresponding to 100 mg. Fe. The injections were made daily, on alternate sides. Every course of treatment comprised 10 injections. Before the clinical trials started, the tolerance for iron-sorbitol was tested by giving 10 subjects increasing amounts of this preparation. As no side-effects were observed in these experiments the full therapeutic dose was given without a preceding test dose.

Material

The series comprised 65 patients who satisfied the clinical criteria for stabilized iron deficiency. In the order in which the patients came in for treatment, every second case was selected for iron-dextran treatment while the others were given iron-sorbitol. Twelve cases in the iron-dextran group and 21 in the iron-sorbitol group received the treatment in the out-patient department and the others were treated in hospital.

The sex-and-age distribution in the groups is shown in Table I. As may be seen, the groups were equivalent in these respects, and women were in the majority. Table II presents the distribution of the material with respect to the diagnosis. As the material included cases

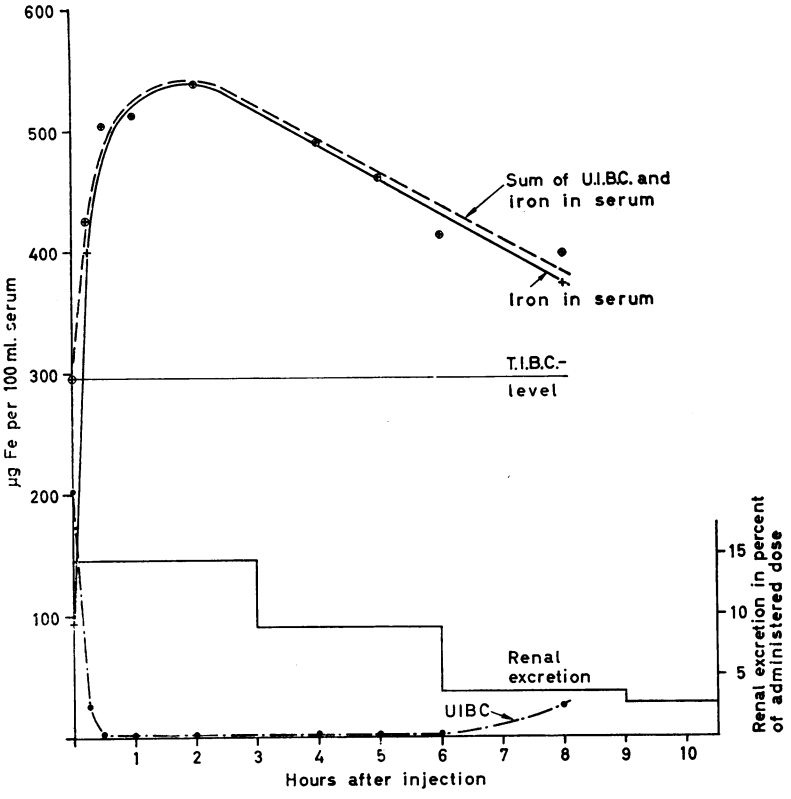

FIG. 1.—Iron concentration in serum, unsaturated iron-binding capacity (U.I.B.C.), sum of iron concentration in serum and unsaturated iron-binding capacity (five healthy subjects, whose level of total iron-binding capacity—T.I.B.C.—is shown), and renal excretion (nine healthy subjects). Mean values

showing a wide diversity in the degree of anaemia, it was divided into three subgroups (Table III) with a view to facilitating assessment of the therapeutic effect.

In order to obtain a better idea of the degree of utilization of the administered iron for the haemoglobin synthesis the total dosage given was slightly on the small side. In all cases with anaemia the dosage given—1,000 mg. Fe—was not sufficient to restore the Hb

TABLE I.—*Age-and-sex Distribution of 65 Patients Treated*

Preparation	Sex	Age (Years) 0–30	31–45	46–60	Over 60	Total
Iron-sorbitol	Females	11	7	8	1	34
	Males	2	3	1	1	
Iron-dextran	Females	5	6	8	3	31
	Males	2	1	5	1	

TABLE II.—*Clinical Diagnoses*

	Iron-sorbitol	Iron-dextran
Acquired haemolytic anaemia (sequel of splenectomy)	1	1
Sideropenia	9	7
Menometrorrhagia	12	11
Duodenal and gastric ulcer	7	8
Sequel of ventricular resection (B II)	3	2
Ulcerative colitis	1	1
Polyposis of rectum	1	—
Diaphragmatic hernia with melaena	—	1

TABLE III.—*Distribution of Cases According to Pre-treatment Hb Value*

Preparation	Hb Value in g./100 ml. Blood ⩽8	8·1–12	⩾12·1
Iron-sorbitol	7	23	9
Iron-dextran	7	16	11

concentration to normal and to fill the body's iron depots. When the increase in Hb was thought to have ceased, eight patients who were still anaemic were given a further series of 10 injections of the same preparation as they had received before; hence the total courses of treatment amounted to 73.

Clinical Methods

The Hb and erythrocyte values were determined twice a week during treatment and subsequently once a week for at least four weeks. In the first 57 patients a daily reticulocyte count was made for 10 to 14 days. All these analyses were carried out by the same assistant.* The serum-iron level was determined by Agner's (1947) method before and 35 days after the start of treatment.

The sedimentation rate, urinary sediment, and non-protein nitrogen were investigated in all patients, and the liver status was followed by bilirubin determinations, thymol turbidity tests, Takata–Ara tests, and determinations of the alkaline phosphatase. In some of the cases the renal function was studied by means of an endogenous creatinine-clearance test.

Results

Therapeutic Effect

The therapeutic effect was assessed from the reticulocyte response and the increase obtained in the Hb and serum-iron values. The rise in the reticulocyte count, which for both preparations reached its maximum six to eight days after the start of therapy with a less-marked peak in the reticulocyte response than is observed in the treatment of pernicious anaemia, was for both preparations most pronounced in the patients showing the lowest initial values for the haemoglobin content (Table IV).

For the group with an initial value of Hb ⩽8 g./100 ml. blood the Hb increase is given for every case in Table V. The group treated with iron-sorbitol consisted of six women and one man; three of the women had their menstruation during the observation period. The iron-dextran group comprised three women and four men; one of the women in this group had her menstruation during the observation period. The Hb value 7, 14, 21, and 35 days after inception of treatment is shown and it is seen that the increase ran parallel in both groups; after five weeks it was 3.8 g./100 ml. blood in the iron-sorbitol group and 3.9 g./100 ml. in the iron-dextran group. The mean serum-iron value before treatment was 17 μg./100 ml. blood for the iron-sorbitol group and 23 μg./100 ml. for those given iron-dextran; after treatment the values were 21 and 37 μg./100 ml. blood, respectively.

Table VI presents the results of treatment of patients with a pretreatment Hb level of 8.1–12 g./100 ml. and of ⩾ 12.1 g./100 ml. blood. There was no difference in

TABLE IV.—*Maximum Reticulocyte Response per* 1,000. *Number of Cases in Parentheses*

Preparation	Hb Value in g./100 ml. Blood ⩽8	8·1–12	⩾12·1
Iron-sorbitol	106 (5)	66 (19)	46 (7)
Iron-dextran	91 (7)	60 (13)	37 (6)

TABLE V.—*Patients with Hb Value ⩽ 8 g./100 ml. Blood Treated with Iron-sorbitol or Iron-dextran*

Sex	Before Treatment	Hb Value in g./100 ml. Blood, Days from Start of Treatment 7	14	21	35
Iron-sorbitol					
F	5·4	6·5	8·7	8·8	9·2
F	6·0	7·6	8·9	9·3	9·4
F	6·2	8·1	9·6	10·5	11·2
F	6·8	8·3	10·3	11·4	11·4
F	7.0	7·6	8·8	9.8	10·3
M	7·6	9·2	9·8	10·0	10·3
F	7·8	9·0	10·0	10·3	11·4
Mean value	6·7	8·0	9·4	10·0	10·5
Increase from initial value	—	1·3	2·7	3·3	3·8
Iron-dextran					
F	5·0	6·2	7·8	8·5	10·1
F	6·0	6·0	7·6	9·0	9·7
F	7·6	9·2	10·6	11·2	10·8
M	7·8	8·7	10·0	11·2	11·4
M	8·0	9·2	9·7	10·8	12·8
M	8·0	9·3	10·3	10·8	11·8
M	8·0	9·0	10·3	11·4	11·4
Mean value	7·2	8·2	9·5	10·4	11·1
Increase from initial value	—	1·0	2·3	3·2	3·9

TABLE VI.—*Increase in Hb Value in the Group with Pretreatment Hb Level* 8.1–12 *g. and* ⩾ 12.1 *g./100 ml. Blood*

Preparation	Hb Range	No. of Cases	Mean Value of Hb in g./100 ml. Blood: Before Treatment	Increase after Start of Treatment: 7 Days	14 Days	21 Days	35 Days	Serum Iron, μg./100 ml.: Before Treatment	Increase 35 Days After Start of Treatment
Iron-sorbitol	8·1–12	23	10·2	0·6	1·2	1·6	2·3	28	34
Iron-dextran	8·1–12	16	10·2	0·6	1·1	1·5	2·5	29	46
Iron-sorbitol	⩾12·1	9	12·9				1·7	44	37
Iron-dextran	⩾12·1	11	13·1				1·0	44	55

*The analyses were made by Mrs. Kerstin Brumark, to whom

therapeutic effect between the two preparations, as the increase in haemoglobin was the same for both. The rise in the serum-iron concentration recorded after treatment was also similar for both preparations. Some illustrative cases from the treatment are seen in Figs. 2–5.

Side-effects

No general reactions in the form of temperature elevation, headache, nausea, vomiting, or chills were observed after the injection of iron-sorbitol in doses equivalent to 100 mg. Fe. Some of the patients reported, however, that at a meal about one hour after the injection their normal sense of taste was affected; this reaction had disappeared completely after about 12 hours.

In five cases treated with iron-sorbitol a mild local reaction at the injection site, in the form of a feeling of distension with moderate tenderness to palpation, arose immediately after the injection. The sensation was described as being similar to the reaction following an intramuscular vitamin or penicillin injection. In no case was the discomfort severe enough to warrant discontinuation of the treatment. In two of the patients the tenderness persisted for about a week after conclusion of the treatment. With the injection technique used no discoloration of the skin was observed.

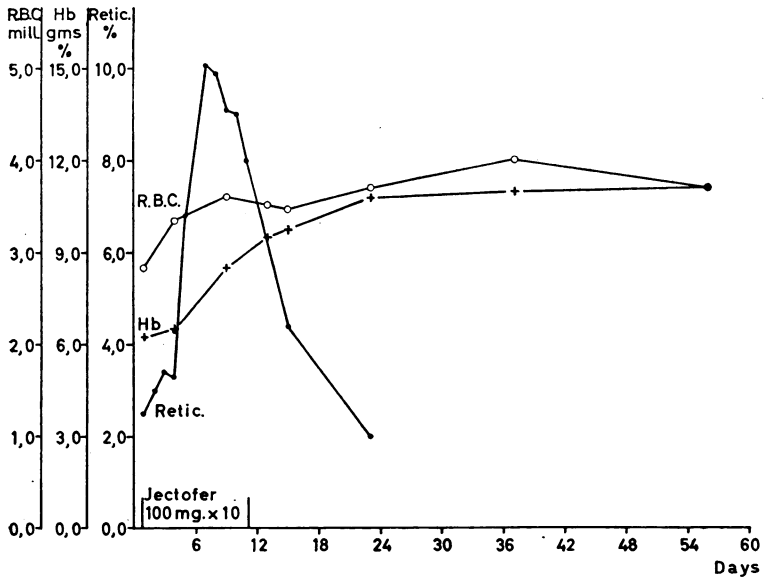

FIG. 2.—Woman aged 46 with abnormally profuse menstruation but in other respects normal.

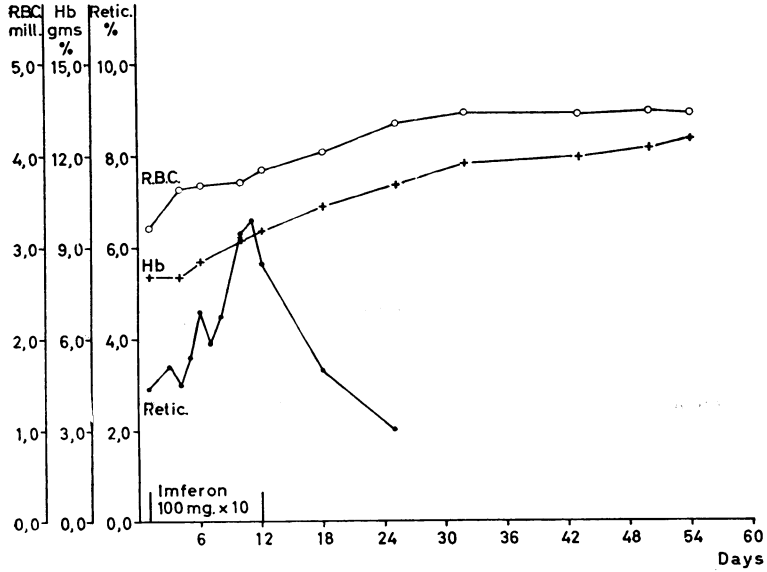

FIG. 3.—Man aged 68 with anaemia after a gastric haemorrhage (duodenal ulcer). No other features of interest obtained from the clinical examination

TABLE VII.—*Renal Excretion of Iron in a Female Patient with Impaired Renal Function. Endogenous Creatinine-clearance 17 ml./min. N.P.N. 60 mg./100 ml. Blood. Intramuscular Injection of Iron-sorbitol in a Dose Corresponding to 50 mg. Fe*

Renal Excretion (%)				
Hours After Injection				Total
0–2	3–6	6–9	9–24	
3·1	4·2	1·9	2·1	11·3

In one patient treated with iron-dextran a temperature rise to 38.2° C. was noted after the tenth injection. Another patient, not included in the therapeutic evaluation, refused to undergo further treatment on account of severe pain at the injection site in association with a general feeling of illness and a temperature rise to around 38° C. Besides these two patients, a further six who received iron-dextran complained of pain around the site of injection; two of them took to their beds for a couple of days with highly inflamed, tender buttocks and thighs. No local discoloration of the skin was, however, observed after the iron-dextran injections.

Effect on Renal Function

As already mentioned, about 30% of the iron is excreted with the urine after an injection of iron-sorbitol. There was no disturbance of the urinary sediment or increase in the non-protein nitrogen in any of the patients. The urinary sediment was normal also at the time when the iron excretion was at its maximum and when the urine was somewhat darkened. The renal function was observed in about 10 patients in an endogenous creatinine-clearance test before and after the treatment; no changes were demonstrated.

Two patients with greatly impaired renal function were also studied. They were given gradually increasing doses, terminating in the one case with a dose of iron nine times and in the other case six times the 100-mg. dose. The first patient had a non-protein nitrogen level of 57 mg./100 ml. blood and a filtration of 10 ml./min. before the treatment. The values were the same after the treatment. In the other patient the filtration value was 17 ml./min. both before and after treatment. The non-protein nitrogen was 60 mg./100 ml. blood before and 47 mg./100 ml. after treatment; the sediment showed no changes. The urine from the latter patient was collected

injection of a dose corresponding to 50 mg. of iron. The result is shown in Table VII. As may be seen, the patient excreted only 11.3% of the amount given, while healthy subjects excrete about 30% of this dose as well.

Discussion

Treatment or iron-deficiency anaemia by intravenous therapy gave, according to Nissim (1949) and Andersson (1950), a rise in the Hb level of 0.64 g./100 ml. blood per 100 mg. Fe; this corresponds to 100% utilization.

Baird and Podmore (1954) stated that an intramuscular injection of iron-dextran in a dose corresponding to 100 mg. Fe produced a rise in the Hb level of 0.24 to 0.48 g./100 ml. blood (mean value 0.34). The results achieved with iron-dextran in this investigation fall within the values mentioned by Baird and Podmore, and in the group with the most advanced anaemia the increase was on an average 0.39 g. Hb per 100 ml. blood. With iron-sorbitol an increase of 0.38 g./100 ml. blood was obtained. Using the same basis for calculation as that applied by Nissim and by Andersson, the values obtained are equivalent to approximately 60% utilization.

In the groups with a pretreatment Hb level of 8.1–12 g./100 ml. blood the utilization of the two preparations was the same, or, applying the aforementioned calculation basis, 36% for the iron-sorbitol and 39% for the iron-dextran group; in the patients with an initial Hb level of over 12 g./100 ml. blood the corresponding figures were 27% and 16% for iron-sorbitol and iron-dextran, respectively. The lower utilization percentage in the last-named group is due to the fact that in a large number of these cases the Hb value had been normalized, and it must therefore be assumed that the excess was present as depot iron. Hence the clinical investigation has shown that in the treatment of iron-deficiency anaemia iron-sorbitol gives the same good therapeutic results as iron-dextran, despite the fact that 30% of the injected iron is excreted with the urine.

As approximately 60% of the iron given in the form of iron-sorbitol had been utilized for the Hb-synthesis in the patients with the highest degree of anaemia, about 90% of the dose administered could thus be accounted for. For iron-dextran about 60% could be accounted for; this may be explained by the fact that a large amount may remain in the muscle. Grimes and Hutt (1957), for instance, when using preparations marked with ^{59}Fe, found that 17–45% remained at the site of injection, and Karlefors and Nordén (1958) reached a similar conclusion. The latter authors noted discoloration of the skin in 25% of their patients after treatment with iron-dextran; no such complications were observed in the present material. The explanation of this may be that mg. Fe, while only 100 mg. Fe was given in the present series. Systemic side-effects were also reported by these authors, but the incidence of such cannot be ascertained from their case reports. In the material with iron-dextran described in the present paper, 4 out of 32 patients had severe side-effects and a further four complained of considerable discomfort after the treatment; hence the total incidence of side-effects amounted to about 25%.

When iron-sorbitol was used, I noted neither systemic side-effects nor local discoloration. Local reactions in the form of a feeling of distension occurred in 5 of the 34 cases treated, or approximately 15%. A few patients also reported a transient effect on the taste. This ran approximately parallel to the absorption of the preparation as reflected in the increase of the iron concentration in serum.

Recently there has been much discussion regarding the possible risk of a carcinogenic action of iron-dextran, since a high incidence of sarcoma was demonstrated in

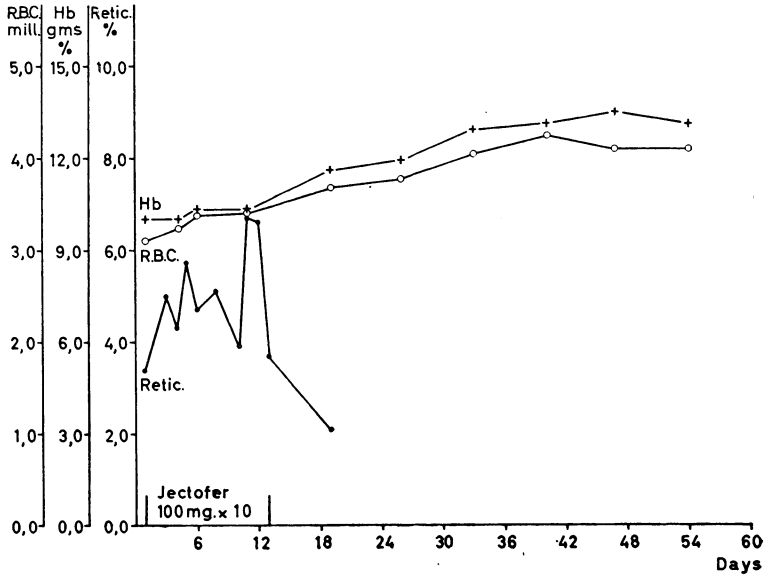

FIG. 4.—Woman aged 68 with hypertension of several years' standing. Severe attacks of haemorrhage from the nose in 1958. Now she had anaemia after a gastric haemorrhage (duodenal ulcer). No other observations of interest.

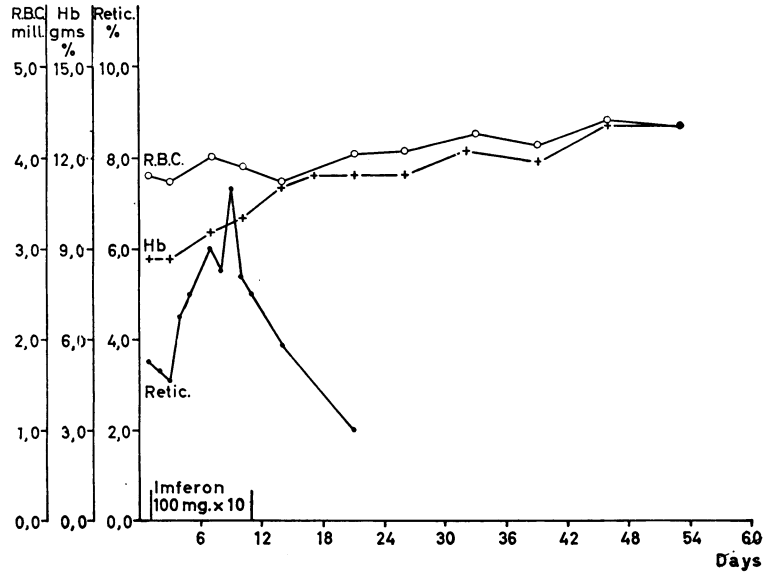

FIG. 5.—Man aged 73 with polyposis of the rectum. No other pathological

animal experiments. The clinical importance of this observation, however, has still to be elucidated. Lundin (1961), using the same technique as Richmond (1959), has confirmed this action of iron-dextran. After iron-sorbitol, on the contrary, no sarcoma developed.

Summary

A preparation containing an iron-sorbitol–citric-acid complex (" jectofer ") and intended for intramuscular injection has been studied from the aspects of tolerance and therapeutic effect in 39 cases. Comparisons are drawn with iron-dextran (" imferon ") (34 cases). The clinical tolerance for the iron-sorbitol complex was good, and only mild local side-effects were noted. The therapeutic result was satisfactory, and in patients with an Hb concentration of less than 8 g./100 ml. blood the increase in the Hb level was 3.8 g./100 ml. for the iron-sorbitol group and 3.9 g./100 ml. for the iron-dextran group. This corresponds approximately to a 60% utilization of the iron in the preparation. About 30% of the dose administered is excreted in the urine without producing any noticeable effect on the renal function.

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INTRAVENOUS IRON-DEXTRIN IN IRON-DEFICIENCY ANAEMIA

BY

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The use of parenteral iron preparations in the treatment of iron-deficiency anaemias has passed through several phases. Baird and Podmore (1954) point out that Claude Bernard used intravenous iron in animals. Many preparations have been tried, including iron gluconate (Reznikoff and Goebel, 1937), ascorbate (Friend, 1938), and triethanolamine (Brownlee *et al.*, 1942), but toxicity and pain precluded their clinical use. Cappell (1930), in an extensive study in mice, demonstrated the reticulo-endothelial uptake of saccharated iron oxide after intravenous injection and its subsequent redistribution. Nissim (1947) established that saccharated iron oxide was an effective therapy by the intravenous route. Its disadvantages were lack of stability in plasma, the risk of severe and painful inflammatory reactions when injected outside a vein, and a moderate incidence of toxic reactions (Nissim, 1954; Ross, 1957).

Cappell *et al.* (1954), Baird and Podmore (1954), Jennison and Ellis (1954), and Scott and Govan (1954) reported favourably on a high-molecular carbohydrate iron complex, iron-dextran (" imferon "), suitable for intramuscular use. This complex has been the subject of many clinical and experimental studies. The ease of intramuscular administration and the relative freedom from general toxic reactions soon made iron-dextran the most frequently chosen preparation when parenteral iron was indicated. Interest in the intravenous route declined. Iron-dextran has also been given intravenously, but, although no large series has been reported, it appears that toxic reactions, including anaphylaxis, often occur (Callender and Smith, 1954; Ross, 1955; MacKenzie and Lawson, 1959; *Brit. med. J.*, 1960b), and no investigator has reported with any enthusiasm on its intravenous use.

Richmond (1957, 1959) reported the induction of sarcomas by iron-dextran in rats, and his findings were confirmed by Haddow and Horning (1960) in mice. There has since been a good deal of speculation on how far this carcinogenic activity for mice and rats is applicable to man (*Brit. med. J.*, 1960a; Golberg, 1960; Haddow, 1960; Duthie *et al.*, 1960). No definite answer can be given to this question at present. One result of this unexpected finding has been a renewed interest in the intravenous administration of parenteral iron. The preparation for intravenous use reported here is not a new one, although it has not until recently been available in this country. Andersson (1950), Lucas and Hagedorn (1952), and Hagedorn (1952) report on its efficacy in iron-deficiency anaemias and its freedom from toxic reactions.

The Preparation.—The preparation used is a dextrin-iron known as " astrafer." The manufacturers describe the preparation as a high-molecular-weight iron-carbohydrate complex. It contains 20 mg. of iron per ml. in isotonic solution, is stable in saline and plasma, and has a *p*H of 7.3. The iron is trivalent. The complex differs from iron-dextran in having a lower-molecular-weight carbohydrate, dextrin, as the protective carrier for colloidal ferric hydroxide.

Methods and Materials

Iron-dextrin was used as astrafer, iron-dextran as " imferon," and saccharated iron oxide as " ferrivenin."

Haemoglobin is estimated as oxyhaemoglobin, using a Unicam SP 300 photoelectric colorimeter. The instrument is frequently checked by chemically estimated blood samples supplied by the M.R.C. and by a glycerin-preserved sample of haemoglobin: 14.6 g. Hb per 100 ml. is referred to as 100% Hb.

Serum-iron estimations on patients not receiving iron complex were made by the method of Kok and Wild (1960), but in the presence of iron-carbohydrate complex a more vigorous hydrolysis is required to liberate all bound iron, and the method of Trinder (1956) was used.

Haemolysis is usually measured by the amount of haemoglobin freed from red cells, or by the haemoglobin content of residual intact red cells. The dark colour and viscosity of iron-complex solutions make measurement of their haemolytic power by haemoglobin methods rather inaccurate and tedious. A red-cell-counting technique was used, based on the EEL electronic blood-cell counter. The greatly improved