

THE CLASSIFICATION OF ANEMIA*

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SUMMARY

A laboratory and clinical classification of anemia has been outlined.

The results of the blood study have been correlated with the clinical classification.

The importance of the clinical and hematologic classification in relation to the treatment of anemia has been emphasized and the lines of treatment indicated.

Changes in the erythrocytes must always occur in anemia since the hemoglobin is constantly decreased. Erythrocytes may be decreased in number, the size may be altered, or the hemoglobin content per cell may vary from normal. No patient with anemia should be treated without a complete laboratory and clinical examination. The blood must be properly studied and classified in the laboratory; the patient must have a careful clinical examination; the results of the laboratory and clinical studies must be correlated. It is my purpose in this paper to describe a method of study of anemia which has proved most valuable in our hands.

No clinical or laboratory classification of anemia suggested in the past has proved satisfactory. Most clinicians have employed only a rough grouping into primary and secondary types. In the primary group have been placed the anemias without apparent cause and those with a color index over 1.00; in the secondary group, those with known cause, and those with a color index less than 1.00. Such a classification confuses clinical and hematological data and is not really workable.

In every animal the blood is undergoing constantly a rapid ebb and flow. Erythrocytes and hemoglobin are always being formed and destroyed. The life span of the erythrocyte of man is about four weeks, which means that every month the entire store of circulating and reserved red cells is replaced. An anemia is simply a loss of balance between this normal process of destruction and replacement. In every anemia it is necessary to know:

1. How many cells and how much hemoglobin have been lost.
2. What qualitative changes, such as variation in size and hemoglobin content of the cells, have taken place.
3. How rapidly the cells are being destroyed.
4. How rapidly the cells and hemoglobin are being replaced.

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This information can be easily obtained by a systematic blood study. A red cell count is done, the hemoglobin is determined in grams per hundred cubic centimeters, and the volume of packed cells per hundred cubic centimeters of blood is measured by centrifugalization of 10 c.c. of blood containing an isotonic anticoagulant. From these data the volume and hemoglobin content of the mean cell can be calculated and also the amount of hemoglobin per unit volume of cell relative to normal. The best index of the rapidity of the blood destruction other than the red cell count is the amount of bile pigment in the blood, provided there is no obstruction of the biliary tract. The activity of red cell formation in the marrow is best determined from the level of reticulocytes in the circulation since these are young cells. (For the technical details of such a blood examination, see the author's paper "The Technique of a Blood Examination," Jour. Lab. & Clin. Med., 17:843-859, 1932.)

The primary classification of anemia from a laboratory standpoint is based on the volume and hemoglobin content of the mean red cell. Only six groupings are possible.

1. *Normocytic and normochromic.* Here the volume and color indices are within normal limits (0.90 to 1.10). It is apparent that the number of cells must be reduced if anemia is present.

2. *Macrocytic and hyperchromic.* In this type the mean cell is larger and contains more hemoglobin than normal so both the volume and color indices are greater than 1.00. Since the amount of hemoglobin per cell is increased, the number of cells is always decreased.

3. *Macrocytic and normochromic.* The cells are large but the mean amount of hemoglobin per cell is normal; the volume index is greater than 1.00; the color index is within normal limits.

4. *Macrocytic and hypochromic.* Here the volume index is still increased, but the color index is below normal.

5. *Normocytic and hypochromic.* The mean cell volume and the volume index are within normal limits but the hemoglobin per cell is decreased as shown by a color index of less than 1.00.

6. *Microcytic and hypochromic.* The volume index is below the lower limit of normal (0.90). The hemoglobin per cell in such a case is necessarily less than normal so the color index is low. Usually the number of red cells shows little if any decrease.

To complete the laboratory study the pigments in the plasma are measured by comparison with a dilute solution of potassium bichromate and recorded as the icterus index or determined quantitatively by the van den Bergh method. A vital stain is made and the reticu-

locytes counted; a film stained by Wright's stain is examined for variations in diameter and shape, basophilia, nucleated erythrocytes, relative number of platelets and a differential count of the leucocytes.

The laboratory classification of anemia is thus simply a descriptive one. An etiologic classification is always the most desirable one, and such a classification may be made from the clinical standpoint. A satisfactory clinical grouping based on method of production is shown in Table I.

TABLE I.

CLINICAL CLASSIFICATION OF ANEMIA BASED ON METHOD OF PRODUCTION

- I. Increased Blood Loss
 - a. Mechanical from acute hemorrhage as in:
 1. Trauma
 2. Peptic ulcer
 3. Uterine bleeding
 4. Disturbance in blood coagulation
 - b. Accelerated destruction as in:
 1. Chronic hemolytic icterus
 2. Hemolytic anemia due to infections and poisons
- II. Decreased Blood Formation
 - a. Depression of marrow function in:
 1. Idiopathic aplastic anemia
 2. Cachexia, chronic intoxication, metabolic disturbances, poisons, radioactive substances, malignancy or infiltration of marrow by tumor or leukemia.
 - b. Deficiency in specific substances necessary for normal red cell formation as:
 1. Deficiency in specific anti-anemic factor of liver leading to pernicious and other macrocytic anemias.
 2. Deficiency in iron and perhaps other unknown substances necessary for hemoglobin formation as in chronic hemorrhage, dietary deficiency in iron, and disturbance in absorption or assimilation of iron (idiopathic, hypochromic and microcytic anemia).

The laboratory and clinical findings may be correlated and in some instances the laboratory findings indicate the etiology of an anemia from a clinical standpoint. If the anemia is caused by an acute mechanical loss of blood, the cells remaining are normal in size and hemoglobin content, and the volume and color indices are normal. The anemia is normocytic and normochromic. The bile pigments in the plasma are decreased and the reticulocytes are increased if the bone marrow responds normally. With increased hemolysis the bile pigments are markedly increased, so the icterus index is high. The

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reticulocytes are usually much increased in a chronic hemolytic anemia since the bone marrow is overactive in an attempt to compensate for the increased blood loss. The volume and hemoglobin content of the mean cell show little change.

In the large group of anemias due to a simple quantitative defect in delivery of the red cells from the marrow, such cells as are formed are normal in size and hemoglobin content. The volume and color indices are normal. Not infrequently, however, the anemia resulting from malignancy, toxemia, infection, and other causes is not simply a quantitative deficiency, but is qualitative also, since the primary disease interferes with the absorption or utilization of the substances necessary for the normal formation of blood. Here the blood findings are a combination of those characteristic of a quantitative and a qualitative deficiency.

The qualitative deficiencies show characteristic findings. With a deficiency in the specific anti-anemic factor of liver, the red cells in the circulating blood are larger than normal, so the volume index is increased. This specific principle is necessary for the normal growth from the megaloblast stage. Megaloblasts are large cells; hence the macrocytosis since maturation is not normal. The bone marrow is red because it is overactive. Many cells die in the marrow because of their inability to mature and thus increase the bile pigments in the plasma. The reticulocyte count is low. With a deficiency in iron, the cells are small and deficient in hemoglobin although the total red cell count is decreased little if at all. Hypochromia as evidenced by a low color index is the first abnormality to develop if the supply of iron is inadequate. If the hypochromia continues, the cells decrease in size and the volume index falls, probably because there is no need for a normal cell mass, since there is no hemoglobin to fill it. The formation of bile pigment is at a low level because less hemoglobin is destroyed and hence the icterus index is decreased. The reticulocyte count is variable but never high.

Not infrequently more than one factor is operative in the causation of an anemia, and so the laboratory findings represent a summation of those characteristics for the different types of anemia. If there is a deficiency in both iron and the anti-anemic factor of liver, the macrocytosis and hyperchromia due to the lack of the anti-anemic factor of liver may be neutralized by the microcytosis and hypochromia of the iron deficiency. The cell size and hemoglobin content may then be within normal limits. Malignant disease may depress the marrow, interfere with the utilization of a specific factor, and also cause hemorrhage. In such a case, there are three factors in the causation of the anemia.

DISCUSSION

With the laboratory and clinical study here outlined a satisfactory classification of almost every anemia can be made, and the proper treatment administered. The classification is more difficult in cases in which more than one factor is operative. It is increasingly evident in the study of anemia that the utilization of a specific factor may be interfered with even when the supply is adequate. Infection often prevents the normal utilization of specific factors. Thus it is well recognized that if an infection develops in a patient with pernicious anemia, the intake of liver or liver substitute must be increased. This fact indicates that the infection interferes with the absorption or utilization of the specific and anti-anemic principle.

It is apparent that the proper treatment is usually indicated if the study is complete. In the specific deficiency anemias the adequacy of treatment must be determined from the laboratory study of the patient's blood. No patient with pernicious anemia is adequately treated if a macrocytosis of the erythrocytes persists, and so the aim of treatment should be to obtain a normal color and volume index. Likewise in a case of iron deficiency anemia, if enough iron be given and if utilization is normal, the cells become larger and filled with hemoglobin, and the color and volume index return to normal.