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On Potential Carcinogenecity of the Iron Macromolecular Complexes

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Introduction

SAUNDERS (1958) provides a brief review of the history of iron in medical treatment. Oxides and carbonates of iron have found a place in therapy from ancient times. Their use is mentioned in the *Ebers Papyrus*, and Dioscorides, Galen, Celsus and Aetius advocated iron therapy in the treatment of splenic enlargement and menorrhagia. In 1661 SYDENHAM described the striking benefit of iron therapy in the treatment of chlorosis. LIEBIG, in 1843, gave the first clear description of the role of haemolgobin, and FORTES and THIVOLLE, in 1925, first demonstrated that plasma-iron is different from haemoglobin. These and related findings demonstrated beyond argument that iron is an essential ingredient of the human diet.

FIGUEROA's (1958) view that "The great majority of patients suffering from iron deficiency can be treated with oral iron" is probably widely acceptable, especially if the word "iron" is interpreted as "bivalent organic iron" (UNDRITZ, 1958). The valid indications for parenteral iron therapy in the very few patients who require it include, according to FIGUEROA (1958): —

1. Where there is a failure to absorb adequate amounts of oral iron.

2. Where a patient cannot tolerate orally administered iron, or is unwilling or cannot be relied upon to continue oral iron therapy.

3. Where it is necessary to replace iron stores in cases of severe, predictable and frequent blood loss not amenable to medical or surgical correction.

4. Cases of iron-deficiency anaemia that have failed to respond to prolonged adequate oral iron therapy.

Of these indications the first is rare, except in patients with idiopathic steatorrhoea, or who have undergone extensive surgical removal of the small intestine, and the second is the most common. Referring to the use of parenteral iron therapy during the third trimester of pregnancy, FIGUEROA (1958) comments that it is debatable whether the small or moderate increase in haemoglobin more readily achievable by the parenteral administration than by the oral administration of iron is justified.

Iron macromolecular complexes suitable for parenteral administration.

1. Saccharated iron-oxide (Ferrivenin, Proferrin, Colliron, Neo-Ferrum, Iviron). — For intravenous injection only.

2. Iron-dextrin (Dextriferron, Astrafer). — For intravenous injection only.

3. Iron-dextran complex (Imferon). — For intramuscular or intravenous injection.

4. Iron-sorbitol-citric-acid complex (Jectofer). — For intramuscular injection only.

5. Iron-polyisomaltose (Ferrum Hausmann). — For intramuscular injection only.

If given in adequate and equivalent amounts these preparations are more or less equally effective in the treatment of iron-deficiency anaemia (Figueroa, 1958) This is at first sight surprising since there are marked differences in the degree of retention of iron at the injection site (Fielding, 1962): iron-dextrin and iron-dextran are both retained locally to a far greater extent than iron-sorbitol-citric-acid complex. However, these differences refer to conditions in which animals are overloaded with iron. In the absence of overloading the somewhat more rapid clearance of the iron-sorbitol complex is, from the point of view of rapidity of haematological response, apparently offset by the more rapid excretion of its iron-content by the kidneys (Lindvall and Andersson, 1961).

General toxicity, other than carcinogenicity, of parenteral iron preparations.

The toxic effects, other than carcinogenicity, of saccharated iron oxide are discussed by Nissim (1954) and Brown and Moore (1956). The material is strongly alkaline and hypertonic and gives rise to marked local inflammation if injected extravascularly. Both immediate and delayed systemic toxic effects are also frequent; the former are thought to be due to individual hypersensitivity to impurities in the preparation, and the latter to the intravascular precipitation of the compound. The incidence of reactions has varied with the technique of administration from less than 0.2% to over 50% of injections. Intravenous iron-dextrin also gives rise to a range of toxic reactions, especially in patients simultaneously receiving oral iron (Blazer and Del Riego, 1962). From the point of view of the incidence and severity of such toxic reactions the introduction of iron-dextran for intramuscular use was a big step forward (Scott and Govan, 1954). Intramuscular injection of iron-sorbitol-citric acid complex (Jectofer) undoubtedly carries more risk of toxic response than does similar treatment with iron-dextran (Scott, 1962), and the simultaneous administration of iron orally seems to enhance this risk. Iron-polyisomaltose is similar to iron-dextran both chemically and in its relative lack of toxicity (Mereu and Tonz, 1961).

Haddow and Horning (1960) described the failure of hair to regrow after clipping over the site of injection of iron-dextran, and Baker, Golberg, Martin and Smith (1961) and Fielding (1962) reported the development of alopecia, brown staining and loss of tissue elasticity at the site of injection of iron-dextran, but not of iron-sorbitol-citric-acid complex. Beresford, Golberg and Smith (1957) reported acute inflammation and degeneration followed by rapid and complete regeneration following the intramuscular injection of iron-polysaccharide complexes of the iron-dextrin/iron-dextran type. Roe and Haddow (1965) found that acute tenderness and swelling at the injection site was more marked in rats injected with iron-sorbitol-citric acid complex than with iron-dextran.

Induction of neoplasms at site of intramuscular or subcutaneous injection of iron preparations

Reports of the induction of sarcomas and histocytomas at the site of subcutaneous intramuscular injection of various iron-carbohydrate complexes is summarised in Table I. The repeated injection of relatively large doses of saccharated iron-oxide, iron-dextrin or iron-dextran may induce such tumours in laboratory rodents: in many tests for carcinogenicity sarcomas have been induced in upwards of 50 per cent of animals injected with these substances. Iron-sorbitol-citric-acid complex (Jectofer), on the other hand, has given an essentially negative result in 3 fairly stringent tests (LUNDIN, 1961; FIELDING, 1962 and ROE and HADDOW, 1965). HADDOW, DUKES and MITCHLEY (1961) obtained a low yield of tumours in both rats and mice following repeated injections of iron-polyisomaltose (Ferrum Hausmann). MEREU and TONZ (1961) referred to negative results in animal tests for carcinogenicity of this product but gave no details.

In most of the experimental studies control animals have been injected with the corresponding carbohydrate moiety of iron-carbohydrate complex under test. Almost without exception entirely negative results have been obtained in such control groups. A problem here is that the carbohydrate by itself has a much smaller molecular size (ca. 2,500) than the iron-macromolecular complex which it forms with iron (ca. 180,000 — see ERIKSSON, 1961). HUEPER (1959), however, tested 11 different dextrans ranging in molecular weight from

Table I. *Carcinogenicity of various iron preparations administered by subcutaneous or intramuscular injection*

Preparation	No. of tests for Carcinogenicity	No. of tests in which positive results obtained	Species	References
Saccharated iron-oxide	3	2	Mouse	RICHMOND (1959); HADDOW and HORNING (1960); HADDOW, DUKES and MITCHLEY (1961)
Iron-dextrin	3	3	Rat Mouse	LUNDIN (1961); FIELDING (1962)
Iron-dextran	19	17	Rat Mouse Hamster Rabbit	RICHMOND (1959); HADDOW and HORNING (1960); GOLBERG, MARTIN and SMITH (1960); LUNDIN (1961); FIELDING (1962); KUNZ, SHAHAB, HENZE and HEINZE (1963); HADDOW ROE and MITCHLEY (1964); HADDOW and ROE (1964); ROE, HADDOW, DUKES and MITCHLEY (1964); ROE and HADDOW (1965)
Iron sorbitol citric acid complex	3	1*	Rat Mouse	LUNDIN (1961); FIELDING (1962); ROE and HADDOW (1965)
Iron polyisomaltose	2	2	Rat Mouse	HADDOW, DUKES and MITCHLEY (1961)

* Solitary benign fibroma among 20 rats.

37,000 to several million in rats, mice and rabbits: injection-site sarcomas were induced by none of these materials.

Sarcoma-induction in relation to amount injected at one site

Roe, Haddow, Dukes and Mitchley (1964) compared the effect of giving 24 weekly injections of 0.5 ml iron-dextran into one, two, four or six subcutaneous sites in comparable groups of rats. A spectrum of local tumours was induced, including benign fibromas, small, slowly growing sarcomas and rapidly growing sarcomas. Table II shows that the incidence of rapidly growing tumours fell and the average latent interval before they appeared rose as the number of injection-sites used increased. Table III demonstrates that, although the risk of tumour development at any one site fell as the number of injection-sites increased, the risk that the animal would develop a tumour at one of its injection-sites actually increased! However, the type of tumour seen in animals injected in 4 or 6 sites tended to be more benign than that seen in animals injected in only 1 or 2 sites. A further interesting observation was that multiple tumours were frequently seen at individual injection sites.

Table II. *Incidence and time of induction of rapidly growing tumours (RGT) at the injection site*

No. of rats	Injection sites per rat	RGT	Time of appearance of first RGT	Average time of appearance of RGT
24	1	14	329	501
24	2	6	460	667
24	4	9	449	706
24	6	3	522	674
32	0	0	—	—

Table III. *Risk of tumour developing at injection site*

Injection sites per rat	Dose of iron-dextran per site	Sites examined at autopsy	Sites with malignant tumours	(per cent)	Sites with benign or malignant tumours	(per cent)
1	12 ml.	22	14	(63.6)	14	(63.6)
2	6 ml.	46	9	(19.6)	11	(23.9)
4	4 ml.	96	20	(20.8)	29	(30.2)
6	2 ml.	138	12	(8.7)	17	(12.3)

Carcinogenicity in relation to iron-overloading

Golberg, Martin and Smith (1960) studied the effects of overloading animals with iron. Their results indicated that the escape of iron from the site of injection was much slower in iron-overloaded animals than in normal animals. In addition, biochemical changes in the liver, serum and region of injection were observed in the former but not in the latter. Finally they asserted that local tumour induction only occurs in iron-overloaded animals. They saw, for example, no sarcomas in response to weekly intramuscular injections of 0.02ml iron-dextran in mice and only one sarcoma in 50 mice injected once weekly with 0.1 ml. However, in the latter case

survival was poor. More recently HADDOW and ROE (1964) reported a high incidence of sarcomas in mice receiving 0.05 ml iron-dextran weekly (total dose 2.35 mls) and one out of 20 rats given 90 weekly injections of 0.01 mls developed a sarcoma (Table IV, V). In a current experiment sarcomas have appeared in response to only 2 injections, each of 0.75 ml iron-dextran (see Table VI).

Clearly the risk of tumour induction recedes as the size of the local dose is reduced, but particularly in the light of the results just referred to it is by no means certain that the degree of general overloading with iron is of any significance.

The relationship of dose to body size

HADDOW and HORNING (1960) and ROE (1961) have argued cogently that

Table IV. *Carcinogenic response to different doses of iron-dextran (imferon) injected subcutaneously in CB ♂ rats (Wistar)*

No. of doses (Imferon)	Size of each dose (ml.)	Total dose (ml.)	Injection site sarcomas	No. of rats injected	Minimum induction time (days)
30	1.0	30	20	30*	145
20	0.5	10	8	20	426
64	0.05	3.2	2	20	478
90	0.01	0.9	1	20	736

* A further 8 rats had local histiocytomas.

Table V. *Carcinogenic response to different doses of iron-dextran (Imferon) injected subcutaneously in CB ♂ mice (Stock)*

No. of doses (Imferon)	Size of each dose (ml.)	Total dose (ml.)	Injection site sarcomas	No. of rats injected	Minimum induction time (days)
30	0.3	9.0	14	30	182
47	0.05	2.35	12	30	168
87	0.01	0.87	0	20	—

Table VI. *Effect of dose in induction of sarcomas at the site of injection of iron-dextran*

Group	No. of S.C. injections of 0.75 ml. iron-dextran into R. flank	Total dose of iron-dextran	No. of rats in group	Position 16 months after start of experiment		
				Survivors	Injection site sarcomas*	Time of appearance of sarcomas (months)
A	16	12 ml.	16	3	5	12, 14, 14, 14, 16
B	8	6 ml.	32	17	2	9, 15
C	4	3 ml.	64	29	0**	
D	2	1.5 ml.	128	71	3	13, 14, 14
E	0	0	64	33	0	

* All histologically confirmed.
** One benign fibroma.

the induction of sarcomas at the site of injection is a "local" phenomenon. Therefore, it is the actual size of the dose and not its size relative to whole body size which matters. The size of individual cells in man is of the same order as in experimental animals and a particular volume of injected material will come into contact with approximately the same number of cells in all species. Thus the ratio of dose to body weight is only of importance if it can be shown that the local induction of sarcomas by the injected material is dependent on a general dose-dependent effect on the body as a whole. So far this has not been demonstrated.

Evidence for carcinogenicity other than locally at the site of injection

Hueper (1957, 1959) examined a wide variety of macromolecular substances for carcinogenicity, administering them intravenously, subcutaneously (by injection or implantation), or intraperitoneally to rats, mice or rabbits. Only one of 30 substances examined, silastic rubber (a silicone polymer), gave unequivocal evidence of tumour induction at the site of subcutaneous implantation. On the other hand, many of the test substances appeared to increase the incidence of tumours of the reticulo-endothelial system. These findings of Hueper and the observations of Haddow, Dukes and Mitchley (1961) that simple iron salts, such as ferric citrate, ferric salicylate, ferrous sulphate, ferrous lactate or ferrous gluconate, do not induce injection-site sarcomas, suggest that the local carcinogenicity of iron-macromolecular complexes is attributable neither to the carbohydrate alone, nor to the iron alone, but to the complexes themselves. On the other hand, the fact that a variety of macromolecules seem able to induce cancer of the reticulo-endothelial system, suggests that there may be a hazard of *distant carcinogenesis*, (i.e. the induction of tumours at sites distant from the point of injection) following the parenteral administration of iron-carbohydrate complexes also.

Most of the tests of iron-carbohydrate complexes for carcinogenicity have been designed specifically to study the induction of tumours locally at the site of injection. For such purposes a control group containing the same number of animals as the test group is appropriate. Much larger control groups are likely to be necessary for studying the effect of treatment on the incidence of tumours of *all* sites and tissues of the body. Haddow and Horning (1960) observed a number of unusual tumours in their iron-dextran treated animals, including a bronchogenic carcinoma in a rat. Haddow (1963), from a survey of his many experiments with iron-dextran, regarded the yield of tumours at sites remote from the injection-site as "unquestionably significant". But Lundin (1961) commented on the absence of liver tumours in his iron-dextran treated animals, despite the large deposits of iron in the organ, and Roe and Lancaster (1964) felt that more information was necessary before such a conclusion could be reached. Roe, Haddow, Dukes and Mitchley (1964) recorded the occurrence of various types of tumour in both iron-dextran treated rats and in untreated control groups. More recently, Roe and Haddow (1965) observed more 'distant' tumours of various types in rats injected repeatedly with iron-sorbitol-citric-acid than with iron-dextran in similar dosage. Langvad (1964) reported an experiment in which 50 male and 50 female mice of the St/El A strain were injected repeatedly with iron-dextran, each animal receiving a total of 2 mls

of the substance. Seven per cent of the males and 58% of the females developed tumours. The corresponding rates for untreated controls were 0% and 20%, respectively. LANGVAD (1964) suggested that oncogenic viruses used in other experiments in the same laboratory at the time might, through contamination, have been wholly or partly responsible for the differences recorded. However, even if it were shown that iron-dextran acts as no more than a co-factor in the induction of tumours of distant sites, its use is hardly to be regarded as being without potential carcinogenic hazard for man.

Obviously the problem cannot be resolved until the results of careful studies on much larger groups of animals are available.

Evidence of carcinogenic effect of iron macromolecular complexes in man

To date there has, to our knowledge, been no fully acceptable report of the occurrence of sarcoma at the site of injection of iron-macromolecular complexes in man. CROWLEY and STILL (1960) reported the occurrence of a metastasis in the buttock at the site of previous iron-dextran injections in a case of cancer of the cervix uteri. ROBINSON, BELL and STURDY (1960) reported a case in which an undifferentiated soft-tissue sarcoma arose at the site of injection of iron dextran into the region of the deltoid muscle $3^1/_4$ years previously. Excess iron was present at the tumour site, though it was not proved to be iron-dextran. It was thought unlikely that the tumour was a metastasis, but the possibility could not be excluded. GOLBERG (1960) subsequently quoted the opinion of Professor R. A. WILLIS that the lesion observed by ROBINSON and his colleagues was not a neoplasm. Where there is a difference in opinion between pathologists on the histopathological nature of a lesion, it is logical to take into account the macroscopic appearances and clinical details. The case history provided by ROBINSON and his colleagues is more in keeping with neoplasia than with any alternative diagnosis.

In any event, as pointed out by many authors, the induction of sarcomas in man by injected iron complexes, if it occurs at all, is likely to take many years. It is still less than 20 years since use of this type of iron preparation became widespread, so that there remains the possibility that the minimum induction period for man has not yet been exhausted.

If the main carcinogenic effect in man is a local one, then it is likely that it will be observed sooner rather than later, since localised soft-tissue sarcomas are relatively uncommon. If, however, the main danger is a slightly increased risk of cancer of many different sites, then nothing short of a major long-term prospective epidemiological survey is likely to reveal the hazard.

BAKER, GOLBERG, MARTIN and SMITH (1961) were interested in establishing the carcinogenic safety of iron-dextran for man. With this intention, they compared the local tissue response to injection in different species. Rabbits and dogs showed less residual iron at the injection-site, and a greater hepatic uptake of iron than mice and rats. Nevertheless, HADDOW, ROE and MITCHLEY (1964) encountered two cases of local sarcoma in 6 rabbits injected with iron-dextran. Most of the specimens obtained by BAKER *et al* (1961) from iron-dextran injection-sites in man showed no evidence of fibrosis, but in 2 cases fibrosis and the heavy accumulation of siderophages were seen. These are precisely the changes which precede

tumour formation in experimental animals.

Is iron, per se, carcinogenic?

There is no evidence that iron as such is carcinogenic, though it is doubtful whether it has been deliberately tested for carcinogenicity to an adequate extent. There have been no reports of an excessive incidence of cancer in animals deliberately overloaded with simple iron compounds, and with possibly one exception, referred to above (see Langvad, 1964), the carcinogenic effect of iron-macromolecular complexes appears to be limited to the site of its injection into the body. Overloading with iron leads to its excessive storage in the liver, i.e. 'haemochromatosis'. In this condition the iron is stored as an organic complex, for which Golberg and Smith (1960) suggested the name "haptosiderin". These workers also suggested that where haemochromatosis arises spontaneously, it does so as an expression of an inborn error of metabolism involving the overproduction of haptosiderin. In induced haemochromatosis, on the other hand, the excess of haptosiderin is secondary to overloading with iron. Cirrhosis tends to accompany both spontaneous and induced haemochromatosis, but according to Golberg and Smith adequate protein and vitamin E in the diet delay or prevent its occurrence. Although in general there is undoubtedly an association between cirrhosis and liver cancer, in the particular case of the cirrhosis which accompanies haemochromatosis the association is very weak (Sheldon, 1935; Willis, 1953). Foulds and Stewart (1956) and Hueper (1956) both observed a high incidence of bronchial carcinoma in haematite miners, and concluded that sidero-silicosis predisposed to neoplasia. Doll (1958) did not regard the evidence for the association as conclusive, but Campbell (1940) reported a higher incidence of adenomatous lung tumours in mice exposed to mixtures of silica and iron oxide than in untreated controls.

The mechanism of carcinogenesis by iron macromolecular complexes

There has been much speculation with regard to the mechanism of carcinogenesis by macromolecular materials in general and by iron-carbohydrate complexes in particular. As pointed out above, the induction of local tumours cannot be attributed solely either to the iron or to the carbohydrate moiety of the various molecules. Carcinogenicity is somehow linked to the nature of the complex itself. In this connection it is of special interest that aluminium-dextran is also highly productive of local sarcomas on injection: Haddow, Dukes and Mitchley (1961) recorded the induction of 11 sarcomas in 40 mice given repeated subcutaneous injections of this complex. Preparations of chromium-dextran, copper-dextran and bismuth-dextran, on the other hand, were more or less inactive. The macromolecular compounds studied by Hueper (1959) were largely ineffective in the induction of local tumours. Hence macromolecularity itself is not a sufficient explanation of carcinogenicity.

Haddow and Horning (1960) suggested that blockage of the reticulo-endothelial system with, perhaps, interference with immune processes might be implicated. Fielding (1962) saw evidence of lymphatic blockage after the injection of iron-dextran or iron-dextrin, but not after injection of iron-sorbitol-citric-acid. Richmond (1959) suggested that the carbohydrate complex might enable the passage of iron across intracellular membranes normally

impervious to it. He subsequently (RICHMOND, 1962) showed that iron-dextran gives rise to cytological changes indicative of intracellular oxidation. He thought that the changes were not dissimilar from some of the effects of ionising radiation, and suggested that they could explain the carcinogenicity of iron-dextran. TURNER (1964) reported that the response of fowl fibrocytes grown *in vitro*, to iron-dextran, resembled that to known carcinogens. HADDOW and HORNING (1960) reviewed the literature concerning the interference with iron metabolism by carcinogenic agents, but came to no real conclusion with regard to the likely mechanism of action of iron-complexes.

It is, perhaps, tempting to regard carcinogenesis by iron-carbohydrate complexes as being related to carcinogenesis by other metals, e.g. arsenic, beryllium, cadmium, chromium, cobalt lead and nickel (see ROE and LANCASTER, 1964). However, on present evidence it would certainly be unwise to presume that this is so. In the cases of all the other metals the evidence strongly suggests that the metal itself is implicated. But in the case of iron, the only acceptable evidence of carcinogenicity relates to iron-carbohydrate complexes and, possibly, combinations of iron with silica. Aluminium alone behaves in a similar fashion.

ROE and LANCASTER (1964) suggested that the induction of cancer by the subcutaneous injection of chemically unreactive materials such as the iron macromolecular complexes may be more akin to the "Oppenheimer effect" than to chemical carcinogenesis. On the other hand, HUEPER (1959) contended that chemical mechanisms have not been excluded in the case of sarcoma induction by the implantation of plastic materials. Moreover, as ROE and LANCASTER (1964) themselves pointed out, by no means all chemically unreactive substances, even those which remain permanently at the injection-site, induce sarcomas.

The consideration of the mechanism of carcinogenesis by iron-carbohydrate complexes should, perhaps, begin with a description of the changes which precede the appearance of tumours. On this subject there is general agreement that the first change is the uptake of the injected material by histiocytes (siderophages). In these cells the iron is thereafter stored as newly formed ferritin (MUIR and GOLBERG, 1961). Siderophages are also found in the local lymph nodes, and other cells of the reticulo-endothelial system, generally, take up and store the iron as ferritin. However, the movement of iron away from the injection site, certainly in animals overloaded with iron, is slow (BAKER, GOLBERG, MARTIN and SMITH, 1961) and both siderophages and extracellular iron-containing material persists locally until tumour development ensues. The development of a mass of siderophages clearly depends on the proliferation of histiocytes and in some instances this proliferation leads to the formation of a histiocytic neoplasm (histiocytoma) in which many of the cells are not laden with iron. After a period of some months, depending on the species, proliferation of histiocytes gives place to fibroblastic activity. It is not certain whether fibroblasts are derived from siderophages or merely stimulated to divide by the presence of the siderophages. The onset of fibroplasia is appreciable, clinically, in that the injection site becomes firm and thickened. Such areas of thickening remain unchanged or enlarge slowly over a period of several months. Suddenly, usually it seems from one edge of the thickened lesion, a rapidly growing nodule appears. The growth of this lesion is progressive

and necessitates the sacrifice of the animal within a matter of days or weeks from the time it first became palpable.

The stage of fibroblastic proliferation appears to be an essential preliminary in the induction of sarcomas. This is true not only of their induction by iron-macromolecular complexes but by all agents, including implanted sponges, plastic films, and metal objects. In our experience chemically unreactive substances which do not induce sarcomas at the site of their subcutaneous or intramuscular injection, also do not stimulate fibroblastic proliferation. This still leaves open the question of whether the induction of tumours by iron-carbohydrate complexes is chemical or physical in nature. Cadmium-precipitated ferritin was shown to be carcinogenic by Haddow, Roe, Dukes and Mitchley (1964), but a similar carcinogenic effect by cadmium itself was also demonstrated. It is not yet known whether cadmium-free ferritin is able to induce sarcomas if injected subcutaneously. If it can be shown that iron complexes induce tumours at sites remote from their injection, then an essentially chemical mechanism will seem more likely. At present, in our opinion, a physical mechanism similar to that which operates in the case of the 'Oppenheimer effect', seems most plausible.

Conclusion

From the point of view of future policy the mechanism of carcinogenesis by subcutaneously or intramuscularly administered macromolecular iron complexes is of academic interest only. In the case of their intravenous administration, however, it is highly relevant. At present there is no clear-cut evidence of carcinogenic hazard from intravenously administered iron-carbohydrate complexes, nor is there adequate evidence of their safety in this respect. Long-term experiments on a large scale in several species are urgently needed to investigate this problem. In the meantime, the possibility of carcinogenic response should be borne in mind by those proposing to administer iron parenterally. The reasons for preferring parenteral administration to the oral route are few (Figueroa, 1958). When administration by this route is justified, the apparently greater carcinogenic risk of some preparations, as compared with others, should be taken into account along with evidence of other types of toxicity in choosing the most suitable preparation. Overloading with iron should be avoided. The size of individual injections should be small and multiple injections should be distributed through several sites and not given all into the same site. Because the latent interval for sarcoma induction in man is likely to be more than 15 or 20 years there need, on present evidence, be little hesitation in administering iron complexes by subcutaneous or intramuscular injection into patients whose life expectancy is shorter than this. Much more caution should be exercised in the case of younger patients. In particular, it is most doubtful whether the administration of iron by the parenteral route to pregnant women, more or less as a routine measure, is at all justified.

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