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Idiopathic hypochromic anemia

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IDIOPATHIC HYPOCHROMIC ANEMIA

BY

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IDIOPATHIC HYPOCHROMIC ANEMIA

INTRODUCTION

In recent years many articles have been published concerning a new type of primary or idiopathic anemia. This disease, characterized by the presence, usually in middle-aged women, of pallor, weakness, atrophied tongue, brittle fingernails, achlorhydria and hypochromic anemia, responding readily to large doses of iron and tending to spontaneous relapse, has been described under numerous synonyms.

Among these may be mentioned simple achlorhydric anemia, Witts (33), Davis (4), and Haden (13); primary hypochromic anemia, Dameshek (5,6,7) and Waugh (30); the idiopathic hypochromemia of Mills (20,19); and chronic chlorosis, Mettier and Minot (17).

Wintrobe and Beebe (31), in a review of the literature, find the following names which also describe this same condition: achylic chloroanemia, achylic chlorosis, late chlorosis, chlorotic anemia, pseudo-pernicious anemia, hypochromic anemia with achlorhydria, idiopathic hypochromic anemia, essential hypochromic anemia, chronic hypochromic anemia and erythro-normoblastic anemia.

Idiopathic hypochromic anemia has been selected in this review because the greater number of articles describing the condition bear this name. The fundamental characteristics which are encountered in all variants of the clinical picture should be used. These seem to be the hypochromic nature of anemia and the absence of any of the accepted...
causes for this type of anemia. Achlorhydria, as will be pointed out, is not found in all cases and therefore this term should not be used in naming this condition. Likewise the term chlorotic should be avoided for it implies a relationship with the disease Chlorosis which is not generally accepted.

In contrast to hyperchromic anemia with achlorhydria, commonly called pernicious anemia, hypochromic anemia with achlorhydria has received comparatively little attention. Waugh (30) believes that it is due principally to three factors: 1. This type of anemia is so readily confused with other hypochromic anemias that often it is not recognized. Many physicians are satisfied to rule out pernicious anemia carefully and then to be content with the diagnosis of "secondary anemia" without further investigation or distinction. A smear is made, a blood count is done, no megalocytes are found, the color index is low, and at once all interest in the anemia disappears.(2).

This condition never reaches the severity of pernicious anemia, and is therefore more readily passed over. The patients do not look as ill as they really are. They show so favorable a picture on physical examination, except for the anemia, and they complain so little except of fatigue, lassitude and perhaps palpitation on exertion that one is inclined to consider them hypochondriac. Moreover, although the anemia is persistent, it rarely, if ever, increases to a sufficient degree to cause death of the patient. While this lack of a possible fatal outcome can not but lessen concern,
it in no way alters the economic importance of the condition (3). The disease has only recently been recognized as a disease entity.

The condition was first described as a disease entity by Faber in his address before the International Congress of Medicine in London in 1913. He drew attention to the fact that not only pernicious anemia, but a simple chlorotic type of anemia might occur, associated with gastric achylia. He described a case and pointed out that 15 of 207 uncomplicated cases of achylia showed percentages of hemoglobin below 50. At this time he considered that the achylia predisposed to the production of hemolytic toxins of bacterial origin in the intestine, which were the direct cause of the pernicious anemia. Later further statistics were published, and the theory arose that congenital predisposition is the deciding factor as to whether in achlorhydria, a hypochromic or hyperchromic type of anemia should arise. Weiner and Kaznelson (16) in 1926 reported the first description of bone marrow sections made at biopsies in these cases. These findings have been substantiated by Witts (33) and Dameshek (6).

Schneider and Cary (1928) found that of 51 cases of primary achlorhydria 7 had a color index higher than 1, and 7 had secondary anemia; of 42 cases of secondary achlorhydria 2 had a color index higher than 1 and 10 had a secondary anemia. Summarising their results, in 93 patients with achlorhydria there were 9 with pernicious anemia and 17 with secondary anemia.
Altschuller, in 1929, reported a similar case, reviewed the work of Faber, and drew the conclusion that the achlorhydria is not the preponderant or exclusive cause of the anemia, but rather the expression of an abnormal constitution in which this type of anemia may develop. According to his views, the real cause lies in a disturbance of the complex regulatory mechanism of hemopoiesis.

Watkins (29) (1929), in his classification of what he refers to as chromic idiopathic anemia, includes as his third group an anemia of middle-aged women, which agrees in many respects with the condition under discussion. He stated, that achlorhydria may or may not be present and did not consider this of primary importance in the disease picture.

Witts (32) in 1930 published an article on the relation of achlorhydria to anemia, called attention to this simple (hypo-chromic) form in contrast to pernicious anemia. He stated that in his experience it is even more common in patients with achlorhydria than pernicious anemia, and it is not often recognized. In his opinion, achlorhydria or at least marked hypochlorhydria is always present and plays a primary role in the pathogenesis of the condition, although the finer details of the mechanism of this development are still in doubt.

Waugh (30) (1931) in the course of several hundred complete morphologic examinations of the blood, encountered this condition on several occasions. At first he paid little attention to it, but as the finer diagnostic features of the blood became clearer, a prediction of achlorhydria was often
possible before gastric analysis was done. His interest became aroused and he published a series of cases describing it as a disease entity.

Since 1931 many reports have been published under a variety of names. Cases have been reported in which achlorhydria has not been present. Instances of hypochromic anemia associated with dysphagia and other cases of such anemia occurring during pregnancy have been recorded. The pathogenesis of the anemia has been discussed and its right to recognition as a disease entity. These discussions cover over 500 cases of this type of anemia.

ETIOLOGIC FEATURES

SEX. The almost exclusive occurrence of idiopathic hypochromic anemia in women (96 per cent) is an extraordinary feature of this disease. Only 26 cases have been recorded in men (35). In 5 of these the anemia developed some years after a gastric operation.

AGE. In review of 260 cases by Wintrobe (31) 60 per cent of the cases were encountered between the ages of 30 and 50, and 82 per cent between 20 and 50 years. The most striking feature is the marked decrease in the incidence of this type of anemia after 30 years of age. These ages represent the age of discovery and not the age at onset of the anemia. It is quite unusual for this anemia to commence in women after the menopause, (31). It has been suggested (30) that this type of anemia is never encountered after reproductive functions have ceased but this fact is disputed by
most authorities.

RACE. No cases of idiopathic hypochromic anemia have been reported among negroes. It has been suggested (31) that most of the publications have come from localities where few members of this race are found. Anemia is also less likely to be discovered in this race and the clinical picture more often may be obscured by associated infections. It is thus difficult to make a proper estimate of the occurrence of idiopathic hypochromic anemia in the negro race. It has been reported among Chinese patients. Most authors believe that there is no racial predisposition, nor does occupation seem to bear a causal relationship.

CONSTITUTIONAL TYPE. Witts (32) and Waugh (30) state that the majority of these patients are slender and asthenic. Wintrobe and Beebe (31) reporting a larger number of cases, believe that most were hyposthenic or sthenic in build. The patient often appears similar to the type encountered in pernicious anemia with light-colored eyes set widely apart, prematurely gray hair and wide costal angles.

FAMILIAL INCIDENCE. As in pernicious anemia, it is not unusual to find a family history of anemia in patients suffering from idiopathic hypochromic anemia. In several instances pernicious anemia has been noted in the male members of a family whereas the female members suffered from a "secondary" anemia. Although special inquiry for familial cases was not made in his cases, a family history of anemia was given by three of Witts' 50 patients (32). A family
history was discovered in 2 of 22 of Wintrobe's cases (31) in which inquiry was made.

Barrow (2), in reviewing the literature to determine the importance of the familial factor, came to the conclusion that it was not an uncommon occurrence to find this type of anemia associated with primary anemia in members of the same family. A family history of secondary anemia of undetermined type is occasionally found, but proved reported cases of achlorhydric anemia in more than one member of a family was rare. Barrow found no record of more than 2 cases in one generation.

Of possible importance from the point of view of etiology is the evidence of a familial form of achlorhydria although there is no known relationship between this and achlorhydric anemia. The specific hematopoietic hormone of normal gastric juice recently demonstrated by Castle which is absent in pernicious anemia was found to be present in some cases of achlorhydric anemia. Nearly all contributors to the subject, nevertheless advance the theory that the anemia is secondary to a gastric secretion deficiency which results in an interference with the maintenance of normal hematopoiesis. Barrow reported a case history of idiopathic hypochromic anemia with actual or presumptive evidence of the same type of anemia in the patient's five sisters and in her mother and her mother's sisters. There was nothing in the history or physical or laboratory findings of these individuals to suggest a common factor of etiological significance.
A second family was reported where there seemed to be a tendency to secondary anemia but where only one case was of the achlorhydric achromic type. If these cases were related etiologically he did not indicate what the etiological factor might be. Barrow concluded that this type of anemia was not uncommonly found in families in which there was evidence of primary or secondary anemia in other members of the same family.

HYGIENIC FACTORS. Although patients have been found in all classes of society, there is little doubt that poor hygienic surroundings contribute to the continuation and aggravation of the anemia. Wintrobe and Beebe (31) mention the frequency of the inadequate convalescence in the cases which commenced during pregnancy.

In a number of instances, the diet has been poor, although examination of case histories does not suggest that defective diet is responsible for the development of anemia in at least the majority of cases. Nevertheless, it is true that in not at least a few cases flatulence, dyspepsia and poor appetite have led to the taking of a poorly balanced, inadequate diet rich in carbohydrates and poor in hemoglobin-building foods, with the result that a vicious circle of anemia, poor diet and more severe anemia may have become established (31).

The underlying cause of idiopathic hypochromic anemia depends upon a number of factors, viz.;

(1) An achlorhydric constitution or the so-called
chronic abdominal invalid of Witts (32);

(2) Iron deficiency;
(3) Nutritional disturbances;
(4) Associated complicating conditions.

There is no doubt that the close association of achlorhydria with iron deficiency etiologically segregates the so-called achylic type from other disturbances, and that associated complicating conditions are of slighter consequence in the pathogenesis of this particular group. In the normochlorhydric group (or chlorosis) such complications are possibly more important, causing a greater iron demand and, therefore, producing an iron deficiency (23).

The more recent opinions regarding the pathogenesis of achlorhydric anemia would seem to incline to an iron deficiency, either as to intake or assimilation. In clinical experiments on achlorhydric patients with anemia Mettier and Minot (17) showed that iron is absorbed best when the reaction of the duodenum and jejunum is acid, and that large doses are necessary for optimal response.

Heath, Strauss and Castle (14,15,4) conclude that "a simple explanation is offered for the effectiveness of iron therapy in certain types of hypochromic anemia, namely, that these types of anemia are due to a deficiency chiefly of iron, preventing adequate hemoglobin formation".

A similar view is expressed by Dameshek (5,6,7) who believes that inadequate gastric digestion of iron may lead to faulty hemoglobin synthesis, and thus result in improper
maturation of the immature red elements of the bone marrow.

Davies (9,10) is of the opinion that iron deficiency arises in achlorhydrics from the ingestion over long periods of concentrated foods because of post prandial discomfort which occurs after the intake of protein foods and vegetables.

In discussing the cases of hypochromic anemia in pregnancy, Strauss (25) concludes that the added demands for hemoglobin during gestation result in an iron deficiency conditioned by gastric anacidity or low acidity.

Witts (32) associates the development of this anemia with the stress of the reproductive era in women who have some inherent inadequacy of the blood forming system, particularly in the synthesis of hemoglobin. In the induced achlorhydria of gastrectomized patients he believes diet, deficiency of iron, together with poor iron assimilation are important factors in the development of the anemia.

Bloomfield (3) is likewise inclined to believe that because of the predominance of this anemia in females, it is in some way linked to the menstrual function in individuals who have some erythropoietic deficiency, either primary or secondary to faulty diet.

It has been held by some that achlorhydric anemia is closely allied to pernicious anemia. Davies (9) described an intermediate group which falls between these two extremes and which responds to both liver and iron. A family has been reported which, through three generations, pernicious anemia or idiopathic anemia occurred in different members. One case
was followed from its inception as a hypochromic anemia to a fully developed pernicious anemia.

Dameshek (6) believes that hypochromic anemia may be an abnormal type of pernicious anemia.

The artificial production of achlorhydria through partial or total gastrectomy may throw additional light on the etiology of hypochromic anemia. Only 5 per cent of 50 cases of subtotal gastrectomy developed anemia (23). These have been hypochromic in type, and in no case has pernicious anemia been observed.

Idiopathic hypochromic anemia, therefore, may be regarded as a disturbance of iron metabolism which occurs chiefly in women during the period of sexual maturity (31).

SYMPTOMATOLOGY

Most of the patients give a history of a healthy childhood and adolescence. Careful questioning as to the anemia coming on at puberty or any evidence of a chlorotic diathesis at this time was generally answered by the statement that they were healthy with good color, (30). One finds, however, in the history of the latter years two outstanding features; (1) often indefinite stomach trouble with possibly an operation for ulcer and (2) always a persistent anemia and general weakness and lassitude. Many of the patients have had several children and have noted that during pregnancy they were particularly weak and compelled to spend the later months in bed. Some had an indefinite anemia during pregnancy, but careful questioning brings out the fact that the anemia
was probably present before the pregnancy began.

ONSET. The onset of idiopathic hypochromic anemia is characteristically insidious. The time at which the patient calls for the physician's help is of course influenced by many factors not concerned with the anemia itself, but it is unusual for the patient to present herself before the hemoglobin falls to 70 per cent and it is often much lower than this (31). The typical story is one of long continued ill-health. In a large series of cases reported by Wintrobe (31), the duration of symptoms varied from 2 to 22 years and averaged 8 years. In Witts' series (33) the average duration was 5 years. In as many as 25 per cent of cases the complaints had been present since early adult life. In an equal number the symptoms were dated from the time of onset of some infection or other debilitating disease, the patients stating that they had never regained their full strength and vigor since that time. In several cases some operation preceded the development of complaints. In 17 per cent of Wintrobe's cases (31) the onset of symptoms were definitely associated with pregnancy.

ENTRANCE COMPLAINTS. Complaints are characteristically vague and indefinite. All writers, however, stress the frequency with which weakness and ready fatigue and an ever-present feeling of "dead-tiredness" are the major complaints. Symptoms which are usually associated with anemia, such as weakness, shortness of breath, palpitation and choking sensations were the entrance complaints of a large percentage of the cases, 84 per cent of a large series (31). In 56 per cent
of this same series, the patients complained of symptoms referrable to the gastro-intestinal tract, while nervous and menstrual symptoms were somewhat less common. A few patients have no complaints, the anemia being discovered accidentally; they seem to become adjusted to a state of chronic ill-health.

**GASTRO-INTESTINAL SYSTEM.** Vague complaints referred to the gastro-intestinal tract are quite common in this disorder and include such symptoms as abdominal pain or distress, loss of appetite, flatulence, eructation, nausea, constipation and sometimes vomiting or diarrhoea. The diarrhoea resulting from the achlorhydria may become a major complaint.

As the consequence of these gastro-intestinal symptoms, many of these patients become extraordinarily careful about their choice of food and, finding that carbohydrates cause least distress, they partake of a diet which is least efficient in blood regeneration.

Sore tongue or sore mouth are frequently encountered. Symptoms referred to the tongue or mouth were noted in approximately 28 per cent of 238 cases (31). Glossitis rarely approaches the frequency and intensity observed in pernicious anemia. Occasionally the stomatitis is very severe. During the attacks the corners of the mouth become sore and cracked and on the mucous membrane of the cheeks small, pale blister-like lesions surrounded by a slight area of erythema may appear. The tongue at the time may become dull red. With relief of the anemia these symptoms disappear.

**DYSPHAGIA.** In the past few years there has been
described a clinical picture, most frequently spoken of as the Plummer-Vinson syndrome, which as more cases are observed and more detailed studies are made, comes more and more to resemble the disease here under discussion. The first cases were reported in 1919. The patients had suffered from dysphagia for years. In some the onset of symptoms was gradual, in others it was sudden but in neither group could any precipitating cause be determined. Occasionally a history of long continued anemia, dyspepsia or impaired general health preceded the onset of symptoms. Some patients considered dysphagia to be the initial symptom. The dysphagia was referred to the level of the larynx. All these patients found it necessary to masticate their food thoroughly and to swallow carefully and deliberately. Food tended to catch in the throat and frequently regurgitation followed attempts to wash the food down with liquids. The condition was more marked when the patients attempted to eat in front of strangers. Frequently the symptoms were continuous and present at every meal, although in a few cases remission took place for several months or even years. Often the condition was found to be worse when the patients were fatigued and improved after rest.

It was noted in a few cases that the mucous membranes of the mouth and throat were pale and waxy and the tongue was smooth and devoid of papillae. Fissures were present at the corners of the mouth in a number of instances. Direct examination of the pharynx revealed muscular spasm and in many cases taut membranous bands could be observed. The
rupture of these bands often brought relief.

Some thought that the dysphagia was not a hysterical manifestation although this was suggested by the occurrence of this anemia in women near the age of the menopause. It was thought that there was a disturbance in the nervous arc concerned with deglutition. It was suggested that the sensory portion of the nervous arc might have become hyperesthetic as the result of irritation by foreign bodies, fissures or inflammation with consequent hyperactivity of the motor fibers and the subsequent development of a "nerve-habit".

The common association of this spasmodic dysphagia with superficial glossitis was observed.

Some authors thought that a streptococcus was responsible; others suggested that a vicious circle might be responsible: debility and anemia associated with the climacteric, changes in the pharyngeal mucosa, dysphagia, limitation of food, accentuation of anemia and aggravation of all the symptoms. Witts argues that the anemia is not due to dysphagia. He has observed a case in which anemia of the same type reappeared without dysphagia after iron therapy had been discontinued.

The occurrence of this syndrome almost exclusively in women 30 to 50 years of age, the presence of glossitis and stomatitis, achlorhydria, splenomegaly, koilonychia, paresthesias without objective neurologic findings, as well as a microcytic hypochromic anemia which responds in a spectacular fashion to the administration of large doses of iron,
makes up a picture indistinguishable from idiopathic hypochromic anemia and differentiated only by the presence of dysphagia. Although in many instances all other symptoms have been reported as commencing after the onset of dysphagia, in numerous cases the anemia has preceded the difficulty in swallowing. The symptoms of anemia are frequently so vague and so unobtrusive that it is difficult to compare their onset with that of a symptom like dysphagia, and it is very probable that the onset of anemia preceded that of dysphagia in many more cases than has been supposed. The rapid improvement of these cases after administration of large doses of iron and the clinical picture makes one believe that the great majority of the so-called cases of the Plummer-Vinson syndrome are simply instances of idiopathic hypochromic anemia in which dysphagia is a prominent symptom (32,33,34).

Davies (9) refers to the occurrence of hematemesis without apparent cause in 3 of his cases. In view of the resemblance of this triad of anemia, splenomegaly, and hematemesis to Banti's syndrome, the recognition of this symptom is of special interest.

Hemorrhoids which bled occasionally were present in some of the cases reported by Wintrobe (19). It seemed clear from their histories, however, that the small amount of blood lost in this way could not account for the severe degree of anemia present.

CARDIO-RESPIRATORY SYSTEM. Dyspnea, palpitation, choking sensations and even edema may be encountered. In two
of Witts' (32) cases true anginal pain on exertion which disappeared on repair of the anemia, was present. These are all symptoms which have come to be associated with anemia of any type.

GENITO-URINARY SYSTEM. Menorrhagia of varying degrees which is not associated with organic pelvic disease, appears to be a symptom of some importance in these patients (31). In no reports has menorrhagia been considered to be more than, at most, a contributing factor in the development of the anemia. Very often this symptom has appeared many years after the onset of symptoms of anemia; in other cases it was not of such severity as would be expected to cause the degree of anemia present. In several cases reported by Wintrobe (31) hysterectomy was not followed, even after two or three years, by relief of the anemia, and this took place only after iron was given. It does not seem, therefore, that in these cases the uterine bleeding is the fundamental cause of the anemia. Haden (13) found that in his patients the abnormal bleeding was relieved when the blood returned to normal under iron therapy.

The patients sometimes bruise abnormally easily, especially when over 40 years of age. Menorrhagia from no well recognized cause and severe post partum hemorrhages are not rare (21). Amenorrhea occurs but apparently less often than menorrhagia. Nosebleeds without any very distinctive reason also may take place. It would appear as if in this disease hemorrhages might be dependent upon improper closure of the capillaries associated with an impoverished nutritional
state of the uterine and other tissues.

Irregularity of the menstrual flow and amenorrhea are less common symptoms.

NEUROLOGIC SYSTEM. Numbness and tingling in the limbs is not unusual in idiopathic hypochromic anemia. This symptom was noted in 17 per cent of 234 cases reviewed by Wintrobe (31); in his only personal cases these changes were present in 36 per cent. This complaint rarely attains the prominence encountered in pernicious anemia.

Objective neurologic findings are very rare in idiopathic hypochromic anemia. Only two cases in which the latter signs were found, have been reported. Wits (32) had a patient with hypochromic anemia, sore tongue and achlorhydria, who complained of increasing weakness of the legs without unsteadiness or paresthesiae. The abdominal reflexes and the right ankle jerk were absent. Dameshek's patient (6) complained of numbness and tingling of the fingers and toes and was found to have a positive Babinski on the left, absent right knee jerk, some hyperesthesia of the lower extremities but vibratory sensation and all other neurological signs were normal.

PHYSICAL EXAMINATION. The appearance of these patients is often quite characteristic. They do not look acutely ill, but appear tired and lifeless, and resigned to a state of chronic invalidism. Their fatigued, listless expression is characteristic. The pallor is striking. The appearance is waxy and bloodless in the more severe cases. The color is
usually white but not infrequently it is mixed with a light brownish coloring of skin. In such instances the conjunctivae will not be found icteric and the sclerae are blue or pearly white. The hair is often scantly, dry and brittle. The skin may be wrinkled to an unusual degree and is inelastic (31).

Equal numbers of the patients are thin, normal and obese (31). Mention has already been made of the frequent similarity in the body build of these patients to the constitutional type described in pernicious anemia.

Papillary atrophy of the tongue is common. The atrophy may be very striking, but usually it is less marked than in pernicious anemia, and may be limited to the edges of the tongue. In 238 cases collected by Wintrobe 39 per cent showed atrophy.

Slight cardiac enlargement may be encountered. Functional systolic murmurs are very common.

The abdominal wall is atonic and inelastic. The edge of the liver has been felt in a small proportion of cases (31). The spleen is palpable in about 50 per cent of cases (33 per cent in review of 255 cases). The size of the spleen is never very great. It has been found to extend at most to three finger-breadths below the costal margin. With successful treatment the spleen frequently recedes within the costal margin (32).

A peculiar flattening and concavity of the fingernails, koilonychia, is sometimes encountered in these patients. In extreme examples of this abnormality, the concavity is so
marked that a drop of water may be held on the nail. Usually the nails of two or three fingers are so affected, while the other nails appear dull and lustreless and are longitudinally striated and irregular.

Extreme changes in the nails are infrequent but it is common to find less marked modifications and a number of patients, when specifically questioned, state that their nails are brittle and break very readily. In a number of cases they have been sore. Witts observed that after successful treatment the nails regained their normal contour.

Koilonychia, while no doubt not specific to this disorder, is nevertheless a characteristic and interesting symptom. It is known that traces of iron are present in all living cells and are necessary for biologic oxidation (31). It has been suggested that the dystrophy of the nails is the result of a poor supply of iron to the germinative cells of the nail root.

Vaisey (27) described a case of Acne Rosacea accompanying this type of anemia. The interest of this case lies in the fact that Acne Rosacea has long been known to be associated with some form of alimentary disturbance. He believes that the study of this case indicates a common etiological factor, since in one patient there occurred two conditions - an anemia and Acne Rosacea - both known to be associated with gastric hypochlorhydria. These conditions both improved on treatment. Vaisey also described thinning of the hair as a finding and explained it on the basis of modification of the
horn cells, the same factor being responsible as for the changes in nails.

COMPLICATING OR ASSOCIATED CONDITIONS. In approximately 30 to 40 per cent of cases of idiopathic hypochromic anemia, some associated or complicating disorder has been present. Thus 11 of Dameshek's 25 cases were complicated; 6 by recent pregnancy, 2 by extensive operations on the stomach, and one by dysphagia, one by myxedema and one by beef-tape-worm infestation. Among 25 cases of Wintrobe the following conditions were found in one case each: arthritis, rheumatic heart disease, chronic cholecystitis, syphilis, uveitis, dysphagia, and gastro-enterostomy. The relation of dysphagia to idiopathic hypochromic anemia has already been discussed. The significance of repeated pregnancies and of extensive gastric operations will be considered in a later section. That some of the other complications above mentioned aggravate the anemia can hardly be doubted; that they are solely responsible for it, seems highly improbable. Although they may be removed the anemia persists and, even when the anemia has subsequently been relieved by rion therapy, it often returns when iron is discontinued.

ABNORMALITY OF GASTRO-INTESTINAL FUNCTION

A great deal of discussion may be found in the literature concerning the relation of the achlorhydria to this type of anemia.

As previously discussed many consider the achlorhydria or decreased amount of hydrochloric acid to be primarily
Achlorhydria persisting in spite of injection of histamine ("absolute achlorhydria") is observed commonly. This achlorhydria usually persists after improvement of the blood. In other cases the achlorhydria is "relative" in that acid is secreted only following stimulus such as given by histamine. Some cases are found where hydrochloric acid is found without a special stimulus but in diminished quantities. Minot (21) makes the statement that the more profound the achlorhydria the severer the case.

Rapid emptying of the stomach accompanies achlorhydria, and it has been suggested that the more quickly the stomach empties, the more likely is the anemia to occur.

Idiopathic hypochromic anemia is not uncommon after gastrectomy and the syndrome may occur following gastro-enterostomy with the development of hypochlorhydria. Castle (4) has shown that patients with idiopathic hypochromic anemia, in spite of "complete" achlorhydria, do not lack the gastric factor which is wanting in pernicious anemia. Many speculations are made concerning the mechanism by which the lack, or decreased secretion, of gastric hydrochloric acid or some associated abnormality favors the development of anemia and probably iron deficiency. One way that the achlorhydria is explained (17) is that the lack of hydrochloric acid in the stomach could lead to a relative increase in the pH in the upper intestine where iron is especially absorbed, which would not favor the best assimilation of iron.
for it is absorbed better from an acid than an alkaline or neutral buffered medium. Long-continued difficulty in obtaining iron for the body and other factors necessary for hemoglobin synthesis could lead to deficiency of such substances and thus anemia. Mettier and Minot (17) have shown that the response of the bone marrow to a given small amount of iron is better when the contents of the upper intestine are rendered acid, rather than alkaline, and maintained as such for some time by "buffered media". The administration of diluted hydrochloric acid in customary therapeutic ways will not enhance the effectiveness of iron or relieve anemia, for it only very temporarily can increase the acidity of the duodenal contents. This acid may give patients some relief from their gastro-intestinal symptoms although occasionally it seems to distress rather than alleviate them (21).

Davis (9) found on examination of the gastric secretion of idiopathic hypochromic anemia the excessive secretion of mucus and decreased secretion of pepsin; and in a certain number of cases the decrease of pH upon injection of histamine. In contrast to these findings, Davies noted in the gastric secretion of cases of pernicious anemia, no mucus, great diminution of pepsin secretion, and no change in the volume or pH after histamine stimulation.

It is thus clear that in idiopathic hypochromic anemia the disturbance in gastric secretion is not as grave as is found in pernicious anemia (31). As more cases are observed and the clinical characteristics of this anemia be-
come more clearly defined, it seems that achlorhydria must not be made too rigid a criterion for differentiation, and it becomes apparent that a few patients without achlorhydria may be encountered whose symptoms, blood findings, response to treatment, and tendency to relapse when therapy is discontinued, make up a clinical picture indistinguishable from idiopathic hypochromic anemia (31).

Wintrobe, in classifying cases with this type of anemia, in which gastric analyses were available, in 334 cases found that the cases could be subdivided on the basis of gastric secretion into four classes:

1. A group in which no free hydrochloric acid was secreted even after histamine stimulation. This was noted in 60 per cent of the cases;

2. Patients who secreted low or normal amounts of free hydrochloric acid after histamine stimulation although the Ewald meal had been ineffective in eliciting acid (23 per cent);

3. Cases of hypochlorhydria (Ewald) (8.5 per cent);

4. Cases in which the secretion of hydrochloric acid seemed to be normal (8.5 per cent).

Mills (20) believes that whatever may be the secretory defects associated with achlorhydria, it seems certain that the individual with a deficiency or absence of free hydrochloric acid in his gastric contents is even more likely to develop a hemoglobin deficiency anemia than he is to develop anemia of the Addisonian type.
THE BLOOD

There is a marked reduction in hemoglobin together with only a slight or moderate reduction in the red blood cell count. The color index is thus markedly reduced and the red blood cells show marked hypochromia. The erythrocytes are also markedly reduced in size, (microcytosis), the average red blood cell diameter being well below 7 microns.

The most common red blood cell count is between 3,500,000 and 4,000,000. Wintrobe and Beebe (31) encountered figures as high as 5,860,000 with markedly reduced hemoglobin. In 90 per cent of Wintrobe's series the red blood cells numbered between 3,000,000 and 5,150,000.

Waugh (30) states that the hemoglobin falls in the greater majority between 30 to 60 per cent. Wintrobe says (31) that in 74 per cent of his series the hemoglobin ranged between 41 to 70 per cent, 41 to 35 per cent most commonly encountered.

The volume of packed red cells was 23 to 35 cc. in 80 per cent of the cases. The cells are pale and stain poorly and irregularly. Morphologically, they vary considerably in size, with occasional forms larger than normal and the greater majority smaller. Poikilocytosis and polychromatophilia vary from slight to moderate. Elliptical erythrocytes are found; these have been mistaken for sickle cells, but true sickling does not occur in fresh preparations of the blood (31). Punctate basophilia has not been observed, and nucleated red cells do not occur except in severe possibly
complicated cases.

Reticulocytes may be normal, or somewhat increased in number. Occasionally small nucleated red cells (microblasts) or normoblasts are seen (31).

The extreme microcytosis and hypochromia are readily demonstrated by calculation of the mean volume and hemoglobin content of the erythrocytes. In the cases examined by Wintrobe the mean corpuscular volume averaged 65 c. µ and in 75 per cent of the patients this ranged between 55 and 74 c. u.

The mean corpuscular hemoglobin is likewise greatly reduced. This constant ranged between 15 and 21 µµ in 70 per cent of the cases and averaged 18 µu. Unlike the majority of anemias, the mean corpuscular hemoglobin in this type of anemia is reduced even more than the mean corpuscular volume (31).

Similar information may be derived by the calculation of the indexes. The volume index is reduced below normal (0.65 to 1.07, average 0.76), the color index even more markedly (0.42 to 0.81, average 0.62) and the saturation index is likewise found to be low (0.64 to 1.00, average 0.80) (31).

The reduction in the mean volume and hemoglobin concentration of the red cells is of considerable assistance in differentiating this from other types of anemia. In pernicious and in other macrocytic anemias the mean corpuscular volume is greater than normal and the mean corpuscular hemoglobin concentration is usually normal. In anemias due to blood destruction such as those caused by the malaria parasite and in a-
plastic anemias there is no significant alteration in the mean volume or hemoglobin content of the erythrocytes. In the anemias associated with the various infections and toxic processes relatively slight microcytosis and only a slight reduction in mean corpuscular hemoglobin is encountered. The very marked microcytosis and hypochromia above described have been found only in idiopathic hypochromic anemia, in the anemia resulting from chronic blood loss, in hookworm disease, and in chlorosis.

In some cases increased resistance of the erythrocytes may be noted by the macroscopic fragility test, but Waugh, using a microscopic technique, has found quite regularly an increased resistance in the lower salt concentrations and increased fragility in the higher concentrations (30).

No evidence of increased blood destruction is to be found. The icterus index is normal or more commonly it is below normal. Urobilin is present in normal or reduced quantities in the urine.

In typical cases there are from 4,000 to 5,000 white blood cells per cubic millimeter: a moderate leukopenia. This is due primarily to a definite reduction in neutrophilic polymorphonuclears (30). Haden (13) and Wintrobe (31), however, state that no appreciable change takes place in the white count.

Waugh (30) says that the monocytes are also actually reduced in number, although their percentage may be slightly increased. There is often a relative, but never an absolute,
lymphocytosis, and these forms may also be reduced in number. In many cases of hypochromic anemia the mast cells may be noticeably increased and occasionally there is a slight eosinophilia (30). The polymorphonuclears do not exhibit toxic changes, but there is often an increase in lobation of the nuclei, that is, a shifting of the index of nuclear segmentation to the right as in pernicious anemia. Minute forms, such as myelocytes, are but rarely seen in typical cases.

The platelets are somewhat reduced in number, though low figures suggesting an approaching hemorrhagic diathesis were not observed (38).

There is no prolongation of the bleeding time. As regards to coagulation, fibrin formation appears to occur more rapidly than normally in the majority of cases, and congealing of the blood both without and in the presence of added calcium chloride tends to be somewhat shortened. Retraction of the clot occurs promptly and to a marked degree.

In severe cases, as occasionally occurring in women during pregnancy, the foregoing picture may be somewhat altered. The anemia is more marked and nucleated red cells and myelocytes appear, but the blood picture as a whole maintains the same essential characteristics.

PATHOLOGY

Kaznelson (1926) first reported the changes occurring in the bone marrow in this type of anemia. He examined marrow obtained from the sternum at biopsy. One patient was re-examined five months later, when a remission had been produced by
treatment with iron. Kaznelson found an excessive increase in erythroblasts which in all cases were exclusively normoblasts. Megaloblasts and erythrogonia could not be found. The number of normoblasts fluctuated between 30 and 47 per cent of the total cells, whereas in normal subjects the value is about 20 per cent. In the case which was examined a second time he observed a decrease of the normoblasts from 47.4 to 32 per cent. He says in comment:

"This normoblastosis is really a surprising thing. There is no sign of hemolysis. One might expect, therefore, to find that the anemia was due to hypoplasia of the erythroblastic apparatus, and that it was analogous to the anemia of chronic infection, which has been shown to be due to hypoplasia of the erythroblastic apparatus of the bone marrow. The fact that, in spite of persistent anemia, the number of normoblasts in the marrow remains high, can only be explained by a disturbance in the maturation of normoblasts into erythrocytes, whilst the new formation of erythroblasts progresses normally. There is in consequence an accumulation of normoblasts in the bone marrow in the florid stage of the disease, and a decrease in their numbers with improvement in the blood picture. In this form of anemia, then disturbance in the maturation of the normoblasts is apparently the factor which leads to a diminution in the erythrocytes in the blood, for the destruction of erythrocytes cannot fall below a certain level."

Mills (20) summarized the morbid anatomical changes
in idiopathic hypochromic anemia by stating that the most striking and constant changes are hyperplasia of the erythroid tissue of the bone marrow. He found no constant change in the other organs. He found the spleen enlarged sometimes, and the available evidence suggested that this enlargement was a pure splenic hypertrophy without histological abnormality.

There is little information from which conclusions may be drawn concerning the state of the bone marrow in idiopathic hypochromic anemia. The sternal marrow is known to be the last to become hypoplastic and, therefore, whether or not the findings reported at sternal biopsy correctly indicate the general state of the bone marrow (31). However, the finding of polychromatophilia and an increased number of reticulocytes in a number of cases, as well as the quick response to iron therapy, indicates that in many instances at least the bone marrow is very active and only awaits a supply of iron in order to replace normal red cells in the blood stream.

In a case which had been characterized by dysphagia, hyperkeratinization of the epithelium with areas of desquamation and atrophic degeneration of the underlying muscle tissue throughout the tongue, hypopharynx and esophagus the intermuscular nerve plexus revealed no abnormality. The condition was not considered to be inflammatory. Atrophy of the mucosa of the stomach and intestines has also been reported. Extreme anemia of the brain and internal organs, fatty de-
generation of the liver and kidneys, pulmonary edema, ecchymoses in the small and large bowel, a firm, enlarged spleen, and circumscribed round cell infiltration in the liver and kidneys, as well as red bone marrow in the humerus were reported by various authors.

DIAGNOSIS

Idiopathic hypochromic anemia is the commonest cause of obscure anemia in middle-aged women (32). A fractional test meal is necessary to complete the diagnosis. Diseases which produce a secondary anemia must be excluded. Malignant disease often presents itself as an obscure anemia and must be considered; they are common at this age and give rise to the same symptoms of dysphagia and anemia. The occult blood test should always be done to exclude the possibility of a malignancy. Alimentary bleeding from other sources, such as hemorrhoids, may be associated with achlorhydria. Many of these patients are treated for hemorrhoids without any benefit to the anemia. It is more common for anemia to be erroneously attributed to hemorrhoids than for hemorrhoids to be overlooked. Menorrhagia is often associated with simple achlorhydric anemia. Pelvic abnormalities must naturally be looked for and corrected, but in most cases the menorrhagia is secondary to the anemia and not primary (32). Oral sepsis is an uncommon cause of anemia and should be considered a satisfactory explanation unless other signs of septic absorption are present.

Many cases of pernicious anemia with low color index
are instances of idiopathic hypochromic anemia. Many symptoms are common to both types of anemia but the lack of evidence of increased blood destruction both on physical and laboratory examination, the absence of objective neurologic signs and the microcytic, hypochromic nature of the anemia as distinguished from the macrocytic anemia so characteristic of pernicious anemia should make differentiation simple (30).

The gastro-intestinal complaints encountered in idiopathic hypochromic anemia may lead to some confusion in diagnosis and in not a few instances they have led to performance of unnecessary operations. As distinguished from peptic ulcer, pain is unusual and never periodic; unlike malignancy, the illness is of longer duration, dyspeptic symptoms are not so pronounced, weight loss is relatively slight, and the appearance is not so cachectic (31).

Great difficulty may be experienced in differentiating cases of idiopathic hypochromic anemia with splenomegaly from cases of Banti's disease. Achlorhydria, glossitis, secondary anemia and leucopenia may occur in both. In idiopathic hypochromic anemia there is no history of jaundice, haematemesis or ascites. There is no pigmentation. Koilonychia may be present, whereas in Banti's disease there may be slight clubbing. The spleen is not greatly enlarged and may only just be palpable. The levulose tolerance test is normal and Van den Bergh's reaction likewise. The anemia responds to iron and the spleen recedes beneath the costal margin. Neurasthenia and psychoneurosis are common diagnoses in cases of idiopathic
hypochromic anemia (32, 31). These patients are often nervous and difficult, but in many cases the anemia is a contributing factor.

Post-hemorrhagic conditions with poor regenerative ability on the part of the hematopoietic system may give a similar blood picture: however, demonstration of the loss of blood completely fails and the maintenance of such a constant level of anemia is against such a conclusion (30).

Similarly such chronic toxic states as tuberculosis or nephritis often show severe cases of hypochromic anemia with poor regenerative ability: the bone marrow is hypoplastic and the body does not appear to respond to the deficiency in blood. There seems to be no evidence that such a primary condition plays a role in this disease (30). Occult tuberculosis, heart disease, infective endocarditis, myxedema, rheumatism, pyelitis, aplastic anemia, leukemia and colitis are some of the diagnoses which have been made in these cases. These conditions should be differentiated without difficulty.

TREATMENT

In contradistinction to pernicious anemia, liver extract and desiccated hogs' stomach are valueless in the treatment of idiopathic hypochromic anemia. Likewise there is no evidence that whole liver possesses any value that may be compared with that of iron, and fetal calves' liver has likewise had little influence (31).

The beneficial effects of large doses of iron in the treatment of idiopathic hypochromic anemia is now well
recognized. Small doses and injections are useless (42). The response to the administration of iron is so consistently observed that, if this does not become manifest within three weeks after treatment has been instituted, the diagnosis may well be questioned (19). There is almost immediate improvement in the well-being of the patient, and a gain in appetite and in strength. The normal color gradually returns, numerous vague symptoms as well as more definite complaints disappear and even such symptoms as menorrhagia may be completely relieved. However, it must be stated that symptomatic relief, while definite in all cases, is not always complete. What role psychoneurotic factors play in the continuation of some complaints is difficult to estimate but there can be no doubt that these play a large part, for the temperament of the patients frequently, as the result of long-continued ill-health, becomes nervous and difficult (31).

The presence of infections may materially delay the action of iron. Menorrhagia may be a very troublesome complication. In certain instances, as soon as the hemoglobin has been raised by iron to about 70 per cent, a previous amenorrhoea gives place to menorrhagia. Omission of iron, rest in bed, calcium gluconate orally, usually arrest this condition and the periods become normal in amount and duration. When the menorrhagia is intractable, it is unwise to await a natural menopause. Treatment by X-ray or subtotal hysterectomy should be recommended early.

The preparations most commonly used in this country
have been ferric and ammonium citrate, reduced iron and the pills of ferrous carbonate (Blaud's). The latter medication, so commonly used in the past, has to some extent been displaced in favor of the other preparations. Recently, the use of ferrous rather than ferric compounds of iron has been advocated.

Dameshek (47) studied 65 patients to compare the therapeutic effects of several iron compounds. The following drugs were used: ferric ammonium citrate, reduced iron, ferrous glutamate, ferrous chloride and ferrous glutamate. In addition two patients were given large amounts of beef blood by mouth.

The patients were carefully studied from various standpoints. The percentage of hemoglobin was estimated by the Sahli method using apparatus calibrated against the Van Slyke-Neill method for determining the oxygen capacity of the blood. The Sahli standard of 100 per cent hemoglobin equivalent to 15.4 gm. of hemoglobin was used. Red blood cell and white blood cell counts were determined in the ordinary way, Bureau of Standard pipettes being used, daily reticulocyte counts also being made. Counts of the blood platelets were frequently made simultaneously with those of the reticulocytes, utilizing the same method. Blood smears stained with Wright's stain were examined at frequent intervals. Gastric analysis was performed on all but a few of the patients. Either histamine 0.5 to 0.7 mg. was injected subcutaneously as the primary procedure, or an alcohol meal
(7 per cent, 50 cc. of alcohol) was given, followed by histamine in the presence of achlorhydria. Several experiments were performed in which the effects of an iron preparation upon the secretion of free hydrochloric acid was determined.

The following results were obtained:

(1) Taste and Gastro-Intestinal Reaction to the Iron Preparation. Ferric ammonium citrate has an unpleasantly astringent taste when taken in water, although this is moderately well masked in milk. Reduced iron was never given except in capsules so that its taste was not a factor. Ferrous glutamate was found to have an unpleasant metallic taste. Mixing with orange juice slightly masked this taste, but a disagreeable after-taste was frequently present. It was finally given in capsules, either alone or in combination with ferrous chloride. The latter drug is extremely unpleasant to the taste, whether given in water, milk or other liquid and it was found necessary to dispense it in capsules.

Nausea, distress and vomiting, probably due to gastric irritation, occurred with ferric ammonium citrate, reduced iron and ferrous chloride; in greatest degree with ferrous chloride, in least degree with reduced iron. Diarrhea was encountered in 38 per cent of the cases treated with ferric ammonium citrate. When the dosage was diminished and then gradually increased, diarrhea did not ordinarily occur. Diarrhea occurred in about 20 per cent of the patients given reduced iron, and in about 15 per cent of those given ferrous
glutamate-ferrous chloride. No gastro-intestinal reactions were encountered in the few patients given chocolate-coated pills, usually 12 tablets per day, of the ferrous glutamate-ferrous chloride compound.

(2) Reticulocytes. Most of the cases treated with ferric ammonium citrate and all the cases treated with ferrous glutamate-ferrous chloride were studied for reticulocyte percentages. Reduced iron was not studied in this fashion.

The percentage of reticulocytes usually began to increase on the second or third day, the peak of reticulocyte response usually occurring on the seventh to tenth day. The reticulocyte "peaks" frequently tended to recur for several days, giving the curve a more flattened appearance than that seen in pernicious anemia following effective therapy. The maximum percentage of reticulocytes obtained varied (1) with the extent in diminution of hemoglobin and (2) with the dosage of iron given. The highest reticulocyte counts were obtained in those patients who, presenting very low hemoglobin readings, were given maximal doses of an iron preparation. It was noted that if an inadequate dosage of an iron preparation was first given, followed by a larger dosage, a secondary rise in reticulocytes took place. As a rule, at the end of 14 to 20 days, the reticulocytes had assumed a normal level (0 to 0.3 %).

(3) Hemoglobin. Usually there was definite rise in percentage of hemoglobin within one week after institution of treatment. In certain cases definite rise did not occur
until the second week. The rapidity of rise in hemoglobin depends on (1) the extent in diminution of hemoglobin before treatment; (2) the dosage of iron given; (3) the type of preparation used; and (4) the individual patient. With an optimal dosage in a patient whose hemoglobin was at a relatively low level (20 to 40 per cent) there was usually an average weekly rise in hemoglobin of at least 7 per cent, a daily rise of about 1 per cent. In general, the higher the initial level of hemoglobin percentage, the less striking was the daily rise in hemoglobin. The weekly rise in hemoglobin was usually greatest during the first three weeks of treatment, gradually becoming diminished as more normal levels were reached. Ordinarily, at the end of sixty days the hemoglobin percentage was at about normal limits (80 per cent), irrespective of the initial level of hemoglobin.

The accompanying table compares the average daily rise in hemoglobin percentage and average daily dosage in available iron for the various preparations used. Taken from the work of Dameshek (5,6,7). Because of the variations in the average initial hemoglobin percentages for the different preparations used, these have all been correlated to an arbitrary level of 43 per cent (the average initial percentage of hemoglobin in the ferric ammonium citrate series).
Average Daily Rise in Hemoglobin (%)

<table>
<thead>
<tr>
<th>Reduced iron</th>
<th>0.65</th>
<th>3000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous glutamate-</td>
<td>0.77</td>
<td>900</td>
</tr>
<tr>
<td>ferrous chloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous glutamate</td>
<td>0.84</td>
<td>1000</td>
</tr>
<tr>
<td>Ferric ammonium citrate</td>
<td>0.84</td>
<td>1000</td>
</tr>
</tbody>
</table>

Optimal Dosage (mgs. of iron)

In about 25 per cent of Dameshek's cases the hemoglobin remained "fixed" at a level between 50 to 60 per cent despite the administration of large doses of iron. This was ordinarily remedied by adding to the regular iron dosage small amounts of copper sulphate (0.005 gm. t.i.d.) or cuprous glutamate. If, however, copper was added and iron discontinued, there was no continued rise in hemoglobin.

Mills (19) used copper with iron in treating this type of anemia. He used a capsule made to contain Blaud's mass, copper sulphate, and phenolphthalein. Three capsules were prescribed daily. The phenolphthalein was added to prevent the constipating effect of the iron but proved too laxative. It was later replaced with cascara. Several of his cases showed improvement when taking iron with calf liver. He explained this by the beneficial effect due to the copper content of the liver which is considerable, 145 mg. per kilo of fresh liver according to a recent analysis.

Any explanation as to why copper is of such value
when combined with iron in the treatment of these cases is largely speculative (19). It may be a catalyst as Wadell and his coworkers suggest. Certain of its salts are known to be good catalysts in vitro and recent observations on the oxygen-combining power of dogs' blood after heavy copper feedings suggest that it may have this same catalytic action in the circulating blood.

When the percentage of hemoglobin reaches normal figures Dameshek (7) suggests that the dosage of iron be reduced to about one-third or one-sixth of its original amount. This dosage was ordinarily found sufficient to maintain the patient at a constant level of hemoglobin. If the dosage of iron was entirely discontinued, the percentage of hemoglobin gradually became diminished.

(4) Red Blood Cells. In general the rise in red blood cells is definite and parallels the rise in percentage of hemoglobin (7). The rapidity of rise depends to a great extent upon the original level of the erythrocyte count. The red blood cells showed, during treatment with iron, gradual diminution in achromia with parallel diminution in the extent of poikilocytosis and anisocytosis.

(5) White Blood Cells, and Blood Platelets. Following successful treatment with iron, the white blood cells usually increased, the rise being due to an increase in polymorphonuclear cells. During this rise, the percentage of immature polymorphonuclear cells ("band" forms) frequently became increased up to 10 per cent.
(6) Clinical Affects. Approximately four to seven days after institution of iron therapy the patient usually develops a marked appetite and begins to feel stronger. With continuance of iron treatment, striking improvement may be noted from week to week. The symptoms of weakness, fatigue, dyspnea, palpitation, anorexia, dysphagia, etc. gradually disappear. Along with these symptoms, the objective signs of pallor, smooth tongue, brittle spooned finger nails, dry skin, etc. gradually diminish. The most striking findings are noted in the tongue which gradually develops a coat and new papillae. The latter at times regenerate in islands (7). The brittle, flattened, spooned finger nails improve more slowly, possibly a year, they regain their normal lustre, lose their brittleness, and become normally rounded (31). The skin becomes less wrinkled and more firm and the hair more lustrous. There is usually marked gain in weight, one patient increasing in weight from 121 to 162 pounds in a period of six months.

Various reasons have been cited for the difference in efficacy of the many iron preparations. Among these may be mentioned (1) differences in solubility, (2) difference between ferrous and ferric iron, (3) difference between organic and inorganic iron.

Wintrobe (31) found that some cases developed a polycythemia after treatment. Some increased to six million and more under influence of iron therapy. This polycythemia was, however, only temporary although it persisted for a
month or two. He found that the red cell count may be above normal even when the hemoglobin reaches normal values before the mean corpuscular volume and the mean corpuscular hemoglobin concentration. Thus the red cell count is not a safe guide in estimating the need for further treatment and even the hemoglobin is not altogether reliable.

Under the influence of adequate iron therapy, polychromatophilic erythrocytes may appear, and an ever increasing number of normal, orthochromatic red cells is found (31).

Wintrobe found that the average weekly gain estimated on the basis of the entire period of intensive treatment is 0.35 to 0.050 grams hemoglobin. On the basis of this value it is possible to make a rough estimate of the length of time required for intensive treatment in a given case.

Disorders contributing to the ill-health of the patient must be treated. However, unless the need is urgent, measures which tax the strength of the patient should be delayed until improvement in the anemia has taken place, (19). This particularly applies to operative measures for the treatment of such conditions as bleeding hemorrhoids and pelvic disease. Not only is the operative risk lessened in this way, but frequently the bleeding may be found to have diminished or abated after treatment of the anemia.

Mettier, Kellogg and Rinehard (17) studied the relationship of diet and nutrition to this type of anemia. They selected a group of cases which showed a diet deficient in the amounts of meats, fruits and green vegetables consumed.
A series of determinations of erythrocytes and hemoglobin was made on a group of patients who were fed a diet rich in iron prior to the administration of large doses of iron. The diet used in the experiment as an "iron-rich" diet was considered to be adequate in all dietary factors and to contain a large amount of organic iron.

The patients who partook of this diet rich in iron showed no significant change in their hemoglobin and no change was noted until large amounts of iron and ammonium citrate were given. They concluded from this that a diet regarded as fully adequate in content of iron is not alone sufficient to restore the blood in these anemia patients.

They also investigated the part played by the achlorhydria or hypochlorhydria in producing the anemia or in preventing its relief by adequate amounts of iron in the diet.

They fed patients a predigested meal consisting of eggs, spinach, lean beef protein, commercial pepsin and hydrochloric acid digested in an incubator at 37 degrees C. for 6 hours. The patients responded favorably to this treatment not unlike those given adequate therapy with iron. They concluded from these studies that chronic idiopathic hypochromic anemia is one presumably due to a deficiency of iron wherein gastric dysfunction leads to failure in utilization of organic (dietary) iron.

Heath (14) followed cases over long periods of time to determine if possible the dose necessary to maintain the hemoglobin at the proper level. He finds that patients with
mild cases of idiopathic hypochromic anemia will sustain their blood level while taking an adequate diet, but when an additional cause for anemia occurs, such as a chronic or an acute blood loss, a considerable degree of anemia may be produced which would not occur in a normal person. He attributes this to the small reserve hemoglobin-building substances in the patient with idiopathic hypochromic anemia, even at a time when the hemoglobin level is nearly normal. On the other hand, certain patients, even while taking a proper diet and one rich in iron-containing foods and protein and not suffering from a chronic blood loss or other causes of anemia, cannot maintain their hemoglobin level for more than several weeks without taking relatively large doses of iron daily (0.3 to 1 gm. of iron as iron and ammonium citrate).

Heath (14) found the maintenance dose thus to vary considerably in different patients and also in individual patients at different times. Much depends on the reserve of iron and possibly other hemoglobin building substances in the body, on the extent of the gastro-intestinal defect and on the composition of the diet. It is therefore necessary in treating these patients to adjust the maintenance dose of iron to the needs of the given patient, frequent hemoglobin determinations being necessary. It is probable, if large doses of iron are persisted in for a long time after hemoglobin reaches normal, that the iron stores in the body may be increased. This would allow the hemoglobin level to be maintained for a certain time without iron being administered
by mouth. One or two courses of iron therapy a year, lasting several months each, designed to maintain the store of iron in the body, will then be sufficient in many cases to keep the hemoglobin at a normal level, but it seems wiser to administer the drug with regularity (14).

PROGNOSIS AND COURSE

The prognosis as regards life is good in simple achlorhydric anemia. The prognosis as regards permanent recovery of health is not so favorable (32). Idiopathic hypochromic anemia is a disease with little tendency to recovery, and continuous treatment is necessary if health is to be maintained.

Unlike pernicious anemia, temporary remissions are uncommon, the anemia gradually progressing or it may become fixed at a low level beyond which it may not progress (31).

Complete symptomatic relief is not always obtained after treatment. Fatigue often persists although the anemia is relieved. Wintrobe (31) believes that psychoneurotic factors play a role in continuation of some of their complaints, although long continued ill-health may be responsible for secondary changes giving rise to a partial permanent disability.

Under the influence of iron therapy there is usually rapid alleviation of symptoms and glossitis, acroparesthesias, koilonychia, enlargement of the spleen, menorrhagia, gastrointestinal and other complaints subside completely or partly (30, 31, 32). Witts (32) estimated that complete cure follow-
ed adequate iron therapy in 80 per cent of his patients.

Infections may hinder the action of the iron and full therapeutic response may not be obtained.

The late therapeutic results, however, are not so good. With discontinuation of iron therapy, relapse is common. The time elapsing before relapse was observed varies from 2 to 9 months (31).

SUMMARY

1. Idiopathic hypochromic anemia is defined as an anemia of unknown etiology occurring especially but not exclusively in women in the third to fifth decades of life, and one which is characterized by an insidious onset, long duration, symptoms such as are common to all anemias and, in addition, glossitis, stomatitis, dysphagia, paresthesias without objective neurological findings, and often splenomegaly and koilonychia.

2. Idiopathic hypochromic anemia is a clinical entity as definite as pernicious anemia but probably no relation to it.

3. It is a common disease; if untreated it becomes chronic but seldom, if ever, is fatal and does not show spontaneous remissions.

4. The gastric analysis always shows an achlorhydria with the simple test meals, although free acid may be found in some cases after the administration of histamine. Gastric ferments are usually present but in dimin-
ished amounts.

5. The blood shows typically a microcytosis and hypochromia of the red cells without marked diminution in the number of erythrocytes. Hence the volume and color indexes are usually low. The stained film shows pallor and anisocytosis of the erythrocytes. The leukocytes show nothing extraordinary, although there is usually leukopenia. The bile pigments in the plasma are never above normal and are usually below normal.

6. The bone marrow shows a normoblastic marrow during the active stages of the disease with a return to normal during treatment.

7. The disease responds quickly and characteristically to treatment with large doses of iron, but recurs unless iron is given continuously.

8. The bone marrow findings, the characteristic response to iron therapy, the achlorhydria and certain of the clinical symptoms suggest that the fundamental disturbance may be defective gastric secretion with faulty utilization or synthesis from the diet of material which is necessary for hemoglobin formation. Anemia develops possibly because the demands for hemoglobin are in excess of the capacity of the individual to meet them. The requirements of menstruation and repeated pregnancies probably explain the preponderance of this type of anemia in women. Such factors as a diet deficient in foods potent for hemoglobin formation, excessive menstrual flow, blood loss from hemorr-
hoids, or dysphagia and consequent lack of food are considered secondary aggravating factors and not primary etiologic agents.
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