# Problems in Family Practice

# The Common Anemias

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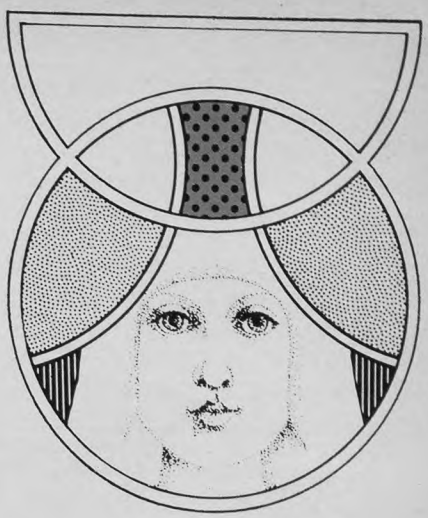

Anemia is a common clinical problem requiring precise diagnosis of its underlying etiology in order to provide effective therapy. Most common anemias are characterized by discrete hematologic patterns. The most useful laboratory studies in most instances are red cell indices, blood film, reticulocyte count, platelet count, serum iron and total iron binding capacity. This paper presents simple guidelines for the rational use of common laboratory tests in the diagnostic assessment of anemia.

Anemia is a common clinical finding that requires explanation. Before appropriate therapy can begin, its etiology must be established. In practice all anemias are due to one, or sometimes a combination of the following mechanisms:

1. Iron deficiency, ie, blood loss
2. Marrow failure
   a) relative – anemias of chronic disease
   b) absolute – aplastic anemia, myelofibrosis, leukemia, lymphoma, myeloma
   c) ineffective erythropoiesis – refractory normoblastic anemia
3. Hemolytic anemia
4. Megaloblastic anemia

Table 1 gives the approximate frequency of anemias in practice. These frequencies change, of course, in a university setting and in subspecialty practice where hemolytic anemias and the anemias of leukemia, lymphoma, and myeloma are more common.

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## Laboratory Work-up of Anemia

When history and physical examination have not explained the anemia, the following baseline data should be obtained before ordering other tests: (1) Red cell indices, (2) A look at the blood film, (3) Reticulocyte count, (4) Platelet count, and (5) Serum iron and total iron binding capacity.

*Red cell indices* (Table 2) are usually supplied automatically if a Coulter S is used. Sometimes they make an immediate diagnosis. MCV above 120 usually means liver disease or megaloblastic anemia. MCV above 110 strongly argues against anemia of chronic disease or acute blood loss. MCV below 100 is *not* pernicious anemia, and MCV below 80 is either iron deficiency or thalassemia minor. MCHC above 36 means hereditary spherocytosis, and MCHC below 32.5 usually means iron deficiency or thalassemia minor.

*Inspection of the blood film* should include a specific check for hypochromic microcytes, oval macrocytes, spherocytes, schistocytes, target cells, hypersegmented P.M.N.'s and abnormal white blood cells. Spherocytes indicate hereditary spherocytosis or autoimmune hemolytic anemia. Schistocytes (contracted cells, helmet cells, triangular cells) usually suggest damage to blood vessels by fibrosis or cancer. Stippled cells are young cells, still containing RNA like reticulocytes, but the RNA is denatured and precipitated by Wright's stain, unlike the reticulocytes whose RNA is precipitated only by supravital stain. Prominent stippling is seen in lead poisoning or thalassemia minor. Howell-Jolly bodies are nuclear remnants and are characteristic of splenectomized patients. Tables 3 and 4 summarize the important elements in the blood films of anemic patients and their diagnostic significance.

The *reticulocyte count* is a most useful test in the evaluation of anemia, as illustrated in Table 5. A very high reticulocyte count (50 percent or more) means autoimmune hemolytic anemia when the Coombs' test is positive; on very rare occasions it means pyruvate kinase deficiency, a red cell enzyme defect associated with a negative Coombs' test. Moderate elevation of the reticulocyte count (ten to 20 percent) usually means hemolysis but occasionally indicates other underlying problems. Acute blood loss can bring the count this high and patients with pernicious anemia or folic acid deficiency may have counts at this level or higher a week after specific therapy was started; their counts, however, show an orderly rise, peak at one week and decline at two weeks, unlike a hemolytic anemia, whose counts, while fluctuating, stay high. If the reticulocyte count is under five percent, the patient probably does not have hemolytic anemia. Very low counts, especially in absolute terms, are characteristic of aplastic anemia and pernicious anemia.

The *platelet count* is also a useful laboratory test in the initial workup of anemia. (Table 6) A low platelet count

in an anemic patient, who does not have frank thrombocytopenic purpura, points to the marrow as the site of disease. In other words, this is not just iron deficiency or anemia of chronic disease, but possible leukemia, aplastic anemia, or some other malignancy. Hypersplenism may also present with moderate anemia, platelet count of 70,000 and white count under 2,000.

*The serum iron and total iron binding capacity* is worth doing early in the work-up because so many anemias are caused by iron deficiency, and finding a low serum iron but high TIBC means iron deficiency. If the serum iron is not low, the patient does not have iron deficiency; if the serum iron is low and the TIBC is also low, one has learned nothing because many of the anemias of chronic disease may have a very low serum iron – as low as 10 mcg/100 ml as seen in hemochromatosis, and often in megaloblastic anemias.

Some hematologic tests are frequently misapplied. The *serum iron/TIBC* (Table 7) should not be done in a patient with fever or infection because it will always be low. It should also not be done in a patient with a high reticulocyte count because iron deficiency is not the patient's problem and serum iron may even be misleading. When a patient with pernicious anemia is treated with vitamin $B_{12}$, the serum iron plummets to very low levels and stays low for weeks, even with ample iron states.

The *Schilling test* is not worth doing in patients with MCV below 100, or in patients with elevated WBC and high reticulocyte counts or spherocytes. Vitamin $B_{12}$ level should, of course, not be done after a Schilling test. The *Coombs' test* is usually not worth doing with a normal reticulocyte count. The *osmotic fragility* is useful only in the diagnosis of hereditary spherocytosis. It is no longer useful in the work-up of patients with hypochromic anemia. *Hemoglobin*

**Table 1. Relative Incidence of Anemia per 1,000**

| | |
|---|---|
| Anemia of chronic disease | 10 |
| Iron deficiency | 10 |
| Sickle cell anemia Black population | 2 |
| Pernicious anemia | .4 |
| Hereditary anemia | .2 |
| Leukemia | .05 |
| Myeloma | .03 |
| Aplastic anemia | .004 |

**Table 2. Red Cell Indices**

| | |
|---|---|
| **MCV** | |
| Above 120 | Liver disease<br>Megaloblastic anemia |
| Above 110 | NOT anemia of chronic disease, chronic blood loss |
| Below 100 | NOT pernicious anemia |
| Below 80 | Iron deficiency<br>Thalassemia minor |
| **MCHC** | |
| Above 36 | Hereditary spherocytosis |
| Below 32.5 | Iron deficiency<br>Thalassemia minor |

**Table 3. Blood Film**

Look for:

- Hypochromic microcytes
- Oval macrocytes
- Spherocytes
- Schistocytes
- Target cells
- Hypersegmented P.M.N.'s
- Abnormal WBC

**Table 4. Abnormal Red Cells on the Blood Film**

| Abnormal Cells | Possible Causes |
|---|---|
| Spherocytes | Hereditary spherocytosis<br>Autoimmune hemolytic anemia<br>Acute alcoholism<br>Hb C disease<br>Burns<br>ABO incompatibility |
| Oval cells | Ovalocytosis<br>Megaloblastic anemia<br>Myelofibrosis<br>Refractory normoblastic anemia |
| Microangiopathic cells (fragmented, helmet cells, etc) | Thrombotic thrombocytopenic purpura<br>Metastatic cancer (stomach, pancreas, ovary)<br>Postcardiotomy<br>Calcific aortic stenosis (?)<br>Drugs (± G6PD deficiency)<br>Hemolytic-uremic syndrome of infants<br>Acute nephritis (rare)<br>Malignant hypertension (rare)<br>Uremia |
| Target cells | Jaundice<br>Thalassemia<br>Iron deficiency<br>Splenectomy<br>Hemoglobinopathies |
| Stippling | Lead poisoning<br>Thalassemia minor<br>Several severe anemias |
| Spur cells | Cirrhosis<br>Acanthocytosis<br>PK deficiency |
| Howell-Jolly bodies | Splenectomy<br>Megaloblastic anemia |

*electrophoresis* is not worthwhile in patients with low platelets and white cells or normal looking red blood cells.

### Patterns of Common Anemias

The most common anemias have their own hematologic patterns.[1-5]

1. *Iron deficiency anemia.* This is characterized by an MCHC below 32.5 and MCV usually below 80, serum iron below 50, TIBC above 350, and an absent marrow hemosiderin. In blood loss of recent onset (ie, within two to four weeks) these laboratory deviations from normal may not as yet have occurred.

2. *Thalassemia minor* must be differentiated from iron deficiency anemia because both conditions feature hypochromic, microcytic red cells; thalassemia minor is a frequent diagnosis in those population areas where many people of Mediterranean, especially Italian, or Cantonese Chinese origin reside. It is always a mild anemia; the hemoglobin is above 9 gm and usually between 10 and 13 gm, but the red cell count is often higher than normal. The MCHC is only slightly low but the MCV is well below 80 and may be below 60. The diagnosis of thalassemia minor may be established definitely by finding an elevated hemoglobin $A_2$ or hemoglobin F on hemoglobin electrophoresis.

3. *Marrow failure.* In *absolute* marrow failure, the normal myeloid tissue has been replaced by fat (aplastic anemia), fibrosis (myelofibrosis), or malignancy (lymphosarcoma, multiple myeloma, or leukemia). The platelet count and absolute reticulocyte count are usually low. Morphologically abnormal white cells help in the diagnosis. A bone marrow aspirate or biopsy is essential for specific diagnosis.

*Relative* failure is exemplified by the anemias of chronic disease. In general, all these conditions have in common normal red cell morphology. White cells and platelets are normal in number and appearance, and reticulocytes are not elevated. The serum iron is low, and TIBC is not elevated. This group is characterized by relative marrow failure, ie, a moderately shortened red cell survival with only suboptimal compensatory increase in marrow activity. The red cell survival is often one-sixth normal, but the marrow only compensates 1½ to two times. By contrast, marrow in chronic blood loss, or marrow in an uncomplicated hemolytic anemia, such as hereditary spherocytosis, can increase its output by six to ten times.

Other abnormal findings have to do with impaired protein synthesis resulting in low transferrin, erythropoietin, and albumin levels. The serum iron is usually also low because of impaired reutilization of iron, that is, the reticuloendothelial cells do not readily release iron obtained from decaying red cells. Another example of the relative unavailability of iron is an increase in red cell protoporphyrin in these conditions.

There are some subtle differences between these entities. Anemia associated with cirrhosis is primarily hemolytic, frequently with target cells; spur cells are seen occasionally; the reticulocytes are usually slightly elevated.

Anemia of azotemia is primarily hypoplastic; because of the striking decrease in the erythropoietin, few red cells are made. Sometimes a few burr cells are seen on the peripheral blood film. Burr cells must be distinguished from spur cells. Spur cells, which are characteristically seen in jaundiced patients with liver disease, have a few long spikes emanating from the cell; the spike is longer than the base is wide. Burrs are short; the bases are wider than the length of the projections.

The anemia of cancer is sometimes complicated by blood loss, sometimes it features contracted cells, schistocytes, a sign of marrow invasion.

Ineffective erythropoiesis or intramedullary hemolysis refers to a phenomenon that combines greatly increased production of erythroblasts with destruction of these nucleated red cells right in the marrow, permitting only few, and often misshapen and poorly made red cells to reach the blood stream. Pernicious anemia is the best known example of this mechanism; the thalassemias also show this form of dyserythropoiesis. In the so-called refractory normoblastic anemias or sideroachrestic anemias, intramedullary hemolysis is a prominent feature and it is associated with characteristic ring sideroblasts in the marrow.

4. *Hemolytic anemia.* Most chronic hemolytic anemias have an elevated reticulocyte count, and slightly elevated indirect bilirubin; they may have an elevated LDH, and an absent haptoglobin. These general signs of hemolysis should be obtained first. After first establishing that hemolysis is present, one goes on to specific tests, such as osmotic fragility to establish hereditary spherocytosis, Coombs' test to establish autoimmune hemolytic anemia, hemoglobin electrophoresis for diagnosis of hemoglobinopathy, and enzyme studies for diagnosis of hereditary non-

**Table 5. Reticulocytes in Anemia**

| Relative Count | Type of Anemia | Absolute Count* |
|---|---|---|
| Over 50% | Autoimmune hemolytic anemia<br>Pyruvate kinase deficiency | Over 1,000,000/cu mm |
| 10 ± 5% | Hemolytic anemias<br>Acute blood loss<br>Escape from depression<br>eg, chloramphenicol<br>following specific therapy<br>(eg, iron or vitamin $B_{12}$) | 2-500,000/cu mm |
| Under 5% | Probably not hemolytic anemia | Under 100,000/cu mm |
| Under 5% | Primary marrow failure<br>Megaloblastic anemia | Under 50,000/cu mm |
| 1 ± .59 | Normals | 25-75,000/cu mm |

*Obtained by multiplying the percent of reticulocytes by the red cell count.

| Table 6. Platelets |
|---|
| Below 150,000: |
| Marrow involved |
| Megaloblastic anemia |
| Aplastic anemia |
| Malignancy |
| Hypersplenism |

spherocytic hemolytic anemia.

The hemoglobinopathies are seen mostly in the black population; target cells are common to all hemoglobinopathies. Red cell indices are usually normal. Sickle cell anemia is the most common, but other variants must be considered. When red cell morphology is normal, hemoglobinopathy is unlikely.

5. *Megaloblastic anemia.* This anemia is easily recognized by the large oval macrocytes, hypersegmented polymorphonuclear cells, the characteristic bone marrow findings, and the appropriately low vitamin $B_{12}$ or folic acid serum levels. Hypersplenism is a syndrome which is usually secondary to some other disease, such as cirrhosis of the liver, rheumatoid arthritis or Gaucher's disease. It is characterized by a large spleen, "empty" blood and full marrow without morphologic abnormalities of the red cells, white cells, or platelets.

With these simple guidelines, the work-up of a patient with anemia is usually neither time-consuming nor expensive and is gratifying to the physician in terms of precise diagnosis of anemia as the basis for effective care of the patient.

| Table 7. | | |
|---|---|---|
| | **Serum Iron** | **TIBC** |
| **Low** | Iron deficiency anemia | Infection |
| | Infection | Collagen disease |
| | Cancer | Rheumatoid arthritis |
| | Renal disease | Cancer |
| | Rheumatoid arthritis | Hypoproteinemia |
| | Collagen disease | |
| | Pregnancy | |
| | Serum levels in the afternoon | |
| **High** | | Iron deficiency |
| | | Pregnancy |
| | | The pill |


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