IRON-DEFICIENCY ANEMIA is the type of anemia most commonly encountered in the world. Its cause is usually blood loss, and in tropical countries worm infections of the digestive tract play an important role in this respect. However, in affluent countries as in North America and Western Europe, iron deficiency is also quite common.

The principal causes of iron depletion in the latter parts of the world are: in children, rapid growth; in women, blood loss during menstruation and increased iron demands during pregnancy; in men, blood loss and/or diminished iron absorption as a result of abnormalities of the digestive tract. In all cases, the occurrence of iron deficiency is favored by a diet which contains insufficient iron. Iron-deficiency anemia, as a rule, responds well to administration of bivalent iron by mouth.

Before iron deficiency leads to anemia, depletion of iron deposits occurs. An iron depletion of this type, which is not yet associated with anemia (also
known as "latent iron deficiency") is quite common even in prosperous countries. Whereas there is agreement as to the need for treatment of iron-deficiency anemia by administration of iron, opinions differ concerning the question of whether measures should be taken in the case of iron depletion not yet associated with anemia.

This paper will first describe changes in iron metabolism which accompany iron depletion. Next, it will consider which population groups frequently show iron depletion and its consequences. Finally, it will discuss whether treatment of iron depletion is necessary before anemia occurs and whether preventive measures should be taken in an effort to avoid iron depletion.

**DIAGNOSTIC METHODS AND CRITERIA**

When iron is lost as a result of blood loss or when more iron than usual is required for rapid growth in children or during pregnancy, the organism resorts to its storage iron for such purposes as hemoglobinopoiesis. When the mobilizable storage iron is exhausted in this process, iron depletion occurs while anemia is as yet not necessarily present (Fig. 1).

The following methods of investigation are used in diagnosing iron depletion:

1. The storage iron is localized for the most part in the liver and bone marrow, in about equal amounts. Under normal conditions the total amount of human storage iron varies widely. Pritchard and Mason found a mean value of 819 mg. in males (range 580–940 mg.) and 254 mg. in females (range 59–502 mg.). These great variations have their reflection in the results of hemosiderin staining of bone marrow fragments from males and females with "normal" iron storage, which can be indicated as ± to ++.

When the storage iron is exhausted, hemosiderin staining of the RES in bone marrow or liver is negative. It has been shown that staining of bone marrow fragments for hemosiderin, in a bone marrow smear, gives the same information as histochemical testing for iron in bone marrow sections. However, even when hemosiderin staining of bone marrow is negative there may still be storage iron available in the form of histochemically unstainable ferritin. The term iron depletion applies when no hemosiderin or only traces are found in the RES of bone marrow fragments.

2. When the iron stores become exhausted, the serum iron concentration gradually diminishes while the serum transferrin concentration increases. As a result, the serum iron saturation percentage diminishes to below 20. These changes in serum iron values do not always occur simultaneously with iron depletion; negative hemosiderin staining of bone marrow may thus be accompanied by normal serum iron values (Fig. 1).
In the course of the day, the serum iron value often diminishes while the transferrin concentration remains about the same. This is why in the afternoon the lower limit of the normal serum iron saturation percentage is 15 rather than 20. When the serum iron saturation percentage has diminished to below 10, iron depletion nearly always exists. In the case of a diminution to values between 10 and 20 per cent, an "infectious" anemia also may be involved.

In iron depletion the serum iron value often diminishes and the serum iron-binding capacity increases due to an increase in the amount of transferrin before anemia occurs. The latent serum iron-binding capacity consequently increases to 300 μg./100 ml. or more, and the serum iron saturation percentage diminishes to below 20.

(3) As the iron stores become exhausted, little iron is bound to a parenterally administered iron-chelating compound such as desferrioxamine (DFOM). When the iron stores are normal, intramuscular injection of 1000 mg. desferrioxamine is followed by excretion of 0.4–1.1 mg. iron in the 24-hour urine when renal function is normal. When the iron stores are normal, intramuscular injection of 1000 mg. desferrioxamine is followed by excretion of 0.4–1.1 mg. iron in the 24-hour urine when renal function is normal. When the serum iron saturation percentage has diminished to below 10, iron depletion nearly always exists. When the serum iron saturation percentage has diminished to below 10, iron depletion nearly always exists. When the serum iron saturation percentage has diminished to below 10, iron depletion nearly always exists. When the serum iron saturation percentage has diminished to below 10, iron depletion nearly always exists. Whenever more than 0.7 mg. iron is excreted, the iron stores usually prove to be sufficient. Hallberg and Hedenberg reached similar conclusions after intravenous injection of 10 mg. DFOM/Kg. body weight.

An excretion of less than 0.4 mg. iron in the 24-hour urine following parenteral administration of desferrioxamine (see above) is suggestive of iron depletion; an excretion of more than 0.7 mg. renders iron depletion improbable.

(4) When the iron supply to the bone marrow is less than normal because iron stores are exhausted, disturbances in heme synthesis occur. Dagg, Goldberg and Lochhead found an increase in the erythrocyte protoporphyrin content even before anemia occurred. A similar increase is observed in infections. This protoporphyrin content is normally 6.5–35 μg./100 ml. erythrocytes. In iron depletion the erythrocyte protoporphyrin content usually rises to above 35 μg./100 ml. erythrocytes.

(5) After intravenous injection of a minute amount of an iron compound labeled with radioactive iron, the disappearance of this iron from the plasma (in which it is bound to transferrin) is abnormally rapid in iron depletion because of the demands of erythropoiesis in the bone marrow. When the plasma iron disappearance curve shows a half-life of less than 50–60 minutes, this suggests iron depletion in the absence of distinct signs of intramedullary or extramedullary hemolysis.

(6) In the case of unusually high iron requirements the percentage of iron absorbed from the food increases. When the iron stores become depleted it is often possible, therefore, that sufficient additional iron is absorbed so that no anemia occurs. This increase in percentage of iron absorbed from a small test dose of bivalent iron (e.g., a ferro-iron compound labeled with 59Fe) proves to be a very sensitive standard of establishing the presence or absence of additional iron requirements or iron depletion even before anemia occurs. An increased iron absorption percentage from such a test dose is found also in the presence of hyperplastic erythropoiesis as a result of abnormal hemolysis. Also during pregnancy, even when sufficient iron stores are available, more iron is absorbed than normal. In iron depletion, even before anemia occurs, the iron absorption percentage from a small test dose of bivalent iron is larger than normal.

(7) When in iron depletion the iron loss (blood loss) and/or additional iron requirements exceed the amount of iron that can be taken up from the food by maximum iron absorption, iron-deficiency anemia occurs. The hemoglobin value at which the term anemia should be applied is dependent on the subject's age and sex.

After the marked diminution in hemoglobin concentration which occurs immediately after birth, a gradual increase prevails until puberty (Fig. 2), after which the mean hemoglobin content remains about the same in females, whereas in males it increases by almost 2 Gm. In females, the mean hemoglobin concentration remains lower than in males even when the females receive long-term iron medication. This difference is probably of hormonal origin and related to the stimulant effect of testosterone compounds on erythropoiesis. There seems to be a correlation also between muscular development and hemoglobin concentration.
IRON DEPLETION WITHOUT ANEMIA

It is difficult to establish the lower limit of the normal range of the hemoglobin concentration particularly in adult females. They prove to show an overlap between low-normal hemoglobin values with optimal iron supply, and abnormally low hemoglobin values which show an unmistakable increase after administration of bivalent iron. Based on observations in Norway it seems to be recommendable in Western Europe and probably also in North America to assume a hemoglobin concentration range of 14–17.5 Gm./100 ml. for normal adult males up to 60 years of age, and one of 12.5–16 Gm./100 ml. for normal adult females up to 60 years of age. Normal hemoglobin values are lower both in males and in females over age 60 (Fig. 2). When the diagnosis of iron depletion without anemia is considered, the hemoglobin concentration must be 14 Gm./100 ml. or more in males and 12.5 gm./100 ml. or more in females.

In summary, the criterion of the existence of iron depletion is a negative staining of bone marrow fragments for hemosiderin. The results of several other methods of investigation described above, can render iron depletion probable within the limitations inherent to these methods.

INCIDENCE OF IRON DEPLETION

Making use of the above described diagnostic methods and criteria, it can be stated that iron depletion without anemia is quite common in Western Europe and North America. It appears, however, that geographic differences exist in this respect, which probably are connected with dietary customs.

After birth, the mean hemoglobin concentration diminishes to about 11.5 Gm./100 ml. at age 3–6 months, whereupon it gradually increases until it averages 12 Gm./100 ml. at the end of the second year of life. At birth, full-term children average about 250 mg. iron, of which about 150 mg. is contained in hemoglobin. During the first few years of life there is a large increase in blood volume and muscular volume and this requires much iron. Until the end of the second year of life the total body iron thereby normally increases from some 250 mg. to an average of 450 mg. This high iron requirement during the first 2 years of life as a rule exhausts the storage iron and iron depletion occurs. This means that, during the latter half of the first year, when most additional iron is required, an average of 0.9 mg. iron per day must be absorbed from the food; during the second year this daily amount...
averages 0.5 mg. Children of this age prove to be capable of absorbing this amount of iron.\textsuperscript{26,27} It is therefore of great importance that infants be given a varied diet containing a sufficient amount of iron as soon as this is possible. A Dutch study of 100 random infants aged 10–24 months disclosed a mean hemoglobin concentration of 12.3 Gm./100 ml. In only 10 was the hemoglobin lower than 11 Gm./100 ml. The daily diet of these infants contained 4.5-6 mg. iron.\textsuperscript{28} Assuming that infants usually absorb about 10 per cent of the nutritional iron, and 20 per cent or more in the case of iron depletion and iron-deficiency anemia,\textsuperscript{29} the amount of iron found in the daily diet of these infants can be considered adequate. Besides the iron content, however, other factors such as the protein content of the diet affect iron absorption. For example a high-protein diet is believed to be less desirable.\textsuperscript{29} However, when the switch from a low-iron milk diet to sufficiently varied baby food with a sufficient amount of iron is made in time, it seems unnecessary in the Netherlands\textsuperscript{28} and probably also in other countries of Western Europe and in North America to enrich the diet by additional iron.\textsuperscript{29} It has been established that additional iron administration to infants of this age may raise the average hemoglobin concentration.\textsuperscript{27,30} But it has not been demonstrated that the health of normal full-term infants is in fact improved as a result.\textsuperscript{24,31}

\textit{From age 2 until the beginning of puberty} there is little iron-deficiency anemia.\textsuperscript{32} The average low serum iron content and low serum iron saturation percentage increase gradually to normal values.\textsuperscript{33} Other investigators\textsuperscript{41} already found in children aged 3 to 6 years, normal or nearly normal serum iron values. In boys and girls alike, the mean hemoglobin concentration gradually increases until at age 10 it reaches about 13 Gm./100 ml.\textsuperscript{35}

\textit{During puberty}, high demands are again made on the iron supply in connection with the menarche and with the marked increase in blood volume and muscular volume, especially in boys. De Wijn and Pikaar\textsuperscript{36} demonstrated that boys frequently develop iron depletion, usually transient, without anemia. In seven of 66 boys examined at ages 9, 13 and 17, they found signs of iron depletion at age 13. In six of these seven boys the iron depletion was no longer demonstrable at age 17 (Table 1). None of these boys showed unequivocal anemia. Iron depletion was assumed to exist when the serum iron saturation percentage diminished to below 15 because Dagg et al.\textsuperscript{12} have shown that such a diminution of the serum iron saturation percentage usually is associated with iron depletion if infections can be ruled out. Natvig et al.\textsuperscript{35} likewise found signs of transient iron depletion in boys of this age.

\begin{table}[h]
\centering
\caption{Semi-longitudinal Examination of 66 Boys*}
\begin{tabular}{|l|l|l|l|l|l|}
\hline
\textbf{Age in Years} & \textbf{Hemoglobin Gm./100 ml} & \textbf{Serum Iron \( \mu g./100 \text{ ml} \)} & \textbf{T.I.B.C. \( \mu g./100 \text{ ml} \)} & \textbf{Serum Iron Saturation Per Cent} \\
& \textbf{Medium Value} & \textbf{Number of Cases} & \textbf{Medium Value} & \textbf{Number of Cases} \\
\hline
9 & 13.6 & 3 & 336 & 2 \\
13 & 14 & 8 & 352 & 7 \\
17 & 15.1 & 2 & 338 & 1 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*} Age 9–17 years in the Netherlands, from 1960–1968 (de Wijn and Pikaar,\textsuperscript{36} with permission of the authors); explanation in text.
Table 2.—Semi-longitudinal Examination of 59 Girls

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Hemoglobin Gm./100 ml. Medium Value</th>
<th>Serum Iron μg./100 ml. &lt; 50 Per Cent Number of Cases</th>
<th>T.I.B.C. μg./100 ml. Medium Value</th>
<th>Serum Iron Saturation Per Cent &lt; 15 Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>13.6</td>
<td>5</td>
<td>350</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>13.6</td>
<td>4</td>
<td>355</td>
<td>5</td>
</tr>
<tr>
<td>17</td>
<td>13.6</td>
<td>9</td>
<td>338</td>
<td>7</td>
</tr>
</tbody>
</table>

* Age 9–17 years in the Netherlands, from 1960–1968 (de Wijn and Pikaar;36 with permission of the authors); explanation in text.

In a follow-up study made by De Wijn and Pikaar36 on 59 girls from age 9 to age 17, five girls showed a serum iron saturation percentage below 15 at age 13; two of these girls were anemic. Unlike a group of boys they studied, the group of girls showed an increased number of individuals with iron depletion with increasing age; at age 17, seven girls showed an iron saturation percentage below 15 (Table 2); again, only two girls were anemic. Natvig et al.35 found anemia in 3.4 per cent of a group of girls aged 14–16, but in only 1.7 per cent of girls aged 17–20. These observations, like those of De Wijn and Pikaar,36 indicate the transient occurrence of iron depletion during puberty. Without administration of additional iron with the food, these signs of iron depletion as a rule disappear at a later age.

In normal adult males up to age 60, iron-deficiency anemia and iron depletion without anemia are not frequent.17 When iron depletion occurs in men, this need not necessarily lead to anemia. Liem, de Laive, Korver, Ossentjuk, van der Beld and Verloop37 examined four groups of men 3–4 years, 5–7 years, 8–14 years and 15 years or more after partial gastrectomy according to Polya-Hofmeister. In the group examined 3–4 years after the operation, 50 per cent showed signs of iron depletion. This percentage gradually increased, to reach 70 per cent in the group examined 15 years or more after the operation (Fig. 3). Only 25 per cent of the men had developed anemia; this means that the majority of the men in whom iron depletion after the gastrectomy was found, avoided anemia by absorption of additional iron from the food. Even after resection of a large portion of the stomach, iron-depleted men are often capable of absorbing sufficient iron from the food to avoid a negative iron balance.

Adult females frequently show iron depletion. The average amount of storage iron in them is much smaller than in men. This is commonly explained by menstrual blood loss and increased iron demands during pregnancies.

In a group of healthy Swedish women with normal dietary habits Hallberg, Högdahl, Nilsson and Rybo28 found a correlation between the incidence of iron depletion and menstrual blood loss. When no stainable iron was found in the bone marrow, the blood loss per menstruation usually exceeded 60 ml.

The percentage of "normal" women without symptoms who "suffer" from iron depletion without anemia has been reported as varying from 20 per cent39 to about 30 per cent. Reports on the percentage of women who suffer from iron-deficiency anemia (hemoglobin lower than 12.5 Gm./100 ml.) also
Fig. 3.—Comparison of the results of iron staining of bone marrow fragments in 19 patients who underwent cholecystectomy 3 years to more than 15 years previously, with the results in 133 patients who were gastrectomized according to Polya-Hofmeister (Billroth II) 3 years to more than 15 years previously. Hatched lines mean hemosiderin staining of the bone marrow is positive. Open spaces mean hemosiderin staining of the bone marrow is negative; n, number of patients.

Vary, from 2 per cent,39 to 10 per cent42 to 25 per cent.43 Dagg, Morrow, MacFarlane and Goldberg44 reported anemia in 10 out of 26 women who had shown iron depletion without anemia 2 years previously.

However, iron depletion in women by no means always leads to anemia. Strengers, Roovers and Olislagers45 examined 24 Amsterdam female blood donors aged 20–30 who in the course of preceding years had donated blood on five occasions. A week after the sixth donation (some 400 ml. blood) the mean hemoglobin concentration diminished from 13.6 to 12.2 Gm./100 ml., the mean serum iron content diminished from 89 to 58 μgm./100 ml., and the mean serum iron saturation percentage diminished from 24 to 15. Six months later, serum iron concentration and mean serum iron saturation percentage had returned to normal (Table 3), although no additional iron had been taken.

Extra severe demands on the iron supply in women are made in pregnancy. The average amount of additional iron required during pregnancy is 250 mg. for the fetus25 and about 90 mg. for the placenta.46 Moreover, the erythrocyte mass increases by an average of 225 ml. during pregnancy, which means that another 225 mg. iron is required.45,47 It is frequently found reported that the erythrocyte mass increases by 400 ml. or more, but this is the case only when additional iron is administered during pregnancy.45,48

At the end of a normal pregnancy it is nearly always found that the storage iron has been exhausted entirely or nearly entirely.15,40 This means that development of iron depletion is the rule during pregnancy. In the case of iron
depletion, much less iron is lost with physiological sloughing of cells from skin and mucous membranes than when normal iron stores are available. Bothwell and Finch estimate that in that case the daily iron loss of about 1 mg. is reduced to about 10–50 per cent of this value. This implies that, during a normal 280-day pregnancy, the total loss of iron is not 250 mg. but averages at best half this amount, i.e., 140 mg. The average total amount of iron required during pregnancy, therefore, is about 700 mg. (see Table 4).

Immediately after labor the additional iron required for the increase in erythrocyte volume during pregnancy, an average of 225 mg., becomes available again. Assuming the average blood loss in parturition to be 300 ml., which entails a loss of 150 mg. iron, we find a postpartum gain of 225 minus 150 which equals some 75 mg. iron.

How do pregnant women acquire the additional iron they need? It has been established that, under the influence of the increased iron requirements during pregnancy, additional iron is absorbed from the second trimester on in principle, therefore, the same happens as in iron depletion outside pregnancy. Normally 5–10 per cent of food iron is absorbed. Moore calculated that 10–20 per cent of the nutritional iron is absorbed in iron depletion. Garby calculated a mean value of 16 per cent (9–24 per cent). Finch, Haskins and Finch, Pribilla, Bothwell and Finch, and Crosby, Conrad and Wheby established the likelihood that up to 30 per cent of the nutritional iron can be absorbed if necessary in the case of increased iron requirements.

The iron content of the normal diet in North America and Western Europe is believed to be 10–15 mg. daily. Taking as a starting point a low average daily nutritional iron content during pregnancy (10 mg.), it is likely that 10–20 per cent of this amount will be absorbed during the course of pregnancy, dependent on the degree of iron depletion and the iron requirements.

### Table 4.—Mean Iron Requirement in Pregnancy*

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expansion of red blood cell mass</td>
<td>225</td>
</tr>
<tr>
<td>External iron loss</td>
<td>140</td>
</tr>
<tr>
<td>Fetal iron</td>
<td>250</td>
</tr>
<tr>
<td>Iron in placenta and cord</td>
<td>90</td>
</tr>
<tr>
<td>Total requirement</td>
<td>705</td>
</tr>
</tbody>
</table>

* Explanation in text.
During the first trimester of pregnancy the iron requirements are only slightly higher than otherwise, and an average of 10 per cent of the nutritional iron is therefore probably absorbed; this means: 1 mg. iron daily or a total of some 90 mg. During the second trimester the iron requirements are increased, and the iron absorption is likely to rise to about 15 per cent. This means an average daily absorption of 1.5 mg. iron or a total of some 135 mg. iron for the entire second trimester. Iron requirements are highest during the third trimester. During this period the percentage of nutritional iron absorbed probably averages 20 or more; absorption of 2 mg. iron daily during the third trimester would mean a total absorption of 180 mg. during this period.

The amount of storage iron with which a woman starts her pregnancy varies. De Leeuw et al. examined nulliparae to quadriparae at the beginning of pregnancy and found that 30 per cent had no or only traces of stainable iron in the bone marrow; these women, therefore, had little storage iron. Hallberg et al. found the same in 40 per cent of women at the beginning of pregnancy. These observations indicate that 60–70 per cent of normal women have a fair amount of storage iron when they enter the period of gestation. Pritchard and Mason calculated a mean amount of storage iron of 254 mg. for a number of normal nonpregnant women. Finch found a mean amount of storage iron of 385 mg. in normal women.

It may be assumed then that on an average some 300 mg. storage iron is available to women who become pregnant. As we calculated above, some 400 mg. iron can be absorbed from the food during pregnancy. With the mean amount of storage iron, this makes some 700 mg. iron available to a pregnant woman. This corresponds with the amount of additional iron believed to be the average requirement in the course of a normal pregnancy (see Table 4). Of course these figures are gross averages, which make understandable how, why in affluent societies relatively few cases of severe iron deficiency anemia in or after pregnancy are observed.

The gravest risk of iron-deficiency anemia during or immediately after pregnancy seems to be run by the women (30–40 per cent of the total) who enter pregnancy with a small amount of storage iron and those who during pregnancy receive insufficient iron from their diet. On the other hand, the iron requirements and iron absorption during pregnancy prove to vary so widely, that no iron-deficiency anemia need necessarily occur in women with a small amount of storage iron, while anemia may well occur in women who enter pregnancy with fair iron stores. Since therefore, the occurrence of anemia during pregnancy is not predictable with certainty, the only reliable approach is that of regular determinations of hemoglobin concentration and/or hematocrit value.

In the course of pregnancy the hemoglobin concentration usually diminishes because the increase in plasma volume considerably exceeds that in erythrocyte volume. It is assumed that the hemoglobin value can fall to an average of 11 Gm. per cent by this dilution. Others accept 10.5 Gm./100 ml. or 10 Gm./100 ml. as the lower limit.

In the U.S.A., a study of some 2500 normal pregnant women using no addi-
tional iron showed that the hemoglobin concentration remained above 10 Gm./100 ml. during and after pregnancy in 89 per cent; in the remaining 11 per cent (with a hemoglobin value of less than 10 Gm./100 ml. on one or several occasions), the concentration nearly always returned to normal values after parturition although no additional iron was given. The children of the latter group of women differed in no way from those of the women with high hemoglobin values during pregnancy; not even the mean hemoglobin concentration was different during the first year of life. Although an assumed 10 or 11 Gm./100 ml. as lower limit of the normal hemoglobin concentration during pregnancy is an arbitrary value, it can nevertheless be stated that the presence of true iron-deficiency anemia during pregnancy is small when the Hb value is 11 Gm./100 ml. or higher.

In "normal" males and females over 65 years of age, the mean hemoglobin concentration and the hematocrit show a gradual decrease with increasing age. However, the difference in hemoglobin concentration between the sexes persists, be it slightly diminishing (Fig. 2). At this age, iron administration is usually followed in both sexes by an increase in hemoglobin concentration. This observation, and the often hypochromic character of the blood picture, indicate that iron depletion is probably often involved.

A cause of the lower Hb values over age 65 is therefore probably to be sought in iron poverty of the diet or occult blood loss; in addition however, hormonal factors probably play role and/or there are changes in body tissues caused by inactivity which result in a lower hemoglobin concentration.

Consequences of Iron Depletion Without Anemia

There are reports on diminution of certain iron-bearing enzymes in iron depletion, even before anemia occurs. Beutler demonstrated that the concentration of the iron-bearing enzyme cytochrome C in the liver and kidneys of the rat is diminished in iron depletion. Dagg, Jackson, Curry and Goldberg found the activity of cytochrome-oxidase in human buccal mucosa frequently diminished. These enzyme deficiencies disappeared after iron administration.

Beutler, Larsh and Gurney reported that symptoms in women with iron depletion without anemia disappeared more frequently after iron medication than after administration of a placebo. Others were unable to corroborate this. A study of 133 men who underwent partial gastrectomy also disclosed that symptoms were independent of the state of the iron stores. Consequently, there is no definitive evidence that iron depletion as such produces symptoms.

It has been established that an average normal hemoglobin concentration in women with iron depletion can increase following administration of bivalent iron, an increase which fails to occur after administration of a placebo. There is no evidence, however, that these women's conditions improve as a result.

A similar problem poses itself during pregnancy. During this period the erythrocyte volume shows an average increase of about 15 per cent. When additional iron is given however, this increase can amount to as much as 30 per cent or more. Therefore, when additional iron is prescribed to normal non-anemic pregnant women the average hemoglobin concentration increases due
to an increased erythrocyte volume. But it has not been established that the increase in hemoglobin concentration improves the conditions of these pregnant women or their children.69-71

**ARE MEASURES TO PREVENT IRON DEPLETION DESIRABLE?**

It has been said in the foregoing that iron depletion as such seems to cause no clinical symptoms in men and seems to have no undesirable side effects. This being so, measures to prevent iron depletion only seem desirable for those population groups, which have a fair chance to develop iron-deficiency anemia. In full-term neonates the hemoglobin concentration diminishes immediately after birth and without administration of additional iron, iron depletion is the rule during the latter half of the first and during the second year of life. This iron depletion disappears however in later years without iron medication, and iron stores are formed by absorption of iron from food (both in girls and in boys). Iron depletion is quite common again during puberty, and again it is usually found to be transient.

In later years, few problems as a rule occur in men. Iron depletion in adult men is rare unless there is blood loss or an intervention such as gastrectomy. Iron depletion often occurs in postgastrectomy patients, but most of these men prove to be capable of absorbing sufficient iron from the food to avoid a negative iron balance.72

Iron depletion is quite common in women, and iron-deficiency anemia occurs in a number of these women.44 During pregnancy, iron depletion is the rule rather than an exception; but, more often than not, anemia can be prevented by additional iron absorption from the food. Iron depletion seems to be quite common also in individuals over 65 years of age. The reasons for this phenomenon have not yet been adequately investigated.

In view of the above considerations, an increased iron supply would at this time seem to be required only for women of reproductive age, at least in North America and Western Europe, for in these women a fair chance exists, that iron depletion is followed by iron-deficiency anemia. The question as to which is the best way to provide women of reproductive age with a sufficient amount of iron, is not easy to answer.

Geographic differences appear to play an important role in the occurrence of iron depletion. These differences do not seem to be based on a difference of the iron content of the diet only. The amount of iron that can be absorbed from food depends, not only on the iron content but also on the composition of the diet.73 Various chelating agents in the diet can prevent absorption of iron, for example from bread;74 the absorption of iron from bread is believed to be unfavorably influenced by simultaneous ingestion of a boiled egg.68 Milk too is believed to impede iron absorption.75 A high-protein diet may be undesirable also.26 The influence of fat on iron absorption from food is a controversial subject. Brodan, Kuhn, Masek, Brodanova, Kordac and Valek76 found that whipped cream has an inhibitory effect on iron absorption. In the USA, Denmark, England and Chili, iron is as a rule added to flour used for bread-making;77 it seems doubtful, however, whether this sufficiently enhances the iron absorption from the diet.58, 78, 79
In South Africa and Ethiopia, some population groups daily ingest 100 mg. iron or more with the food by contamination with iron from iron cooking utensils or by contamination of the food with iron-containing earth. Pregnant women in these groups usually have sufficient iron stores, and anemia is rare both in pregnant and nonpregnant women. Therefore, iron depletion in women probably can be avoided if food contains so much additional iron. Enrichment of the food with so much additional iron entails, however, a risk of hemosiderosis and hemosiderosis can gradually lead to tissue damage which may result in hemochromatosis. The manner in which foods should be enriched with iron in order to ensure a higher iron absorption from the daily diet proves to be a complex problem which remains to be solved.

Iron depletion, even when no anemia has yet occurred, entails a larger iron absorption from normal food than occurs in the case of sufficient iron stores. At the moment, therefore, it seems best to make efforts to ensure that women, especially pregnant women, receive a diet which contains sufficient iron by nature, thereby trying to prevent anemia.

In pregnant women, however, regular determinations of hemoglobin concentration and/or hematocrit value remain an indispensable aid in the early diagnosis of iron-deficiency anemia. Whenever the hemoglobin value diminishes to below 11 Gm./100 ml. it is advisable to prescribe a bivalent iron compound which must be continued until a few months after parturition in an attempt to replenish empty iron stores. When a large percentage of iron-deficiency anemia during pregnancy is noticed in a population group, it may be advisable prophylactically to prescribe additional oral or parenteral iron for all pregnant women in the group. Lowenstein, De Leeuw, Cantlie and Brunton maintain that 80 mg. bivalent iron daily by mouth during the latter half of pregnancy is sufficient to prevent iron depletion. According to Pritchard, 30 mg. bivalent iron daily during pregnancy throughout the 9 months is sufficient for that purpose.

The disadvantage of routine prescription of iron compounds to pregnant women, however, is that hemoglobin checks are often omitted in these cases. This means that anemia from other causes (e.g. folic acid deficiency or a complicating (urinary) infection, etc.) is overlooked or discovered too late. Moreover many women for whom iron is prescribed during pregnancy fail to take the medication and omit to mention this at follow-ups. This is why, in my opinion, the best approach remains that which ensures frequent check-ups on the blood picture during pregnancy without routine prescription of iron. They ensure early diagnosis and adequate treatment of anemia.

ACKNOWLEDGMENT

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IRON DEPLETION WITHOUT ANEMIA


Clinical Review: Iron Depletion Without Anemia: A Controversial Subject

M. C. VERLOOP