CHAPTER 7

IRON DEFICIENCY ANAEMIA

Iron deficiency anaemia is one of the commonest nutritional deficiencies very widely prevalent throughout the world (Moore and Dubach, 1956). It is extremely common in the tropics and in India (Woodruff, 1955; Foy and Kondi, 1957; Foy, Kondi and Sarma, 1958).

DEFINITION

In health, the number of the red cells and the percentage of haemoglobin depend on a delicate balance between fresh formation and destruction. This balance may be upset in disease or other conditions, e.g.,by decreased production or increased wastage. The resulting deficiency in the oxygen carrying capacity of the blood, which mainly resides in the haemoglobin content of the red

cells, is called "ANAEMIA".[41] Thus, anaemia refers to the concentration of oxygen carrying substance in a certain volume of blood. The term anaemia, as is generally used in clinical medicine, refers to a reduction below normal in the number of red corpuscles per c.mm., the quantity of haemoglobin and the volume of packed red cells per 100 ml. of blood.[138]

In iron deficiency anaemia the haemoglobin and to a lesser degree the volume of packed red cells, are reduced much more than is the red cell count. This is due to the fact that the majority of red corpuscles making up the blood are smaller than normal (microcytic) and are poorly filled with haemoglobin (Hypochromic).

AETIOLOGY AND PATHOGENESIS

A clear cut response to administration of iron, makes it evident that, lack of iron is of great significance in the pathogenesis of iron deficiency anaemia.

Factors concerned with the absorption of iron, the relative value of different foods, iron transport and storage and the requirements for iron have already been discussed in Chapter 4. On theoretical grounds the circumstances under which iron deficiency might occur can be enumerated as follows :

(I) Inadequate intake

(II) Impaired absorption.

(III) Increased requirements

(IV) Imperfect utilization

(V) Excessive loss

(VI) Inadequate protein supply

In many instances, more than one of these factors is involved. Time is an additional factor. Until the body stores of iron have been drained, iron deficiency anaemia will not develop.

I. Inadequate Intake :

It is rare in ordinary practice to find cases of iron deficiency anaemia in which the consumption of a diet lacking in foods containing iron, is the only discoverable etiological factor. It is true, however, that food idiosyncrasies, bad dentition, gastro-intestinal disturbances or well-intentioned but misguided treatment of such disorders, poverty, exigencies of war, cultivation of "money crops" to the exclusion of farm products necessary for home consumption, or religious tenets and caste practices result in the use of a diet which can furnish little haemoglobin-building material. As economic conditions improve, such grades of deficiency become less and less common, but in many parts of the world, and particularly

in India, they are still prevalent.

Iron deficiency anaemia was found to be common in regions where the soil was deficient in iron and the vegetables grown were low in iron content.

II. Impaired Absorption :

The facilitation of iron absorption attributed to the normal acid secretion of stomach is real, but, nevertheless, relatively unimportant under normal circumstances. However, when the requirement of iron becomes relatively high, the presence of free hydrochloric acid may be important in making additional dietary iron available for absorption. Thus, hydrochloric acid is only of minor importance except perhaps when iron requirements are high and therefore even minor factors may be significant. It is noteworthy that chronic iron deficiency anaemia is not unusual in men following gastrectomy even though this type of anaemia is rare in the male sex otherwise. Achlorhydria alone rarely causes iron deficiency but, when other factors are contributing to the development of iron deficiency and, in consequence, iron requirements are high, the handicap of achlorhydria may be of some importance.

In addition to gastrectomy other defects in the gastro-intestinal tract may contribute to the development of iron deficiency. Thus, this type of anaemia is often

associated with sprue, steatorrhea, celiac disease, pellagra and sometimes seen in other disorders characterised by diarrhea and impaired absorption.

Inspite of high dietary intake of iron, iron deficiency anaemia can be produced by impaired absorption. Among the several factors which interfere with digestion and absorption of food iron the phytic acid and phytate content of the diet are important.[5] It was shown that high phytate level of 40 per cent in the diet gave rise to increased faecal excretion and considerable dimination of iron absorption.[18]

Infection is one of the most important factors responsible for impaired iron absorption. The absorption of iron from gastro-intestinal tract is considerably diminished in presence of infection.[82]

III. Increased Requirements :

In the absence of disease, requirements of iron in a male adult vary little. In infancy, childhood and adolescence, on the other hand, the requirements of iron are increased because of the greater needs for the rapidly growing tissues. Similarly, in females from menarche to menopause, the requirements of iron are increased because of menstruation, pregnancy and lactation.

In infants from four to six months until three years of age, iron deficiency anaemia is common. The anaemia is particularly common in premature infants and in twins, and is more frequent in artificially-fed infants as compared with breast-fed infants. A similar type of anaemia is observed in older children with abnormal eating habits. The development of iron deficiency anaemia in infancy is not a matter of surprise when it is recalled that during the first year of life the total blood volume must be tripled and the quantity of haemoglobin doubled. It has been rightly said that "the infant bleeds into his own increasing blood volume."

The greater demands for iron in the female readily account for the prevalence of iron deficiency anaemia in female sex. After the age of puberty, such anaemia is much more common in the female than in the male. The iron requirement in female during reproductive period is four times that of the male.

Iron deficiency is, therefore, common in pregnancy and in lactating women and particularly so in multiparous women. This is to be expected if consideration is given to the fetal requirement, the quantity of blood in the placenta and uterus and the ultimate loss as at parturition, especially if these drains involve a person whose stores may already have been taxed by a number of years of

menstrual losses and perhaps several preceding pregnancies. It may be added that child-bearing represents a drain of about 725 mg., which is by no means made up by the saving of menstrual losses which is on an average 30 mg. per period in normal women.

Thus, it is clear from the foregoing considerations that when one considers the increased requirements of iron needed by growing children and young women, it is evident that many of them are living on a razor's edge in respect to their iron content, and that a negative iron balance can readily develop to produce iron deficiency anaemia.

IV. Imperfect Utilization :

A theoretically possible additional factor is the role of faulty utilisation of iron. It is known that iron balance is disturbed when there is an infection. There is no evidence that infections are ever a primary cause of iron deficiency. In fact, the iron which is unused remains in the body stores. Nevertheless, impaired utilization of iron as the result of infection might possibly serve as a contributory factor in the development of anaemia.

Thus, in certain cases, inspite of the presence of iron in large quantities in the body; iron deficiency anaemia is present. In such instances, the iron stores in

the liver or spleen may be unavailable for haemoglobin synthesis, iron may fail to enter the red cells, or finally iron utilization may be blocked in the interior of the red cells.[15]

Anaemia tends to be greater in degree in the more serious and in suppurative infections. There is some evidence that greater the number of organisms, the more severe the anaemia. In most instances, infections of less than a month's duration are not accompanied by significant anaemia. There is no direct correlation, however, between duration of infection and severity of anaemia. In general, anaemia gradually progresses while the infection persists, but after a time the degree of anaemia becomes relatively constant. There are exceptions to this pattern, of course.

It seems most likely that the anaemia of infection is the resultant of impaired erythropoiesis and shortened survival of red corpuscles. It is well-known that profound metabolic alterations accompany infection and these have now been shown to include alterations in iron, copper and porphyrin metabolism.

V. Excessive Loss :

Chronic blood loss, open or concealed, is an important etiological factor for the causation of iron

deficiency anaemia. This may be only as an exaggeration of physiological blood loss, as by menstruation, or because of some disease. Thus, common causes are menorrhagia and metrorrhagia from uterine fibroids, or peptic ulcer, hernia at the esophageal hiatus, non-specific ulcerative colitis, carcinoma of the stomach or colon, cirrhosis of liver with bleeding varices or bleeding hemorrhoids. Sometimes, such anaemia may result from recurrent severe epistaxes, as in multiple hereditary telangiectasia, or from recurrent attacks of microscopic or macroscopic haematuria. It is possible to a certain extent to make up for the loss of blood by consuming an adequate diet, as the absence of anaemia in many men with chronically bleeding hemorrhoids indicates. Nevertheless, if sufficiently great and when continued for a long enough time, the chronic loss of blood will result in iron deficiency even when other demands for iron, as in men, are small. Since the chronic loss of blood in the male, if detected, would usually lead to his seeking attention, the discovery of iron deficiency anaemia in a male patient almost always signifies the presence of an occult source of chronic blood loss, such as peptic, ulcer or carcinoma of the ascending colon or stomach.

Hookworm infection is one of the most important etiological factors for the causation of iron deficiency anaemia, and this is particularly true for the tropical

countries. The role of hookworm in the production of anaemia along with the amount of blood loss are specially considered in detail in the next chapter. In cases of hookworm infestation, besides the blood loss caused by the worm, there may be other contributory factors like deficient diet, other drains of iron stores, as for example from repeated pregnancies, and achlorhydria. Marked reduction in serum vitamin B_{12} levels and impaired intestinal absorption of folic acid in persons with heavy hookworm infestation give further evidence of their impaired state of nutriation. Amongst the other parasites, subtertial malarial parasites, which is not common now, at least deserves a passing reference.

Salicylate administration is put forward as a possible cause of anaemia which is sometimes referred to as "Salicylate anaemia" (Summerskill and Alvarez, 1958). Consumption of salicylate compounds causes occult gastrointestinal bleeding in a considerable proportion of patients (Lange, 1957; Alvarez and Summerskill, 1958), and much less frequently, haemetemesis or malena occurs as a result of medication (Muir and Cosar, 1955; Alvarez and Summerskill, 1958). It has been suggested that the bleeding may be responsible for the decrease in circulating haemoglobin. In addition, it has been shown that during the administration of salicylate the survival time

of red cells is diminished. Thus, the combination of blood loss and increased red cell destruction may account for the anaemia which develops following salicylate administration. It is further suggested that xkk salicylates might produce anaemia not only by gastro-intestinal bleeding but also by interference with the metabolism of iron through some unknown mechanism.[66]

The role of the skin as an additional and important channel for iron loss in relation to iron deficiency anaemia has not received as much attention as the problem deserves. The skin and sweat glands are important xx excretory organs for iron. It has been shown that under conditions of profuse sweating together with desquamation of epithelial cells significant amount of iron could be lost from the body. Hence, this could be one of the etiological factors in the widespread prevalence of iron deficiency anaemia in the tropics, (Hussain et al., 1960).[64] Foy and Kondi (1957) have also suggested that excessive dermal loss of iron may be the probable etiological factor in the genesis of iron deficiency anaemia in the tropics.[18]

VI. Inadequate Protein Supply :

Although it is obvious that the adequate supplies of protein are required to build up the globin or the protein portion of haemoglobin, this aspect has been on the whole neglected because anaemia due to or contributed

by protein deficiency is rare and is usually masked by other deficiencies.[131]

Anaemia aggravated by or partly due to protein deficiency is more common in women than in men, and is prone to occur in pregnancy. Anaemia arising fundamentally from gross protein deficiency is well shown by the liver-disease and Kwashiorkor so prevalent in Nigeria and other parts of Africa.[131] A poor protein diet, however, may not always cause anaemia, probably because of the fact that haemoglobin formation takes precedence over the formation of even plasma protein in the body.

From the above considerations, it is clear that a multiplicity of factors may be involved in the production of iron deficiency anaemia. Often, in a given case, more than one factor has played a role. Whichever, of the above single or multiple factors is involved in a given case, the ultimate result is the same, namely, a negative iron balance with ultimate depletion of the iron stores of the body.

The severity of symptoms of patients with iron deficiency anaemia is often not proportional to the degree of anaemia. This can be admitted readily and could be well expected in persons who have developed anaemia over a long period of time and under a great variety of social

and economic circumstances.

SYMPTOMATOLOGY

Certain features are common to all forms of hypochromic microcytic anaemia. Their onset is insidious and their progress is gradual. The duration of symptoms usually varies from 2 to 22 years. Symptoms common to all anaemias may be found, such as, weakness, fatigability and pallor. An ever present feeling of "dead-tiredness" is a frequent symptom. Nevertheless, in some cases the onset is so slow that the patient becomes adjusted to the chronic state of ill-health and severe grades of anaemia may be maintained with remarkably few complaints. In infants with iron deficiency anaemia, edema of extrimities, as well as enlargement of liver, spleen and lymph nodes, may develop when the anaemia is marked.

1. Gastro-intestinal Symptoms :

Gastro-intestinal symptoms include loss of appetite, flatulence, heart burn, vague and often shifting and irregular epigastric distress after meals, and hunger pain are prominent features. Constipation is troublesome and relatively constant symptom. Diarrhoea is a common symptom in iron deficiency anaemia of later life.

Soreness of tongue and mouth are common but are less severe than those found in pernicious anaemia. There

may be pain or spasm in the throat or actual dysphagia. Difficulty in swallowing, also known as Plummer-Vinson Syndrome, though uncommon and late, is a striking feature of the disease, when present.

A relatively rare symptom is hematemesis, which, when it is associated with anaemia and spleenomegaly, suggests the diagnosis of Banti's syndrome.

2. Cardio-respiratory Symptoms :

Cardio-respiratory symptoms include palpitation which is common, persistent and troublesome; arrhythmias of the simpler variety; dyspnea on exertion, and choking sensations. Edema around the ankles and, less frequently, puffiness of the face when present, may produce a clinical picture which suggests congestive cardiac failure or chronic nephritis.

3. Genito-urinary Symptoms :

Disturbances of menstruation are frequent. The periods may appear late, they may be vary profuse, or there may be dysmenorrhea or irregularity of flow. Amenorrhea is quite frequent. Pruritis vulvae occurs but is uncommon. Urinary complaints are rare unless there is complicating cystitis.

4. Endocrinal Features :

In addition to the disturbances of menstrual function already mentioned, there may be signs of mild hypothyroidism which do not disappear as the anaemia is relieved but require specific treatment.

5. Neuro-muscular Symptoms :

Nervous irritability, deficient mental application, headache and disturbances of sleep are common symptoms. There may be neuralgic pains, vasomotor disturbances, or tingling and numbness. The last-mentioned complaints are found in about 15 to 30 per cent of the cases of iron deficiency anaemia, but, like glossitis, they rarely attain the prominence found in pernicious anaemia. More serious symptoms such as disturbances of gait and objective neurological findings are quite rare.

In addition to the symptoms described above, in patients in whom the anaemia is primarily due to blood loss, there may be complaints referrable to the system where the blood loss is occurring. Thus, there may be signs and symptoms indicative of peptic ulcer. It is important to note that the symptoms of anaemia may completely obscure those of the underlying condition.

6. Symptoms of Hookworm Anaemia :

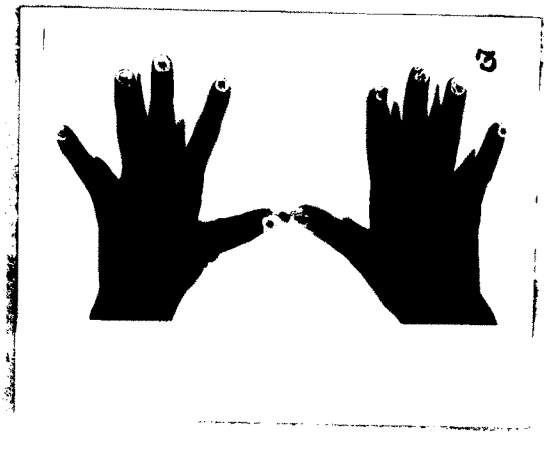
In hookworm anaemia the symptoms, in general, are similar to those already outlined. Epigastric pain,

abdominal cramps, vomiting, diarrhea or constipation are common. The history of "ground-itch" is usually not obtained. Long infested children show retarded development, both physical and mental.

PHYSICAL SIGNS

The appearance of these patients is often quite characteristic. They do not look acutely ill but appear tired and lifeless. Pallor, when present, is the most striking outward sign and is observed in skin, mucous membrance and nails. There may be no evidence of weight loss and some patients are actually obese.

Skin is enelastic, wrinkled and dry. The hairs usually feel dry and lusterless and are often scanty. The nails are soft, thin, brittle, lusterless and flat. In advance cases the normal convexity is entirely lost and replaced by hollowing which is so great that in some cases 8 drops of water can be run into the concavity of the nail without overflowing. [62] Such spooning of the nails appears first in the lower limbs and then in the upper limbs, and is known as 'Koilonychia' (Photograph No.3).



Fingers of one of the patients
showing Koilonychia

The mucous membranes of the gums and pharynx are pale, as are the nail-beds and the ocular conjunctivae. The last mentioned are blue or pearly white instead of icteric as in pernicious anaemia.

The tongue is usually pale. It may show papillary atrophy. This, however, is rarely if ever as striking as is found in pernicious anaemia. There may be a swelling, a blotchy, irregular denudation of the papillae or dusky red irregular spots on the tongue. Fissures may be present at the angles of the mouth. On the mucous membrane of the mouth there may also be small, blister-like lesions surrounded by areas of erythema.

Slight cardiac enlargement may be present. Functional systolic murmers are very common. The presence of edema

around the ankles has already been mentioned. The abdominal wall is often atonic and inelastic. The "potbelly" of hookworm disease is a classical feature of advanced cases of that condition. The liver is often palpable and in some patients with marked anaemia, it has been quite large. In about one-third of the cases of iron deficiency anaemia in later life, the spleen has been palpable but excessive enlargement is unusual.

LABORATORY FINDINGS

The changes in the blood necessarily vary with the severity of anaemia.

The peripheral blood smear shows micro-cytosis, hypochromasia, anisocytosis, poikilocytosis and occasional target cells. However, the chief characteristic feature is the poverty of haemoglobin in the individual corpuscles. This is indicated by an exaggeration of their central pallor. The more severe the anaemia, the greater the degree of this change and the more numerous the corpuscles affected. In extreme grades of iron deficiency anaemia, most of the red cells are mere rings (Photograph No.3A).

A Microphotograph of the peripheral blood smear from one of the patients

In almost all cases, however, a variable number of well-filled red corpuscles are present and some macrocytes, often polychromatophilic, can be distinguished. These probably represent the feeble effort to form haemoglobin-containing corpuscles. The number of such cells is increased as the iron is made available.

The morphological changes are reflected in the quantitative data. The haemoglobin is reduced out of proportion to the red cell count and volume of packed red cells. The red cell count may be normal or even somewhat above normal when the haemoglobin is as low as 8 gm. per cent. Extreme reduction in red cell count, such as seen in pernicious anaemia, are not found. It is the haemoglobin and volume of packed red cells which are markedly reduced. Cases are recorded in which the haemoglobin was as low as 2.5 gm. per 100 ml. and the volume of packed red cells 10 ml.

In majority of the cases M.C.V. ranges from 55 to 74 cu (normal 82 to 92 cu), M.C.H. ranges from 15 to 21 uug (normal 27-31 uug), and M.C.H.C. ranges from 25 to 30 per cent (normal 32 to 36 per cent).

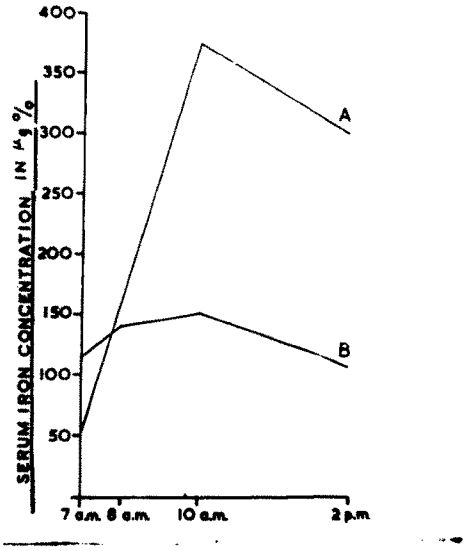
Mean diameter of red corpuscles is reduced and ranges from 6.2 to 6.7 u (normal 6.6 to 7.7 u), and the Price-Jones distribution curve shows a broadened base and is swung to the left of normal.

Reticulocytes are normal in number or reduced, unless a recent haemorrhage has occurred. A large haemorrhage may induce temporary reticulocytosis.

Serum iron content is markedly reduced (usually below 35 mcg. per cent) and serum iron-binding capacity is increased. Moreover, there is a good response to the oral iron absorption test in which serum iron estimation is carried out at intervals after the administration of a test dose of an iron salt. The following curve shows the response to the administration to a fasting patient of 1.6 gm. of ferrous gluconate, with serum iron determinations after 1, 3 and 7 hours. If the rise in serum iron is small (B), the patient has sufficient stores of iron, but if the serum iron concentration rises rapidly (A) and greatly exceeds the approximate maximum normal value of 220 mcg. per cent, a state of iron deficiency requiring

iron therapy is indicated (Photograph No.3B).

3B



Response to the Iron Absorption test in a patient with iron deficiency (A) and one with adequate iron reserves (B).

Blood plasma is very pale and no evidence of increased blood destruction is found in the urine or stools.

Leucocytes may be normal in number or slightly reduced. A few multisegmented neutrophils may be found, and there may be slight absolute granulocytopenia as well as relative lymphocytosis in long-standing cases. A fresh haemorrhage of large size, however, may cause

slight leucocytosis of the neutrophilic type. In hookworm anaemia, eosinophilia is common.

Platelets are usually normal in number. However, in long standing cases of chronic iron deficiency anaemia in adults, the number of platelets may be slightly reduced.

Plasma protein content is quite often reduced, total proteins being less than 5 gm. per cent (normal range 6 to 8 gm. per cent).

Bone marrow is hyperplastic and shows a relative as well as absolute increase of normoblasts. Unlike the pernicious anaemia, megaloblasts are not found, although young normoblasts are in evidence. The predominant cell is a small polychromatophilic normoblast. The increase in normoblasts is roughly proportional to the degree of anaemia. The percentage of these cells increases after the administration of iron but as the blood is restored to normal, the cellularity of the marrow likewise returns to normal. The granulopoiesis, in general, is slightly reduced but does not show any significant deviation from the normal. There is, however, a remarkable absence of stainable iron.

Gastric analysis shows achlorhydria which is a common finding in chronic cases of iron deficiency anaemia. Frequently, there is an excessive secretion of mucous and decreased formation of pepsin. The volume of the gastric secretion is generally less than normal.

Other laboratory findings are not noteworthy except those which may reveal occult bleeding, as for example, from the gastro-intestinal tract. The urine shows no significant changes.

COURSE AND PROGNOSIS

The disease is chronic and the average duration of symptoms before treatment is 5 years. It is rarely fatal but in the absence of proper treatment many patients remain invalid for years together.[103]

Under the influence of iron therapy, the blood returns to normal and many of the symptoms disappear. This is particular true so far as glossitis is concerned. Tongue papillae and nails return to normal. The cardiac murmers may persist for a long time although dyspnea disappears. Failure to respond to oral iron therapy and a subsequent need for parenteral iron therapy is very rare. In some patients a certain degree of fatigability or other complaints may persist for a long time. Since many of these patients have been ill for many years and have acquired faulty habits of various kinds, it sometimes requires all the art of the physician to bring about complete restoration of health.

There is strong tendency to relapse, which can only be avoided by re-examination at frequent intervals or by persisting with iron therapy, at least in small doses.[103]

PREVENTION

Iron deficiency anaemia can be greatly prevented by increasing the iron intake of the population either by encouraging the use of foods known to be rich in iron through a programme of health education or by administering supplemental therapeutic iron. Aykroyd et al. observed that iron medication was more effective in the treatment of iron deficiency anaemia rather than consumption of iron rich foodstuffs, whereas iron rich diet was valuable for the prevention of iron deficiency anaemia.[109]

Foy and Kondi observed that 85 per cent of their anaemia cases responded to iron administration and suggested that some thought should be given to the fortification of the diet with iron.

The eradication of hookworm and the resultant chronic blood loss, would also help in maintaining the normal haemoglobin levels.

In addition to all these considerations, therapeutic iron should be given during the periods of rapid

growth as in infancy and childhood, and to women during pregnancy. Prophylactic administration of iron in professional blood donors not only prevents the onset of iron deficiency, but also hastens the regeneration of haemoglobin.

TREATMENT

In recent years, there has been a vast improvement in the treatment of iron deficiency anaemia. From a period when nonspecific measures represented all that was available for the treatment of anaemia, we have passed to a period in which several types of anaemia can be treated specifically and dramatic recoveries can be expected. Yet it is by no means unusual even today to encounter cases of anaemia which have been treated ineffectively, inadequately, and incorrectly.

I. General Measures :

It is not very necessary to dwell on general measures in the treatment of anaemia for they are similar to those employed in the treatment of all acute and chronic diseases. Physical rest, mental serenity, fresh air, sunshine and massage are valuable and important. As the patient improves in strength and well-bing, exercise should be started gradually and persisted in systematically.

physical exersion to the point of actual fatigue should be avoided.

Gastro-intestinal disturbances must be treated as they arise. Constipation is common in anaemic patients. Drastic purgatives should be avoided. Contrary to the effect of small doses of iron, the larger amounts which are now employed may cause diarrhea. The latter can be prevented by commencing with about half the ultimate dose and gradually increasing the amount. If this is done, an anaemic patient, formerly constipated, may regain normal bowel movements. In achlorhydric patients, diarrhea may be troublesome or nausea may occur. These symptoms are sometimes relieved by the administration of Mist Acid pepsim ounce 1 B.D.P.C. Glossitis can be relieved by appropriate therapy, depending on the type of deficiency, but this may have to be given parenterally to be effective (e.g. vitamin B Complex or B_{12}).

Respiratory and circulatory symptoms will be alleviated as the anaemia is effectively relieved. Sometimes, the development of anaemia is sufficient to precipitate failure in a diseased cardio-vascular system which is able to function adequatenly when the oxygen supply is normal. Digitalis therapy may be necessary. Anginal symptoms will often vanish as the blood count rises.

As regards the nervous system, the management is the same as in the treatment of nervous conditions unrelated to anaemia. As indications arise, it is permissible to use the sedatives.

II. Diet in Anaemia :

Dietary management in cases of iron deficiency anaemia is carried out by encouraging the patients to take a well-balanced, high protein, rich vegetarian or non-vegetarian diet containing foodstuffs rich in iron (vide Chapter 4). The concentrated carbohydrate foods, such as, cakes, puddings and the like, should be avoided since their ingestion necessarily lessens the appetite for more valuable foods. For similar reasons, fats should not be given in excess.

The consistency of the diet and the number of feedings must be adjusted to the state of health of the patient. All food should be tastefully served and seasoned while cooking, and monotony in meals must be avoided. A proper diet helps to prevent relapses.

If the anaemia is severe, bland diet consisting of milk and milky foods, fruits and vegetables should be given. It is preferable to give small frequent feeds at 2 to 3 hours intervals and gradually increased as the appetite improves.

III. Iron Therapy :

The administration of adequate amounts of inorganic iron salts is so regularly followed by a well-marked therapeutic response that such treatment can be regarded as specific.

1. Relative value of various forms of Iron :

Clinical experience is consistent regarding the effectiveness of inorganic iron salts, given by mouth, in the treatment of iron deficiency anaemia and the greater efficiency of bivalent salts as compared with trivalent forms.

A great variety of compounds for use in oral iron therapy have been promoted from time to time, with claims of greater effectiveness, greater tolerance and less toxicity. No convincing evidence has been provided so far that any one of the compounds proposed is better in any way than FERROUS SULPHATE, which is also the cheapest available compound. There is also no evidence that supplementation of ferrous sulphate with other substances, whether they may be metals, such as copper or cobalt, or vitamins, such as vitamin B_{12}, folic acid or ascorbic acid, is of any value in acceleratig the response to therapy with iron in cases of iron deficiency anaemia. These mixtures only add to the cost.

2. Preparations and Doses :

The most commonly used iron preparations are ferrous sulphate and ferri et ammonium citrate. However, the choice of preparation is a matter of convenience and tolerance. The

average effective dose of the common preparations of iron, along with the amount of Elemental Iron administered, and the percentage used for haemoglobin formation are given below :[132]

TABLE NO. 4

EFFICIENCY OF VARIOUS IRON PREPARATIONS IN RELATION TO DOSAGE

Sr. no.	Iron preparation	Daily dose in gm or ml.	Elemental iron in mg.	Daily utilisation of ingested iron	
				mg.	percent
1	2	3	4	5	6
FERROUS PREPARATIONS :					
1.	Ferrous sulphate(EXC.)	0.6	180	27.2	15
2.	Ferrous Carbonate	0.3	150	15.0	10
3.	Ferrous Chloride	0.25	100	12.0	12
4.	Ferrous Lactate	1.0	190	15.2	8
5.	Ferrous Gluconate	0.9	104	11.5	11
6.	Ferrous Succinate	0.45	111	16.5	15
7.	Ferrous fumarate	0.6	195	—	—
FERRIC PREPARATIONS :					
8.	Ferric citrate	2.0	400	24.0	6
9.	Ferri et.ammon.citrate	4.0	800	12.0	1.5
10.	Colloidal Ferric hydroxide	5.2	600	84.0	14

Sr. No.	Iron preparation	Daily dose in gm. or ml.	Elemental iron in mg.	Daily utilisation of ingested iron	
				mg.	percent
1	2	3	4	5	6
CHELATED PREPARATIONS :					
11.	Ferrous aminoacetosulphate	0.9	150	7.5	5.0
12.	Iron Choline citrate (Ferric)	0.96	120	18.0	15
13.	Sodium iron edetate (ferric)	1.1	165	12.5	7.6
INTRAVENOUS PREPARATIONS:					
14.	Saccharated Ironoxide (Ferrivenin)	5.0	100	85 +	85+
15.	Iron-dextran complex (Imferon)	5.0	250	212 +	85 +
16.	Iron-dextrin complex (Astrafer)	2.0	40	27.2+	68+
INTRAMUSCULAR PREPARATIONS:					
17.	Iron-dextran complex (Imferon)	5.0	250	150+	60+
18.	Iron-sorbitol complex (Jectofer)	2.0	100	60+	60+

3. Oral Iron Therapy :

Until recent years, the only practicable route for iron administration was by mouth, and it is still the

route of choice in the great majority of cases, the reason being the ease of administration besides the fact that the actual administration is free of cost. Moreover, the time-honoured ferrous sulphate which is the cheapest and more effective than, or at least as effective as, any other oral iron compound is still the drug of choice.

The effective daily dose of ferrous sulphate is 0.6 to 0.8 gm. per day, given in form of tablets of 0.2 gm. size. To avoid gastric irritation ferrous sulphate should be given immediately after the meals. The daily dose should be divided roughly in accordance with the size of the meal. Two tablets may be readily tolerated after a large meal whereas one may cause discomfort if the stomach is empty.

Tablets, pills or capsules containing iron salts are preferable to solutions of iron for the latter may oxidise, generally stain the teeth and are distasteful. Tablets of ferrous sulphate are usually specially coated to prevent oxidation to the ferric form.

Therapeutic doses of oral iron preparations may induce gastric distress, nausea, vomiting, diarrhea, constipation or heart burn. The incidence and severity of these symptoms can be reduced by starting at low dosage levels, say about one-third of the maximum, and gradually increasing to the required level in the course of 3 to 4 days. For the same reason, it is customary to give the drug after

meals. Thus, the tolerance for oral iron salts is increased by post-prandial administration of gradually increasing doses.

The response to oral iron therapy is somewhat variable and, although it is sometimes as dramatic as that of pernicious anaemia to cyanocobalamin, it may be two to three months before normal blood levels are reached. Treatment at full dosage levels should be continued for at least one month thereafter, and preferably for longer in order to provide for replenishing of the body stores.[26] Rarely, the patient is intolerant to oral iron in any form, and iron has to be given parenterally.

4. Parenteral Iron Therapy :

Parenteral iron therapy should not be used if oral administration is possible. There are few legitimate Indications for parenteral therapy. These are :

(a) Patients with iron deficiency anaemia who are unable to tolerate iron by mouth, e.g. cases of ulcerative colitis, persistent vomiting (as in pregnancy), disordered gastro-intestinal function after gastrectomy and carcinoma of stomach. In such patients iron by mouth may seriously aggravate the symptoms. However, most patients with these and similar gastro-intestinal disorders can take iron orally if proper instructions are given(vide supra).

(b) Inability to absorb adequate amounts of iron taken by mouth. Such cases in which steatorrhea is usually present are rare. However, in many cases of steatorrhea and even in sprue and after gastrectomy, iron is usually absorbed satisfactorily from the gastro-intestinal tract.

(c) Need for rapid restoration of normal haemoglobin level e.g. later stages of pregnancy or when blood transfusion is contraindicated. It is rare that the need is this much urgent.

Recently, two compounds have been shown to be more effective. One, however, iron-dextran was found to be markedly sarcogenic in the rats and its use has been abandoned. Thus, there remains only the Saccharated oxide of iron which must be given intravenously. This is an iron-sucrose complex containing 2 per cent ferric or ferrous iron, colloidally suspended.

If parenteral iron therapy is indicated, the total quantity given should not be more than the amount required to restore the haemoglobin to normal. There are two methods[104] for calculating the amount of iron required :

(a) Give 250 mg. for every 1 gm. of haemoglobin deficiency. The formula for calculating this is:

Normal Hb (gm.%) - Patient's Hb (gm.%) x 250 = mg. Fe

(b) Another method is to estimate the haemoglobin deficit in gm. per 100 ml. (e.g. normal is 15 and the patient has 6 gm. per 100 ml., then the deficit is 8 gm. per 100 ml.). Considering the hypothetical blood volume as 5 litres, the total haemoglobin deficit will be 50 x 8 = 400 gm. Considering that each gm. of haemoglobin contains 3.4 mg. of iron, then the iron needed to replace the total haemoglobin deficit will be 400 x 3.4 = 1360 mg. Fe. Then add 1000 mg. to fill the iron stores. This gives a total dose of approximately 2360 mg.

Because of the possible toxic effects, only 50 mg. of iron should be given at the time of the initial injection. Subsequent daily doses of 100 mg. are given until the calculated dose has been administered.

EFFECTS OF IRON THERAPY

If severe iron deficiency is present, a vigorous response can be expected. The speed and magnitude of this effect depend on the route of administration and the amount of iron absorbed.

A rise in the percentage of reticulocytes follows the institution of iron therapy and the increase is maximal usually on 8th to 12th day after the institution of iron therapy. Following the reticulocyte rise the haemoglobin, volume of packed cell increase and the size and haemoglobin content of the red cells gradually return to normal.

Symptomatic improvement occurs rapidly along with the blood regenration. The colour improves, the skin becomes less dry and wrinkled and more elastic. Appetite is better and the patient's strength is regained. The tongue papillae become normal in appearance. If koilonychia has been present, the brittle concave nails are eventually replaced by convex, smooth and shiny ones. The enlarged spleen recedes and, although it is quite rare, secretion of free hydrochloric acid is restored. The 'hemic' cardiac murmers are slow to disappear.

REFRACTORINESS

When the established case of iron deficiency anaemia fails to respond to the prescription of an oral iron preparation, the first step should be to ascertain that the prescribed dosage is actually being taken. Sometimes bed rest seems to provide the needed stimulus.

It is essential to ensure that the original cause

of the anaemia is not still operating. A pathological source of blood loss may remain unnoticed, or menstruation may be excessive. Dietary factors are not of great importance at this stage. Defective absorption is rarely the cause of failure to respond to therapeutic doses of iron, and when it is present, parenteral administration of iron will soon provide the answer and the cure.

What is more important in a refractory case of iron deficiency anaemia is the presence of a complicating factor like infection, neoplasm, or chronic hepatic or renal disease. In such circumstances the anaemia may actually be due to iron lack, and the refractoriness may be due to toxic inhibition of haemopoiesis. On the other hand, there may not be a true iron deficiency and the anaemia may be attributable wholly to the direct interference with haemoglobin formation in the presence of adequate iron stores.

TOXICITY OF IRON

The toxic manifestation resulting from iron therapy may be described under three headings as :

(1) Toxicity of oral iron,

(2) Toxicity of intramuscular iron

(3) Toxicity of intravenous iron.

1. Toxicity of Oral Iron :

Chronic intoxication from orally administered iron therapy is practically unknown.

Acute toxicity can occur from ingestion of large doses of iron. Ferrous carbonate appears to be the least toxic of the inorganic salts (D'Arcy and Howard,1960) and ferrous sulphate the most toxic. Organic iron salts are less toxic than inorganic salts and the chelated forms are least toxic.[132] Thus, 3 grams of ferrous sulphate may be a fatal dose for a child aged 1 to 2 years.

Many iron pills unfortunately have attractive appearance and a preliminary taste suggestive of sweets. Numerous instances of iron poisioning have been reported in young children who have been attracted by the appearance and flavour of the tablet-coatings. Duffy and Diehgl observed three cases of ferrous sulphate poisioning in children. Fatal cases have also been reported by Luongo and Bjornson (1954)."Iron encephalopathy" following the administration of 11 gm. of iron and ammonium citrate daily has been reported, as well as a case in which paralytic ileus occurred from retention of iron in the caecum.[136]

The ill effects of excessive amounts of iron are attributable to the rapid absorption of the metal in amounts far above the iron-binding capacity of the plasma.

Serum iron values as high as 3000 mcg. per cent have been observed. The iron also has a local astringent action on the gestro-intestinal mucosa and, in the liver, hemorrhagic necrosis of the peripheral or periportal portions of the lobules has been described. Iron has also got toxic effects on the central nervous system.

The signs and symptoms of acute toxicity consist of three phases :

(a) An earlier phase developing after ingestion which is marked by pallor, restlessness, nausea, vomiting, diarrhea, haematemesis and malena. This is followed by drowsiness and ultimately semiconsciousness and coma and finally by signs of peripheral circulatory collapse.

(b) A period of rapid improvement for 12 to 24 hours may be followed by sudden death 24 to 48 hours after the ingestion of iron. Thus, such a misleading period of clinical improvement precedes the final phase.

(c) The final phase precedes the death and is characterised by obvious metabolic, hepatic and cerebral injuries, convulsions and coma.

As a first-aid measure vomiting must be induced by pressing a finger to the back of the tongue preferably

after a drink of milk. This removes any iron tablet remaining in the stomach and thereby reduces further tissue damage. Gastric lavage is repeated with 1 per cent sodium bicarbonate or 10 per cent disodium orthophosphate (Shafir, 1961).

Further treatment consists of measures to combat shock. Shock is combated by warmth, oxygen and intravenous fluids.

Intravenous infusions of 500 mg. of calcium disodium versenate (Ethylenediamine tetra-acetic acid or E.D.T.A.), which is a synthetic polyamino acid, in isotonic glucose solution (Simpson and Blunt, 1960), given slowly over 6-12 hours reduces the level of circulating iron and this should be repeated daily until the serun iron level is normal.[132]

2. Toxicity of Intramuscular Iron :

Intramuscular administration of iron often causes pain at the site of injection and occasionally may be dangerous. Immediate reactions include nausea, vomiting, pallor and fall in blood pressure, but as a rule, they are transient. Recently, iron-dextran complex (Imferon) has been reported to have carcinogenic effect.

3. Toxicity of Intravenous Iron :

Intravenous administration of iron often causes mild to severe reactions. Paravenous injections are painful and

cause tissue damage. Local induration, thrombophlebitis, transient venospasm may be produced.

Systemic reactions may be alarming and include headache, sneezing, flushing, hypotension, pain in chest, back or extremities, symptoms suggestive of sympathetic stimulation (tachycardia, pallor and faintness), or of parasympathetic stimulation (sweating, intense burning, lacrimation, nausea, bronchospasm, dyspnea), and, more rarely symptoms of circulatory collapse. Encephalitis has been reported.

The excessive administration of parenteral iron can induce a syndrome somewhat similar to hemochromatosis. It also resembles siderosis produced by repeated blood transfusions and can result in fibrosis of liver and pancreas.