THE MECHANISM OF ANEMIA*

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Anemia is a reduction below normal of the capacity of the blood to transport the oxygen necessary for all animal life. The body tissues must be supplied with many times as much oxygen as can be carried in physical solution in the plasma. The hemoglobin normally present (15 to 16 gm. per 100 c.c. of blood) increases one hundred times the power of the blood to transport oxygen by carrying it in chemical combination. This amount of hemoglobin in solution in the circulating blood would greatly increase the osmotic pressure of the plasma beyond that of the surrounding tissues and so dehydrate the tissues. Hemoglobin in a red cell is outside the plasma, does not affect the osmotic pressure, and yet functions efficiently as an oxygen carrier since absorption and release of oxygen is as efficient as if the hemoglobin were in solution in the plasma. The red cell is thus simply a container[1] for the necessary hemoglobin and functions as a cup on an endless-chain conveyor. It is normally filled with hemoglobin and is constantly making round trips from the lungs to the tissues. This conception of the function of the red cell applied to the different laboratory types of anemia is illustrated in Fig. 1. In addition to thinking of the red cell as a cup on an endless-

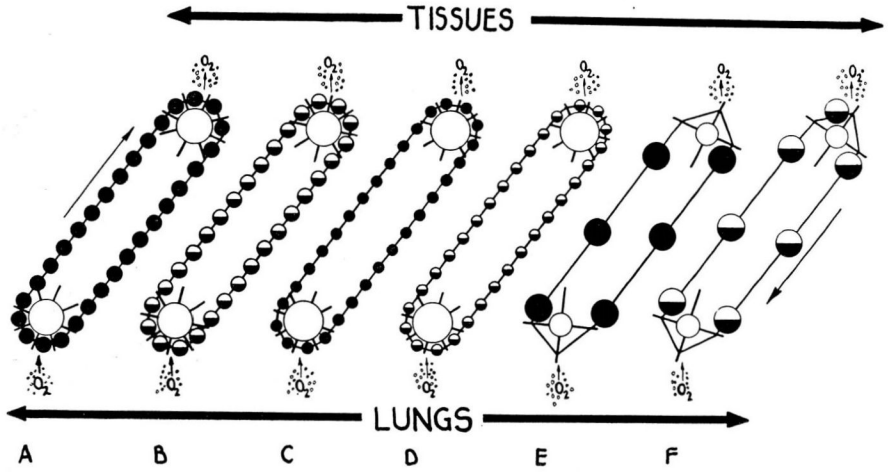

FIG. 1.—Schematic illustration of red cells functioning as units (cups) on an endless-chain conveyor. *A*, Normal red cells. *B*, Red cells of normal size partly filled with hemoglobin (normocytic, hypochromic anemia). *C*, Small red cells completely filled with hemoglobin (microcytic, hypochromic anemia). *D*, Small cells, partly filled with hemoglobin (microcytic, hypochromic anemia). *E*, Large cells, completely filled with hemoglobin (macrocytic, hyperchromic anemia). *F*, Large cells containing a normal amount of hemoglobin (macrocytic, normochromic anemia).

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chain conveyor, we should also visualize the total mass of circulating red cells as a vessel containing hemoglobin. The size of this vessel varies enormously in blood dyscrasias affecting the red cell as illustrated in Fig. 2.

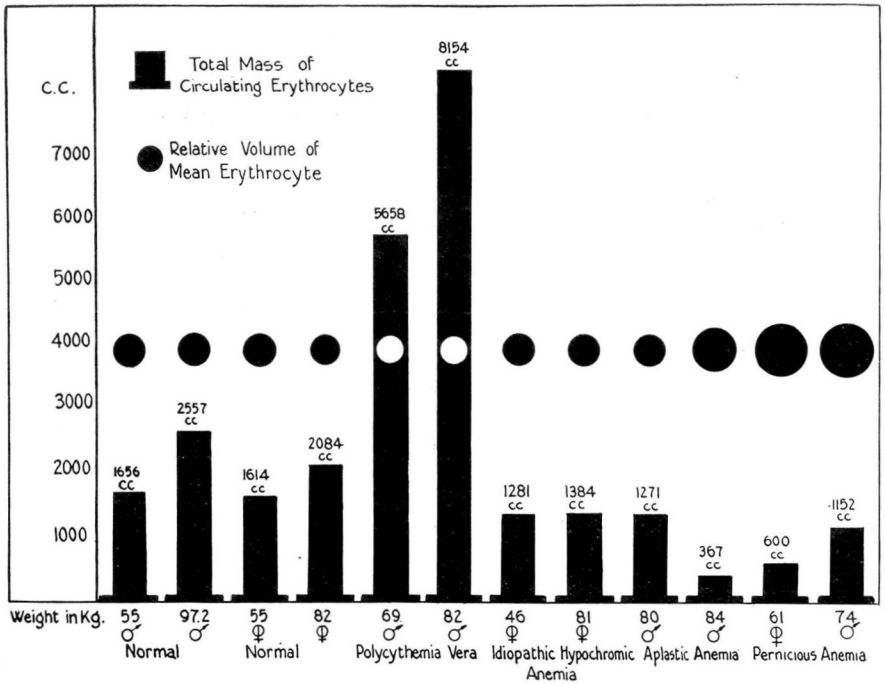
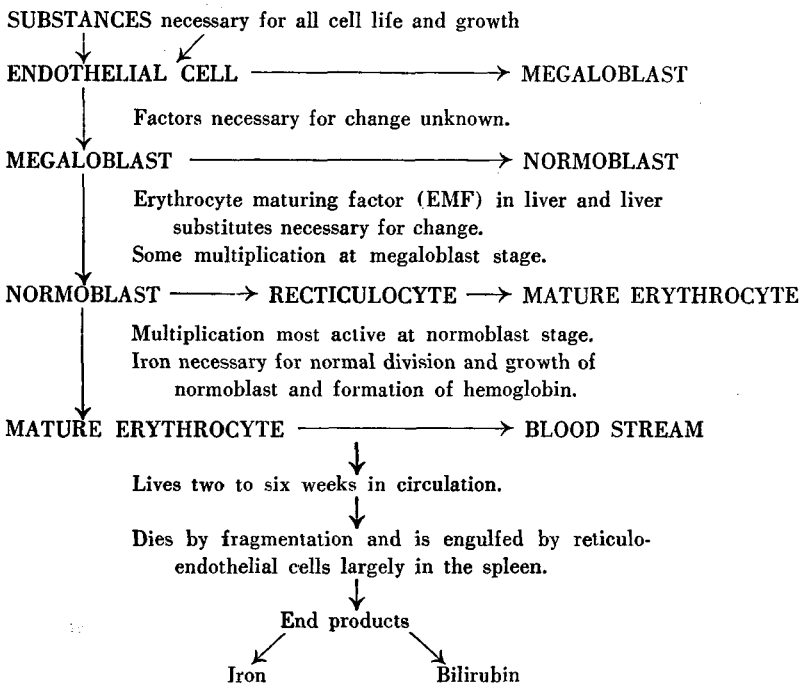


FIG. 2.—Variation in total mass of circulating red cells in various conditions. The circle indicates the relative volume of the unit of mass (the red cell) in each instance.

The problem of anemia is primarily concerned with hemoglobin and its carrier, the red cell. The span of life of a red cell averages thirty days. About a trillion red cells are formed and destroyed each day since the number normally in the circulation shows little variation. The life history of the erythrocyte is shown in Table I. To form red cells, nonspecific substances necessary for building all cells are needed. These are protein, fat, carbohydrate, water, vitamins, and mineral salts. Two specific substances are also required, the iron necessary for hemoglobin formation and the substance supplied by liver and liver substitutes necessary for the maturation of red cells. To evaluate an anemia, we must understand red cell formation in the marrow, know the level of circulating elements, and visualize the rate of red cell and hemoglobin destruction.

TABLE I

LIFE HISTORY OF THE ERYTHROCYTE



Certain indicators of red cell activity are necessary to evaluate the formation, circulation, and destruction of red cells. The red cell count and the hemoglobin content record only the balance between red cell formation and red cell destruction. Young red cells have the property of staining with certain dyes before they are fully matured. The number of reticulocytes or young cells which take this stain is an index of the rate of production of red cells ready to function in the blood stream or at least the rate of delivery of such cells from the marrow. The marrow may be hyperplastic or hyperactive with a low reticulocyte count in the circulation if the delivery of cells from the marrow is impaired. If the reticulocyte count in the circulation is high, the marrow is necessarily hyperplastic; if below normal the marrow may be aplastic, hypoplastic, or hyperplastic.

When a red cell is destroyed, hemoglobin is set free, iron is split off from the hemoglobin molecule, and bilirubin is formed as the end product of the pigment metabolism. Bilirubin so formed is adsorbed

by protein and is not easily excreted by the kidney. The capacity of the liver cells to excrete bilirubin so formed is also quickly exceeded, so an excessive destruction of red cells and hemoglobin is soon reflected in an increased bile pigment content of the plasma. In the absence of biliary obstruction and liver disease, the amount of bilirubin present in the plasma is an indicator of the rate of red cell and hemoglobin destruction. A correlation of the bilirubin content of the plasma and the reticulocyte level is shown in Table II.

TABLE II

RELATION OF BLOOD FORMATION AND DESTRUCTION TO BILIRUBIN AND RETICULOCYTE LEVEL

BILIRUBIN CONTENT (ICTERUS INDEX)	RECTICULOCYTE COUNT		
	INCREASED (OVER 1.5%)	NORMAL (0.5-1.5%)	DECREASED (UNDER 0.5%)
Increased (over 6 units)	Increased blood destruction with active bone marrow	Increased destruction without good marrow response	Increased destruction with inactive bone marrow or impaired delivery of red cells
Normal (4-6 units)	Active bone marrow without excessive destruction	Decreased marrow without excessive destruction of red cells	Decreased formation or impaired delivery of red cells without excessive destruction.
Decreased (under 4 units)	Decreased destruction of hemoglobin due to iron deficiency; active cell formation in marrow	Decreased destruction of hemoglobin. Decreased formation of hemoglobin; normal cell formation in marrow	Decreased destruction of hemoglobin. Decreased formation of hemoglobin. Decreased cell formation in marrow or impaired delivery of cells

If all elements necessary for red cell formation are deficient, the marrow cannot make the normal number of cells at the normal rate. The marrow functions at a low rate of speed but such cells as are delivered into the circulation are usually normal. The two specific elements, iron and erythrocyte maturing factor (EMF), are necessary if the marrow is to make a normal cell with a normal complement of hemoglobin. As the red cells develop in the bone marrow, they multiply actively at the megaloblast stage but are not ready for delivery from the marrow until completed by a substance formed by the interaction of a secretion of the stomach (the intrinsic factor of Castle) on food elements (the extrinsic factor of Castle) and stored in the liver. This substance has been designated by many names, as "liver principle," the "antianemic principle of Castle," the "pernicious anemia principle," and "anti-megalocyte principle." Its fundamental action is to mature the red cell, or prepare it for emergence from the marrow, so we have designated it

erythrocyte maturing factor (EMF). Since it is always necessary to know, in studying an anemia, whether there is a sufficient supply of this essential factor, we must have some indicator of its lack. The cell to which this substance (EMF) is supplied becomes smaller so a decrease in volume of the cell is characteristic of the maturation effected by the erythrocyte maturing factor and a macrocytosis is indicative of its lack. While a macrocytosis is usually an indicator of a deficiency of the erythrocyte maturing factor (EMF), cells of increased size may be due to other causes. A hyperplastic marrow, overactive in response to a great demand for red cells, may deliver red cells larger than normal. These are large because of rapid removal from the marrow before maturation is complete rather than a lack of erythrocyte maturing substance (EMF). Thus the hyperplastic marrow in response to rapid destruction of red cells in phenylhydrazine poisoning or in spherocytic jaundice may deliver macrocytic cells. A chronic hyperplasia of marrow in response to increased cell loss usually leads in time, however, to the formation of cells smaller than normal. Iron is the second specific element necessary for normal red cell formation. Without iron, hemoglobin cannot be formed. It is most probable also that iron stimulates the growth and multiplication of red cells at the normoblast stage where division is most active. With a decrease in the normal amount of hemoglobin in the blood, there is first a decrease in the concentration of hemoglobin in the red cells or decreased color index. Since there is no value in having red cell stroma without hemoglobin to fill it, if the color index continues low, the cells become smaller and the volume index decreases. The hypochromia shown by the lessened color index and volume index is a measure of the lack of iron.

Thus we have accurate indicators to show the balance between red cell formation and cell destruction (the red cell count and hemoglobin content), the rate of destruction of red cells (the icterus index), the rate of regeneration or delivery of red cells (the reticulocyte count), the lack of the erythrocyte maturing factor or EMF (macrocytosis), and a deficiency of iron (hypochromia and microcytosis) as tabulated in Table III. I have described elsewhere the technic of the blood exami-

TABLE III

MEASURES OF RED CELL ACTIVITY

FACTOR	INDICATOR
Balance of red cell and hemoglobin formation and destruction	Red cell count and hemoglobin content
Rate of destruction of red cells	Level of bile pigment in plasma
Rate of regeneration of red cells	Level of reticulocytes in circulation
Deficiency of iron	Hypochromia and microcytosis of red cells
Deficiency of erythrocyte maturing factor (EMF)	Macrocytosis of red cells

nation to supply such data.[2] A careful laboratory study is first necessary in every anemia to furnish the data outlined above. From the laboratory examination the anemia is classified on the basis of the number, size, and hemoglobin content of the mean red cell.[3] These studies are illustrated in Fig. 3. The relation of the blood findings to red cell formation and destruction is shown in Table IV.

TABLE IV

RELATION OF BLOOD FINDINGS TO RED CELL FORMATION AND DESTRUCTION

Active bone marrow	Increased number of reticulocytes, basophilia, nucleation. Slight increase in mean erythrocyte volume if reticulocytosis is marked. Often an increase in leucocytes and platelets unless destruction is more active than normal. The number of cells is increased
Inactive bone marrow	Decrease or absence of reticulocytes, basophilia and nucleation. If blood destruction is normal or increased, the cell count decreases
Increased red cell and hemoglobin destruction	Increase in bilirubin content of plasma; decrease in number of cells unless compensated for by increased marrow activity
Decreased hemoglobin destruction	Decrease in bilirubin content of plasma
Deficiency in erythrocyte maturing factor (pernicious anemia)	Anemia with increase in mean erythrocyte volume (increased volume index)
Deficiency in iron (iron deficiency anemia; chronic hemorrhagic anemia)	Anemia with hypochromia of red cells (decreased color index); microcytosis (decreased volume index); if hypochromia continues
Hemolytic anemia	Anemia with increased icterus index; reticulocytosis if marrow responds to increased need
Anemia due to decrease in amount or activity of marrow (aplastic or hypoplastic anemia)	Anemia with cells of normal size and hemoglobin content; decrease in reticulocytes

Since an anemia represents a loss of balance between red blood cell formation and destruction, an anemia can result only from increased blood loss without a compensating increase in blood formation, by decreased formation with a normal or accelerated blood loss, or by a combination of increased blood loss and decreased formation. A clinical classification of anemia on the basis of method of production with the more important clinical causes is given in Table V. In every anemia it is necessary to make both a laboratory and clinical classification.

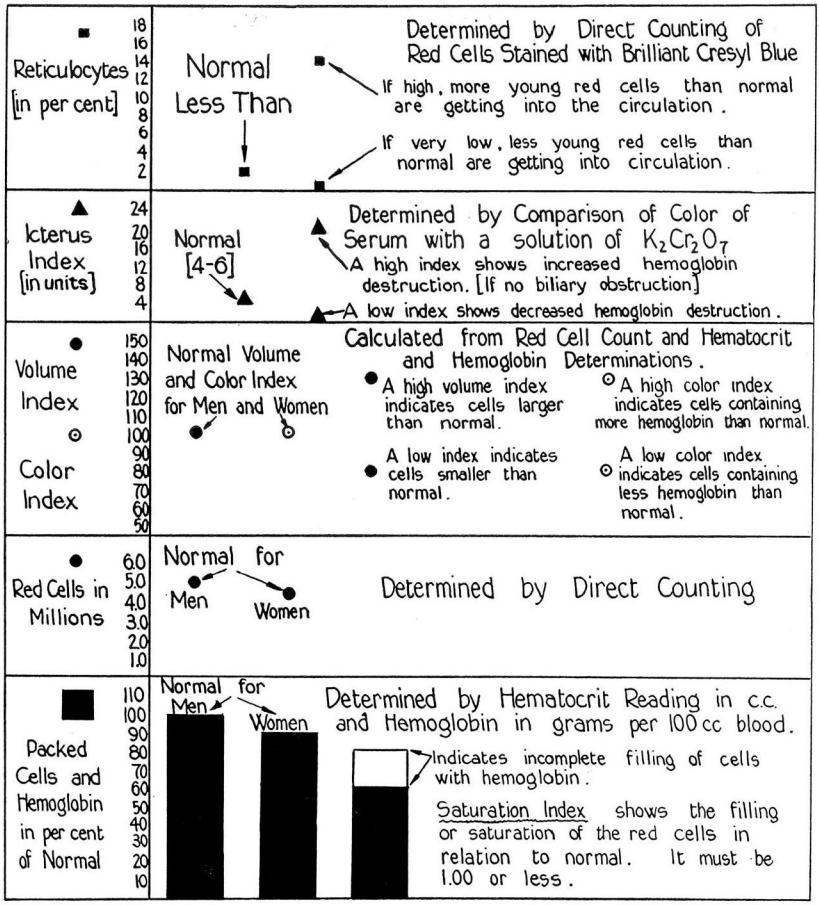


FIG. 3.—Study of blood and interpretation of findings in anemia.

TABLE V

CLINICAL CLASSIFICATION OF ANEMIA

I. Increased blood loss
   1. Mechanical loss from hemorrhage
   2. Accelerated red cell destruction by:
      a. Hemolytic agents (as phenylhydrazine or bacterial toxin)
      b. Rapid red cell removal from an abnormality of cell shape (as congenital hemolytic icterus), overactivity of reticulo-endothelial system, or defect in cell structure

II. Decreased blood formation
   1. Quantitative decrease in red marrow from aplasia as in benzol poisoning, or crowding out of erythrogenic tissue as in leucemia or myeloma
   2. Quantitative depression of marrow activity as by malignancy, hypometabolism, chronic toxemia such as nephritis or cachexia
   3. Qualitative decrease in marrow activity from deficiency of specific substances necessary for normal marrow activity
      a. Deficiency in supply, absorption, or use of erythrocyte maturing factor (EMF) as in pernicious anemia or sprue
      b. Deficiency in supply, absorption, or use of iron as in chronic hemorrhage, dietary lack, and idiopathic hypochromic anemia

With a careful study of the blood and determination of each of the indicators of red cell activity, a clinical study of the patient and a clinical classification of the anemia, the different types of anemia can be visualized by means of diagrams. In each diagram, the blood is depicted in relation to the three phases of the red cell, viz., (1) formation, (2) circulation, and (3) destruction. The fundamental fault in the production of the anemia is apparent in such a diagram, so the point of attack in treatment is evident.

In Fig. 4, the normal cell is shown in relation to formation, circulation, and destruction. The bone marrow is thought of as a gristmill with three hoppers supplying materials for making red cells. One hopper supplies the nonspecific elements and the other two the specific elements. Normally, the hoppers are full. The level in the mill indicates the relative fullness of the bone marrow. To maintain the normal balance between formation and destruction, nearly one trillion cells and 25 gm. hemoglobin must be formed daily. In the circle showing the normal circulation are 100 red cells with one reticulocyte. The cells are of normal size and hemoglobin content. The normal findings are shown below the circle. Old red cells are taken out by the reticuloendothelial cells, largely those of the spleen. If the blood count remains constant as it normally does, the same number must be taken out as are delivered to the blood stream by the marrow. As the hemoglobin is destroyed, iron is split off. Some of the iron is excreted but the larger part (85 per cent) is returned to the marrow to be used again. The end product of hemoglobin destruction is bilirubin which is excreted by the liver. The normal amount of bile pigment and iron formed is indicated by the level of these substances in the containers in which they are received. We think of the mill as functioning at a constant rate of speed so as to supply the same number of cells with the same hemoglobin content as are destroyed each day. The normal mean elapsed time between the beginning of formation of the cell and the ultimate disposal of it is thirty days.

Every anemia can be illustrated by such a diagram. In Fig. 5 is shown the red cell mechanism immediately after a large hemorrhage from the uterus. The cells remaining in the circulation are normal and the process of formation and destruction is unaltered. This state persists for only a short time, however, after the hemorrhage, when there is increased activity of the marrow to compensate for the blood lost. The icterus index falls (2 units) and the amount of bilirubin and iron set

free decreases, and the picture is now one of an iron deficiency anemia, shown in Fig. 6, where there is a defect in the supply of iron to the

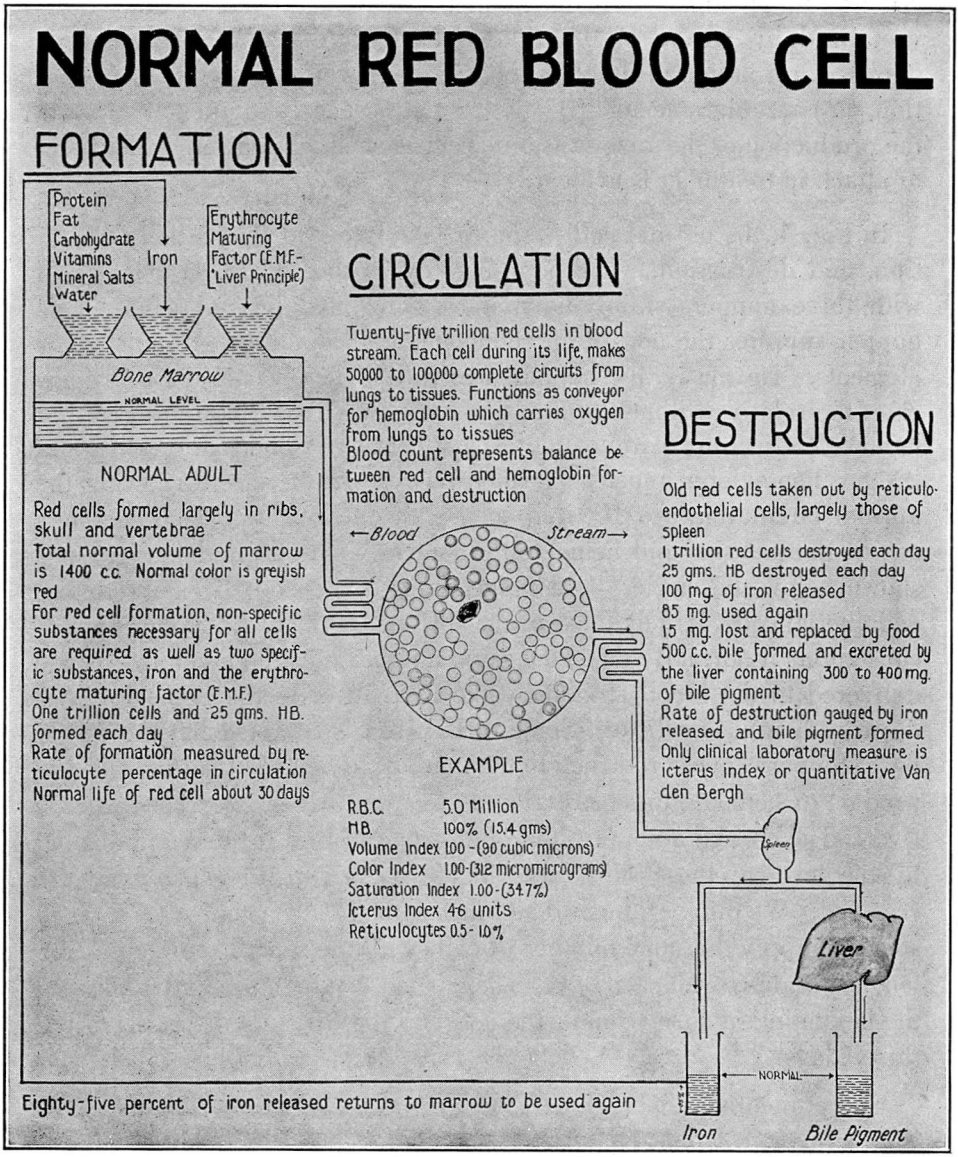


Fig. 4.—Normal red cell physiology.

marrow with the result that the cells are small (volume index 0.067) and have a decreased hemoglobin content (color index 0.4). The therapeutic indication is to stop the blood loss and supply an adequate amount of iron.

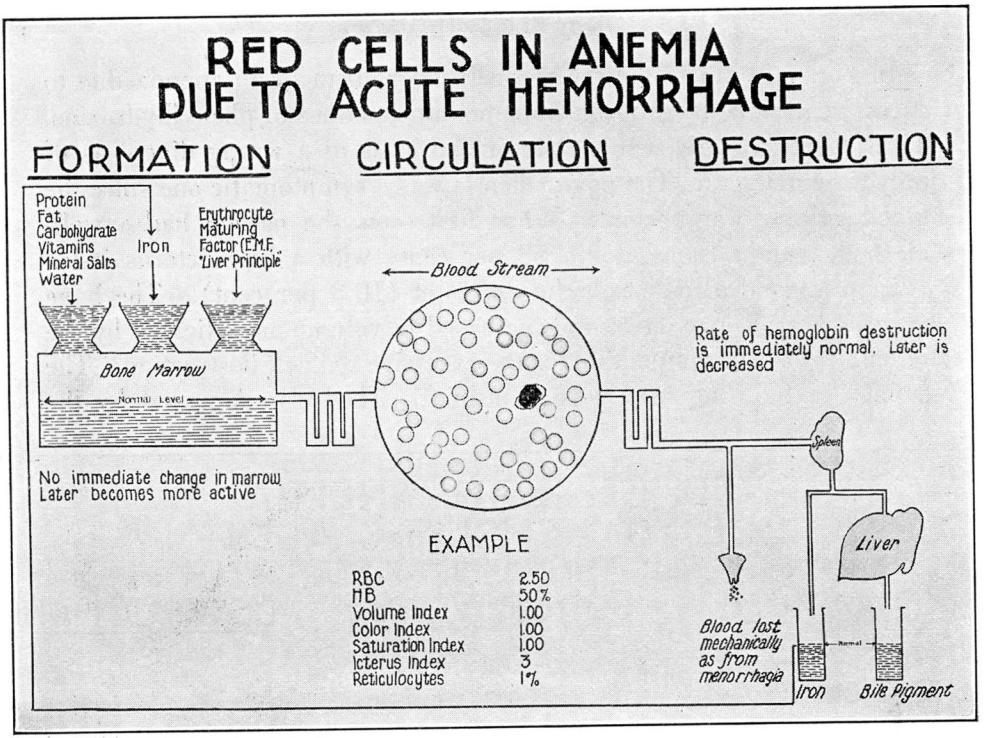


Fig. 5.—Physiology of red cells after an acute hemorrhage.

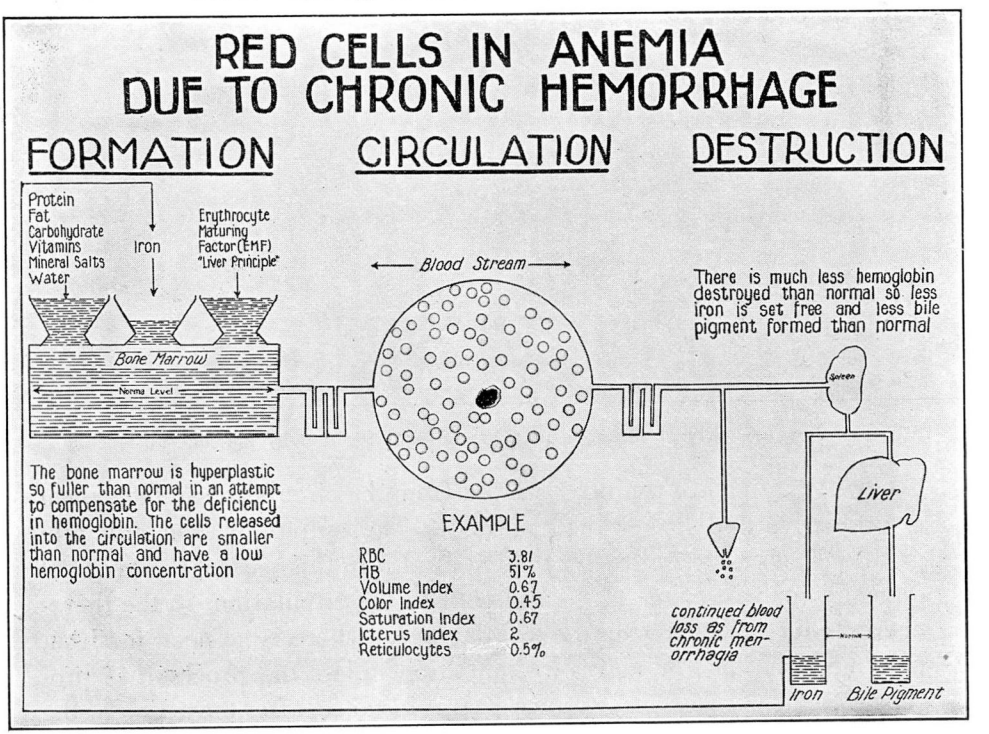


Fig. 6.—Physiology of red cells after a chronic hemorrhage.

In Fig. 7 is illustrated the red cell mechanism in an anemia due to excessive hemolysis resulting from the improper use of phenylhydrazine. This patient was given this drug on the basis of a wrong diagnosis of polycythemia vera. The polycythemia was a symptomatic one since the blood volume was normal. When first seen, the patient had a well-marked anemia (hemoglobin 58 per cent) with a high icterus index (25 units) and a high reticulocyte count (10.3 per cent). The bone marrow here is overactive and increased in volume as indicated by the reticulocytosis to compensate for the excessive red cell destruction. The supply of building materials is normal. The cells damaged by the

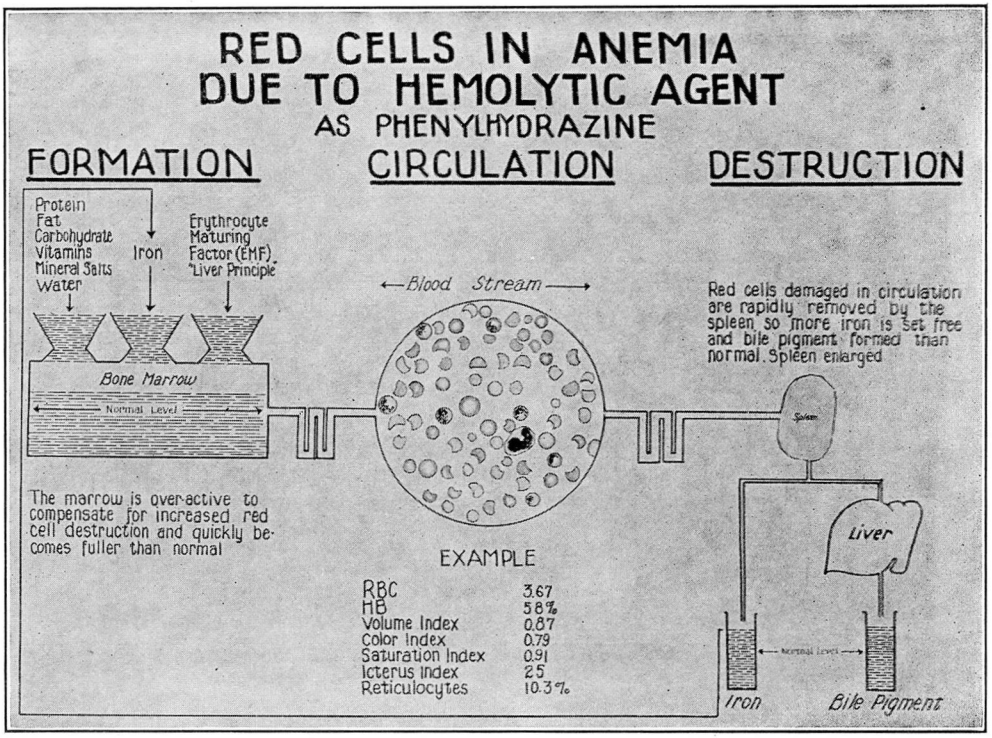


FIG. 7.—Physiology of red cells with excessive destruction by a toxic substance.

phenylhydrazine are rapidly removed from the circulation so the spleen is overactive and larger than normal. The output of iron and bile pigment is necessarily greater than normal. In this patient the primary difficulty is the damage to the red cells in the circulation, so the therapeutic indication is to stop the cell damage. There is no need for iron, liver preparations, or marrow stimulation unless the process has proceeded to the point of exhaustion. In this instance, after the action of the

drug was past, the spleen, icterus index, the reticulocyte count, the red cells, and hemoglobin all returned to normal.

In Fig. 8 is shown the red cell mechanism in congenital hemolytic icterus and spherocytic jaundice. This patient had a well-marked anemia with a high icterus index (15 units) indicating excessive blood destruction and a high recticulocyte count (10.8 per cent) showing good marrow response. The supply of building materials is ample so the hoppers are full and the active marrow is fuller than normal. The fundamental difficulty in this disease is an anatomic defect in the shape of the red cells which are spherocytic rather than normal biconcave

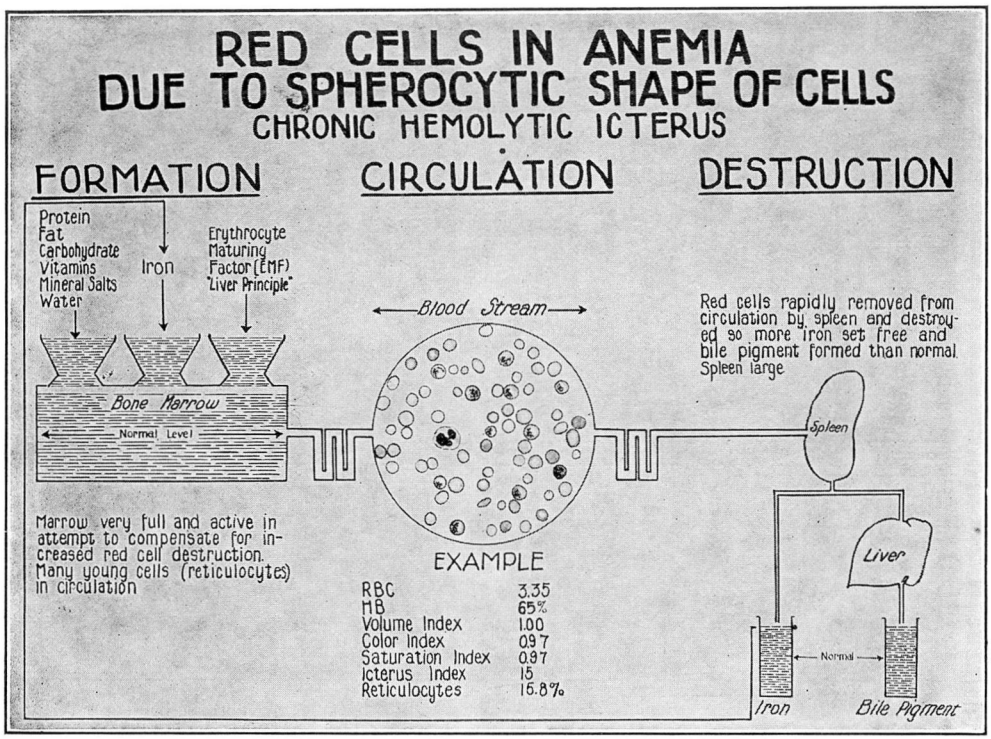


FIG. 8.—Physiology of red cells with excessive filtration by spleen (spherocytic anemia).

disks. As a result of this abnormal shape the cells are more fragile than normal[4] and are rapidly removed from the circulation by the spleen which is enlarged as a result of the increased activity. More iron and bilirubin than normal are poured out. Here the average length of life of the red cell is a few days instead of the usual thirty days. There is a rapid stream of cells from the site of origin, the bone marrow, to the place of destruction, the spleen. We cannot correct the anatomic defect

so the patient is treated by removing the filter. The abnormally shaped cells function normally if allowed to remain in the circulation. The anemia, reticulocytosis and jaundice all disappear after splenectomy, showing that the increased activity of the spleen is the cause of the anemia although the fundamental defect is in the bone marrow.

Sickle-cell anemia, shown in Fig. 9, has much in common with spherocytic anemia (congenital hemolytic icterus). Here also, there is a fundamental defect in the marrow with the delivery of cells of abnormal shape and probably with a greater tendency to

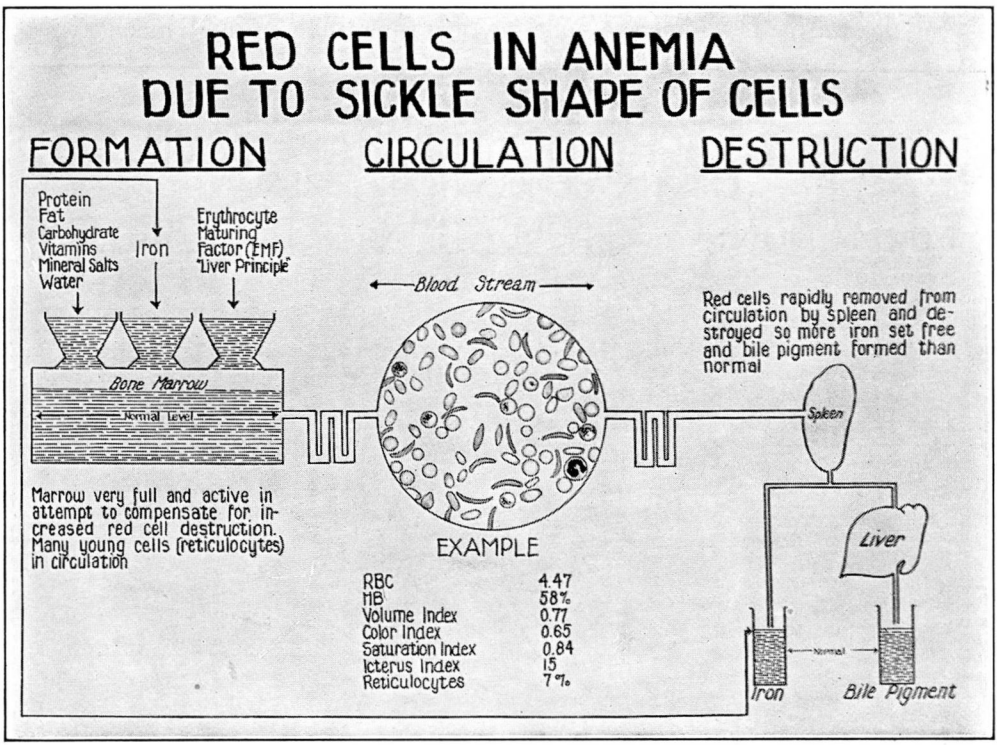


FIG. 9.—Physiology of red cells with excessive filtration by spleen (sickle-cell anemia).

fragment. The supply of building material is adequate, the marrow is overactive as shown by the reticulocytosis, and red cell destruction is excessive as shown by the increased icterus index. The spleen is enlarged at least early in the disease due to overactivity in removing excessive numbers of abnormal cells from the circulation. Splenectomy helps the anemia[5,6] but here the result differs from that seen in spherocytic anemia in that the patient continues to have some anemia after removal of the spleen. The increased cell destruction and formation also continue so the excessive activity of the spleen cannot be the

sole cause of the anemia. It is most probable that the red cells fragment more easily than normal and this fragmentation continues after splenectomy. There is no treatment for this phase of the disorder. Splenectomy removes only one factor in the anemia.

Fig. 10 illustrates the anemia due to marrow aplasia caused by the prolonged use of arsphenamine. The amount of functioning marrow tissue is decreased. In this instance the blood examination shows a marked anemia with cells of normal size (volume index, 0.97) and

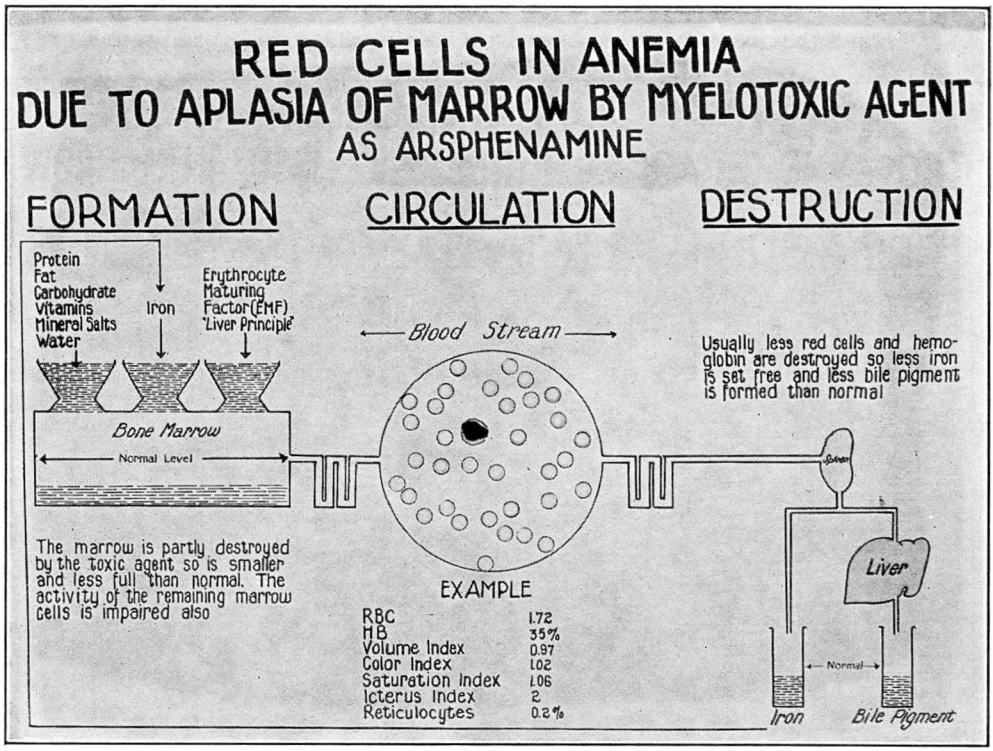


FIG. 10.—Physiology of red cells when formation of cells is decreased by aplasia of marrow.

hemoglobin content (color index, 1.02). The reticulocyte count is very low (0.2 per cent). The marrow is at a low level as indicated by the low red cell, white cell, reticulocyte, and platelet counts. The mill is greatly decreased in size although the supply of raw material is ample. There is less destruction of cells so the iron and bile pigment output are much below normal. It is apparent that this anemia can be treated only by measures designed to improve the size and function of the marrow. In this instance the marrow was permanently damaged and the patient finally died of the anemia.

Another type of anemia due to marrow deficiency is illustrated in Fig. 11. This is a myeloid leucemia with a marked anemia (hemoglobin 42 per cent). Here the marrow is full, but the increase in size is due to the hyperplasia of myeloid tissue at the expense of erythrogenic tissue, so there is a great decrease in red-cell-forming tissue and a consequent anemia. The spleen is also enlarged from infiltration of myeloid tissue and not from overactivity due to excessive cell destruction. There is less red cell destruction and so less iron is set free and less bile pigment formed. Here again, the indication for treatment of the anemia is to decrease the mass of myeloid tissue in the marrow by radiation or

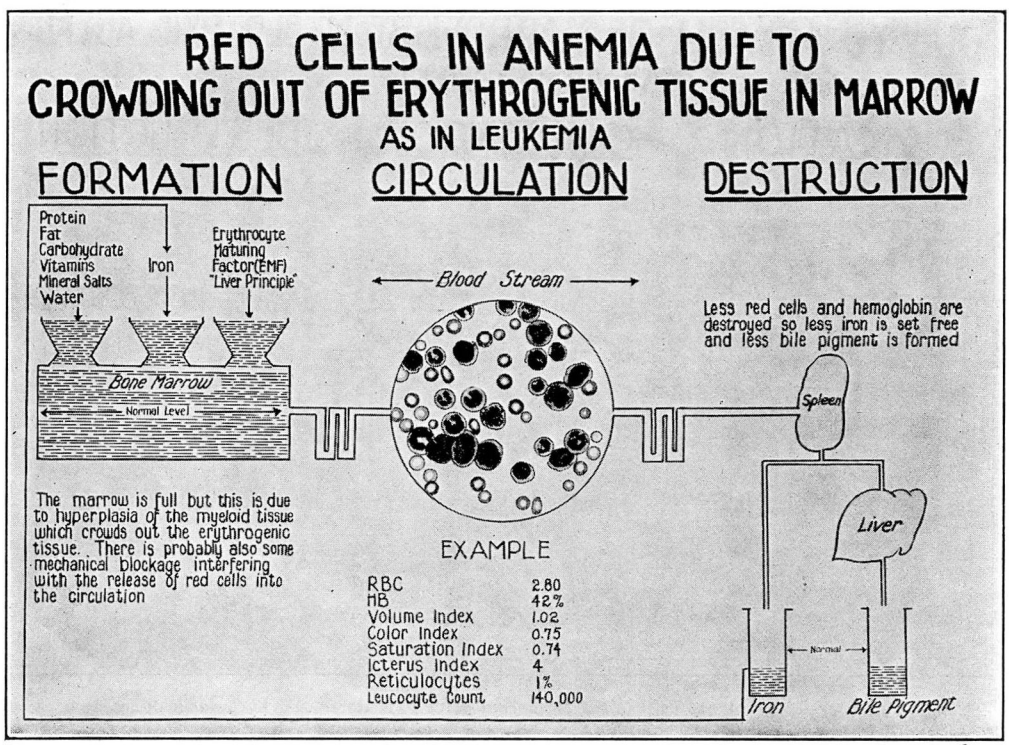


FIG. 11.—Physiology of red cells where the formation of red cells is diminished by crowding out of erythrogenic tissue.

medication to make room for the erythrogenic tissue. The red cell count often reveals more in leucemia than the number of white cells as it gauges the state of hyperplasia of the marrow which is more important than the white cell count.

Instead of a quantitative decrease in erythrogenic tissue, the total amount may be unchanged but the function be quantitatively depressed.

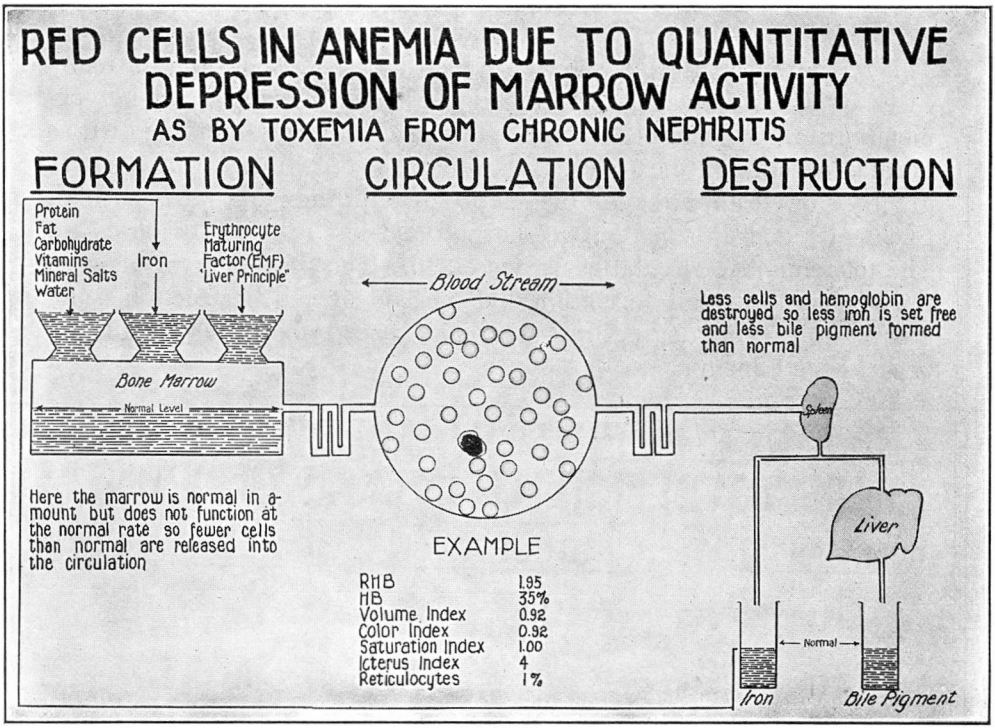


FIG. 12.—Physiology of red cells when the function of marrow is slowed up.

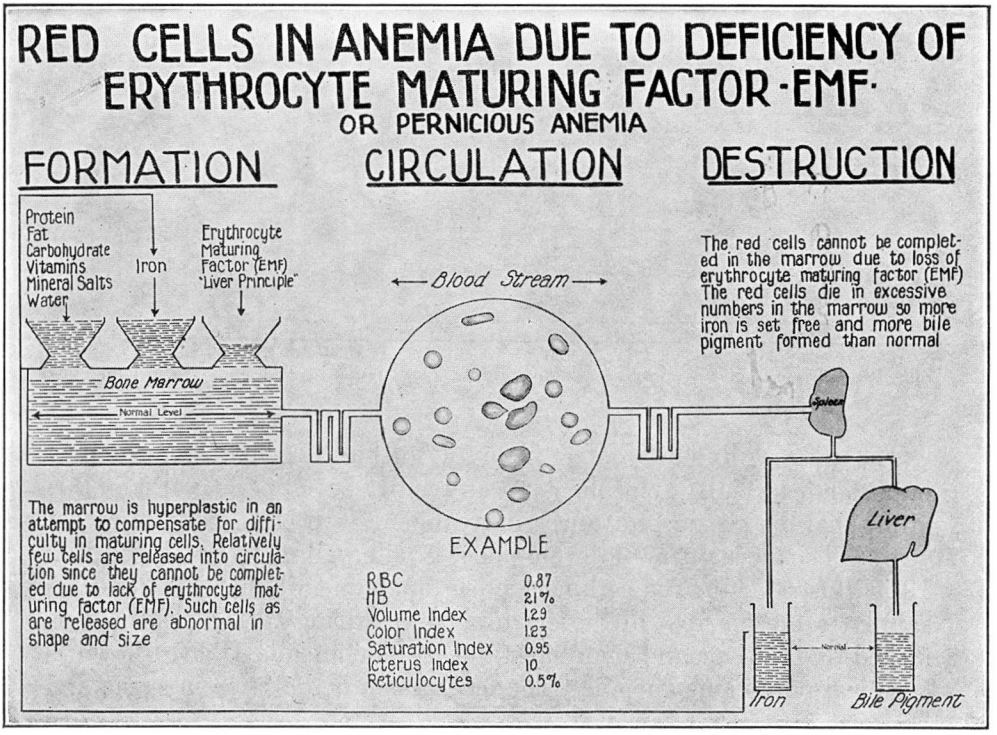


FIG. 13.—Physiology of red cells when building materials are deficient (pernicious anemia).

This type of mechanism is shown in Fig. 12. It is responsible for many cases of anemia such as malignancy, infections, toxemia, and hypometabolism. We can best visualize this mechanism by thinking of it as normal except for the speed with which the apparatus works. It is greatly slowed up, although the supply of building material is normal. Such cells as are turned out are normal and less cells are disposed of. The total number circulating is decreased. The time interval between the beginning of cell formation and the end of cell destruction is increased to varying degrees just as it is decreased in spherocytic anemia or sickle-cell anemia.

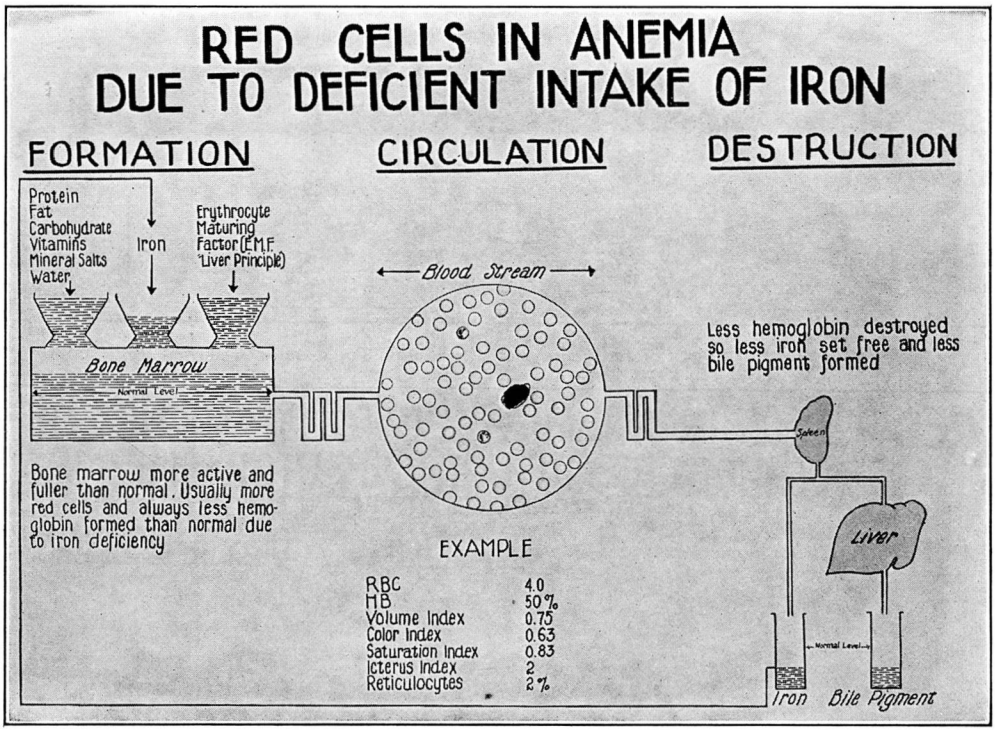


FIG. 14.—Physiology of red cells when building materials are deficient (iron deficiency anemia).

The anemias due to a defect in supply of building material are most important especially since the lack can readily be supplied. It is in this group that the greatest advances in treatment have been made in recent years. The mechanism of development is now well understood. In Fig. 13 is illustrated the red cell mechanism in an anemia due to a defect in supply to the marrow of the erythrocyte maturing factor (EMF) furnished by the liver and liver substitutes. The anemia I have shown is a typical pernicious anemia. The mechanism is the same in sprue and

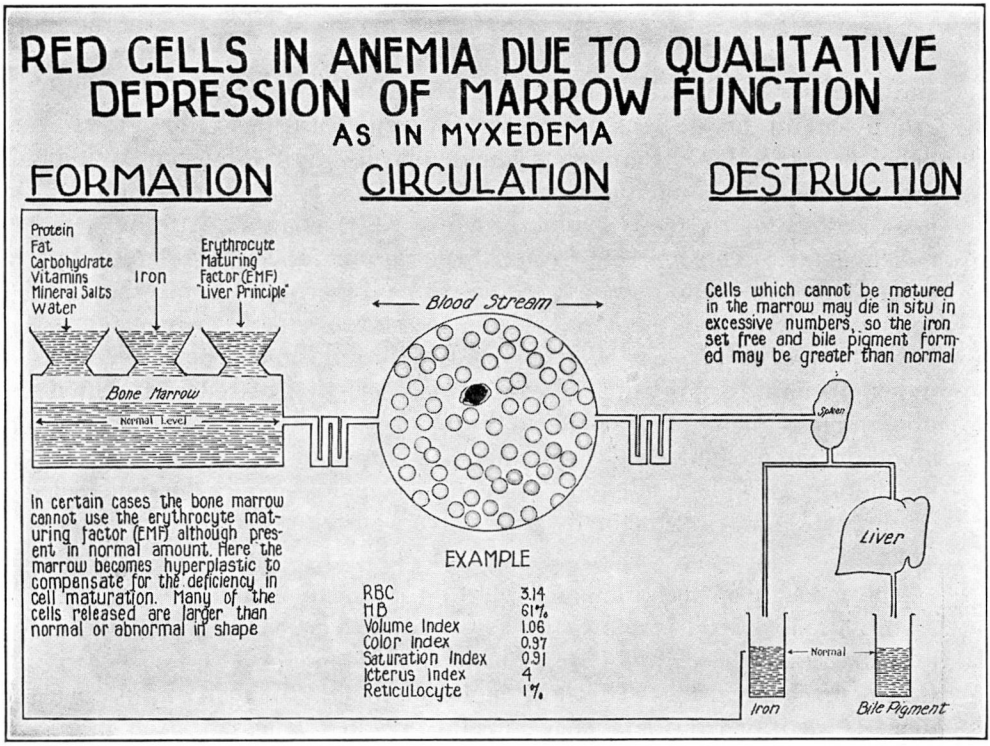


FIG. 15.—Physiology of red cells when the marrow is unable to utilize the erythrocyte maturing factor (EMF) normally.

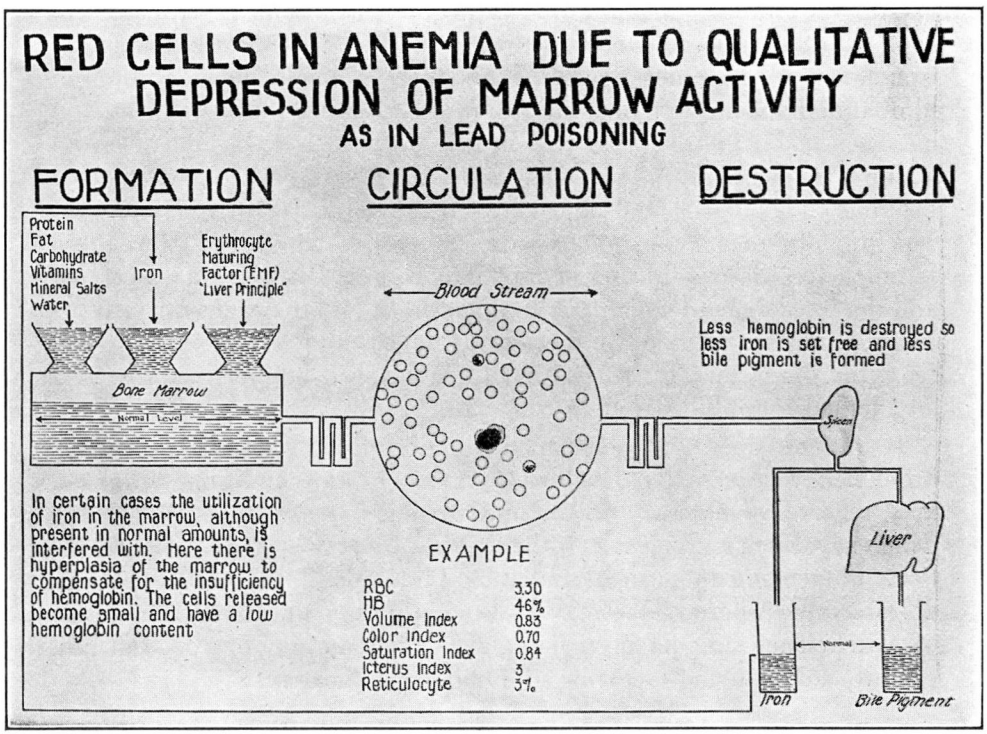


FIG. 16.—Physiology of red cells when the marrow is unable to utilize iron normally.

similar disorders in which the macrocytic anemia occurs. This whole group should be designated the erythrocyte-maturing-factor (EMF) deficiency anemias. Pernicious anemia is the most important of the group. The patient cited during the active phase of the disease had the macrocytosis of red cells (volume index, 1.29) characteristic of such a deficiency. The marrow in active pernicious anemia is shown by marrow puncture and necropsy studies to be hyperplastic, but very few cells are delivered to the blood stream so the reticulocyte percentage is low (0.5 per cent). The bile pigment of the plasma is high (icterus index, 10 units), indicating an excessive destruction of red cells which in pernicious anemia takes place in the marrow and not in the circulating blood or reticulo-endothelial system. The output of iron is high. Here the therapy is evident. It consists in supplying adequately the deficient erythrocyte maturing factor by giving liver, gastric tissue, or liver concentrates.

The mechanism in an anemia due to a deficient intake or impaired assimilation of iron is shown in Fig. 14. The mechanism is similar to that already shown in a chronic hemorrhagic anemia (Fig. 5) except for the mechanical loss of iron in the hemorrhage. In such an instance there is also an iron deficiency anemia due to the loss of iron more rapidly than it is normally supplied by food. If sufficient iron is given, the hemorrhage may continue, but the anemia is relieved so long as the marrow is able to stand the added strain. The bone marrow has to cope with the same deficiency if there is a defect in assimilation so the iron taken in does not reach the marrow. This is the condition in idiopathic hypochromic anemia. In the example cited, insufficient iron has been taken in. The marrow in this instance is hyperplastic in an attempt to compensate, but such red cells as do get out are small (volume index, 0.75) and deficient in hemoglobin (color index, 0.67). The low volume and color index indicate the iron deficiency. Here there is much less destruction of hemoglobin so very little iron is set free and the bile pigment content of the plasma is less than normal (icterus index, 2 units). Again the therapy of the anemia is clearly indicated from the diagram. It consists in filling the iron hopper by providing an adequate supply of iron.

If an organ does not receive an adequate supply of a necessary factor, a deficiency necessarily develops. Under certain conditions an organ may receive a necessary factor and for some reason not use it so a deficiency state results just as if the factor were not supplied. The conditions influencing the use of nutritional factors in general have been discussed elsewhere.[7] We may find the clinical and laboratory picture of a deficiency anemia even though an adequate amount of iron and erythrocyte maturing factor be supplied to the marrow.

It is well known that myxedema may show the typical blood picture of pernicious anemia. Such a state is illustrated in Fig. 15. This patient had an anemia with a mild macrocytosis in myxedema. The defect is in the normal completion of the red cells just as it is in idiopathic pernicious anemia. In such a case, the addition of thyroid extract alone should relieve the anemia since the marrow can then use the erythrocyte maturing factor (EMF) already supplied in adequate amounts.

It is quite common to encounter an iron deficiency anemia which will not respond to adequate dosage of iron. There seem to be many more extraneous factors influencing the use of iron by the marrow than of the erythrocyte maturing factor. The example cited in Fig. 16 is the case of a patient with lead poisoning. The giving of iron does not influence the anemia, although the laboratory findings of low volume and color index are characteristic of an iron deficiency anemia. The lead seems to prevent the normal utilization of the iron by the marrow, so treatment must first consist of removing the influencing factor before iron is given. The findings here are exactly like those shown in chronic hemorrhagic anemia (Fig. 6), and an anemia due to a deficient intake of iron (Fig. 14). The laboratory findings indicate the fundamental defect so far as the marrow is concerned but do not show whether the marrow defect is due to excessive loss, deficient intake, or impaired utilization of iron.

Summary

In every case of anemia, the rate of red cell formation and delivery from the marrow, the rate of destruction, and the balance between these two factors must be determined.

Measures are available for gauging accurately the state of the marrow and all important factors in red cell activity.

The anemia must be studied and classified from both the clinical and laboratory standpoints.

Red cell formation, circulation, and destruction in all the common anemias are illustrated by diagrams.

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