CHAPTER 3

HISTORY OF IRON THERAPY

The story of the development of our knowledge of iron deficiency anaemia and the therapeutic use of iron, is a fascinating one which dates from early Greek civilization.

The empirical use of iron in the treatment of anaemia dates from ancient time. Iron salts have been used by physicians since the time of Hippocrates.[138] It has been stated that iron therapy takes its origin in sympathetic magic, the weakly sufferer having hoped to assume something of the strength of steel by drinking the water in which a sword had rusted.[138] The Greek physicians employed iron for the cure of weakness, a prominant symptom of anaemia, with a view to impart to the patient the strength of iron.

The calcinied iron preparation of ancient Hindu medicine, known as 'Lauha Bhasma', was prepared by roasting sheets of iron and then macerating them to a fine white powder in oil, whey, vinegar, cow's urine and milk.[51]

Sydenham was probably the first physician to employ iron in a manner that would be approved even today. Three centuries ago he introduced iron into clinical medicine for the treatment of "Chlorosis" for which he found iron or steel of great value.

In 1681, Sydenham wrote the following concerning the treatment of chlorosis: ".....The pulse gains strength, the face (no longer pale and death-like) a fresh ruddy colour." He prescribed "Steel in substance" or "iron or steel filings steeped in cold Rhenish wine," the dose amounting to 0.5 to 1.0 gram of iron daily.

In 1684, Sydenham introduced iron as a therapeutic agent in clinical medicine. Since then, the number of iron preparations available for the treatment of iron deficiency anaemia has steadily increased. A rational basis for the use of iron was provided almost one hundred years later when iron was demonstrated in the ash of the blood, and it was shown that the iron of the blood could be increased by feeding iron-containing foods.

In 1831, the French physician, Pierre Blaud recognised the nature of the malady chlorosis and also that the

failure in the treatment of chlorosis was due to the use of two small doses of iron, and reported the rapid cure of 30 patients by the use of large doses of the metal.[51] Thus Blaud reported the success of iron therapy with ferrous carbonate pills.

In 1832, Blaud emphasized the specific action of iron in the treatment of chlorosis and described the use of his deservedly famous pills known as Blaud's pills.[138] Blaud's original pills consisted of a mixture of equal parts of Ferrous sulphate and potassium carbonate, and he gave sufficient and gradually increasing dose to supply 0.4 to 1.6 grams of ferrous carbonate daily.[51] This would be considered adequate therapy today. Many excellent observers, including Niemeyer and Osler, confirmed his findings.

For many years, Blaud's nephew distributed throughout the world "Veritable Pills of Doctor Blaud." The Blaud's pills incorporated in the U.S.P. and B.P. differ somewhat from the original, both in composition and recommended dose.

In 1832, Fodisch /reported that the amount of iron in the blood of chlorotics is greatly diminished.[51]

In 1836, Ashwell, while discussing the treatment of chlorosis, said that the sulphate of iron was "probably the most efficacious and possessed more specific properties than any of the rest."[123]

In 1842, Andral et al., with the advent of methods for properly examining the blood, noted that iron therapy caused an increase in red cell corpuscles in anaemia.[51]

In 1891, Sir William Osler, realised that, with oral iron therapy there is much need for prolonged treatment. He stated "The important feature in the treatment of chlorosis is to persist in the use of iron for at least three months and, if necessary, subsequently to resume it in a smaller doses as recurrences are so common." [128]

In 1893, Stockman tried subcutaneous iron citrate in the treatment of chlorosis. Since then several investigators have tried to improve upon parenteral iron therapy, by way of increasing the doses or minimising the toxicity by the use of refined preparations.

Macallum in 1894 and Hall in 1896, studied the absorption of iron by microchemical methods and proved that iron can be absorbed in the inorganic form.

In 1899, Abderhalden claimed that, even though the inorganic iron can be absorbed, it cannot be converted into haemoglobin, and its beneficial effect in anaemia was as a result of the stimulation of the blood forming organs for the better utilisation of organic iron. Later on he found that the above objection was untenable and finally it was abandoned.

A possible reason for the delay in admitting the superiority of medicinal inorganic iron was the disappearance of chlorosis, the syndrome in which iron therapy was most dramatic. Further more, the failure of iron to benefit patients with pernicious anaemia and other anaemias not caused by iron deficiency, as well as the lack of knowledge concerning proper dosage, tended to confuse the status of iron therapy.

Until the last decade of nineteenth century, iron therapy of anaemia followed the principles enunciated by Sydenham and Blaud, and was comparable to modern practice. At that time, however, the teachings of Bunge, Quincke and Von Noorden, and others caused a radical departure in the use of iron in anaemia, and it came to be accepted that the metal either was not absorbed in the inorganic form or was necessary only in small doses. The clonical failure of small doses soon brought discredit on the iron therapy, and it was not until the end of second decase of the present century that the lessons taught by the physicians of old were relearned.

Thus, in the period 1890 to 1920, iron therapy became discredited, thanks to dogmatic statements by Bunge that inorganic iron is valueless in therapy and that only organic preparations should be used, as well as the result of Von Noorden's teaching that not more than 0.1 gm. of metallic

iron is necessary. Further more, physicians failed to distinguish between iron deficiency in anaemias and anaemia due to other causes. It was not until chronic hypochromic anaemia resulting from iron deficiency became a clearly defined syndrome and methods for its recognition came into general use that the value of large doses of inorganic iron, resurrected by Lichtenstein and by Meulengracht, once again received general recognition.

Upto the second decade of the nineteenth century there was a controversy about the place of iron therapy in the treatment of iron deficiency anaemia. But since then, iron therapy has been regarded specific for the treatment of iron deficiency anaemia.

With the establishment of the antianaemic value of iron, the metal was employed rather indiscriminately in the treatment of all types of anaemias. With the recognition of the iron deficiency anaemia as a distinct clinical syndrome and with the knowledge of its diagnostic criteria, iron therapy has claimed a firm place in clinical medicine. Once the other problems were solved, the question arose about the superiority of the various salts of iron as regards their absorption, therapeutic efficacy, side effects and toxicity.

Ferrous carbonate (Blaud's Pill) has been displaced by an array of various iron compounds like ferric

ammonium citrate, ferrous sulphate, gluconate, succinate, fumarate, molybdate, glutamate, chelates etc. These iron preparations have been used singly or in combination with other elements like copper and cobalt, and vitamins like, ascorbic acid and folic acid to enhance the therapeutic value either by aiding their absorption and/or increasing their utilisation.

Many alternative potent preparations of iron have been used in order to avoid the undesirable side effects and dangers to children. There was, however, a wide-spread belief amonst the patient that iron inevitably causes gastro-intestinal disturbances, particularly constipation.

In general it has been thought that the best preparations are those containing iron in the divalent (ferrous) form, but trivalent (ferric) preparations such as ferri et ammonium citrate, have had their advocates. Again some workers have insisted on high dosage of iron, while others have been satisfied with much smaller doses.

The inorganic salts were regarded to be superior to the organic salts of iron. However, it has been claimed by some that organic salts of iron are as efficient as the inorganic salts and the side effects of the former are much less than those of the latter. For last two decades of the present century, therefore, the organic salts of iron have come into lime-light in the treatment of iron deficiency

anaemia. Accordingly, in past few years organic iron preparations, such as salts of organic acids and chelate types, have been introduced and strongly recommended for the treatment of iron deficiency anaemias.

It was the opinion of Thomas Sydenham that "iron may be given in largest doses without inconvenience." His optimistic view has been shared in later generations by the originators of a large number of oral iron preparations which now compete for favour in the advertisement columns in the medical press.

The use of larger doses of Ferrous Sulphate e.g.upto 2 gm. of Ferrous Sulphate or 720 mg. of elemental iron, daily, as recommended by some workers dates from the time when iron by mouth was the only practical means, apart from transfusion, of treating iron deficiency anaemia. However, since the introduction (Nissim 1947, Slack and Wilkinson 1950) of a stable and relatively non-toxic intravenous preparation, and with the subsequent development of a reliable intramuscular preparation of iron, the treatment of cases resistant to oral iron has few difficulties either in hospital or in general practice.

In early days, iron was given subcutaneously or intramuscularly. These injections were painful and the preparations used were toxic. Attempts were, therefore, made to find new iron preparations for parenteral use.

In 1930, Cappel for the first time showed that iron could be given intravenously as a saccharated iron oxide without the usual dangers of parenteral therapy.[69]

In 1932, Heath et al. claimed that 32 mg. of iron and ammonium citrate given intramuscularly was equivalent to 1 gram of the same administered orally.[41]

In 1933, Davidson urged the use of Ferrous Sulphate tablets, adequate treatment with which still costs only one penny a week.[123] It was suggested that ascorbic acid given by mouth may itself aid in the Haemoglobin synthesis. Thus, in 1936, Heilmeyer and Plotner[100] found that intravenous injection of ferrous ascorbate produces Haemoglobin regeneration in excess of that calculated from the amount of iron injected.

In 1936, Ruskin and Katz tried ferrous adenylate, but it was found to be toxic.[69]

In 1937, Reznikoff and Goebel for the first time recommended the use of ferrous gluconate which has lately became one of the most popular iron tablets.[123]

In 1945, Little and others used ferrous ascorbate intravenously but this was not found to be very satisfactory. Hann in 1946, introduced a colloidal ferric hydroxide for intravenous use.

In 1946, Goodman and Gilman summarised the figures upon which the estimations of the amount of iron required and the calculations for the dosage of different iron preparations are based.

In 1947, Nissim reported that a solution of saccharated iron oxide was better tolerated and could be given intravenously in large enough amount to treat anaemia effectively, without untoward reactions.[3] Nissim showed satisfactory use of intravenous injections of saccharated iron oxide (Ferrivenin) in doses of 25 to 200 mg.[41] nearly all of which could be utilised for haemoglobin synthesis. Govan and Scott, in 1949, recorded 8 per cent increase of haemoglobin concentration in a pregnant woman treated with ferrivenin for one week. [41]

In 1949, Slack an Wilkinson showed how effective was such a preparation in the chronic "resistant" cases of iron deficiency anaemia. Since then several reliable preparations of iron for intravenous administration have been marketed, and much more has been learnt about these anaemias. Nissim and Robson in 1949 gave a detailed account of the method of preparation and standardisation so as to have a uniform preparation.

The utilisation of iron given intravenously has been studied Dubach and others in 1946 with the help of radio-active iron and also by Finch and cthers in 1949.

Many papers have been published showing the effects of iron given intravenously. The preparation commonly used is a 2 per cent solution of saccharated oxide of iron, one millilitre containing 20 mg. of iron. Nissim and Robson in 1949 and Slack and Wilkinson in 1949 reported very satisfactory haematological response. Govan and Scott in 1949 tried ferrivenin on 25 anaemic pregnant women and recorded a 1 per cent rise for every 40 mg. of iron injected. Sinclair and Duthie in 1949 noted a good response to intravenous iron in hypochromic anaemia associated with rheumatoid arthritis with a low erythrocyte sedimentation rate.

In 1952, Girdwood drew attention to a strong psychological intolerance shown by his patients towards the tablets of ferrous sulphate, but only when they were quoted green.

In 1954, Baird and Podemore showed that iron-dextran complex injected intramuscularly is less toxic, more stable and easier for administration than the saccharated iron oxide.

In 1955, O'Sullivan et al.[94] compared the relative costs of treating iron deficiency anaemias with Ferrous Sulphate, Ferrous Succinate and Ferrous Gluconate in equivalent doses and concluded that ferrous sulphate is much cheaper than others and equally efficacious. It maintains its position as a satisfactory therapeutic agent.

In 1956, Edgar and Rice found that the usual high rate of intolerance to Ferrous Sulphate reported in pregnant women was reduced to less than 5 per cent when the product was given in the form of a white tablet instead of the well-known green form, thus suggesting the psychological element.

Jhatakia [67] in 1956 showed that the simultaneous administration of iron and cobalt intravenously in iron deficiency anaemia gives better results than the administration of iron alone.

For many years the mainstay of iron therapy has been Ferrous Sulphate. In 1957, Ferrous Fumarate, an organic iron compound, was introduced as a new contestant in the field.

Parekh et al.[95] in 1958 showed that Ferrous Succinate is a useful additional compound in the treatment of hypochromic anaemia, its special merit being its good tolerability.

In 1958, Kerr and Davidson, in a double blind trial, found that none of the iron preparations (ferrous sulphate, ferrous gluconate, ferrous succinate and ferrous calcium citrate) induced toxic effects more frequently than did the "unknown" control lactose pills,[132] thus suggesting that the intolerance was mainly psychological in origin.

Chelation has been used before, but mainly to try to prepare safe and effective parenteral iron drugs. Will and Vilter used sodium iron edetate, a chelated compound, as an oral substitute for ferrous sulphate. They found that it released iron satisfactorily and was notably free from unpleasant side-effects, but interchange between iron and calcium occurs with this compound, and though the effect is small, it is probably best avoided.

Recently, a number of chelated iron compounds have been introduced, viz. iron aminoates (Cope and Gillhespy, 1959), ferric sodium salt of ethylenediamine tetra-acetic acid (sodium iron edetate) (Herridge, 1958), ferrous amino-acetosulphate (Jennison, 1958) and iron choline citrate (Franklin et. al.,1958).[132] Hayhoe (1960) in a review of iron preparations for anaemia stated that they appear no better absorbed or tolerated than similar doses of Ferrous Sulphate.

In 1959, Swan and Jewett[123] suggested that ferrous gluconate, ferrous succinate and ferrous fumarate are all efficient preparations but not significantly more efficient than ferrous sulphate.

In 1960, Rajsuriya et al., in a controlled clinical trial observed that ferrous fumarate gives better results than ferrous succinate, but there was no difference between ferrous fumarate and ferrous sulphate.

Robinson et al. in 1960 reported about the possible association of malignant neoplasm in a case treated with iron-dextran injection.[41]

Iron deficiency anaemia is one of the commonest diseases that practitioners are called on to deal with; and if it is not secondary to some other disorder, it responds well to proper therapy. Until 1949, iron was almost always given orally. The injectio ferri of the British Pharmacopoeia caused much pain and had an iron content far below the therapeutic level. Ferrous-sulphate preparations were the most used and were very successful; but some patients preferred a liquid medicine to pills or capsules, and for them iron and ammonium citrate was prescribed.

These preparations sufficed for most patients with primary iron deficiency anaemia. Nevertheless, there remained a group who seemed resistant to iron treatment, and whose blood picture continued to show the characteristic changes.

The introduction of intravenous iron preparations solved the problem for the resistant cases. But intravenous iron solution is not easy to give because it is dark coloured, and owing to its alkalinity any leak outside the vein causes an unpleasant reaction. Another difficulty is the invisibility of the vein particularly in obese patients.

For these reasons the introduction of an iron-dextran solution that could be administered intramuscularly was welcome. It helped in treating all patients who failed to respond to oral iron, and it has been useful as a time-saver for example, in the late stages of pregnancy where there is no time to risk failure to respond to oral iron. In the form of 'Imferon,' intramuscular iron-dextran became deservedly popular.

In man the doses given for therapy are very small compared to the experimental doses, and histological examination of the sites of iron-dextran injections shows only a few scattered iron-containing macrophages. But Baker et al[46] examined tissues from two patients who over a period had received several hundred times the recommended therapeutic dose. In both cases early formation of fibrous tissue was found, but "no evidence of focal fibroblastic proliferation, which is regarded as the precursor of subsequent sarcomatous change."

Brown and Moore have suggested the possibilities of haemosiderosis and haemochromatosis after parenteral iron therapy. The current opinion, however, is against the possibility of such remote complications, with parenterally administered iron in therapeutic doses.

Haddow[55] and associates administered iron-dextran complex to a variety of animals, producing sarcomas in mice,

rats and hamsters. The iron-dextran complex given subcutaneously over a period of time produced sarcomas in 9 to 14 months at the site of injection. This has caused a great deal of emotional debate in British Medical literature. Haddow has stated that since this substance is carcinogenic in animals, it has a definite hezard in man. Subsequently, it was taken off the market for use in man in England and has not returned. It has, however, recently returned and has been approved by the Food and Drug Administration in this country.[104]

A case has been reported in man in which iron-dextran administration was associated with the development of an indifferentiated liposarcoma of the left deltoid region.[111] This tumour followed six injections (11 mg. each) of iron-dextran into the deltoid region. The tumour occurred 44 months after the injections, and has been pathologically corroborated by many pathologists. There have also been instances of metastatic carcinoma occurring at the site of both penicillin and iron-dextran administration.[39,141] On the other hand, iron-dextran complex has given in large amounts to another patient and a biopsy was taken 46 days after the last injection; iron was found at the site, but no sarcoma had developed.[8]

Iron preparations can be administered in three ways - orally, intravenously and intramuscularly. Oral therapy is

the safest and best method of ferrotherapy. Oral administration has the advantage of being more or less self regulating. Thus overdosage in the sense of presenting more iron to the haemopoietic organs than they can deal with is thus not possible after oral iron therapy. The parenteral route by-passes the natural barrier and is thus open to the objection that an excess of iron can be deposited in the tissues, where it may exert its deleterious effects (Piney 1957).

It is now generally accepted that oral iron is the treatment of choice in iron deficiency anaemia. Plain ferrous sulphate, in tablets or capsules, is still as efficient as any preparation, and it is very cheap. Iron preparations for intramuscular injection are still about five times as expensive as those for intravenous injection, and their absorption may be less regular. Intramuscular iron is, at present, essentially a therapeutic weapon to be kept in reserve.

In spite of the fact that orally administered iron is effective in a large number of cases, parenteral iron therapy may be given in certain cases like the anaemias of late pregnancy and for the correction of severe anaemias before major surgical operations, as the rapid restoration of Haemoglobin is essential in these cases. Similarly, in patients of iron deficiency anaemia with very low haemoglobin levels coming from a large section of the population of this country, parenteral iron therapy becomes important on social and economical grounds.

Considering the relative merits of intramuscular over intravenous route, Cope et. al.[128] have obtained equivalent results with both the methods, even though the response was slightly slow with intramuscular iron. Intravenous iron therapy is best suited for the patients in hospitals where rapid rise of haemoglobin will shorten the hospital stay and so the cost. This is not so for patients treated in private practice as it will be more costly in such conditions. However, in all where tolerance or absorption is at fault this is the ideal therapy. This therapy should not replace oral therapy in the ordinary run of cases but should be reserved for suitable subjects.

In comparing the intramuscular and the intravenous routes of iron therapy, the pain and tenderness at the site of injection, the longer time taken for maximal response and the larger quantity of iron required to raise the haemoglobin by 1% with intramuscular treatment, have to be weighed against the toxic reactions met with in intravenous iron therapy. It has been pointed out that toxic reaction can be reduced to minimum if cases associated with infection are excluded and if four successive test doses of 10, 20, 50 and 100 mg. of iron can be administered safely.

The history of iron therapy reveals that with ferrous sulphate or ferric hydroxide for oral administration, iron-dextran complex for intramuscular administration and

saccharated iron oxide for intravenous administration, every patient with primary iron deficiency anaemia can now be successfully treated. Nevertheless, the overall impression of the history of ~~mx~~ iron therapy lends support to believe that iron therapy illustrates adequately the axiom, "where there is a host of remedies, no one of them is completely satisfactory."