Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Iron Deficiency Anemias

Volume IX | Friday, January 21, 1938 | Number 13

STAFF MEETING BULLETIN
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INDEX

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William A. O'Brien

I. LAST WEEK

Date: January 14, 1938

Place: Recreation Room
Nurses' Hall

Time: 12:15 to 1:15

Program: Movie: "The Romance of Radium"

Carcinoma of Esophagus
N. Logan Leven
Warner F. Bowers

Discussion: O. H. Wangensteen
K. W. Stenstrom
J. C. McKinley
Edw. A. Loeb
N. Logan Leven

Present: 122

Gertrude Gunn,
Record Librarian

II. MOVIE

Title: "Spiders"

Released by: Erpi Corporation

III. GOSSIP

John J. Boehrer, our author today was born in Minneapolis and attended grade and high school here. He received an A.B. from the University of Minnesota and M.D. from Johns Hopkins' University. After a straight internship on medicine at the University of Minnesota Hospitals he was appointed to a fellowship in the department. He is married and lives in Minneapolis. While an undergraduate he did investigative work in psychology on the learning ability of animals. This won him election to Sigma Xi. Keen, alert, industrious, well-liked by his associates, all predict that he will go far. His scholarly presentation today is characteristic of him - Next Friday we will hold a joint meeting with the Institute for Hospital Administrators. They will spend Thursday, Friday and Saturday, January 27, 28 and 29, at the Center for Continuation Study. The program on Friday afternoon will start at noon with our meeting, and continue with demonstrations in the amphitheatre during the afternoon. Among others there will be one on the technique of blood transfusion. For this special occasion we are putting on a contribution from the Department of Pediatrics on a clinical study of the last outbreak of poliomyelitis. With the rapid development of small hospitals throughout Minnesota there has been corresponding interest in improving these institutions. Many of them represent, in miniature, hospitals of much larger size in medical centers. In the small hospital in Bemidji, as an example, I was privileged to see their annual report. It was a model for all institutions, no matter what the size - The first February staff meeting, scheduled for Friday, February 4th, will be changed to Thursday, February 3rd, because of the visit of Dr. Penfield to give the Judd Lecture and also to address the Minneapolis Surgical Society. Dr. Peyton's division will have the program on this day, and we are looking forward to this meeting. The change in date will be for this meeting only, so be sure to mark it on your calendar - We have received a note from one of our old subscribers telling us that he misses the inclusion of discussion abstracts by our staff men. Until a few years ago we printed these remarks the following week. As time went on it became more and more difficult to include them. Now they are kept on file in the record room as part of the proceedings - The Institute in Ophthalmology and Otolaryngology at the Center for Continuation Study has been most successful. It is the first "specialty" institute we have offered, as all those enrolled limit themselves to this specialty. It is also the largest, with an enrollment of over 40, and the widest spread of students, Wisconsin, Minnesota, Iowa, North and South Dakota, Montana, Nebraska and Washington.

IV. IRON DEFICIENCY ANEMIAS

John J. Boehrer

1. Clinical descriptions of disease bearing a close resemblance to iron deficiency anemia are found in the earliest medical writings. The AAA disease of the Ebers papyrus is believed to be a hypochromic anemia probably secondary to infestation with ankylostoma duodenale, which afflicted a fourth of the Egyptians. The writings of Hippocrates and Galen as well as the Arab Rhazes each contain references to rather vaguely described conditions associated with puberty and characterized by pallor, weakness, and irregular menses, which probably represent iron deficiency anemia of the chlorotic type.

In 1746 Menghini discovered that iron was a characteristic constituent of the blood and that it was contained solely in the "globular part." In 1832 Födisch examined the blood ash and made the fundamental observation that the iron content in chlorosis was greatly reduced. It is of interest that it was in this same year that Blaud introduced his now famous pill as a specific for chlorosis.

Following the advent of methods for hemoglobin determination and enumeration of the red blood cells, Duncan and Hayem noted the lowering of the color index in some anemias, and Laache, in 1883, recognized the importance of determining the proportion of hemoglobin to the number of red blood cells in differentiating the anemias.

In spite of increasing knowledge concerning the morphology of anemias, however, the relationship of iron to anemia continued to be a matter of dispute until comparatively recent times. It is worthy of note that such excellent investigators as Musser, and Whipple as late as 1921 were convinced that orally administered iron was inert, and quite useless in the treatment of anemia.

In 1925, however, Whipple and Robscheit-Robbins published the first of their classical experiments on anemic dogs. They maintained dogs in a state of severe anemia by means of repeated venesections, and measured the effect of various foods and iron on hemoglobin production. They proved conclusively that iron was essential for new hemoglobin formation, and were responsible for the fundamental concept of hypochromic anemia as a deficiency disease. It is this concept which permits the inclusion of a variety of anemias in the single category of iron deficiency anemia.

2. Modern Concepts of Iron Metabolism

Iron is a constituent of every living cell. From the standpoint of its availability for blood production, it may be considered as being present in 3 different forms. By far the bulk of the body iron is retained as an essential part of the hemoglobin molecule; another portion is stored in various depots, mainly liver, spleen, and bone-marrow, and may be termed "latent iron"; and a third portion is an integral part of the cell, the so-called "tissue iron," which is unavailable for blood production. The total iron in these 3 forms is not known exactly, but has been estimated by various investigators as in the neighborhood of 5 grams. Of this amount about 3 grams is contained in the circulating hemoglobin; about 1½ grams is stored as latent iron; and the remaining ½ gram is retained as tissue iron. It is of importance to note that the quantity of latent iron represents the body's iron reserve against emergency, and that its size determines whether or not anemia will appear when excessive demands are made for iron.

The exact sites of absorption and excretion of iron are unknown. From the work of Schmidt and others, however, it would appear that the duodenum is responsible for at least a portion of the absorption.

The absorption of iron from the intestinal tract is influenced by a variety of factors, some of which are of considerable importance in the etiology of iron deficiency anemia. Per-

haps the foremost of these is gastric acidity. Mettier and Minot have shown that the response of the bone marrow to iron in hypochromic anemia is greater when the contents of the upper intestinal tract are acid than when they are neutral. Heath found in the first 30 days of treatment a utilization of 11.8% of iron administered to patients with hypochromic anemia due to chronic blood loss. During that same time only 3.1% of the iron administered to patients with "idiopathic" hypochromic anemia with gastric anacidity reappeared as newly formed hemoglobin. Fowler found that 72% of his cases of hypochromic anemia and achlorhydria were in negative iron balance, as compared with 35% of the cases of anemia without achlorhydria. Kellogg and Mettier have shown that hemoglobin formation following hematemesis from duodenal ulcer is inhibited by excessive alkaline therapy, and is resumed following its discontinuance. Dameshek, and Mettier, Kellogg, and Rynehart found that a diet rich in organic iron was ineffective in causing a reticulocyte response in anemia with anacidity. After pre-digestion with hydrochloric acid and pepsin, however, they observed reticulocyte responses, and an increase in the hemoglobin. Experimentally the number of ferric and ferrous ions in a solution has been shown to be inversely proportional to the Ph of the solution. The mechanism of this inhibition of absorption in alkaline solution appears to be the formation of insoluble alkaline salts of iron.

Since achlorhydria is relatively common (Wintrobe found an incidence of 17% in females and 12.5% in males in 11,000 adults of all ages) it may be asked why achlorhydria is not always associated with anemia. As will be shown later, the answer to this lies in the factor of excessive blood loss. Without increased demand for iron deficient absorption is not usually responsible for anemia.

It should be mentioned also in this connection that the relation of achlorhydria to anemia may in some cases be a vicious circle. It is known that anemia can depress the secretion of hydrochloric acid, and in a few patients free hydrochloric acid returns following treatment of the anemia.

Other gastro-intestinal disorders may also be of importance in relation to the absorption of iron. Keefer, Huang and Yang have emphasized the importance of diarrhoea as a factor in the production of iron deficiency. Other variables such as the alkalinity of the pancreatic juice and the relative insolubility of the iron salts of the bile acids may also play a role in this regard.

The presence of other substances may also be essential for the absorption or utilization of iron. Hart and Steenbock have demonstrated that copper is essential for hemoglobin production in the nutritional anemia of rats. Josephs has shown an additive effect of copper and small doses of iron in the nutritional anemia of infants. Fowler has described a decrease in the retention of iron when copper is given simultaneously, but an increase in its utilization. Filmer and Underwood have proven that a nutritional anemia of cattle in Australia is due to a deficiency in cobalt. Other metals, such as arsenic, zinc, nickel, and manganese in very small amounts, perhaps influence iron metabolism similarly to copper. There is a peculiar relationship between calcium and iron. Sherman has shown that retention of iron from the food is favored when the calcium content of the food is high.

It is doubtful, however, if deficiencies in any of these elements play any role in the etiology of human anemia. Mackay and others have emphasized that the dietary of man is so varied, and the required amounts of these substances so small, that their administration therapeutically is useless.

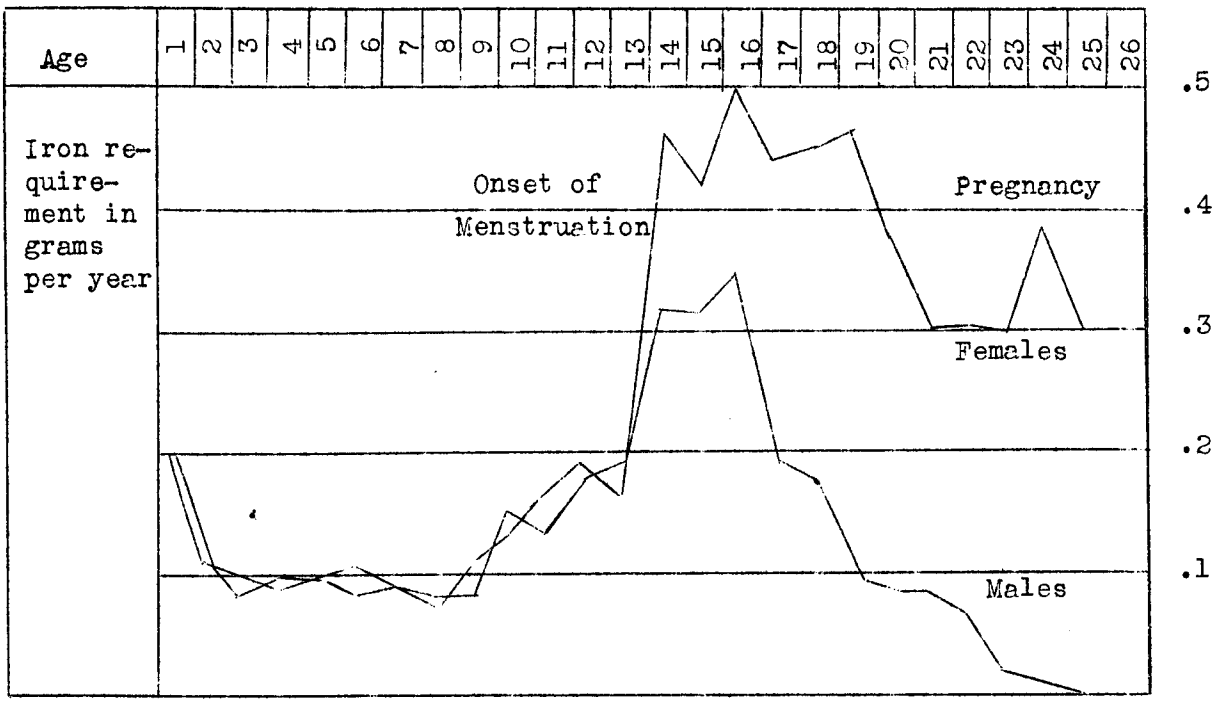
Following the absorption of iron from the intestine, it is carried to the depots in the liver, spleen, and bone marrow to be stored as latent iron, from which it is given up on demand. The mechanism and site of its transformation into hemoglobin is unknown.

3. The Physiological Requirements of Iron

Because of the difficulties inherent in iron balance studies, an exact knowledge of the iron requirements of man is still to be attained. However, an intake of about 10 mgm of iron a day is probably sufficient for the average individual, assuming normal absorption. Fowler found that five patients receiving 4-6 mgm of iron a day were in negative balance, but when the intake was increased to 12-16 mgm a day, they were in positive iron balance. The growth requirement has been variously placed at from .2-.6 mgm a day, and is of course greatest during infancy and adolescence. The advent of menstruation places an additional load upon the growing girl, with an estimated iron requirement of from 1-2 mgm a day. The iron requirement of females is further increased by the demands of pregnancy and lactation, in an amount estimated as about 3 mgm a day for the entire period. As the menopause approaches, the frequent occurrence of menorrhagia adds a further burden which is impossible to estimate. The following chart illustrates the differences and variations in the iron requirements of the sexes.

Figure 1

The Iron Requirements of Males and Females



(After Heath and Patek)

Thus it is seen that the body's requirement of iron may be represented by a succession of peaks; the 1st in infancy, affecting males and females equally; the 2nd in adolescence, affecting females only; the 3rd in pregnancy; and the 4th about the time of the menopause. With each of these peaks a type of iron deficiency anemia is associated, and if one adds to these the anemia of chronic blood loss, the roster of the iron deficiency anemias is complete.

4. The Blood Picture in Iron Deficiency Anemia

Since all these anemias have fundamentally the same etiology, it is to be expected that the blood picture in the 5 types would be similar. As a matter of fact, all of them, with the exception of one or two minor differences, are morphologically indistinguishable.

The essential feature is the proportionately greater reduction of hemoglobin than of red blood cells. The achromic red blood cells average smaller in diameter and the concentration of hemoglobin is markedly reduced.

In order to assay the above changes quantitatively, Wintrobe in 1931 introduced a method for the exact determination of the above factors, utilizing the hematocrit. The methods of calculation, the normal values, and the changes in several types of anemia are tabulated below.

The mean corpuscular volume (M.C.V.) is a measure of the average volume of the red blood cell, expressed in cubic microns. It is computed by dividing the percentage of packed red blood cells (in the hematocrit) X 10, by the number of red blood cells in millions.

The mean corpuscular hemoglobin (M.C.H.) is a measure of the average weight of hemoglobin in each red blood cell, expressed in micro micro-grams. It is computed by dividing the grams of hemoglobin per 100 cc. X 10, by the number of red blood cells in millions.

The mean corpuscular hemoglobin concentration (M.C.H.C.) is a measure of the average concentration of hemoglobin in each red blood cell, expressed in per cent. It is computed by dividing the grams of hemoglobin per 100 cc. X 100, by the per cent of packed red blood cells (in the hematocrit).

	M.C.V.	M.C.H.	M.C. H.C.	R.B.C. diameter
Normal	80-94	27-32	33-38	6.7-8.0
Pernicious anemia	95-160	30-52	31-38	7.5-9.6
Hypochromic	50-71	14-21	21-29	5.8-7.5

It is obvious that the above differences are considerable, and that the determination of these indices, which replace the less helpful volume, color, and saturation indices, is of considerable aid in the differentiation of anemias.

Variations in the size and shape of the erythrocytes in iron deficiency anemia may be marked, but macrocytes are relatively few in number, and are usually round rather than oval, as in pernicious anemia. Normoblasts are occasionally seen. The white blood cells are usually normal in number or slightly increased. In severe hypochromic anemias, however, there may be leukopenia with relative lymphocytosis and reduction in the number of the blood platelets. The nuclear configuration of the neutrophil is normal. The reticulocytes are usually normal, except in the anemia of chronic blood loss, although the bone marrow usually reveals a moderate degree of hyperplasia, of a normoblastic type. The resistance of the red blood cells to hemolysis by hypotonic saline is either normal or slightly increased.

In addition to the above findings the plasma bilirubin is usually decreased, and urobilinogen is excreted in markedly diminished amounts in the stools. Values of 10-20 mgm./day are not infrequently seen, in contrast to the normal value of about 200 mgm. These latter 2 findings are an expression of the depletion of the

body's stores of pigment, and the effort to conserve these blood-building materials by a diminution in the rate of blood destruction.

5. The Incidence of Iron Deficiency Anemia

The incidence of iron deficiency anemia is difficult to determine with certainty. There is no doubt a relation with the economic status and resultant dietary standards. Donaldson, Fullerton, and Campbell examined the blood of 3500 individuals from the poorest classes of Scotland. They reported the presence of anemia, which they believed due to iron deficiency, in 41% of infants under the age of 2, in 2% of school children, in 16% of adolescent girls, and in 45% of adult women. Anemia was absent in adolescent and adult males, except in the presence of organic disease.

6. The Iron Deficiency Anemia of Infancy

The factors responsible for the development of hypochromic anemia in infancy are those of decreased supply of, and increased demand for iron. During the first year of life the total blood volume is approximately tripled, and the total circulating hemoglobin is doubled. Figuratively speaking, the infant bleeds into his own blood supply. In addition, growth is relatively much more rapid during the first year of life than subsequently. It will be remembered that the growth requirement is from .2-.6 mgm iron a day. As human milk contains .17 mgm./100 cc, it is obvious that the infant must draw on his store of latent iron.

The diminution in iron stores may be brought about in a number of different ways. A mother whose iron supplies are deficient may endow her child with an insufficient iron store. Also, the infant's iron stores are laid down in the latter months of pregnancy, and prematurity may result in inadequate iron endowment. Anemia of the hypochromic type is so common in premature infants that it has received the name "anemia of prematurity." Cow's milk contains even less iron than human milk, and artificially fed babies are particularly susceptible to iron deficiency. And finally, infection or gastro-intestinal disturbances may result in a decrease of the iron supply, either because of decreased intake, or because of faulty absorption.

The importance of sufficient iron stores in the prevention of hypochromic anemia in infancy is further emphasized by the work of Josephs, who found that normal, healthy infants were capable of passing through the first year of life on an exclusive cow's milk diet without developing anemia. Strauss showed that there was no significant difference between the hemoglobin level at birth of infants born of anemic and non-anemic mothers, but that moderate to severe degrees of anemia developed in the former infants during the first year of life. This anemia did not occur in infants born of mothers who received iron during their pregnancies.

The hypochromic anemia of infants does not usually appear before the 4th month, and is not to be confused with the physiological fall of hemoglobin which commences immediately after birth and proceeds until the second or third month of life. This is believed to be due to the destruction of red blood cells which are no longer necessary in the presence of the greater oxygen supply of extra-uterine life.

The disease is rare also after two years of age, when supplementary foods have largely replaced milk, although it may appear at any time in response to deficient diet or gastro-intestinal abnormalities.

The general nutrition of these patients is not often disturbed. Pallor, enlargement of the liver, spleen, and lymph nodes, and edema of the extremities are the common physical findings. These physical signs are of course not characteristic and indeed may cause confusion with infection, leukemia, and so-called erythroblastic anemia.

Achlorhydria is a more common finding in the iron deficiency anemia of infants

than is generally recognized. Hawksley, Lightwood, and Bailey studied 13 children with hypochromic anemia, and found 12 to have achlorhydria after an alcohol meal. In 9 of these free acid returned after treatment with iron.

7. Chlorosis

Chlorosis may be defined as an iron deficiency anemia occurring in adolescent girls. Historically, it was the first to be recognized. The classical description was written by Johannes Lange in his "De Morbo Virgineo" in 1554. It was a common disease, and references to the "green sickness" are common in the literature of the past few centuries (as in Capulet's tirade against Juliet in "Romeo and Juliet").

The etiology of chlorosis is to be found in the failure of diminished iron stores to meet the increasing demands for iron by girls at the time of puberty.

The causes of the increased demand for iron in adolescence are largely those of growth and menstruation. In girls there is an acceleration of growth after 9 years of age with an accompanying increase in blood volume and total circulating hemoglobin. Increased growth at puberty is of course found in both boys and girls, and the important feature of adolescence, insofar as the development of iron deficiency is concerned, is the advent of menstruation. It is this phenomenon which is responsible for the sex incidence of chlorosis.

Hoppe-Seyler, and Ohlesen and Daum have shown that each catamenia results in a loss of about 25 mgm of iron, on the basis of an average blood loss of about 50 cc. This amounts to about 300 mgm per year. In addition, of course, there is the growth requirement of 60 to 180 mgm a year.

It is certain, however, that if no iron deficiency has been present in infancy or childhood so that the iron stores at the time of puberty are large, if the appetite is good and the dietary intake adequate in iron, then these increased demands for iron will be met, and no anemia result.

In the presence of inadequate iron stores, however, either because of poor endowment from an anemic mother, or because of inadequate or capricious diet, or because of malabsorption due to gastro-intestinal disease, then the demands of adolescence will prove excessive, and iron deficiency anemia result.

It seems, therefore, that the basis of chlorosis is the development of iron deficiency because of chronic blood loss in young girls whose iron stores are deficient.

Although formerly a common disease, chlorosis is now seen only infrequently. In 1931 Witts could find only five cases of chlorosis among all the anemias admitted to Guy's Hospital in the preceding 9 years. The average age of incidence is about 20 years.

The onset is usually gradual over a period of 3 to 8 months, although it may appear quite suddenly. The symptoms are those of anemia. Weakness and breathlessness appear early. Palpitation and arrhythmias are common. Frequently there is dyspepsia, and a perverted appetite with a persistent craving for unusual foods is the rule. Suppression and irregularity of the menses is often seen.

There are no specific physical signs. The green color, which gives the disease its name, is seldom pronounced, and then only when the anemia is very severe. Pallor is a more common finding, and the puffy appearance of the face often suggests nephritis. Edema of the extremities may be present, and the spleen is palpably enlarged in 10% of the cases.

Thrombosis is the only complication, and is the cause of the extremely rare fatalities. This occurs particularly in the legs and occasionally in the cerebral sinuses. The number of blood platelets is increased in the recovery phase and this may contribute to the development of thrombi.

In contrast to other hypochromic anemias, gastric hyperacidity is common

and achlorhydria rare. Arneth found normal or high values for hydrochloric acid in 23 cases. Fever is not infrequently present and may cause confusion with such infections as tuberculosis and rheumatic fever.

The reason for the practical disappearance of chlorosis is not known with certainty, but most investigators agree that it is probably related to the increasing dissemination of knowledge concerning proper dietary requirements, both in the pregnancy woman, and in the young girl. The adolescent girl thus begins menstruation with adequate iron stores and is able to handle the increased demand satisfactorily.

Hypochromic anemia in young males is extremely uncommon, and is then usually associated with markedly deficient diets, or chronic blood loss. Reynolds has observed hypochromic anemia in two school-boys who grew very rapidly, and in whom he could find no evidence of bleeding. Generally, however, hypochromic anemia in males is strong presumptive evidence of pathological blood loss.

8. Iron Deficiency Anemia of Pregnancy

Anemia is very frequent in pregnancy and is usually of the hypochromic type. Bland, Goldstein, and First found red blood cell levels below 3.5 million in a third of 200 pregnant women in the first six months of pregnancy, and in over half in the last three months. Part of this reduction, of course, is due to the hydremia of pregnancy, but on the average the reduction from this cause seldom exceeds 500,000 red blood cells and 10% hemoglobin.

The average fetus at term contains about 500 mgm of iron. Since hemoglobin contains .335% iron, it is a simple matter to calculate that the maximum hemoglobin loss from the demands of the fetus is about 150 grams, or roughly one liter of blood. Assuming a blood volume of 5 liters, this reduction is approximately 20%. Adding to this the normal "physiological anemia" of 10%, one obtains a figure of 30% as the maximal reduction possible in normal pregnancy. Since anemias of the hypochromic type of 50% or less are relatively common, it is obvious that other factors in addition to the demands of the fetus must play a role, and that uncomplicated pregnancy is incapable of producing severe anemia.

Strauss and Castle have shown the relationships between dietary deficiency, poor gastric secretion, and malabsorption, to blood formation during pregnancy. They showed that the secretion of hydrochloric acid and pepsin was commonly diminished during pregnancy, particularly during the latter third. Anemia occurred only in those patients who had a prolonged defective dietary, and gastric anacidity or related gastro-intestinal disturbances. They concluded that the hypochromic anemia of pregnancy was due essentially to 3 factors acting together: dietary deficiency; malabsorption from the gastro-intestinal tract, associated usually with diminution in the gastric acidity; and the demand by the fetus for blood-building materials.

Repeated and frequent pregnancies predispose to "idiopathic" hypochromic anemia. Post-partum bleeding may be excessive, and productive of hypochromic anemia of chronic blood loss. In addition, prolonged and frequent periods of lactation may aid in the production of profound iron deficiency.

9. "Idiopathic" hypochromic anemia

So-called "idiopathic" hypochromic anemia may be defined as a hypochromic anemia appearing usually in middle-aged women who have a reduction or absence of free hydrochloric acid in the stomach.

Since the original descriptions by Faber in 1909 and 1913, a voluminous literature has appeared on this subject. Many writers have questioned that it is a specific entity, but the clinical picture is usually rather typical, and probably justifies its classification as a special type of anemia.

As in other iron-deficiency anemias, the etiology is multiple. In general, however, the factors are again those of iron loss associated with deficient iron stores.

Achlorhydria is characteristic of idiopathic hypochromic anemia. At least 83% of the cases fail to secrete free hydrochloric acid after the Ewald test meal, and 50-60% have achlorhydria after histamine. Practically every case has a diminished output of hydrochloric acid. Gastric abnormality is further evidenced by frequent excessive secretion of mucus and diminished pepsin formation. The volume of the gastric contents is diminished, but the intrinsic factor of Castle is present, although usually in lessened amounts. There is apparently an unknown relationship between idiopathic hypochromic anemia and pernicious anemia, as evidenced by the similarity of many of the symptoms, and by the occurrence of numerous cases of transition from one to the other. Heath has described a family in which both idiopathic hypochromic anemia and pernicious anemia occurred in each of three sisters.

Frequent pregnancies are often a feature of idiopathic hypochromic anemia. In Heath and Patek's series of 60 cases, 28 had more than four pregnancies, and in 16 of these the average time interval between successive pregnancies was only a year and 10 months. In Wintrobe's series the onset in 17% was definitely related to pregnancy.

As in other types of iron deficiency, pathological blood loss plays an outstanding role. In Heath and Patek's series they were able to demonstrate excessive bleeding in 88%, usually from menorrhagia, although bleeding hemorrhoids and epistaxis were also common. Gray and Wintrobe have also stressed the frequency of menorrhagia in this disease. Fowler studied the iron balance and blood loss from menstruation in normal women and in women with idiopathic hypochromic anemia. He found that 73% of the latter group had excessive menstrual blood loss, and that in 82% this loss was sufficient to place them in negative iron balance. It is significant that most of these women did not consider their menstrual blood loss to be excessive.

Dietary deficiency may play a role in the etiology of idiopathic hypochromic anemia also. Many of these patients give a history of a diet low in hemoglobin building materials. An aversion to meat is a common finding.

Some authors have suggested that faulty iron metabolism may be of importance in the development of this anemia. The careful iron balance studies of Fowler seem to disprove this. He found no significant difference in the utilization of iron in normal and anemic women.

In summary, then, it may be said in all probability the etiology of idiopathic hypochromic anemia is pathological blood loss occurring in middle-aged women whose iron stores have been depleted by the combined effects of dietary deficiency, achlorhydria, and pregnancy.

96% of these cases occur in women, and 60% occur in women between the ages of 30 and 50. It has been described in nearly all countries and races. Many of these patients present constitutional features regarded as typical of pernicious anemia, e.g., light-colored eyes, set widely apart, prematurely gray hair, and wide costal angles.

The onset is typically insidious. The usual story is one of long-continued ill health, often of from 5-10 years duration. The primary complaints are characteristically vague, and include weakness, ready fatigue, shortness of breath, dysphagia and choking sensations. Idiopathic hypochromic anemia in which the latter two symptoms are prominent has been described as the "Plummer-Vinson syndrome." Frequently there is a history of "anemia as a girl."

Abdominal pain or distress, loss of appetite, flatulence, eructation, nausea, and even vomiting and diarrhoea may be encountered. Sore tongue or sore mouth is present in approximately 28% of the cases, but the glossitis rarely approaches the severity of pernicious anemia.

Dyspnoea, palpitation, and edema may suggest abnormalities of the cardio-vascular system. Numbness and tingling of the extremities occur in 15-30% of the cases. As with glossitis, these symptoms are seldom as prominent as in pernicious anemia. Rarely, if ever, are there objective neurological findings.

Physical examination of these patients presents a striking and often typical picture. Characteristically, the patient is a chronic invalid, weak, ambitionless, querulous, and complaining of a variety of physical ailments. There is no icterus, and the skin has a remarkable, pale, waxy hue. The sclerae are bluish. Ectodermal changes are common. The skin sometimes appears atrophic, particularly over the hands. The hair is dry and fine, and pulls out easily. The finger-nails, rarely the toe-nails, are dry and brittle, and characteristically concave, (koilonychia). This concavity may be so prominent that several drops of water can be held on the backs of the nails. Fissures, or rhagades, at the corners of the mouth may be present, and their healing leaves small scars which tend to make the mouth smaller.

A brownish, light pigmentation, particularly on the neck and upper thorax, is frequently observed. Often there is a history of easy bruising, and ecchymoses are occasionally seen, rarely petechiae.

Almost complete atrophy of the tongue papillae, especially at the edges and tip, is common. Examination with the gastroscope may reveal atrophy of the gastric mucous membrane.

The heart may be slightly enlarged, and functional murmurs are often heard. The liver and spleen are frequently enlarged. As in all anemias, dependent edema is not rare.

10. The Iron Deficiency Anemia of Chronic Blood Loss

The hypochromic anemia of chronic blood loss is the result of the same factors that have been seen to be responsible for the development of the other types of iron deficiency anemias, but their operation is seen with greater clarity. The factor of iron loss, however, assumes relatively greater importance, because bleeding in this anemia is usually quite severe. Coincident with this the factors influencing intake and absorption of iron are of lessened significance.

Iron deficiency may follow blood loss from any source, and at any age. To lose blood is to lose iron, and blood contains more iron than any other tissue (53 mgm per 100 grams). And corollary to this is the fact that hypochromic anemia in an adult male is an almost certain sign of pathological blood loss.

The majority of cases of hypochromic anemia in this category are due to bleeding from the gastro-intestinal tract. In Heath and Patek's series of 122 cases of this type of anemia, bleeding from peptic ulcer accounted for 25%, from carcinoma of the stomach 17%, from hemorrhoids 13%, and from gastro-intestinal bleeding of unknown origin 6%, a total of 61%. In addition their "miscellaneous group," constituting 10% of the cases, was made up largely of cases of bleeding of gastr-intestinal origin, such as carcinoma of the colon, ulcerative colitis, and amebic dysentery.

Menorrhagia, metrorrhagia, abortion, miscarriage, and post-partum bleeding accounted for 23% of the cases.

Rarer causes are repeated epistaxes, purpura, hemophilia, and other blood dyscrasias, as well as multiple hereditary telangiectasia.

Hookworm infestation is a common cause of hypochromic anemia in the South. Smillie has shown that the average number of worms in infected individuals is from 25-100, and Wells has shown by direct observation of the intestines of infected dogs, that the parasites actually suck blood from the intestinal mucosa at a rate which he estimated as totalling 85 cc. a day per 100 worms.

Achlorhydria is not uncommon in the hypochromic anemia of chronic blood loss, and serves to accentuate it. In Heath and Patek's series, 37% of the 58 cases on whom a gastric analysis was done had anacidity. In Rhoad's cases of hookworm anemia 23 of 54 were found to have achlorhydria.

The blood picture in the anemia of chronic blood loss differs slightly from that of other iron deficiency anemias in that there is usually a slight reticulocytosis, associated with other evidences of mild bone marrow stimulation such as leucocytosis and slight increase in the blood platelets. These differences are due to the fact that the individual amounts of blood lost are usually larger, and serve as a more effective stimulus to the bone marrow. As iron deficiency becomes more pronounced, however, exhaustion of the bone marrow ensues, and reduction in the number of these elements occurs.

Very occasionally this anemia may have a superficial resemblance to pernicious anemia. The mean size of the cells may be normal or even slightly increased, and there may be many macrocytes. The cells are obviously not well-filled with hemoglobin, however, and the plasma and feces reveal no evidences of increased blood destruction.

11. The Occurrence of Iron Deficiency in Other Anemias

Any anemia may present hypochromic features from time to time. It is a frequent observation in the treatment of pernicious anemia to find the hemoglobin level lagging behind the red blood cells. Indeed the rise in the red blood cells may be temporarily halted at a moderately low level because of iron deficiency. The exhibition of iron at this point allows the resumption of the recovery process.

12. The Pathology of Iron Deficiency Anemia

Since hypochromic anemia is rarely fatal, knowledge of its pathology is scanty. In experimental animals the poverty of the tissues in iron has been demonstrated. As has been stated, the bone marrow is hyperplastic with a predominance of cells of the normoblastic series.

Suzman reported the autopsy of a case of "Plummer-Vinson syndrome" in which death was due to traumatic rupture of the esophagus and subsequent infection. During life the red blood cells were 3.5 million, and the hemoglobin 30%. At post-mortem the tongue was found to be atrophic and the mucous membrane smooth and glistening. There was a constriction at the superior esophageal orifice, and it was felt that during life a mucosal band had been present. Microscopic examination of the spleen showed numerous, large, immature unrecognized cells in the pulp with occasional mitotic figures. The epithelium of the tongue and esophagus showed thinning and hyperkeratinization. Schnehle and Schmidt reported another case in which there was widespread atrophy of the mucous membranes of the tongue, esophagus, and stomach.

13. The Diagnosis of Iron Deficiency Anemias

The demonstration of an anemia of the hypochromic type which responds to iron is sufficient evidence of iron deficiency. The presence of hypochromic anemia alone, however, is not sufficient for the diagnosis of iron deficiency. Hemoglobin production is a complex process, and other factors may be lacking.

Hypochromic anemia, in which there is little or no response to iron, may be found in a number of conditions. It may be seen in chronic infections such as chronic osteomyelitis; in chronic nephritis, in lead poisoning, and in cancer. In these conditions, lack of response may be due to either the absence of iron deficiency, or to the inability of a toxic bone marrow to respond.

There is ordinarily no difficulty in differentiating iron deficiency anem-

ia from pernicious anemia if the various quantitative indices are carefully carried out, although the diagnostic trial of liver extract may be required.

It should be emphasized again that the diagnosis of hypochromic anemia in adults, especially males, should be the basis for a thorough investigation of the gastro-intestinal tract, in a search for sources of chronic blood loss.

14. The Treatment of Iron Deficiency Anemia

The value of iron in the treatment of anemias was recognized long before there was any rational basis for its use. It has been said that the Greeks recognized anemia, and that the treatment consisted in the drinking of water in which a sword had been allowed to rust. Sydenham, the great English physician, described the symptomatology of chlorosis in 1661, and wrote, "I order the patient to take, for thirty days, some remedy drawn from Mars (iron was Mars in the old pharmacopoeias).... the pallor disappears and once again the face is rosy and ruddy."

The rationale of iron therapy was obscured, however, in the first quarter of this century by the belief of Bunge, and Abderhalden that inorganic iron acted only as a "stimulant," and could not enter quantitatively into the formation of hemoglobin. This led to the use of minute quantities of inorganic iron and complex iron compounds.

Barkan, and Meulengracht were the first to break away from this view. They recognized that iron must be given in large doses to be effective. The basis for the use of iron in large dosage is to be found in iron balance studies, and in careful clinical observations, which have demonstrated the extremely low level of percentage utilization of iron.

Heath, Strauss and Castle found that the usual utilization of orally administered iron was a little over 3%, as compared with 96% utilization of parenterally administered iron. With minute doses of orally administered iron, utilization may be as high as 50% but the total gain in hemoglobin is so slight as to make these doses impractical.

There has been considerable discussion in the literature as to whether ferrous or ferric iron should be administered. Iron is present in the hemoglobin molecule in the ferrous state, and Witts and others have noted that weight for weight ferrous iron is more effective than ferric iron. However, Heath, Strauss, and Castle showed that the parenteral administration of ferric iron resulted in its quantitative return as hemoglobin, indicating that the body is capable of utilizing iron in any form, and that dosage differences are primarily related to differences in absorption.

The following table gives the daily amounts of iron in various forms regarded as necessary to produce a maximal effect in hypochromic anemia:

Substance	Dose	Fe content	Cost per month
Ferric ammonium citrate	90 grains	15 grains	$1.80
Ferrous carbonate (Blaud's pills)	60 grains	30 grains	1.08
Ferrum reductum	45 grains	45 grains	1.01
Ferrous sulphate	12 grains	5 grains	.36
Ferric ammonium citrate	1 cc of 10% sol. i.m.		
	3 grains	½ grain	7.50
Lextron	12 capsules	36 grains	9.36

In infants the oral administration of the 10% solution of ferric ammonium citrate is most suitable, and is given in a dosage of 1 cc per pound of body weight, in the milk.

Smaller doses than the above are often effective, but no case should be considered as "resistant" until maximal iron therapy has been tried.

The oral administration of iron has occasional undesirable effects. Iron in solution may stain the teeth, and taken on an empty stomach any form of iron in large doses may cause gastric irritation, vomiting, and diarrhoea. With small doses constipation is more common. Iron should be administered in divided doses immediately after meals. The smaller doses required with ferrous sulphate, and its low cost, make it the preparation of choice.

In rare cases these unpleasant side actions may force the use of iron parenterally. This is usually given in the form of a 10% solution of ferric ammonium citrate, in doses not to exceed 16 to 32 mgm of iron intramuscularly a day. Parenteral administration of iron is dangerous and reactions are common, consisting in local pain, palpitation, precordial pressure, and nausea. With more severe reactions, vomiting, tachycardia, and hyperpnoea may appear. Reactions usually subside within an hour.

Various compounds of iron and other substances have been exploited from time to time as "ideal" in the treatment of iron deficiency anemia, on the basis of certain experimental work on anemia.

It has been shown by Hart and Steenbock that copper is essential to hemoglobin formation in nutritional anemia of rats, and Josephs showed that copper plus small doses of iron was more effective in the hypochromic anemia of infants than small doses of iron alone. Murphy and Powers, and Keefer and Yang showed that whole liver promoted blood formation in hypochromic anemia when associated with hemorrhage, but whole liver is rarely effective in hypochromic anemia associated with anacidity. Whipple, Robscheit-Robbins, and Walden showed that the liver fraction precipitated by 70% alcohol had some effect in hypochromic anemia, but that the fraction precipitated by 95% alcohol, which was effective in pernicious anemia, had no effect.

While the above findings are of interest, they have no practical importance in the treatment of hypochromic anemia. The amounts of liver necessary to produce these effects are many times those that are combined with iron in the various proprietary remedies such as Lextron, and copper is a contaminant of almost every iron preparation. Rarely, the administration of liver extract may be of value, especially in those cases of hypochromia associated with macrocytosis, in which a coincident deficiency of the anti-pernicious anemia principle is suspected, or in those few cases in which maximal iron therapy has resulted in a less than maximal hemoglobin and red blood cell response.

Although the value of iron therapy is primarily related to hemoglobin

production, it is also productive of an increase in the reticulocyte percentage and an increase in the red blood cell count. This response has been used as an index of the effectiveness of iron therapy, and as a means of comparing the efficacy of various iron compounds. Heath has shown that with large doses of iron in severe hypochromic anemia, the increase in hemoglobin may be as great as 2-3% a day, after the initial lag preceding the reticulocyte response. With less severe anemias the rate of hemoglobin production is slower. In patients with hemoglobin values of 50% or less, the hemoglobin increase following maximal doses of iron will usually be about 35% in 30 days. It is to be noted that the presence of infection, nitrogen retention, or persistent blood loss will modify the response to iron. When the hemoglobin level is 20%, the reticulocytes usually reach a maximum of 8-16%, when 40%, from 4-12%, when 60%, from 2-6%. The increase begins in about 3 days after iron therapy is begun, and reaches the peak in 5-10 days. Since the red blood cell count is relatively higher at the beginning of therapy, it usually reaches normal before the hemoglobin, in spite of the more rapid increase in the latter. The red blood cell count may even rise above normal, either because the bone marrow is more responsive to hemoglobin depletion, or because the amount of bone marrow suddenly restored to normal activity is greater than normal.

With the rise in hemoglobin and red blood cells, the changes in size of the red blood cells previously described disappear.

Other features of hypochromic anemias are also affected by iron therapy. Splenomegaly is usually diminished; glossitis disappears, and new papillae may appear on the tongue. The brittle and concave finger-nails return to normal, and the whole clinical picture and emotional attitude of the patient are improved. Ability to secrete free hydrochloric acid occasionally returns, but only rarely. The effect on the menstrual flow is inconstant.

15. Adjuncts to Iron Therapy

Faulkner has shown that in certain individuals, without clinical scurvy, but in whom infection has interfered with vitamin C intake, that the daily administration of several ounces of orange juice or small amounts of cevitamic acid, will cause definite reticulocyte responses and improvement of the blood status when the anemia is of the hypochromic type.

Since the formation of red blood cells and hemoglobin requires protein as well as iron, it is obvious that an adequate protein intake is essential.

The administration of dilute hydrochloric acid may be of benefit in promoting digestion, and especially in the alleviation of the diarrhoea of achlorhydria. It is not necessary, however.

16. The Prevention of Iron Deficiency Anemia

The prevention of iron deficiency consists in the further spread of dietary information; in the prompt detection and removal of sources of chronic blood loss; and in the administration of prophylactic iron in adolescence and pregnancy.

Summary

1. Iron deficiency anemias result when increased demand for iron occurs in an individual whose iron stores are deficient.

2. Inadequate iron stores result from inadequate supply of iron, poor absorption, or both.

3. Inadequate supply of iron may occur in infancy as a result of poor endowment from an anemic mother.

4. Inadequate supply of iron may occur in later life because of faulty diet.

5. Poor absorption of iron is largely due to increased alkalinity of the gastro-intestinal tract (chiefly because of achlorhydria).

6. Poor absorption of iron may be due to other abnormalities of the gastro-intestinal tract, such as diarrhoea, or the sequelae of gastric surgery.

7. Copper and other elements may play a role in the absorption and utilization of iron, but actual deficiency in them in human anemia is doubtful.

8. Increased demand for iron occurs in infancy, in adolescence, in pregnancy, at the menopause, and as a result of chronic blood loss. With each of these periods of increased demand, a type of iron deficiency anemia is associated.

9. Increased demand for iron in infancy occurs as a result of rapid growth, and the iron deficiency anemia of infancy occurs equally in the two sexes.

10. Increased demand for iron in adolescence occurs as a result of rapid growth and menstruation, and chlorosis occurs almost entirely in girls.

11. Increased demand for iron in pregnancy occurs as a result of the demands of the fetus for iron.

12. Increased demand for iron around the time of the menopause is chiefly due to menorrhagia, and idiopathic hypochromic anemia occurs chiefly in women.

13. Increased demand for iron occurs as a result of chronic blood loss, chiefly as a result of bleeding from the gastro-intestinal tract.

14. Hypochromic anemia in an adult male is due to chronic blood loss, until proven otherwise.

15. Iron deficiency may be a feature of any anemia.

16. The pathology of iron deficiency anemia is uncertain. Atrophy of the mucous membranes of the gastro-intestinal tract has been observed. The bone marrow shows hyperplasia, of the normoblastic type.

17. The diagnosis of iron deficiency anemia rests on the demonstration of a hypochromic anemia which responds to iron.

18. Hypochromic anemia may occur without iron deficiency, as in chronic infections, nitrogen retention, and cancer, but the lack of response to iron is probably due to inability of the toxic bone marrow to respond.

19. The treatment of iron deficiency anemia is iron in large doses.

20. Ferrous sulphate is the preparation of choice.

21. Combinations of iron with copper or liver are no more effective than iron alone.

22. Liver extract intramuscularly may rarely be necessary, in addition to iron.

23. Adequate vitamin and protein intake are essential adjuncts.

24. The prevention of iron deficiency consists in the elimination of sources of chronic blood loss, and in the prophylactic use of iron during the periods of increased demand.

CASE REPORTS

1. Female, 21 years of age.

Admitted 10-28-36
Discharged 12-23-36.

History

The presenting complaints were weakness, fatigue, pallor, and edema.

Ten months prior to admission she had noted swelling of the eye-lids and ankles, which had been present intermittently since. Shortly following this she noted that she became fatigued and breathless on very little exertion.

This increased until she became unable to do housework. Her family noted that her face was becoming very pale. There had been a loss of 16 lbs. in weight. Because of these symptoms she had visited a physician who told her that she had "kidney trouble," and gave her medication which afforded no relief.

The past history had been uneventful. There was no history of pathological blood loss, and the patient considered her menstrual periods to be normal, an opinion which was justified by the details of her menstrual history. She felt that her appetite had always been good, and her diet adequate, but specific information on this point was not available, from the record.

The patient's mother had had eight pregnancies.

Physical Examination

The patient was an asthenic white female, aged 21. The skin and mucous membranes were extremely pale. Over the backs of the hands this pallor had a greenish cast. There was no icterus. There was no atrophy of the tongue. There was a soft, blowing systolic murmur all over the precordium. The blood pressure was 98/46, the rate 96, and the rhythm regular. The liver and spleen were not palpable. There was definite koilonychia. The neurological examination was negative. There was no edema. Proctoscopic examination to 26 cms. was negative except for small internal hemorrhoids.

Laboratory

The urine was negative. The hemoglobin was 27%. There were 2.9 million erythrocytes. The leucocytes were 9,100, with a differential of 62% neutrophiles, 28% lymphocytes, 7% monocytes, and 3% eosinophiles. The M.C.V. was 57, the M.C.H. was 18, and the M.C.H.C. was 27. The reticulocytes averaged about .8%. Examination of the stained smear showed microcytosis, marked hypochromasia, and slight poikilocytosis. Examination of the stools revealed small amounts of occult blood 4 times in 9 examinations. The blood creatinine was 1.2 mgms%. The icterus index was 5, and the urobilinogen in the feces averaged 28 mgms./day. Gastric analysis revealed free hydrochloric acid. X-ray examination of the stomach, duodenum, and colon was negative.

Course

In connection with a study of hemoglobin metabolism, this patient was given a sub-optimal dose of iron, amounting to only 3 grains of ferric ammonium citrate a day. Even with this dosage, however, she had a reticulocyte response of 3.5%, and the hemoglobin and RBC level slowly rose, so that at the time of her discharge the hemoglobin was 58%. At the time of discharge the patient was ordered to take iron in therapeutic dosage; and when seen in the medical dispensary at a later date, her hemoglobin was 80%.

Impression

It was felt that this patient had a chlorotic type of anemia, probably complicated by chronic blood loss from hemorrhoids.

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2. Female, 23 years of age.

Admitted 2-24-37
Discharged 5-7-37.

History

This patient was first seen in the obstetrical out-patient department where she came for examination relative to pregnancy. At that time she was found to be at term, and to have a severe anemia. There had been no symptoms referable to the anemia. Her face had been pale as long as she could remember. She stated that she had felt very well during pregnancy, and had experienced no unusual fatigue. There had been no history of pathological blood loss, and the menstrual history was normal. The patient stated that her appetite was good, and not unusual, but details of the dietary intake were not

available.

The patient's mother had had four pregnancies.

Physical Examination

The patient was a fairly well-nourished white female, aged 23. The skin and mucous membranes were quite pale. There was a discrete, papular, excoriated eruption over the face, trunk, abdomen, and legs, which was interpreted by the dermatological consultant as urticaria of pregnancy. The heart was not enlarged. There was a soft systolic murmur at the apex, and a loud, rough systolic murmur in the pulmonic area, which disappeared on pressure, and which was interpreted as a vascular murmur arising in a branch of the left internal mammary artery. The blood pressure was 124/72. The abdomen was enlarged to the size of a 38-40 week pregnancy. There was no edema.

Laboratory

The urine was negative. The hemoglobin was 26%. The erythrocytes were 2.5 million. The leucocytes were 12,200, with a differential of 68% neutrophiles, 27% lymphocytes, 3% monocytes, 1% eosinophiles, and 1% basophiles. The reticulocytes averaged 1.7%. The M.C.V. was 74, the M.C.H. was 17, and the M.C.H.C. was 14. The blood volume was 4.1 liters. The feces contained 75 mgm./day of urobilinogen. Gastric analysis revealed achlorhydria after histamine. Two examinations of the stools were negative for blood.

The blood of this patient's child was examined on the first day of life, and found to contain 109% hemoglobin and 6.5 erythrocytes.

Course

The patient went into spontaneous labor 9 days after admission and was delivered of a normal female infant. The blood loss was 50 cc. The puerperium was normal. Following delivery it was noted that the spleen was palpably enlarged. This patient was also a member of a group being studied from the standpoint of hemoglobin metabolism, and iron therapy was deferred in order to note the effect of the termination of pregnancy on blood formation. Following delivery the reticulocytes rose to an average of 2.2%, and one month later the hemoglobin was 44% and the erythrocytes were 3.8 million. She was then given iron in sub-optimal dosage, amounting to 3 grains of ferric ammonium citrate a day, following which the reticulocytes rose to 5.2% on the 16th day. At the time of discharge the hemoglobin was 59%, and the patient was then ordered to take iron in therapeutic dosage. She has not returned for further examination.

Impression

Severe iron deficiency anemia of pregnancy, possibly complicated by chlorosis.

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3. Female, 45 years of age.

Admitted 7-7-37
Discharged 7-22-37.

History

The presenting complaints were weakness, numbness and tingling of the hands and feet, intermittent abdominal pain, and sore tongue.

The patient stated that she had felt "run-down" and very tired for the past 15 years, following a premature birth with massive hemorrhage. She was able to work, however, until six months prior to her admission, when the fatigue and weakness increased, and she began to complain of abdominal pain. This appeared to be rather generalized, not radiating, and occasionally associated with nausea and vomiting. There was no relation to meals, particular kinds of food, and there was no food relief. There had never been any chills, fever, jaundice, or urinary symptoms. She stated that she was habitually constipated, and the attacks of pain appeared to have

some relation to exacerbations of constipation. Occasionally the attacks would be followed by a moderate diarrhoea. The patient also stated that she had moderate dyspnoea on exertion, and marked palpitation, which often interfered with sleep. The tongue had been sore at intervals in the past year. She complained of some difficulty in swallowing, which appeared at intervals. There had been occasional numbness and tingling of the hands and feet, but she had had no difficulty in walking. There was no history of melena, but the menstrual periods had always been rather profuse. In the past few months the periods had been prolonged, lasting 10-12 days. There had been 5 pregnancies. The patient felt that her appetite was fairly good and her dietary intake adequate, but stated that she did not care for meat.

Physical Examination

The patient was a white female, aged 45, who appeared much older. The hair was white, the eyes blue. The tongue was reddened and the lateral margins were atrophic. There was a marked pharyngeal reflex. The liver and spleen were not palpable. Examination of the pelvis was negative. The thumb-nails were flattened and brittle, but there was no true koilonychia. The neurological examination was negative.

Laboratory

The urine was negative. The hemoglobin was 54%, the erythrocytes 3.7 million. The leucocytes were 7,600, with a differential of 65% neutrophiles, 32% lymphocytes, 1% monocytes, and 2% eosinophiles. The M.C.V. was 100, the M.C.H. 24, and the M.C.H.C. 24. Examination of the stained smear showed marked anisocytosis, poikilocytosis, and hypochromasia. The reticulocytes averaged .6%. The icterus index was 3.6, and the urobilinogen in the stools was 104 mgms./day. Gastric analysis revealed achlorhydria after histamine. 6 examinations of the stools were negative for blood. X-ray examination of the gall-bladder, stomach, duodenum, and colon was negative. X-ray examination of the chest revealed an old fibroid pulmonary tuberculosis at the left apex.

Course

Three months prior to her admission to the hospital this patient had been sent to the medical dispensary with a diagnosis of gall-bladder disease. It was thought in the dispensary that she had pernicious anemia, and she was given a total of 60 cc. of liver extract intramuscularly without relief of her symptoms, or alteration in the blood picture. After admission she was given 90 grains of ferric ammonium citrate a day, and her reticulocytes rose to 7% on the 11th day. One month later the hemoglobin was 85% and the erythrocytes 4.3 million. She stated that her general health had been markedly improved.

Impression

Plummer-Vinson syndrome. Idiopathic hypochromic anemia of the macrocytic type.

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