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.

REFERENCES

- Agner, Kj. (1947). *Kliniska Laborationsmetoder*, 5, 573. Astra, Södertälje.
— Andersson, N. S. E., and Nordenson, N. G. (1948). *Acta haemat. (Basel)*, 1, 193.
Andersson, N. S. E. (1950). *Acta med. scand.*, Suppl. 241.
— and Bergström, I. (1956). *Svenska Läk.-Tidn.*, 53, 13.
Baird, I. M., and Podmore, D. A. (1954). *Lancet*, 2, 942.
Brown, E. B., and Moore, C. V. (1956). In L. M. Tocantins's *Progress in Hematology*, 1, 22.
Fletcher, F., and London, E. (1954). *Brit. med. J.*, 1, 984.
Grimes, A. J., and Hutt, M. S. R. (1957). *Ibid.*, 2, 1074.
Haddow, A., and Horning, E. S. (1960). *J. nat. Cancer. Inst.*, 24, 109.
Karlfors, T., and Nordén, A. (1958). *Acta med. scand.*, Suppl. 342.
Lindvall, S., and Andersson, N. S. E. (1961). To be published.
Lundin, P. M. (1961). To be published.
Nissim, J. A. (1947). *Lancet*, 2, 49.
— (1949). M.D. thesis, University of London.
Richmond, H. G. (1959). *Brit. med. J.*, 1, 947.
— (1960). In R. V. Raven's *Cancer Progress*, p. 24.
Svärd, P. O. (1961). To be published.

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 pH 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 "ferriovenin."

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

consistency of red-cell counts attainable by electronic counting makes it suitable for measuring haemolytic activity of both opaque and coloured fluids which are particle-free. The size of the colloidal iron-complex particle is too small to activate the counting mechanism and does not interfere with the red-cell count.

To 4-ml. volumes of serial dilutions of iron complex in saline are added 0.02-ml. volumes of a washed suspension of human red cells. After three hours at room temperature the red-cell count is measured. The mean of the counts in four 0.2-c.mm. volumes is taken. Thus for an original suspension of 5 million per c.mm. 20,000 cells are counted. The difference in counts between iron-complex suspensions and a saline control suspension is the measure of haemolysis.

Results

Haemolytic Activity

Golberg (1958) calls attention to the *in vitro* haemolytic activity of iron complexes as a measure of the amount of dissociation of free ferric ions. The presence of free ions with consequent saturation of the iron-binding capacity is believed to be one cause of toxic reactions (Klopper, 1951; Librach, 1953). Thus haemolytic activity may be a useful index of toxicity for these complexes.

Table I shows the haemolytic activity of three iron complexes as measured by the red-cell counting technique described above. At the highest concentration used the amount of red-cell lysis induced by iron-dextran was only just perceptible and could not be detected by methods based on haemoglobin measurements.

Saccharated iron oxide has the highest haemolytic activity; under the conditions tested it is eight to sixteen times as haemolytic as iron-dextran. Iron-dextran occupies an intermediate position.

TABLE I.—Haemolytic Activity of Three Iron Complexes

	Concentration of Iron Complex (Mg. Fe/100 ml.)					
	1,000	500	250	125	62.5	Saline Controls
Iron-dextran	4.95	5.21	5.44	5.34	5.48	5.41
Iron-dextran	0.32	3.8	4.43	5.0	5.26	5.29
Saccharated iron oxide	—	—	0.01	0.23	5.25	5.40

Red-cell counts in thousands per 0.2 c.mm. after three hours' exposure to varying concentrations of iron complexes in saline. Three saline controls show the small variability of the cell count by this method.

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Plasma clearance of iron complex in four cases of iron-deficiency anaemia given 100 mg. iron intravenously as iron-dextran, and in three cases given same dose of iron-dextran. FIG. 2.—Serum-iron levels 5 minutes (white columns) and 1 hour (black columns) after 10 intravenous iron-dextran (100 mg. Fe) injections. FIG. 3.—Serum-iron levels 5 minutes (white columns) and 1 hour (black columns) after nine intravenous iron-dextran injections.

Rate of Plasma Clearance

Single Intravenous Dose.—Fig. 1 shows the rate of plasma clearance after intravenous injection of 100 mg. of iron as iron-carbohydrate complex in four cases of iron-deficiency anaemia given iron-dextran and in three similar cases given iron-dextran. Iron-dextran is rapidly cleared from the circulation. The rate of fall is of exponential form, and half the maximum concentration is reached in about one hour, with virtually complete clearance in 24 hours. This is the general form of clearance described for saccharated iron oxide. The rate of clearance is unrelated to anaemia or to the degree of utilization of iron eventually achieved. In contrast, iron-dextran is removed rather slowly from the circulation. The maximum concentration achieved is maintained for periods up to six hours, and about half remains at 24 hours. Serum-iron levels do not approach pre-injection levels for about three days. This characteristic has been used to estimate plasma volume (MacKenzie and Tindle, 1959); the rapid clearance of iron-dextran makes it unsuitable for this purpose.

Multiple Intravenous Doses.—A common pattern of treatment in parenteral iron therapy is a daily intravenous injection, and it is of interest to observe the serum-iron concentrations under these conditions. Figs. 2 and 3 show the serum-iron levels five minutes and one hour after intravenous doses of 100 mg. of iron as iron-dextran and as iron-dextran respectively on 10 and 9 successive occasions. Repeated injections of iron-dextran produced no accumulation of iron in the circulation. There was no significant increase in the maximum serum-iron levels after each injection, and the rapid rate of clearance on each day was maintained as for a single dose. In the case of iron-dextran a break of three days was made between the fourth and fifth injections. There is seen a well-defined trend to increasing maximum serum-iron values each day, reflecting the persistence of the circulating complex at 24 hours. After the 72-hour break between the fourth and fifth injections the maximum level fell to its original value, but again the trend to increasing plasma concentrations is seen on subsequent injections.

Therapeutic Results

Group 1. Iron-deficiency Anaemia

Twenty-five cases of iron-deficiency anaemia are recorded here (23 female, two male), selected for intra-

venous therapy with a haemoglobin of 66% or less, M.C.H.C. 29% or less, and well-marked hypochromia in the stained blood film. One patient with Hb 68%, M.C.H.C. 30%, was included because she had failed to respond to oral iron. The time of observation was sometimes limited by discharge from hospital or failure to attend clinics, and the observed responses to treatment are thus not always maximal.

The objective chosen was to correct anaemia without regard to replacement of iron stores, and the total dosage was calculated on the conservative side, so that the anticipated haemoglobin response fell short of 100%. Intravenous injections of 100 mg. of iron were given daily or on alternate days to a total dosage which varied from 550 to 1,500 mg. Details are shown in Table II.

Twenty-four cases showed haematological improvement. One case of carcinoma of the bronchus failed to respond.

The mean haemoglobin before treatment in these 24 cases was 51.2% (range 38–68%); after treatment it was 81.6% (range 65–97%).

In this group as a whole the utilization of the injected iron for haemoglobin synthesis appeared as 1% increase in haemoglobin for every 36 mg. of iron (or 0.4 g. Hb% per 100 mg. of iron). In the 10 patients observed for over 50 days and in whom it could be assumed that the maximum response had already occurred, the utilization was 1% Hb increase for 33 mg. of iron (or 0.44 g. Hb% per 100 mg. of iron).

The best utilization obtained in an individual case was 28 mg. of iron for 1% rise in haemoglobin (0.52 g. Hb % per 100 mg. of iron). The response in this case is illustrated in Fig. 4.

Group 2. Anaemia of Pregnancy

Forty-five women with anaemia of pregnancy of less than haemoglobin 70% (10.2 g./100 ml.) were treated with iron-dextrin. Almost all were out-patients and included all stages of pregnancy between the twelfth and thirty-sixth weeks. Twenty-six are reported here. Those

TABLE II.—Iron-dextrin in Iron-deficiency Anaemia

Case	Sex and Age		Total Fe Given Mg.	Hb %			M.C.H.C. %		Serum Iron µg./100 ml.	
				Before	After	() Days	Before	After	Before	After
1	F 30	Pulm. tuberculosis	1,200	58	93	(44)	27	29	13	109
2	F 72	High gamma-globulin	1,200	54	84	(54)	26	28	26	61
3	F 36		1,500	42	97	(112)	23	30	34	82
4	F 55	Menorrhagia	1,000	38	86	(91)	25	30	—	72
5	F 48	Haemorrhoids	1,060	31	82	(37)	24	—	29	35
6	F 32	Menorrhagia haemorrhoids	1,150	54	86	(21)	24	27	24	32
7	F 20		1,100	54	78	(59)	28	28	22	95
8	F 75	Varicose ulcers	1,200	46	70	(21)	27	28	42	—
9	F 61	Hiatus hernia	920	65	82	(27)	25	28	44	87
10	F 36		1,200	32	82	(82)	26	—	—	—
11	M 73	Urinary infection	800	68	86	(74)	30	31	—	—
12	F 46		550	66	77	(21)	26	27	6	23
13	F 77		1,100	34	65	(24)	24	—	—	—
14	F 73	Carcinoma of bronchus	1,100	65	63	(21)	27	25	—	—
15	F 43		1,500	43	75	(43)	23	29	15	50
16	F 67		1,100	34	86	(46)	24	30	—	—
17	F 57		1,030	43	70	(28)	23	—	18	32
18	F 33	Menorrhagia	600	50	77	(23)	27	30	—	—
19	F 34		1,000	32	84	(42)	27	32	54	92
20	F 42		1,200	32	94	(79)	23	33	22	34
21	F 16		1,400	42	82	(64)	21	29	—	—
22	M 76	Carcinoma of bladder	1,200	41	80	(31)	21	—	10	36
23	F 81	Cholecystitis	1,000	38	80	(63)	20	28	14	38
24	F 71		900	50	71	(31)	28	29	49	—
25	F 54		1,400	43	92	(65)	23	32	17	70

100% Hb = 14.6 g./100 ml.

TABLE III.—Iron-dextrin in Pregnancy Anaemias

Case	Age	Total Fe Given Mg.	Hb %			Remarks
			Before	After	() Days	
1	19	720	65	77	(28)	
2	29	840	60	84	(37)	
3	32	950	54	80	(42)	
4	27	840	65	80	(26)	
5	40	740	58	82	(34)	
6	30	1,040	54	86	(63)	
7	24	950	61	84	(55)	No response to oral iron
8	30	640	61	77	(17)	" "
9	34	440	58	77	(27)	" "
10	21	1,000	51	73	(33)	Intolerant of oral iron
11	26	1,000	51	80	(92)	Hookworm infestation
12	20	1,140	60	90*	(65)	No response to oral iron and folic acid
13	21	1,040	58	75	(34)	
14	35	1,140	56	88	(90)	
15	28	640	58	71	(18)	" "
16	25	1,040	56	80	(47)	
17	30	740	65	77	(13)	
18	23	1,040	69	95*	(35)	
19	22	950	63	84	(28)	No response to oral iron
20	37	1,240	49	84	(32)	
21	29	640	69	71	(28)	folic acid " and
22	24	1,040	58	82	(48)	
23	27	1,040	58	80	(46)	" "
24	23	860	56	90*	(38)	
25	23	640	69	80	(31)	
26	29	840	60	77	(22)	

* Post-partum. 100% Hb = 14.6 g./100 ml.

FIG. 4.—Woman aged 54 with iron-deficiency anaemia. Haematological response to intravenous iron-dextrin given in a divided course of 900 mg. and 500 mg. Fe.

excluded were patients whose course of treatment was interrupted by delivery, who received concurrent folic acid, or who failed to receive more than 300 mg. of iron. Dosage was estimated on the same basis as for group 1, although it is realized that the apparent utilization of iron for haemoglobin synthesis in pregnancy is lower than in the non-pregnant group. This was consistent with a limited objective of preparing the patient for safe delivery, and no attempt was made to achieve the highest levels of haemoglobin or to replace diminished iron stores or account for foetal needs or loss of blood during delivery. No case received more than 1,240 mg. of iron as iron-dextrin. An initial dose of 40 mg. of iron in 2 ml. was given in most cases, followed by daily or alternate daily doses of 100 mg. of iron. In some cases the course of treatment was spread over a longer period, depending on the patient's ability to attend. The results are summarized in Table III. Of these 26 cases, 25 showed haematological improvement. The mean haemoglobin before treatment was 59.3% (range 49–69%); after treatment it was 80.9% (range 71–95%).

Oral iron had previously failed in 7 of these 26 patients. One failed to improve, and the cause of this was not subsequently elucidated. It should be noted that the

maximum response to treatment was probably not observed in all cases owing to short periods of observation.

In this group as a whole, 100 mg. of iron as iron-dextrin produced an increase of 0.35 g. Hb per 100 ml. (1% Hb for 41 mg. of iron).

Clinical Toxicity

At Site of Injection.—In a few cases some leakage of injected material occurred from the vein which gave rise to a minor inflammatory reaction subsiding in 24 to 48 hours and did not interfere with subsequent injections. No thrombophlebitis or pain along the course of the vein was observed.

General Reactions.—Among the non-pregnant anaemias there were two mild general reactions. The first, in a woman aged 34 who had already received 11 ml. of iron-dextrin in three days, consisted of a feeling of skin heat and flushing, accompanied by slight nausea which abated in three minutes. The second, in a woman aged 42, began an hour after the first 5-ml. dose. She complained of a cramping pain over the left loin, accompanied by slight nausea and a taste in the mouth. The pain was not severe and lasted about two hours. The following day 2.5 ml. produced a little immediate skin-flushing, but the next three injections were uneventful. The fifth dose gave a similar reaction to the first, and, although the symptoms were mild, intravenous therapy was discontinued.

There were no general reactions of any kind among the 45 pregnant women treated with iron-dextrin.

Discussion

The characteristics of iron-dextrin are in several ways intermediate to those of the saccharated oxide and iron-dextran. Its neutral reaction, pH 7.3, may be compared with the strongly alkaline saccharated oxide, pH 9, and the mildly acid iron-dextran, pH 6.2. The low degree of ionic release resulting from the firm union of colloidal ferric hydroxide and its carbohydrate carrier is a property it shares with the dextran. On the other hand, it resembles the saccharated oxide in its rapid plasma-clearance.

Utilization

The evaluation of utilization of iron for haemoglobin synthesis should be based on measurements of total red-cell mass rather than on haemoglobin concentration. Individual variation in normal total red-cell mass, and the change in the ratio of plasma to red-cell volume in iron-deficiency anaemia, make assessment of utilization based on haemoglobin concentration only an approximate guide.

In the adult with a blood volume of 5 litres and haemoglobin concentration 15 g./100 ml., the circulating red-cell mass contains 2.5 g. of iron. Thus 25 mg. of iron is contained in 1% of the total haemoglobin. Nissim (1947) and Slack and Wilkinson (1949) obtained this order of utilization for saccharated oxide in iron-deficiency anaemia. Brown *et al.* (1950) obtained values varying from 0.33 to 0.5 g. Hb % per 100 mg. of iron. The mean utilization of iron as iron-dextrin in the non-pregnant cases reported here, as measured by the increase in haemoglobin concentration, was 0.44 g. Hb % per 100 mg. of iron (1% haemoglobin increase for 33 mg. of iron).

In pregnancy the increase in plasma volume diminishes the apparent utilization of iron for haemoglobin synthesis. In the pregnant group reported here,

100 mg. of iron as iron-dextrin gave a mean increase of 0.35 g. Hb per 100 ml. (41 mg. of iron for 1% haemoglobin), which compares with an increase of 0.3 g. Hb % reported by Scott and Govan (1951) and 0.44 g. Hb % by Klopfer and Ventura (1951) for the saccharated oxide.

Toxicity

Comparison of the clinical toxicity of iron complexes as described in various trials is often vitiated by the varied selection of cases and dose schedules. A useful baseline, however, is the extensive survey of one preparation by Ross (1957), who analysed the toxic reactions in 779 patients receiving saccharated iron oxide (ferrivenin) in 100-mg. doses. He found an overall incidence of toxic reactions in 7.5% of cases; 344 pregnancy anaemias provided the lowest incidence of 5%. Of all case series published, perhaps the most comparable groups are the iron-deficiency pregnancy anaemias. In the present series, using the same 100-mg. dose, no general reactions occurred among the 45 cases of pregnancy anaemia treated, and it would appear that iron-dextrin compares favourably in this respect with saccharated iron oxide. The two general reactions among the non-pregnant iron-deficiency anaemias were mild, and support the conclusion from the pregnancy series that iron-dextrin is a complex of low clinical toxicity.

It is unlikely that a single property of iron complexes can be made to account for all the toxic manifestations of different preparations. Instability of the complex in plasma with possible *in vivo* precipitation, the amount and rate of ionic iron release *in vivo* with consequent saturation of iron-binding capacity, antigenic power, the rate of reticulo-endothelial uptake and release, and the variability of molecular size in the preparation are probably all factors operative in varying degrees. A compound with, for instance, a relatively low release of ionic iron into the circulation, could have this advantageous feature offset by a slow plasma clearance.

Two characteristics with implications for toxicity have been investigated here: the *in vitro* haemolytic action and the plasma clearance rate. The negligible haemolytic power of iron-dextrin, indicating little ionic release, combined with its rapid plasma clearance which is maintained on repeated injections, are possible explanations of the low incidence of clinical toxicity.

Indications

The majority of simple iron-deficiency anaemias respond as well to oral iron as to parenteral treatment. The mucosal block theory (Granick, 1949) led to the belief that, once anaemia has been corrected, replacement of iron stores by oral administration was inadequate. This theory is now in doubt. It has been shown, for instance (Pirzio-Biroli and Finch, 1960), that in normal subjects whose iron stores have been depleted by repeated phlebotomy, but whose haemoglobin, serum iron, and iron-binding capacity have remained in the normal range, absorption of labelled iron from the intestinal tract, measured at intervals over a period of two years, was of the same order, 19%, as in established iron-deficiency anaemias. This compared with an absorption of only 3% in normal subjects given a parenteral iron load. Clearly neither anaemia nor serum-iron concentration directly controls intestinal absorption and there is no need to doubt that iron stores are replaceable by oral iron, given over a sufficient period of time.

When properly indicated parenteral iron is an irreplaceable remedy, but it should be reserved for cases of iron deficiency in which oral iron has failed. Such failure may be the result of poor intestinal tolerance, to malabsorption, or to the patient's inability to sustain oral treatment for an adequate time. There are also situations, such as late pregnancy, in which the efficiency of intestinal absorption is in doubt and time does not permit an adequate trial of oral therapy, when parenteral iron may be justified.

Intravenous or Intramuscular?

The intramuscular route for parenteral iron has obvious practical advantages in ease of administration, and while general toxic reactions to intramuscular iron-dextran are known, they appear to be uncommon.

Of greater importance are two observations which are perhaps connected. Firstly, the relatively high proportion of iron remaining at the site of injection, and therefore not available for haemoglobin synthesis, variously estimated at from 10 to 20% of the injected dose. Secondly, the carcinogenic action demonstrated in mice and rats presents at the moment an unknown hazard for man. In experiments still in progress I have so far found one sarcoma at the site of injection after six months of weekly iron-dextrin by subcutaneous injection in mice. It is likely, therefore, that iron-dextrin will prove to be of the same order of carcinogenicity as iron-dextran in experimental animals, and thus does not commend itself to intramuscular use.

The intravenous route has the merit of encouraging careful attention to the indications for parenteral iron. In the presence of iron deficiency, the high utilization for haemoglobin synthesis ensures that no undue excess of iron is deposited at any site. The main disadvantages have been the risk of severe local inflammation and general toxic reactions which seem to have been minimized with iron-dextrin at the 100-mg. dose level.

Summary

The response to treatment with intravenous iron-dextrin in 51 cases of iron-deficiency anaemias, including 26 in pregnancy, is described. A satisfactory haematological response was obtained in 49 of these cases, with a mean utilization of iron for haemoglobin synthesis in the non-pregnant group of 0.44 g. Hb % per 100 mg. of iron (1% Hb increase for 33 mg. of iron). In the pregnant group, apparent utilization was 0.33 g. Hb % per 100 mg. of iron (1% Hb increase for 41 mg. of iron).

With doses of 100 mg. of iron clinical toxicity was infrequent and mild in degree. There was no instance of thrombophlebitis or pain along the vein used for injection. No general reactions occurred among the pregnancy anaemias.

Indications for, and the administration of, parenteral iron are discussed.

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REFERENCES

- Andersson, N. S. E. (1950). *Acta med. scand.*, Suppl. 241.
 Baird, I. M., and Podmore, D. A. (1954). *Lancet*, 2, 942.
Brit. med. J., 1960a, 1, 788.
 — 1960b, 2, 406.
 Brown, E. B., Moore, C. V., Reynafarje, C., and Smith, D. E. (1950). *J. Amer. med. Ass.*, 144, 1084.
 Brownlee, G., Bainbridge, H. W., and Thorp, R. H. (1942). *Quart. J. Pharm.*, 15, 148.
 Callender, S. T., and Smith, M. D. (1954). *Brit. med. J.*, 2, 1487.
 Cappell, D. F. (1930). *J. Bact. Path.*, 33, 175.
 — Hutchison, H. E., Hendry, E. B., and Conway, H. (1954). *Brit. med. J.*, 2, 1255.
 Duthie, J. J. R., Girdwood, R. H., Hubble, D., Macgregor, A. G., Wayne, E. J., Wilson, A., and Wilson, G. M. (1960). *Lancet*, 2, 155.
 Friend, D. G. (1938). *New Engl. J. Med.*, 219, 910.
 Golberg, L. (1958). In *Iron in Clinical Medicine*, p. 77, edited by R. O. Wallerstein and S. R. Mettler. Univ. California Press, Berkeley.
 — (1960). *Brit. med. J.*, 1, 958.
 Granick, S. (1949). *Bull. N.Y. Acad. Med.*, 25, 403.
 Haddow, A. (1960). *Brit. med. J.*, 1, 1734.
 — and Horning, E. S. (1960). *J. nat. Cancer Inst.*, 24, 109.
 Hagedorn, A. B. (1952). *Proc. Mayo Clin.*, 27, 277.
 Jennison, R. F., and Ellis, H. R. (1954). *Lancet*, 2, 1245.
 Klopfer, A. (1951). *Ibid.*, 1, 531.
 — and Ventura, S. (1951). *Brit. med. J.*, 2, 1251.
 Kok, D'A., and Wild, F. (1960). *J. clin. Path.*, 13, 241.
 Librach, I. M. (1953). *Brit. med. J.*, 1, 21.
 Lucas, J. E., and Hagedorn, A. B. (1952). *Blood*, 7, 358.
 MacKenzie, A., and Lawson, I. R. (1959). *Lancet*, 2, 462.
 — and Tindle, J. (1959). *Ibid.*, 1, 333.
 Nissim, J. A. (1947). *Ibid.*, 2, 49.
 — (1954). *Brit. med. J.*, 1, 352.
 Pirzio-Biroli, G., and Finch, C. A. (1960). *J. Lab. clin. Med.*, 55, 216.
 Reznikoff, P., and Goebel, W. F. (1937). *J. clin. Invest.*, 16, 547.
 Richmond, H. G. (1957). *Scot. med. J.*, 2, 169.
 — (1959). *Brit. med. J.*, 1, 947.
 Ross, I. P. (1955). *Lancet*, 1, 51.
 — (1957). *Ibid.*, 2, 77.
 Scott, J. M., and Govan, A. D. T. (1951). *Ibid.*, 1, 367.
 — (1954). *Brit. med. J.*, 2, 1257.
 Slack, H. G. B., and Wilkinson, J. F. (1949). *Lancet*, 1, 11.
 Trinder, P. (1956). *J. clin. Path.*, 9, 170.

CYCLOPHOSPHAMIDE IN ADVANCED BREAST CANCER

A CLINICAL AND HAEMATOLOGICAL APPRAISAL

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Nitrogen mustard was introduced into the treatment of cancer in 1946, and its derivatives and allied compounds, the alkylating agents, still maintain a leading place in cancer chemotherapy. Their effect on the cell is both cytotoxic and nucleotoxic, vital enzymes in the synthesis of protein being blocked. The cytostatic activity of these compounds is probably due to the reactivity of the chloroethyl group attached to the nitrogen atom, and most of them are associated with high toxicity in the body.

In the development of these compounds, attempts have been made to widen the toxic-therapeutic ratio, and modifications of the basic compound have decreased the toxicity. Thus in nitrogen mustard oxide ("nitromin") and mannomustine ("degranol") there is a delayed activity of the functional group, and therefore a lower toxicity. The concomitant therapeutic results are, however, not outstanding. The ethylenimine compounds—for example, tretamine (triethylene melamine), thiotepa (triethylene thiophosphoramidate) and the ethylene-iminoquinone (E.39)—are very active cytotoxic agents but are at the same time very toxic to all elements of haemopoietic tissue. Watson and Turner (1959) suggested a possible modification of thiotepa toxicity by concomitant administration of androgens.