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Nutritional anemia

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NUTRITIONAL ANEMIA.

RALPH W. BIGGER.

A review of recent literature on
nutritional anemia of infancy with
special reference to the therapeutic
effect of copper in such cases.

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THE INFANT BLOOD PICTURE (1,2,3,4,5,6,7)

The formation of blood cells in the human embryo is at
first erythrocytic in nature, and begins in the body stalk and
more general connective tissues. Later it involves the liver
and spleen and finally the bone marrow. During the first half
of foetal life the liver is the chief site of production of the
corpuscles. The bone marrow which is destined to be the chief
site of blood formation in the adult begins to form at about the
third month of foetal life but does not become of much importance
in corpuscle formation until late uterine life. In fact, the liver
and spleen are at their maximum as blood forming organs in the
last two months of gestation. The activity of the lymphatic glands
and other lymphatic tissues is not marked until well after the
middle of intra-uterine life.

As mentioned above, blood formation is at first entirely
erythrocytic. Moreover, these red blood cells are nucleated and
polychromatophilic. As the bone marrow begins to take an active
part, myelocytes, and a little later leucocytes, appear in the
blood, as well as some platelets. Lymphocytes are at first rela-
tively few but during the later months they predominate.

At birth hemopoesis is still somewhat extramedullary but to
a lesser extent. Gradually the bone marrow replaces the extramedul-
lary areas as blood forming organs. This change commencing in

foetal life and continuing up through post-natal life. At this
time blood formation is essentially the same as in the adult.
The erythrocytes however, are predominently polychromatophilic
and there are a few nucleated red cells and an occasional myelo-
blast or myelocyte. The marrow of the long bones and skull is
red at birth. The change to the fat marrow of the adult begins at
about four years, is marked at seven years and complete at fourteen.

There is much difference of opinion as to whether the red and
white cells originate from a common ancestral cell or from various
cells. From a clinical standpoint the question is of little import-
ance, although it does appear that monophyletism is the theory of
choice.

The common ancestral cell is the lymphoidocyte or hemocytoblast
and is the forerunner of all other blood cells. The type of cell to
develope from this common parent depends on the environment to which
the cell is subjected. Thus under certain conditions lymphocytes
will develop. Under other conditions the cell will eventually
become a granular leucocyte, going first through the premyelocyte,
myelocyte and metamyelocyte stages. During this passage through
these stages the cells become granular, smaller, and their nucleus
becomes more irregular. There are three types of granular leucocytes ,
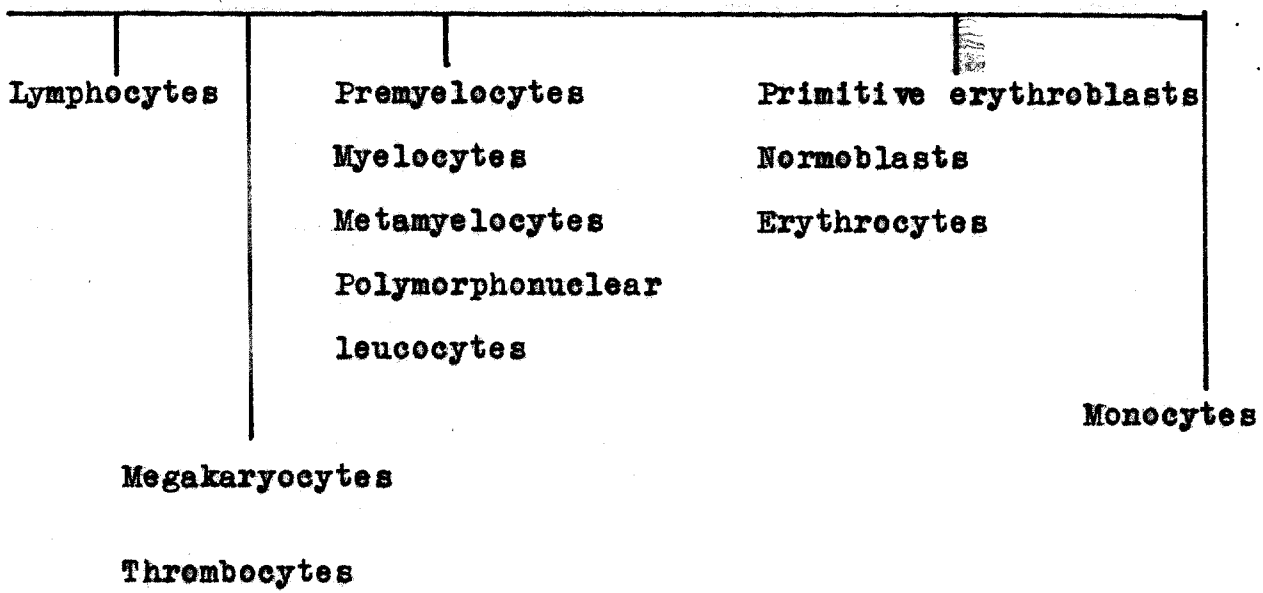namely; the neutrophilic, basiphilic and eosinphilic.

The blood platelets or thrombocytes, which seem to have something
to do with blood clotting are derived from a giant cell, the mega-
karyocyte, which develops directly from the haemocytoblast. These
platelets are thought to be detached portions of the cytoplasm of
the megakaryocyte.

Erythrocytes develope from the common parent cell through large nucleated primitive erythroblasts or megaloblasts and then smaller nucleated cells or normoblasts.

Monocytes or the large hyaline leucocytes are derived directly from the parent cell.

Such a conception of hemopoesis can be illustrated by the following geneological tree.

LYMPHOIDOCYTE   OR   HEMOCYTOBLAST

Lymphocytes

Premyelocytes   Primitive erythroblasts

Myelocytes   Normoblasts

Metamyelocytes   Erythrocytes

Polymorphonuclear

leucocytes

                                                Monocytes

Megakaryocytes

Thrombocytes

The blood vessels of the bone marrow are larger in calibre than the capillaries and they have a very thin wall composed of endothelial cells and the membranous extensions of their cytoplasm.

The cells of the marrow parenchyma are crowded closely against this wall which under normal conditions acts as an effective barrier to the entrance of immature marrow cells into the circulation. Mature cells however, are allowed to pass. The polymorphonuclear neucocytes pass through by virtue of their ameboid activity. The continued multiplication of the erythrocytes and resultant increase in pressure in a limited space forces these cells through the barrier into the circulation. The large nuclei of the immature cells prevent their passage. Megakaryocytes may pass as a result of their ameboid activity, the thrombocytes being broken off in the capillaries. In anemias calling for increased activity of the bone marrow the proliferation may be of such an extent to so increase the pressure sufficiently to break down this natural barrier with a resultant appearance of immature forms in the circulating blood. Such a condition may be observed in pernicious anemia where a long standing hyperactivity and hyperplasia of the bone marrow has resulted in this phenomena.

Various investigators have estimated that from one-tenth to one-thirtieth of the total blood is destroyed daily. Thus calling for a compensatory blood regeneration, which will be discussed later. The life of the erythrocyte is approximately twenty-eight days. The red cells become fragmented, forming in the blood stream a fine hemoglobin containing dust. These fragments or the older cells are taken up and destroyed by the phagocytic endothelial cells of the spleen. Under abnormal conditions when blood destruction is excessive, similar cells in the liver, bone marrow and lymph knodes may share in this process.

The hemoglobin from the destroyed erythrocytes is broken up by the liver cells and is in part secreted as iron-free bile pigment. The iron is largely retained by the body and is doubtless utilized in the reformation of hemoglobin to be contained in newly formed erythrocytes. This function may also be supplemented by other tissues, but under normal conditions it is confined largely to the liver.

White cells die in the blood stream, the lymphocytes being more resistant and longer lived than the granular cells. Blood platelets exhibit an average life of about four days.

Under normal conditions blood regeneration is equal to blood destruction, so that a resultant equilibrium is established. Small losses of blood or temporary slight increases in blood destruction are quickly compensated for by an increase in blood regeneration, thereby maintaining the equalibrium.

If the loss of blood, which may be by increased intravascular blood destruction or hemorrhage, and the demand on the hemopoetic organs is not too great it may be met by an increase in the output of normal red and white cells. If the blood loss is excessive and the demand is greater than can be met in this manner, a hyperplasia and hyperactivity of the bone marrow will result. The barrier will break down and unripe cells will be thrown into the circulation.

The type of response of the hemopoetic system to an increased demand for increased function depends on the age level and the intensity of stimulus. In infancy there is more rapid reversal to embryonic forms. Hence, enlargement of the spleen, lymph glands and liver more rapidly and readily occurs. Bone marrow substance

is also more easily stimulated in infancy, and its reaction is
more rapid and intensive. As a result, less serious conditions of
blood loss will result in the exodus of immature forms from the
marrow more readily than in the adult. Thus, young forms in the
infant are usually of less signifigance. The tendency of the infant
bone marrow to revert to the embryonic condition helps to account
for the abundance of young forms in many anemias of infancy.

Bone marrow substance as a result of continued stimulation,
may increase to the point of causing pressure atrophy of the imperfectly
calcified bone. Moreover, if the demand on the bone marrow is ex-
cessive or continued for a sufficient length of time the regenerative
powers may finally become exhausted. The result would be an anemia
of the aplastic type.

The appearance of immature forms in the blood stream is inter-
preted as a sign of blood regeneration. Reticulated red cells or
reticulocytes furnish a fairly dependable index of blood regeneration.

A discussion of blood is not complete without mention of hemo-
globin, a substance of vital importance, whose complex molecule
contains iron and a protein radical. This substance is contained
in the erythrocyte and imparts to it its red color. By virtue of
its ability to combine oxygen in a loose manner its function is that
of carrying oxygen from the lungs to the tissues. Any reduction in
the normal hemoglobin content would therefore decrease the efficiency
of internal respiration. In cases of low hemoglobin the red cells
become pale or achromic.

Since iron is a constant component of hemoglobin, it is of
interest to review what is known of iron storage in the human body,
and iron metabolism.

During the later part of foetal life iron is stored in the liver, that organ serving as a reservoir during early life when iron intake is usually at a low level. This storage of iron is not, however, as large as has probably been supposed in the past. Sidney A. Gladstone[8] has shown by a series of determinations that the amount of iron in the liver exclusive of hemoglobin is about 32 mgm. for the entire organ. Iron was found in the liver and spleen in almost all cases under the age of three months and it was rarely present in cases over that age. The largest amounts were found from one to ten weeks after birth and it is proposed that this increase is due to the post-natal intravascular blood destruction. In adults Gladstone found that following blood transfusions there was a noticeable increase in the iron content of the liver and spleen. Such an observation rather serves to parallel and support the above findings. Thus it is quite conclusively shown that the liver and spleen act as depots of iron and conserve that element for future hemoglobin synthesis. Some iron is excreted by the bowel but normally the amount is negligable, although a negative iron balance will eventually result in a deficiency of iron, and necessarily then, a diminution of hemoglobin.

The normal mature new born has a high hemoglobin content of the blood, and this value rapidly drops for the first two weeks. As the hemoglobin is broken down the iron so freed is retained by the liver cells and is probably utilized later by the hemopoetic organs in further hemoglobin synthesis.

Hugh Josephs[9], following a study of iron metabolism in rats, has offered a working hypothesis of iron metabolism. He takes cognizance of two types of iron in the body. Function iron of the general body tissues which may be called the non-hemoglobin iron.

It may be divided into two parts; a variable or mobile portion and a fixed portion. The fixed portion remains at two or three mgms. percent in the liver and 0.5 mgms. percent in the body as a whole, and this concentration is maintained at all costs, and probably corresponds to iron of cell nuclei including muscle hemoglobin. The variable portion corresponds to the portion of non-hemoglobin iron which is in the "stores", and which is available for hemoglobin synthesis or excretion. Hemoglobin iron is the blood iron as the name implies and depends on the mobile iron and the organisms' ability to synthesize it, and thus keep it at a proper level.

Josephs suggests that, "ingested iron reaches the liver where it is rapidly removed from the circulation by the neticulo-endothelial cells. It may, however, re-enter the circulation to be distributed as needed in the body, or to be excreted. Breakdown of hemoglobin and of the cells of the body returns the function iron to the circulation, to be taken up again by the cells capable of storing it, or to be excreted, thus there is established within the body a sort of internal circulation which tends to conserve the body store of iron so that the slight loss by excretion may easily be made up by fresh absorption."

The hypothesis may be diagrammatically represented as follows:

Function Iron
of Tissues   Hemoglobin

Ingested ———→ Liver ——————————→ Circulation

Iron

Stores   Excretion
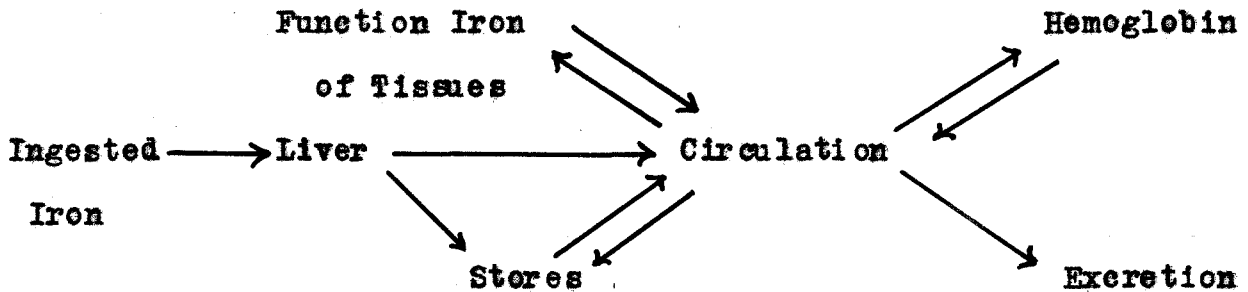
Under normal conditions, infants are born with a store of iron
in the liver. In addition there is normally a high hemoglobin content
of the blood which lowers rapidly during the first few weeks of post
natal life, thereby adding materially to this hepatic storehouse for
iron.[8] In most instances perhaps this stored iron is sufficient to
supply the needs of the infant for hemoglobin synthesis for the first
six to eight months, when the diet is composed largely of milk.

Both human and cows milk are notoriously low in iron and supply
an insufficient intake. Cows milk contains approximately 0.08 mgm.
of iron calculated as fe. per pint. Human milk has only a slightly
higher iron content.

Just what the iron requirements of the new born infant really is
has not been definitely determined.

Leichsenring and Hanson [11] have studied the iron requirements
of children between the ages of 35 and 56 months. The iron require-
ment for growth in their studies was observed as approximately 0.2
mgm. per kilogram of body weight per day. The observed maintenance
need was approximately 0.12 mgm. per kgm. of body weight. These
investigators also noted a wide variance in iron content of various
foods as compared with Shermans[1] tables, as well as pronounced

individual differences in the iron requirements of the children studied.
As a result, they recommend a 50% margin of safety to be allowed over
the total requirements of 0.32 mgm. per kgm. of body weight. This
would make a standard requirement for children of 0.48 mgm. of iron
per kgm. of body weight per day. It is evident then, that milk can-
not supply the infant with enough iron for mere maintenance to say
nothing of the growth requirement.

The hemoglobin at birth is quite high, varying from 95-140%, with
an average of around 130%. There is a sudden drop during the first
two weeks to about 100% and then a more gradual fall to about 80%
during the next six months, where it remains throughout childhood.
This fall in hemoglobin is considered physiologic and is associated
with icterus neonatorum when it occurs. It is during this period
that an increase in the iron content of the liver and spleen has
been noted.

The percentage of hemoglobin in icteric babies is little, if at
all, lower than in babies that are not jaundiced. The normal variations
in the percentage of hemoglobin in different children, and at different
times in the same child are quite marked. Hemoglobin percentage is
somewhat higher in boys than in girls.

Erythrocytes in the first few hours are variously reported at
from five to eight million per cubic m. m. There is an increase
during the first six hours, then a rapid fall for the next three or
four days to five or six million where they remain during infancy and
childhood. Some authors report slightly lower levels. The transient
rise is probably due to a combination of loss of fluid and starvation.

Lucas[6] found nucleated red cells in 52% of all cases on the first day, and 5% on the second day. During the first few days there is often considerable variation in the size of the red cells. They not infrequently show basiphilic granules and lose their hemoglobin easily. Nucleated cells are normally not present after the first six days. They do, however, appear with less provocation during infancy. Anisocytosis, poikilocytosis and polychromatophilia develope much more quickly in infants and younger children than in older children and adults.

Leucocytes are high at birth and during the first few days there is a marked increase to as high as 30,000 per c. mm. At birth, there are 15,000 to 25,000, a transient rise, then a fall to about 8,000 to 13,000 after the first week. The increase in the total leucocyte count is due to an increase in polymorphonuclears. At birth these cells constitute about 40 to 75% of the total. There is a rise for the first twelve hours and then a fall to 20 to 50% in the subsequent two weeks. Remains here for two years and then increases to 40 to 60% at six years and 50 to 70% at twelve years.

Eosinophils and basiphils are more numerous during the first two weeks than at any other period.

Lymphocytes are about 20 to 40% at birth. Thereafter the number increases as neutrophilic polymorphonuclears decrease. First two years they are about 40 to 65% of total white count, 30 to 50% at six years and 20 to 40% at twelve years.

Monocytes are numerous at birth- about 10 to 15%, but diminish

rapidly after the first ten days to 4 to 6%. During early child-hood they approach the percentage seen in adults.

Blood platelets average between 350,000 and 400,000, although figures as low as 100,000 have been observed. The average after the first two weeks is 200,000 to 400,000, being practically the same as in the adult.

Following, is a chart of values with reference to blood components at various ages.

From Ordway[1]   Page 535

| | First Month | | | | | 6 Mo. | 1 Yr. | 2 Yrs. | 4 Yrs. | F-12 Yrs. |
	At Birth	2 Days	5 Days	10 Days	2 Wks.					
R.B.C.	6,000,000	5,800,000	5,800,000	5,500,000	5,250,000	4,800,000	5,000,000	5,000,000	5,000,000	5,000,000
Hemoglobin	130	132	120	110	100	80	80	85	90	90
W.B.C.	15,000	23,000	16,000	16,000	11,000	12,000	10,000	9,000	8,000	8,000
Platelets	400,000	300,000	300,000	300,000	300,000	300,000	300,000	300,000	300,000	300,000
Neutrophils	45	55	40	35	35	40	40	40	50	60
Eosinophils & Basophils	3	5	5	4	4	3	2	2	2	2
Lymphocytes	30	20	40	50	55	51	53	50	40	30
Monocytes	12	15	12	10	6	6	5	6	8	8
Immature W.B.C.	10	5	3	1	0	0	0	0	0	0
Nucleated R.B.C.	++	+	+	0	0	0	0	0	0	0
Reticulocytes	1	3	1.5	1	0.5	0.5	1	1	1	1

NUTRITIONAL ANEMIA

Nutritional anemia (alimentary anemia, dietary anemia, simple anemia of infancy, chlorosis of infancy, cows' milk anemia, goats' milk anemia) is a rather common disease of infancy and has not in the past received much recognition by writers in this country. Workers in Europe however, have recognized this condition for some time and have called attention to it repeatedly.

Nutritional anemia is a metabolic disorder characterized by pallor, irritability, peevishness, persistant anorexia, low hemoglobin and achromia, and reduced red cell count.

The disease occurs especially in premature infants, twins, and in infants who have been maintained exclusively on a milk diet for a long period of time. Usually it does not appear before the age of nine months or after two years.

The more common occurrance of the disease in the premature is perhaps due to a deficiency of iron at birth. Nicholas[12] has shown that iron accumulation in the foetus occurs mainly during the final third of intra-uterine life. In 1899 von Bunge[12] showed that the amount of iron in the liver and spleen of young mammals was highest in the new born and at a minimum at the end of the suckling period, which is evidence that during the suckling period these iron depots served as sources of iron for the building of hemoglobin. Gladstone[8] on the other hand found that iron storage in the last part of foetal life was not so marked as previously contended. Gladstone based

his findings on the iron content of the liver and did not take
into consideration the high hemoglobin level of the new born, an
available store of iron. Our primary observation then, that iron
storage is high in the later months of pregnancy is not erroneous
when both liver and hemoglobin content are considered. Thus the
premature is deprived of the benefits of iron storage normally
occurring in the final trimester of pregnancy. Another factor
which may play a part in the etiology of nutritional anemias in
prematures, is a diminished efficiency of hemoglobin synthesis.
We know that nutritional disorders are more common in prematures,
due to their decreased ability to utilize food. Therefore, it does
not seem so far afield to conjure a hemoglobin deficiency on this
basis.

The higher incidence in twins is probably due to the fact that
the occurrance of prematures in twins is notoriously high. Moreover
the maternal supply of iron for foetal storage must be divided
between two organisms, each receiving approximately half the avail-
able amount. Thus we have prematures and twins beginning life with
deficient iron stores, and almost certainly a diminished ability to
utilize foods and synthesize hemoglobin.

The affection may occur in breast fed infants, but here it is
much less common. The incidence in the artifically fed infant is
higher, especially those fed exclusively on a milk diet. The low
iron content of milk, which is considered the main factor in these
cases, has been previously mentioned. Here we are perhaps also
concerned with a congenitally inferior infant as well as a diet
deficient in iron, although, as will be shown later, a proper diet

containing sufficient iron, will usually prevent or cure the condition.

Rate of growth may also play a part in the production of nutritional anemias. Rapid growth favors anemia while anemias may stunt growth. The premature may quadruple its weight while an eight pound baby doubles his weight. As the rate of growth increases the hemoglobin tends to fall.[13]

Thus in considering the etiology of nutritional anemia we are concerned chiefly with iron deficiency and decreased hemoglobin synthesis. Iron deficiency seems to be the most important, although cases of nutritional anemia have been observed in infants that are receiving diets containing sufficient iron. Some factor influencing hemoglobin synthesis is probably concerned in these cases. Conversely, the disease does not occur in all infants maintained on dificient diets. Such factors as larger stores of iron or slower rate of growth are concerned in these cases.

The onset of the disease is insidious. The striking physical sign is pallor. In fact, not infrequently, no other physical signs can be observed. There is rarely a yellow tinge to the skin. The spleen and liver are usually not noticeably enlarged, which lead us afield from the assumption that the decreased hemoglobin level is due to an increased rate of blood destruction. The physical state may remain surprisingly good, but usually if the anemia becomes of sufficient long standing the muscles become flabby and eventually growth is affected. Pulse rate and rate of respiration are unreliable. The child is usually irritable and peevish. The superficial lymph glands, tonsils, liver and spleen may become

enlarged, although this is by no means the rule.

The blood picture is essentially that of chlorosis. In most early cases a lowering of the hemoglobin and achromia are the only blood changes of note. The hemoglobin level is usually below 60% and may be as low as 10%. Values around 30% to 50% are most common. The red cells for the most part are not affected in number and in most early cases are just slightly below the normal level. In cases of long standing in which anorexia is marked a low red count may be expected. Undoubtedly the bone marrow suffers as a result of the existant malnutrition. In such cases red cell counts as low as 1,000,000 have been observed.

The color index, however, is usually on the negative side. Achromia is the rule and is present in varying degrees. Poikilocytosis and anisocytosis may be seen at times, as well as various degrees of basiphilic stippling. These changes however are usually not marked and when they do occur are usually associated with diminution of red cells. The presence of neticulocytes in abnormal numbers as evidence of active blood regeneration is as a rule not marked.

Immature white blood cells of myeloid or lymphoid series are not usually present. In fact, the bone marrow is seldom affected enough to produce a change in the white cells or platelets. The resistence of the red blood cells to hypotonic saline is normal. There is no evidence of blood destruction. Gastric analysis shows normal or reduced acidity but not achlorhydria.[1]

To diagnose nutritional anemia, secondary anemias due to an infectuous or toxic process must be excluded. The absence of a thermal reaction, sudden onset and rapid course, with evidence of definite bone marrow involvement will usually exclude these conditions.

A blood picture showing many immature forms and a positive color index would tend to exclude nutritional anemia and point to a disease causing a primary disturbance of the hemopoetic organs. The absence of the bizarre blood picture tends to exclude von Jaksch's anemia.

The disease is more common in twins, prematures, and infants maintained solely on a milk diet. Thus a history of these conditions will aid in the diagnosis of nutritional anemia.

Diagnosis from the anemias associated with congenital lues may be made by the absence of the usual luetic stigmata and a negative Wassermann.

The chlorosis or chloranemia of infancy may be considered identical with nutritional anemia if a poor dietary is the chief eteologic factor. This condition is either due to hereditary lues or prolonged feeding on milk [14] Lucas [15] does not consider the so-called infantile type of chlorosis a true chlorosis. He contends that they are due to an iron deficiency and occur most commonly in twins and prematures, and that in true chlorosis the anemia is due to an increase in the blood plasma.

Not infrequently secondary anemias are observed in conjunction with scurvy and rickets. Cases of nutritional anemia do not exhibit the clinical picture of these affections. It is true that scurvy and rickets are nutritional disorders and that the anemias are secondary to a poor dietary, however, nutritional anemia is concerned chiefly with an iron deficiency, is a clinical entity in most cases, and is not primarily concerned with a avitaminosis.

Nutritional anemia tends to be chronic, is seldom fatal, and

under proper therapeutic measures the prognosis is quite favorable.
Response is less striking in cases of long standing, and in those
cases complicated with infections, to which such patients are particu-
larly susceptable. Death, if it occurs, is usually due to an inter-
current infection. Cases occuring before nine months tend to
recover spontaneously as the child begins to consume a varied dietary.

In considering the treatment of nutritional anemia it will be
well to recall that in this disease we are primarily concerned
with a hemoglobin deficiency and not a reduction in the red cell
count. Thus the therapeutic measures must first be directed towards
hemoglobin synthesis. It has been necessary then to exclude to some
extent, that portion of the literature which deals with therapy of
mere secondary anemias of children, which are not purported to be
on a nutritional basis.

In the main the treatment consists of a regulation of the diet
and hygenic habits. A well balanced diet of the needed amounts of
protein, fats, carbohydrates, inorganic salts, water and vitamins
in proportion to satisfy the structural and energy requirements of
the growing infant is indicated. The attack is largely from a
dietary standpoint, however, in cases where the anemia is complicated
by an infectuous or toxic process and reduction in red cells is
alarming, transfusions are indicated. Frequent small transfusions
(5- 10 c.c. per pound of body weight) seem to stimulate the bone
marrow better than single large transfusions. Clinical condition
and severity of anemia should determine if transfusion is necessary.
Moreover, transfusions may be used to protect against intercurrent

infections or to shorten the period of dietary treatment. The
most important indication for transfusion is cardiac embarrassment.[1]

Iron is of definite value and may be administered as reduced
iron, iron and ammonium citrate, iron citrate or chloride or Blauds'
mass. Iron and ammonium citrate has advantages, as larger amounts
may be given, it is readily saluable, and may be added to milk. The
taste of the milk so treated is altered very little and if sweetened
is well taken. The drug has no astringent action on mucous membranes
and no discoloration of the teeth occurs. There are no ill effects
except an occasional occurrence of slight diorrhea. The feces will
be black due to excretion of excess iron. The recommended dosage is
3 to 4 grams given daily over a period of three weeks and continued
small doses for many weeks to maintain the beneficial results.[1]

As far back as 1899 Abderhalden [12] produced nutritional anemias
experimentally, but found that the addition of inorganic iron did not
bring about any increase in hemoglobin. This seems to be the usual
observation in strict nutritional anemias. Secondary anemias on
infectuous or toxic basis, however, usually respond well to inorganic
iron after the infectuous or toxic agent has been irradicated.
Concerning this failure of iron Abderhalden says; "the mere fact
that the addition of iron, to nutriment poor in iron does not have
any distinct influence upon the formation of hemoglobin in no way
speaks against the participation of inorganic iron in the synthesis
of hemoglobin in the case of normal nutrition, but it indicates that
other building material is wanting as well as the iron."

From that time until 1928 when Hart and Steenbock [15] published

their observations on experimentally produced nutritional anemia
on rats, there is no evidence in the literature as to the exact
nature of this other building material. Such food stuffs as liver,
egg yolk, beef, green vegetables and cereals were found to enhance
the curative powers of iron but the substance primarily concerned
was not known.

Hart, Steenbock et al began a series of experimental studies
on iron metabolism in the rat.[15] During the course of their experiments
they found, that young rats when weaned at three or four weeks of age
and placed on a diet of cows' whole milk, that a profound anemia,
characterized by very low hemoglobin would develope in the course of
a few weeks.

These same investigators then administered inorganic iron salts
to the anemic rats. The chloride, sulphate, acetate, citrate and
phosphate were all used and were fed at such a level as to introduce
0.5 mgm. of fe. daily, six times per week. These preparations failed
to increase materially the hemoglobin level in rats made anemic by a
cows milk diet. The ashed residues from dried beef liver, dried
lettuce and yellow corn, and acid extracts of the same, when fed at
such a level as to introduce 0.5 mgm. of fe. six times per week were
found to be fairly effective in alleviating the anemia. They con-
cluded then that the ashes and ash extracts contained in addition to
iron some other inorganic substance, or substances vitally concerned
in the building of hemoglobin.[18]

The Wisconsin workers then studied the effect of a liver prepara-
tion from Eli Lilly and Co. It was essentially the same as that
found so effective in the treatment of pernicious anemia. They wanted

to study it especially, because it is low in iron. At the same time they studied the effect of the addition of 0.25 mgm. of copper as Cu S 0 4 to the 0.5 mgm. of fe. and whole milk diet. This was done at first in but one animal and the response was surprising. "Hemoglobin at the beginning of the experiment was 2.68 gm. per 100 c. c. - in two weeks it was 9.35 gm. - in four weeks 10.94 gm. and in six weeks 13.34 gm. Without the copper addition the rise in hemoglobin would not have occurred." [15] Further experiments on copper, by the same men gave similar results and strengthened this view. [17-18-25-26]

This of course attracted the attention of a number of scientists who immediately began experiments on the supplementary effect of copper and other inorganic substances on iron in the synthesis of hemoglobin.

Titus et al [19] in 1928 reported that manganese added to a milk iron diet seemed to give almost, if not quite, as good results in the building of hemoglobin as did copper added in the same way.

Mitchell and Miller [20] in a study of iron, copper, and manganese reported a slow but definite response to pure iron salts when fed to anemic rats. The response was directly proportioned to the amount of iron fed. They did however confirm the supplementary action of copper on iron in hemoglobin synthesis, but observed that manganese did not share this faculty with copper.

Beard and Meyers [21] in a series of investigations found little reason to believe that copper has any specific action in hemoglobin synthesis, and held that iron alone is capable of causing hemoglobin regeneration.

Later Keil and Nelson [23] after a series of experiments on
nutritional anemia in rats came to the conclusion that pure iron
as ferric chloride when added to milk collected in glass does not
cause hemoglobin regeneration. They also found that salts of
vanadium, titanium, manganese, nickel, arsenic, germanium, zinc,
chromium, cobalt, tin and mercury also failed to stimulate regen-
eration of hemoglobin when added to milk collected in glass (to
prevent copper contamination) and supplemented with pure iron as ferric
chloride. Also that copper was the only element of those tested which
had a positive effect on hemoglobin building, thus supporting the
view that copper plays a specific role in hemoglobin regeneration.

Orten, Underhill and Lewis [24] studying the effect of certain
metals in the prevention of nutritional anemia in rats came to the
following conclusions;

1. "Inorganic iron fails to prevent the development of a
nutritional anemia in the rat on a milk diet, whereas, iron supple-
mented by copper permits the maintenance of an approximately normal
hemoglobin level."

2. "Iron supplemented by manganese fails to prevent the develop-
ment of nutritional anemia."

3. " A mixture of manganese, cobalt, nickel and zinc supple-
menting iron has no prophylactic action in nutritional anemia, while
the same mixture plus copper prevents a decrease in the hemoglobin
level."

4. "Of all the metals studied copper alone has the ability
to supplement iron preventing the nutritional anemia of the rat."

Levine, Culp, and Anderson [38] studied the value of various

vegetables in the treatment of nutritional anemias on rats, from
the standpoint of iron and copper content of the various foods.

Dried spinach when fed ad libitum and yielding an average
daily intake of 0.43 mgm. of iron and 0.0061 mgm. of copper effected
hemoglobin regeneration in three to four weeks, turnip greens fed
at a level furnishing 0.425 mgm. of iron and 0.0179 mgm. of copper
brought about a rapid regeneration in three to four weeks. Lettuce
plus tomatoe mixture, lettuce, spinach and broccoli, all fed at a
level affording 0.20 mgm. of iron but different amounts of copper,
permitted hemoglobin regeneration in four to five, five to six,
six to seven, six to seven, and seven to eight weeks respectively
in the order of the decreasing copper intake. With the iron intake
remaining the same the hemoglobin regeneration increased as greater
amounts of copper were ingested. All other sources of iron and
copper were eliminated. The above vegetables are, according to
this experiment, important sources of minerals concerned in normal
blood function. These same workers found that iron alone or copper
alone when fed in the form of inorganic salt solutions permitted
only partial blood regeneration whereas solutions containing both
iron and copper effected rapid recovery of hemoglobin.[38]

Levine Remington and Culp [41] studied the effect of oysters
in nutritional anemia. The oyster is a good source of vitamins
A. B. C. and D. and contains iron, copper, manganese, zinc, lead
and arsenic. They found the oyster to be of definite value in
correcting nutritional anemia and were able to show that its effects
were due to its iron, copper and manganese content, but did not
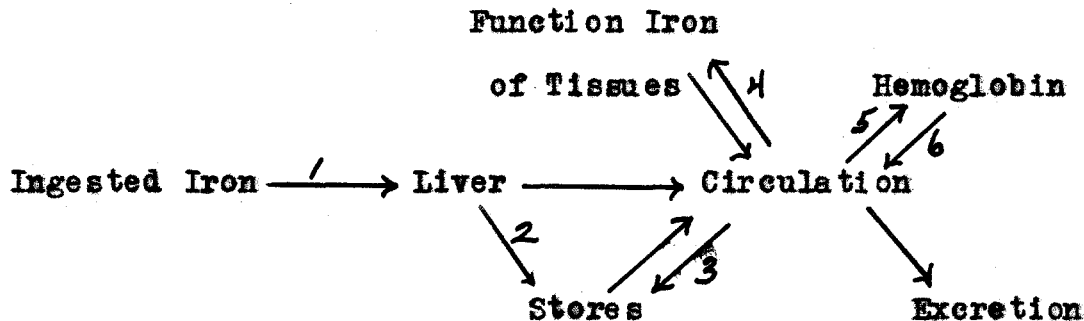determine whether or not manganese was necessary in supplementing

the iron and copper.

Hart, Steenbock, Waddell and Elvehjem, following additional experiments on rats [25] and pigs [26] continue in their contention that copper plays a specific role in supplementing iron in hemoglobin regeneration, and that copper is the only such element.

It is plain to see that the subject of copper in nutrition has become controversial and that there are some differences of opinion. To explain this discrepancy would be difficult and rather out of the question at the present time. The greatest concensus of opinion seems to substantiate the hypothesis that copper is effective in preventing and curing experimentally produced nutritional anemias in rats, when added to a diet of iron and milk.

The beneficial effects of liver in the treatment of anemias may be due as pointed out by Hart et al[15] to the high copper content of liver. Three hundred grams of fresh ox liver was assayed to contain 4 mgm. of copper. The same amount of fresh calves liver contains 30 mgm. of copper. The Eli Lilly liver preparation contained 0.016% copper.[15]

Hugh Josephs has been one of the most active men in dealing with the problem of copper in hemoglobin synthesis. He has studied the effect of copper on iron metabolism and suggests the possible manner in which copper acts.[9] Previously, in this paper a partial review of Josephs work on iron metabolism has been made (see p.9). For purposes of clarity a repreduction of his diagram of iron metabolism follows:

Function Iron

of Tissues   Hemoglobin

Ingested Iron ⟶ Liver ⟶ Circulation

Stores   Excretion

Josephs' observations led him to suspect that copper has no
effect on the "fixed" or function iron of the tissues while it
does appear to influence the mobile portion of the iron "stores."
He concludes that the effect of copper may be produced in one of
three ways as follows:

1. "Copper may act at the arrows 2 and 3 preventing the cells
that ordinarily store iron from taking it up, or causing them to
give it up if it is already there, or in other words changing the
conditions of equilibrium in the direction of a decrease in the
ordinarily great affinity of these cells for iron."

2. "It may act at arrow 5 either by generally stimulating the
hemopoetic tissue or by specifically increasing the rate of hemo-
globin formation by catalytic action or by other means."

3. "It may act at arrow 6 by decreasing the rate of hemoglobin
breakdown. Nothing in this work helps in deciding where the action
takes place."

His work has shown that during the nursing period the retained
iron was sufficient to account for the increase (total) in hemoglobin,
but that if a milk diet was continued beyond the nursing period all

the retained iron went to maintaining the tissue iron at a
constant minimal concentration which he considers the "function
iron" of the tissues. When extra iron was given it was divided
between the hemoglobin and the tissues most of it going to the
hemoglobin. When copper was added a still greater portion of the
iron went to the hemoglobin and the tissue iron was reduced in
amount but never went below that concentration level considered
to represent the function iron of the tissues. Copper had no effect
on iron retention.

Thus it is quite evident that copper does play a definite role
in iron metabolism. The exact manner in which it functions is not
known, perhaps catalytic. Copper is not a part of the hemoglobin
molecule itself but is a normal component of blood and has an import-
ant function in the formation of hemoglobin and in metabolism.[30]

The work of Hart and others proved to be a stimulus to men in
the clinical field, and recent literature is not wanting of reports
of the effect of copper on nutritional anemia in human infants.

Hill [27] in 1929 published an interesting paper on twenty-eight
cases of nutritional anemia. Although he makes no mention of copper
his work is considered here for it serves to describe nutritional
anemia from a laboratory standpoint and point out the shortcomings
of iron therapy alone. Moreover, it serves to parallel some of the
work done on rats. After investigating and treating twenty-eight
cases Hill came to the following conclusions:

1. "Nutritional anemia in infancy is a definite deficiency
disease comparable to rickets or scurvy."

2.   "There is no reason for supposing that there is any active
injury to the blood ----ei hemolysis."

3.   "Inorganic iron alone (ferricum reduction) will in some cases
bring about a satisfactory rise in hemoglobin indicating that
inorganic iron can be used in hemoglobin synthesis."

4.   "Liver alone is also sufficient in some cases, but the most
rapid hemoglobin synthesis is effected by the use of iron and liver
together."

It is evident, that although in some cases iron alone will aid
in hemoglobin synthesis, that there is some other substance which
is capable of definitely enhancing it's value. This substance is
undoubtedly contained in liver.

Hill recommends reduced iron, grains two, twice a day and two
to four tablespoons of liver daily. Finely ground raw liver is
placed in a cheese cloth bag and dipped in boiling water for two
minutes. Then made finer by mashing with a spoon and feeding as a
thick soup.

Following is the list of Hills twenty-eight cases with age,
hemoglobin percentage, red cell count and apparent etiology. Note
the preponderance of color indices on the negative side, and the
high incidence in twins and prematures.

	Age	Hemoglobin	Erythrocytes	Apparent Etiology.
1.	5 mo.	64	3,120,000	Twin
2.	5 mo.	63	3,600,000	"
3.	23 mo.	43	2,952,000	Milk diet
4.	2 mo.	54	3,216,000	"

	Age	Hemoglobin	Erythrocytes	Apparent Etiology
5.	4½ mo.	52	3,500,000	Twins
6.	19 mo.	41	4,600,000	Milk Diet
7.	7 mo.	21	3,700,000	Twin
8.	13 mo.	31	5,616,000	Premature
9.	8 weeks	27	3,900,000	"
10.	11 mo.	67	4,300,000	--
11.	13 mo.	38	--	--
12.	14 mo.	35	5,600,000	Premature
13.	14 mo.	57	--	Premature-twin milk diet
14.	14 mo.	40	--	Premature-twin milk diet
15.	20 mo.	32	2,656,000	Premature milk diet
16.	21 mo.	50	2,000,000	Milk diet
17.	17 mo.	60	4,200,000	Twin
18.	17 mo.	70	4,000,000	"
19.	11 mo.	55	2,700,000	--
20.	19 mo.	44	4,656,000	Milk diet
21.	17 mo.	36	3,724,000	Premature
22.	17 mo.	46	4,110,000	--
23.	11 mo.	35	4,320,000	Milk diet
24.	27 mo.	38	4,650,000	"
25.	14 mo.	35	2,352,000	"
26.	3 7/12 yrs.	31	3,416,000	"
27.	3 4/12 yrs.	25	3,660,000	"
28.	16 mo.	40	3,800,000	Premature Milk diet

Keefer and Lang [36] noted a similar beneficial effect of the use of iron and liver together in the treatment of secondary anemias in infants.

A. Hymanson[37] also noticed the shortcomings of iron alone in the treatment of his cases of alimentary anemia. He considers the disease on the basis of a constitutional predisposition and supports the view by calling to attention the fact that it has occurred repeatedly in only one of a pair of twins. He recommends a varied diet of fruits and vegetable preparations and the early administration of them when indicated. He also uses ferri carbonas saccharatus and out of door life and sunlight as valuable adjuvants. Good results were obtained by this dietary regime in his hands.

It would be of interest to know if the value of iron has any relation to the severity of, or the length of time the anemia has existed. Perhaps if hemoglobin synthesis depends on copper in some manner we should find a greater amount of copper in the hemopoetic centers of the growing infant than in the adult. Also in infants with anemias the copper storehouse should be depleted.

Morrison and Nash[28] in the analysis of the livers of twenty-five infants found an average of 24.0 mgms. of copper per kilogram of fresh tissue, or six times the average for seven adults. The highest value for any adult was lower than any of the values for the infants with the exception of one, who died with a severe anemia. This infant showed a copper value of 6.9 mgm. per kilogram of fresh tissue. Here we have one case in which the copper stores of the liver were depleted during a severe anemia. Also a good indication at least, that infant livers contain more copper than those of adults. The single case of copper depletion in anemia is

of course insufficient evidence but it does suggest that copper is used in hemoglobin synthesis or blood regeneration.

Hugh Josephs [29] studied a group of anemic infants between the ages of three months and two years. His investigation was concerned with the treatment of secondary anemias, no attempt being made to classify them as to etiology or pathogenesis.

He administered a 10% solution of ferric and ammonium citrate giving 2 c.c. per kgm. of body weight per day. Also 1 c.c. of a 0.5% solution of Cu. S O 4.5 H 2 O per kgm. of body weight per day. The copper was always given in milk and usually divided into two doses. No disagreeable results were noted -- ei no vomiting or diorrhea.

On all his cases Josephs allowed a period of observation when no treatment was given in order to establish the diagnosis of secondary anemia and allow some time for spontaneous cure, which would exclude that case from the experiment. Following this period of observation iron alone was given in some cases and in others iron was given for a time and then copper was added.

After the iron was commenced the author noted in most cases a "latent" period of a few days when the hemoglobin did not rise or rose very gradually and was then followed by a more marked rise. This more abrupt rise did not occur until there had been a rise in reticulocytes. Thus it appears that the rise in reticulocytes is fairly reliable evidence of the end of this "latent" period.

In cases without copper the hemoglobin did rise but as the hemoglobin curve reached 50% it tended to flatten out. In cases

on copper and iron a continued rise up to about 70% was noted.

Josephs concluded that the effect of iron was first on the reticulocytes then on the hemoglobin and that copper appeared to accelerate hemoglobin formation but had no effect on reticulocytes.

In 1931 Lewis [31] reported a study of the effects of iron and copper in the anemias of infancy. He noticed that post-hemorrhagic anemias recovered as well with iron as without it, but that the same did not hold true for nutritional anemias. In his hands a child with nutritional anemia would improve under dietary treatment alone if vegetables, eggs and broths were added to the diet at eight months. Under copper and iron however, the recovery was more rapid. Thus, recovery under dietary management was a matter of months while with copper and iron the recovery was markedly hastened.

Lewis used saccharated ferrous carbonate in amounts varying from 15 to 60 grains daily and copper sulphate 0.5% solution one to two drams three times a day.

Cases were observed for three weeks without treatment. They were then put on iron alone for two weeks and then iron and copper. In the presence of infection treatment was of no avail but response was always good as soon as infection was irradicated. Thirty-four cases were observed.

		Before Treatment	After Treatment.
Maximum	r. b. c.	3,500,000	5,500,000
Minimum	r. b. c.	2,800,000	3,100,000
Average	r. b. c.	3,000,000	4,700,000

Maximum hemoglobin	60%	95%
Minimum hemoglobin	33%	60%
Average hemoglobin	45%	85%

from Lewis [31]

No case of nutritional anemia failed to respond to iron and copper. Clinical improvement was gradual in all cases, and the earliest signs of improvement were, an increase in appetite, gain in weight and increase in general well being. Red blood cells showed a prompt rise, in some cases going up to 4,500,000 in one month. Hemoglobin rose more slowly. There was always a marked improvement in the blood picture except in cases of infection during which there would be a drop in blood regeneration, and after subsidence of infection blood regeneration again occurred at a normal rate. In one case with T. B. of the hip the patient showed no improvement after fourteen weeks of treatment with iron, copper and transfusions.

Fifteen cases were followed for six months after treatment and in all, the red blood cells and hemoglobin remained normal. Lewis concludes his article by saying; "Iron and copper given in combination to children with nutritional and secondary anemia was more effective than iron alone. This was particularly noticeable in the nutritional series."

Caldwell and Dennett [32] have also conducted clinical experiments on the effect of copper and iron in the treatment of secondary anemias of children. They studied one hundred cases from the out-patient department of the New York Post Graduate Medical School and Hospital of Columbia University. Their patients ranged in age from

one month to twelve years. All showed no evidence of physical
defect except in many cases a noticeable degree of pallor, loss
of appetite, flabby muscles and retarded or stationary weight.
Thus, it may doubtless be assumed that at least a majority of the
anemias were on a nutritional basis. They also noticed that diorrhea,
intercurrent infection, or an active foci of infection caused a drop
in the hemoglobin and red blood cells regardless of treatment.

Dosage used was 0.25 mgm. of copper and 32 mgm. of elemental
iron in milk three times a day. Although 32 mgm. is less than the
usual dosage of iron they contended that much less iron was needed
when accompanied with copper.

In their cases under iron and copper therapy the hemoglobin
increased from 64% to 84% in four weeks and the red blood cells
increased from 3,605,000 to 4,408,000 in the same time.

They conclude that "iron is best utilized in presence of copper
which is necessary for hemoglobin synthesis."

Bloxsom [33] has made an enlightening study of the iron and copper
requirements in infancy. A series of fifty-seven infants taken at
random from his private practice were fed copper and iron daily in
the form of $CuSO_4$ and iron and ammonium citrate. This group of
fifty-seven infants showed an average increase of from 5% to 15%
in hemoglobin over a group of 104 infants not receiving copper and
iron. Thus, he noticed a marked increase in hemoglobin when copper
and iron were added to the diet.

Edward S. Mills [34] reports very beneficial results in his cases
of idiopathic (hypochromic) anemia in women with an iron copper
therapeusis.

Hugh Josephs [35] in a discussion of nutritional anemia, its prevention and treatment, concludes that copper appears to act as a catalyst in the synthesis of hemoglobin rather than in the formation of red blood cells, and that it has no effect on reticulocytes or urobilin excretion. He uses iron in the form of iron and ammonium citrate and contends that inorganic iron is far superior to iron in food for the rapid cure of patients with anemia probably because of its stimulating effects. He failed to observe any change in recovery from anemia when vegetables and eggs were included in the diet.

Following the administration of copper Josephs saw vomiting and diorrhea only in older children. Dosage of one c.c. of 0.5% solution of CuSO4 per kilogram of body weight was used, given in milk. He has never seen any pathological effect on the urine but admits that the effect has not been followed closely. Copper was never given for more than 7 to 10 days in his cases unless the hemoglobin was around 20 or 30% and then for not more than three weeks.

No other writers have mentioned any deleterious effects from copper except for an occasional case of diorrhea or vomiting, which cleared immediately on discontinuing or reducing the copper intake.

Apparently we have made an important step forward in the treatment of nutritional anemias. Several clinical trials of the iron-copper have been made and reported with universally beneficial results. In all cases the results coincided with those of Hart, Steenbock and others. Of course the work may be said to be still in its infancy, but the outlook is encouraging. The ultimate fate of this treatment will depend upon further clinical trial.

Another treatment of interest is the intraperitoneal injection of iron or whole blood.

Grulee and Sanford [39] recommend the intraperitoneal injection of iron in doses of 5 mgm. at three day intervals combined with one or two transfusions of blood. They have obtained good results with this treatment in secondary anemias but report that it apparently has no effect on the hemoglobin or red cells in primary anemias.

It is a question if such heroic treatment is advisable when a dietary regime has produced such good results in so many instances. In cases with very low red cell counts, or when there is evidence of circulatory failure perhaps such treatment is more clearly indicated.

Cecil Lorio [40] advocates the use of intraperitoneal injections of whole blood, adding that the procedure can easily be carried out without harm. An enlightening description of the fate of the injected blood is given in his article. [40]

The red blood cells of the citrated blood are absorbed quantitatively without disintegration, into the general circulation. They are first absorbed through the lymphatic vessels which establish drainage between the peritoneum and cisterna chyli. Cross sections of diaphragmatic peritoneum shows the red cells being taken up between the endothelial cells. Serum is rapidly absorbed but it may take a week before all of the red blood cells are completely removed from the peritoneal cavity.

In Lorios' opinion agglutination determinations prior to intraperitoneal transfusion is safer. He states further, that the accepted maximum dose of 15 c.c. of blood to the pound of body weight should

permit an increase of 20% to 30% in the hemoglobin. He further states that this treatment should be supplemented with a dietary sufficient in iron and hematin containing foods.[40]

With regard to additional factors Mayerson and Laurens [42] noted that regeneration of red blood cells and hemoglobin was faster in animals irradiated with carbon and mercury arcs, both being equally effective.

Foster[43] reports a slight but definite increase in hemoglobin and red blood cells following irridiation with a quartz mercury arc, but no effect from irradiation with a flaming carbon arc from "Sunshine" carbons.

Koessler et al [44] venture that blood regeneration cannot take place without the presence of vitamin A, and that addition of vitamin A to the diet of animals long depleted in their vitamin A reserve brings about a rapid formation of new blood cells. Further that the rate and intensity of blood regeneration is a function of the amount of vitamin A added, and that a definite relationship exists between a state of chronic vitamin deficiency and certain anemias. They recommend the routine use of a rationally balanced diet in all cases of anemia.

It is difficult to believe that vitamin starvation is the main etiologic factor in nutritional anemias after observing the work of others on iron and copper, although it is quite feasible that vitamin deficiency does play an important role. It may perhaps account for the differences seen in apparently parallel cases when treated in the same manner. Moreover, the factor of vitamin starvation may

serve to effect an inroad on the group previously captioned constitutionally predispositioned.

Since the treatment is largely concerned with iron and copper a brief resume of the iron content of various common foods will be given. Liver and green vegetables have been found to contain copper.

One ounce of beef juice contains 0.2 mgm. of iron but is not of much value since iron contained in hemoglobin and its derivatives is poorly absorbed by the gastro-intestinal tract.[4]

Yolk of egg contains	1.4 mgm.	of	iron
3 drams of oatmeal	0.3 "	"	"
1 ounce of cooked strained spinach	0.59 "	"	"
1 ounce of string beans	0.3 "	"	"
1 ounce of carrots	0.15 "	"	"
1 ounce of prune pulp	0.70 "	"	"

Egg yolk and prune pulp contain more iron than green vegetables and according to Morse[4] are less disturbing to the infant. Morse advocates the use of inorganic iron preparations in place of green vegetables, which he contends are liable to upset the gastrointestinal tract of the infant. Organic iron is not absorbed more readily than inorganic iron.[4]

Summary:

Blood formation in the infant, and the infantile blood picture have been touched upon. The main facts to be noted are that the

infant hemopoetic system reverts more readily and rapidly to
the embryonic condition, and that changes in the blood picture
are of less relative significance in the infant than in the adult.

Iron is stored in the foetus in the latter months of pregnancy
in the form of available iron in the liver, and an excess of hemoglobin.
The excess hemoglobin breaks down early as a physiologic process and
the iron so freed is stored in the liver as available iron for hemo-
globin synthesis during the early months of infancy when iron intake
is usually at a low level. Thus, prematures and twins are deprived
to a variable degree, of the iron normally stored in the latter months
of intra-uterine life.

Both human and cows' milk are notoriously low in iron and infants
fed solely on a milk diet receive an insufficient iron intake for
normal hemoglobin synthesis. This insufficient intake is compensated
for in the normal child by the iron stored during foetal life. In
children who begin life with deficient iron stores such as prematures
and twins, or those who are kept on a milk diet for long period of
time develope an iron starvation which becomes evident in the form
of a nutritional anemia which has been discussed.

Since nutritional anemia may occur at times in spite of the
presence of sufficient iron it is suggested that there is perhaps
a deficiency of some other factor vital to hemoglobin synthesis.

Iron, either organic or inorganic has been found to be beneficial
in most cases of anemia, but in the nutritional types its effect is
almost nil in some cases, and somewhat disappointing in the majority.

In the laboratory copper was found to enhance the curative

powers of iron in the treatment of nutritional anemia. This observation has been confirmed in the clinics. Since copper is not a component of hemoglobin it is infered that it acts as a catalyst. The possible manner in which copper may effect iron metabolism has been described.

In the more advanced cases it was found of value to administer intraperitoneal or intravenous blood transfusions. Such a measure was also recommended as a method of shortening the dietary treatment.

During infections or toxic reactions or if complicated by an active foci of infection the dietary treatment was found to be of no avail. Transfusions are recommended as a measure to combat these conditions as well as removal of the noxious agent.

Conclusions:

1. Nutritional anemia is a deficiency disease and a distinct clinical entity.

2. Nutritional anemia occurs most commonly in twins, prematures, and infants maintained on a milk diet for a long period of time.

3. The elements concerned in the deficiency are iron and copper. Iron assumes the role of a building material for hemoglobin while copper assumes the role of the builder.

4. Iron supplemented with copper is more effective in the treatment of nutritional anemia than iron alone.

5. Nutritional anemias can usually be treated successfully by a proper dietary regime, but advanced cases may require intraperitoneal or intravenous blood transfusions.

6. In the presence of an infectuous or toxic condition even iron- copper therapy is of no avail until the infectuous or toxic agent has been irradicated.

7. Nutritional anemia is not a fatal disease. Death usually occurs, if at all, due to an intercurrent infection.

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