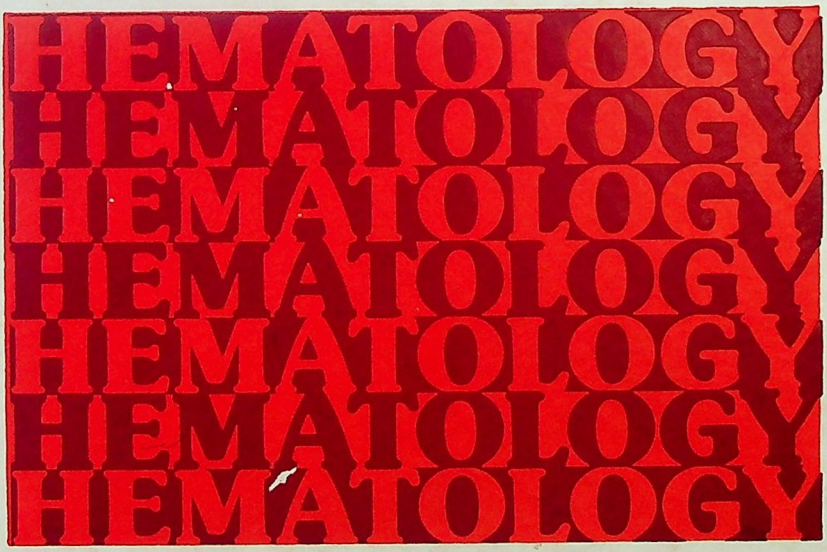
PRACTICAL HEMATOLOGY



William G. Hocking, M.D., editor

PRACTICAL HEMATOLOGY

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PRACTICAL HEMATOLOGY

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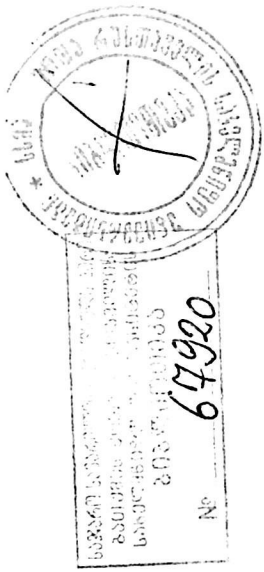

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To Karen and Erin, with appreciation of their help and patience

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Preface

The practice of hematology encompasses a wide spectrum of clinical disorders that includes anemias, disorders of hemostasis, and hematologic malignancies. Many systemic illnesses have prominent hematologic manifestations that may be detected on routine laboratory testing and, if recognized and properly interpreted, may provide important clues to the underlying disease. Some patients with hematologic disorders will require consultation from a specialist who can provide expertise in developing a diagnostic or therapeutic plan. Most patients consult initially with their primary care physician, and in many of these patients the diagnosis can be established and appropriate therapy instituted without referral to a specialist.

The goal of this book is to provide a framework for the primary care physician in approaching patients with hematologic illness. The emphasis of the chapters is on the practical approach to diagnosis and therapy. Although extensive discussions of pathophysiology are not included, sufficient background is provided to facilitate understanding of the diseases. Most of the common hematologic disorders and several less common illnesses are discussed. More detailed discussions of many disorders will be found among the selected readings at the end of each chapter or in the standard hematology subspecialty textbooks.

W.G.H.

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PRACTICAL HEMATOLOGY

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WILLIAM G. HOCKING

Approach to the Anemic Patient

Anemia is defined as reduction of the red blood cell mass below normal. The normal range for the red cell mass is higher for men than for women and is dependent upon the altitude. Residents of higher altitudes have a higher red cell mass than sea level inhabitants. However, this effect does not substantially alter the normal ranges of the red cell mass unless the resident altitude is above 2,000 meters (6,500 feet). For inhabitants of altitudes less than 2,000 meters the normal erythrocyte values derived from sea level residents can be applied.

Determination of the red cell mass requires labeling of autologous erythrocytes with an isotope, usually chromium-51 (^{51}Cr), reinfusion of the tagged cells, and measurement of the dilution of the labeled cells within the circulation. When the ^{51}Cr study is performed correctly, it accurately measures the circulating red cell mass and the values are not affected by variations in the plasma volume. However, there are a number of drawbacks to this test, including radiation exposure and expense. The usual initial method of evaluating the red cell mass of a patient is by determination of the hematocrit and hemoglobin levels.

Hemoglobin, the oxygen-carrying protein of blood, is transported within erythrocytes and is routinely measured by a spectrophotometric method. The hematocrit (packed red cell volume) is measured directly by centrifugation of the blood to determine the proportion composed of erythrocytes. The "microhematocrit" technique employs capillary tubes filled with anticoagulated blood (heparin, oxalate, or ethylenediamine

tetra-acetic acid [EDTA] are suitable) and centrifuged at high speed. This technqiue has the advantage of rapid availability of results and can be performed at the bedside if the appropriate equipment is available. In patients with microcytosis or an elevated red cell mass, the microhematocrit may be falsely elevated due to an increase in the amount of plasma trapped within the packed red cell column. Therefore, the microhematocrit should be corroborated by an additional measurement in patients with microcytosis or an elevated red cell mass. Some automated systems (e.g., Coulter S) provide a hematocrit value determined indirectly, by calculation from the measured red cell count and mean corpuscular volume. The accuracy of this hematocrit is generally equivalent to the directly measured microhematocrit.

In summary, direct measurement of the red cell mass by radioisotopic methods is the most accurate method of detecting a quantitative abnormality of erythrocytes. For patients with erythrocytosis (see Chapter 3) the ^{51}Cr red cell mass must be measured to confirm the diagnosis. However, anemia is usually accurately detected by the measurement of hemoglobin and hematocrit values and radioisotope studies are rarely required in the evaluation of anemia. The normal red cell values are shown in Table 1.

HEMOGLOBIN

Hemoglobin is a tetramer composed of four globin polypeptide chains: two identical alpha chains, and two identical beta chains. Each globin chain contains a prosthetic heme group capable of binding one molecule of oxygen. Thus, each tetramer is capable of transporting four molecules of

Table 1 Normal Erythroid Values for Adults

Test (units)[a]	*Female*	*Male*
Hemoglobin (g/dl)	14 ± 2	16 ± 2
Hematocrit (1/1)	0.42 ± 0.5	0.47 ± 0.5
Erythrocyte count ($\times 10^{12}$/1)	4.8 ± 0.6	5.2 ± 0.8
Mean corpuscular volume (fl)	80-100	80-100
Mean corpuscular hemoglobin (pg)	27-32	27-32
Mean corpuscular hemoglobin concentration (g/dl)	32-36	32-36
Chromium-51 red cell mass (ml/kg of body weight)	25.3 ± 3.0	28.2 ± 4.0

[a] g/dl, grams per deciliter; 1/1, liter per liter; fl, femtoliter; pg, picogram.

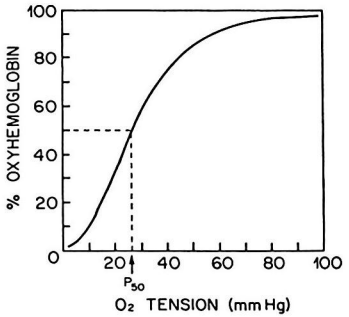

Figure 1 Normal oxyhemoglobin dissociation curve. The P_{50} is the partial pressure of oxygen at which the hemoglobin is 50% saturated with oxygen.

oxygen. As oxygen is sequentially bound to the four heme groups of deoxyhemoglobin, changes in the structure of the molecule occur that stabilize oxyhemoglobin. It is these changes in structure occurring with oxygenation that are responsible for the ability of hemoglobin to accept oxygen in the lungs, transport it through the circulation, and unload oxygen to the tissues. These properties are reflected in the sigmoid shape of the oxyhemoglobin dissociation curve (Fig. 1). The position of the oxyhemoglobin dissociation curve is indicated by the partial pressure of oxygen at which the hemoglobin becomes 50 percent saturated with oxygen (P_{50}). The P_{50} is altered by certain physiologic processes and these changes in hemoglobin oxygen affinity can have an impact on the delivery of oxygen to the tissues. An acute decrease in pH (acidosis) or increase in the erythrocyte 2,3-diphosphoglycerate concentration increase the P_{50} (lowered affinity of hemoglobin for oxygen). Acute alkalosis or decreased 2,3-diphosphoglycerate decrease the P_{50}. Increase in the intracellular 2,3-diphosphoglycerate concentration is an important mechanism for improving oxygen delivery in anemia. In some hereditary hemoglobinopathies, the P_{50} is abnormal due to the structurally abnormal hemoglobin.

RED CELL PRODUCTION AND DESTRUCTION

Erythropoiesis

In the adult, erythrocytes are produced in the bone marrow. The bone marrow contains nucleated red blood cells (normoblasts) at several stages of maturation. Normoblasts are derived from more primitive precursors

committed to erythroid differentiation and these precursors are in turn descended from more primitive multipotential stem cells. These multipotential cells also give rise to cells of the neutrophil, monocyte, and platelet series. The multipotential stem cells and early erythroid progenitors are not morphologically recognizable. As the normoblast matures, it extrudes its nucleus and becomes a reticulocyte. The reticulocyte is a large, anucleate erythrocyte with cytoplasmic RNA that imparts a bluish color to the cells in Romanowsky-stained (e.g., Wright's) blood smears. A reticulocyte count uses a supravital stain to precipitate the RNA as dark blue strands and permit accurate enumeration. Over a period of 2 to 4 days the reticulocyte loses this RNA and becomes a mature erythrocyte. Normally, erythroid cells are not released from the bone marrow into the peripheral blood until they reach the reticulocyte stage. However, when the demand for production of red cells increases, normoblasts may be released into the peripheral blood. Under basal conditions the ratio of normoblasts to granulocytic cells in the bone marrow (E:M ratio) is 1:2 or 1:3. When the demand for red cell production increases, the rate of erythropoiesis can increase six to eight times the basal level, and this is reflected in an increased E:M ratio.

Erythropoietin acts upon erythroid cells within the bone marrow to stimulate proliferation and maturation. The production of erythropoietin by the kidney is regulated by a poorly defined tissue oxygen sensor. Under normal conditions, when tissue oxygen delivery is adequate, basal erythropoietin secretion provides a stimulus to the red cell progenitors sufficient to replace red blood cell loss and maintain a stable red cell mass. When tissue oxygen delivery is inadequate, increased erythropoietin secretion occurs. If the bone marrow is capable of responding to the erythropoietin stimulus, the production of red blood cells increases (Fig. 2).

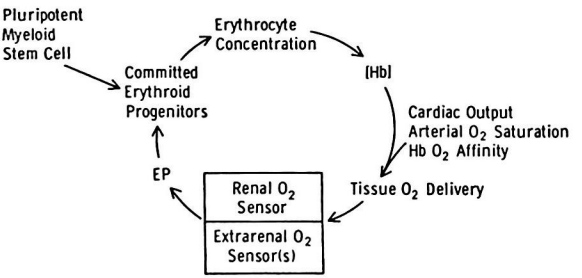

Figure 2 Regulation of erythropoiesis. Erythropoietin secretion is regulated by tissue oxygen concentration.

Red Cell Catabolism

Circulating red blood cells have a life span of approximately 120 days. The erythrocyte, because it is anucleate, cannot replace essential enzymes or structural proteins. Attrition of essential cellular components in senescent erythrocytes leads to the removal of these cells by the reticuloendothelial system. Hemoglobin is degraded within the macrophage to its components—heme and globin. The globin chains are degraded and returned to the amino acid pool. The iron is removed from heme and largely reutilized. The protoporphyrin component of the heme is further catabolized to bilirubin and excreted. During this process, carbon monoxide is produced leading to the formation of small amounts of carboxyhemoglobin. Bilirubin excreted by the liver into the bile is further metabolized within the intestine. One of the products of this process is urobilinogen, which is excreted in the feces as well as reabsorbed and excreted into the urine.

Effective and Ineffective Erythropoiesis

Effective erythropoiesis refers to the production of hemoglobin (or erythrocytes) that is released into the circulation. Ineffective erythropoiesis indicates production of hemoglobin or erythrocytes not released into the circulation. Ineffective erythropoiesis accounts for 10-20% of red cell production under normal circumstances and reflects the destruction of erythrocyte precursors within the bone marrow. Megaloblastic anemias and thalassemias are characterized by markedly increased ineffective erythropoiesis. Total erythropoiesis is the sum of effective and ineffective erythropoiesis.

Measurements of total, effective, and ineffective erythropoiesis can be used clinically and are often helpful in the classification of an anemia. An estimate of total erythropoiesis can be obtained by evaluation of marrow cellularity and the relative number of erythroid cells (E:M ratio).

The reticulocyte count is a measure of effective erythropoiesis. In order to use the reticulocyte percentage as an absolute index of effective red cell production, correction for the degree of anemia is required. This can be done by using the ratio of the patient's hematocrit to a normal hematocrit, 0.45, (Formula 1).

$$\text{Corrected reticulocyte count} = \text{Patient reticulocyte count} \times \frac{\text{Patient Hct.}}{0.45} \quad (1)$$

Under conditions of increased erythropoietic demand, reticulocytes are released from the bone marrow at an earlier stage and undergo an extended maturation time in the ciruculation. The prolonged reticulocyte half-life, which can be estimated to be twice normal, is accounted for by dividing the corrected reticulocyte count by 2. The resultant reticulocyte

production index (RPI) (Formula 2) is a measure of effective erythrocyte production.

$$\text{Reticulocyte production index} = \frac{\text{Corrected reticulocyte count}}{2} \quad (2)$$

A reticulocyte production index less than 2 indicates decreased effective erythropoiesis, whereas a value greater than 3 indicates an increased effective erythrocyte production.

The total catabolism of erythrocytes can be estimated by measurement of fecal urobilinogen. Urinary urobilinogen measurement is more convenient but less reliable. The survival of circulating erythrocytes can be evaluated with a ^{51}Cr red cell survival.

There is no widely available direct test to evaluate ineffective erythropoiesis. However, increased ineffective erythropoiesis usually can be recognized by the findings of anemia, bone marrow erythroid hyperplasia, an RPI less than 2, and elevated fecal urboliniogen excretion. Red cell survival in the circulation is normal.

GENERAL EFFECTS OF ANEMIA

The clinical presentation of a patient with anemia is determined by the underlying disease process, but clinical manifestations also result from tissue hypoxia or the physiologic compensatory changes induced by the anemia. Tissue hypoxia is responsible for such symptoms as angina pectoris, headache, lightheadedness, and fainting. Pallor is due to the reduced hemoglobin concentration in dermal blood vessels and to cutaneous vasoconstriction that results from diversion of blood to vital organs. The resting cardiac output increases with moderately severe anemia and is manifest clinically, by tachycardia, a hyperdynamic precordium, and "flow" murmurs. High output cardiac failure may supervene. Exertional dyspnea and orthopnea are common symptoms of anemia and may occur in the absence of other evidence of cardiac failure.

CLASSIFICATION OF ANEMIAS

Anemias can be classified according to the etiology and pathophysiology (Table 2) or by the morphologic appearance of the red cells (Table 3). The pathophysiologic classification is based on the predominant mechanism of anemia, although multiple mechanisms may be involved. For instance, the anemia of chronic renal failure is predominantly due to impaired production of red cells by the bone marrow, but there is usually an element of shortened erythrocyte survival and chronic blood loss as

Table 2 **Anemias: Pathophysiologic Classification**

I. Impaired erythrocyte production
   A. Disturbance in stem cell proliferation or differentiation
      1. Aplastic anemia
      2. Pure red cell aplasia
      3. Anemia of endocrine deficiency (pituitary, thyroid, adrenal, testicle)
   B. Disturbance in erythroblast proliferation and maturation
      1. Defective DNA synthesis (megaloblastic anemias)
         a. Vitamin B_{12} deficiency
         b. Folic acid deficiency
      2. Defective hemoglobin synthesis (hypochromic anemias)
         a. Defective heme synthesis: iron deficiency; sideroblastic anemias
         b. Defective globin synthesis: thalassemias
      3. Multiple mechanisms
         a. Anemia of chronic disease (inflammatory, infectious, neoplastic)
         b. Anemia of renal failure
         c. Myelophthisic anemia (bone marrow infiltration)
         d. Refractory anemia with cellular bone marrow
         e. Protein malnutrition

II. Increased erythrocyte destruction
   A. Intrinsic erythrocyte abnormalities
      1. Hereditary cell membrane abnormalities
         a. Spherocytosis
         b. Elliptocytosis
         c. Stomatocytosis
      2. Paroxysmal nocturnal hemoglobinuria
      3. Erythrocyte enzymopathies (e.g., glucose-6-phosphate dehydrogenase deficiency)
      4. Hemoglobinopathies
         a. Sickle cell anemia
         b. Hemoglobin C disease
      5. Porphyrias
   B. Extrinsic abnormalities
      1. Antibody

Table 2 (Continued).

a. Warm-reacting (autoimmune hemolytic anemias)
b. Cold-reacting
c. Drug-induced
2. Mechanical
a. Prosthetic cardiac valve
b. Microangiopathic
c. Burns
3. Infection
a. Bacteremia
b. Parasitemia (malaria, bartonellosis)
4. Reticuloendothelial sequestration or destruction (hypersplenism)
5. Oxidant chemicals or drugs
6. Venoms (snake, insect)
III. Blood loss (acute or chronic)

well. Anemias occur by three basic pathophysiologic mechanisms: (1) impaired erythrocyte production; (2) reduced erythrocyte survival; and (3) blood loss.

The morphologic classification divides the anemias into three groups based upon the red cell size and hemoglobin content. The erythrocyte indices provide estimates of the average volume (mean corpuscular volume, MCV) and the hemoglobin content (mean corpuscular hemoglobin, MCH, mean corpuscular hemoglobin concentration, MCHC) of the red cells. These indices can be calculated from the erythrocyte count, hematocrit, and hemoglobin but are also widely available from automated counters used in many clinical laboratories. It is important to recognize that the red cell indices are average values. In some patients with anemia the indices remain normal despite the presence of a subpopulation of red cells with abnormal erythrocyte volume or hemoglobin content.

In summary, there is considerable overlap between these subgroups. The classifications are useful in guiding the diagnostic approach, as long as ridigity is avoided in their application.

Table 3 **Anemias: Morphologic Classifcation**

- Microcytic and hypochromic (MCV $<$ 80; MCH $<$ 27)
  - Iron deficiency anemia
  - Sideroblastic anemia
  - Thalassemias
  - Anemia of chronic disease (~25%)
  - Lead poisoning
  - Unstable hemoglobins
- Macrocytic (MCV $>$ 100)
  - With megaloblastic bone marrow
    - Vitamin B_{12} deficiency
    - Folic acid deficiency
    - Thiamine deficiency (rare)
  - With normoblastic bone marrow
    - Reticulocytosis
    - Liver disease and obstructive jaundice
    - Postsplenectomy
    - Hypothyroidism
    - Aplastic anemia
    - Myeloproliferative diseases
    - Alcohol abuse
- Normocytic and normochromic
  - With RPI greater than 3
    - Acute blood loss
    - Hemolysis
  - With RPI less than 2
    - Anemia of chronic disease (~75%)
    - Mild iron deficiency
    - Sideroblastic anemia
    - Refractory (nonsideroblastic) anemia
    - Anemia of renal disease
    - Myelophthisic anemia
    - Anemia of endocrine dysfunction
    - Hypoplastic and aplastic anemias

DIAGNOSTIC EVALUATION OF THE ANEMIC PATIENT

General Principles

Recognition that anemia exists is the first step in evaluation. While this is obvious, it has been demonstrated that many physicians fail to pursue the diagnostic evaluation, particularly in mildly anemic patients who are often asymptomatic and in whom anemia may be an incidental finding. This tendency to ignore anemia may reflect several factors: concern over cost-effectiveness, uncertainty about the normal values for men and women, and a propensity to subconsciously redefine "normal values" to fit a given patient population. As a general principle all patients with anemia should undergo a diagnostic evaluation to establish the etiology. This approach is justified by two factors: anemia, even when mild, may be a clue to a serious underlying disease (e.g., bacterial endocarditis); the etiology can frequently be established by relatively simple and inexpensive tests.

Anemia is usually diagnosed when the hemoglobin or hematocrit is below the normal range (Table 1). However, relative anemia, characterized by a normal red cell mass occurs when plasma volume expands sufficiently to dilute the hemoglobin concentration into the anemic range. This phenomenon occurs during pregnancy and in patients with macroglobulinemia, congestive heart failure, splenomegaly, or cirrhosis. These relative (dilutional) anemias do not represent a physiologic disadvantage since the oxygen-carrying capacity is not reduced. However, each of the causes of relative anemia can be associated with absolute anemia. The clues to an absolute anemia superimposed are anemia greater than would be expected from dilution alone (a hemoglobin below 10 g/dl or hematocrit below 0.30 should not be attributed solely to dilution) and morphologic abnormalities on the peripheral blood smear. If uncertainty remains, a ^{51}Cr red cell mass will distinguish relative from absolute anemia, although this study is contraindicated in pregnancy.

Once the presence of anemia is established, an investigation to determine the etiology of the anemia is indicated. When the etiologic diagnosis is known, appropriate therapy for the anemia and the underlying disease can be given. The initial diagnostic procedure is a careful history and thorough physical examination, which often provide important clues to the etiology of the anemia (Table 4). The initial laboratory tests that are recommended for all patients with anemia are listed in Table 5. The data obtained from these initial tests allow preliminary classification of the anemia. The red cell indices and evaluation of the peripheral blood smear permit the morphologic classification. Variations in erythrocyte size and shape (Table 6), intracellular inclusions, leukocyte and platelet abnormalities can provide

Table 4 History and Physical Examination in the Diagnosis of Anemia

History
Symptoms of systemic illness (fever, chills, sweats, weight loss)
Previous anemia or use of hematinics
Chronic blood loss (menstrual, epistaxis, melena, purpuric)
Gall bladder disease or surgery
Jaundice or dark urine
Back pain
Neurologic symptoms (paresthesias, ataxia)
Change of bowel habits
Symptoms of endocrine dysfunction
Rheumatic symptoms
Underlying diseases (e.g., renal disease, prosthetic heart valve)
Toxin or drug exposure (including alcohol)
Dietary habits (e. g., vegans)
Cardiovascular (dyspnea, palpitation, claudication, dizziness)
Family history
Physical examination
Funduscopic
Purpura or petechiae
Jaundice
Lymphadenopathy
Heart murmurs or signs of heart failure
Splenomegaly
Hepatomegaly
Rectal and stool guaiac test

important clues to the etiology of the anemia. The reticulocyte count distinguishes anemias due to impaired erythrocyte production by the bone marrow (normal or low reticulocyte count, RPI less than 2) from anemias due to accelerated erythrocyte destruction or loss (reticulocyte count normal to elevated, RPI greater than 3). One caveat is necessary for the interpretation of reticulocyte counts. Many anemias are multifactorial and the reticulocyte count, when normal or low, may not reflect all of the pathogenetic mechanisms involved. For instance, patients with autoimmune hemolytic anemia may have a normal or low reticulocyte count although the primary mechanism of anemia is increased red cell destruc-

Table 5 Initial Laboratory Studies in the Evaluation of Anemia

Complete blood count (including Hb, Hct, erythrocyte count, leukocyte count)
Red cell indices
Differential leukocyte count
Platelet count
Reticulocyte count (calculate RPI)
Examination of peripheral smear
Stool guaiac
Creatinine

tion. The low reticulocyte count in this instance reflects impaired bone marrow response due to the effects of the underlying disease or deficiency of folic acid. In summary, the reticulocyte count reflects the capacity of the bone marrow to increase erythrocyte production in anemia. The leukocyte and platelet counts are obtained to determine if the anemia is an isolated abnormality or if other bone marrow cell lines are involved. Finally, the stool guaiac and creatinine are obtained because of the important role of gastrointestinal blood loss and renal failure in the etiology of anemia.

In some patients with anemia, the etiology may be evident after these initial data are obtained. In other patients, the differential diagnosis may be reduced to a few possibilities, while in other patients the initial studies may only eliminate a few of the etiologic possibilities. Subsequent evaluation should be guided by the initial results.

Microcytic Hypochromic Anemias

The differential diagnosis of microcytic hypochromic anemia is limited (Table 3). The hypochromic anemias (Fig. 3) are due primarily to impaired hemoglobin biosynthesis, most commonly as a result of iron deficiency. Iron deficiency is suggested by a history of abnormal blood loss or excessive menstrual bleeding. Although iron deficiency anemia is usually considered microcytic, hypochromic, mild iron deficiency anemia (Hb greater than 10g/dl) is often normocytic, normochromic. The presence of iron deficiency may be confirmed by measurement of the serum total iron-binding capacity (TIBC) and serum iron. In uncomplicated iron deficiency the serum iron is reduced, the total iron-binding capacity is in the high normal range or elevated and the saturation of the iron-binding capacity (serum iron divided by total iron-binding capacity) is less than

Table 6 Erythrocyte Morphologic Abnormalitites in Anemia

Erythrocyte Abnormality	*Description*[a]	*Associated Conditions*
Basophilic stippling		
Coarse	Large deep blue granules	Lead poisoning, thalassemias
Diffuse	Fine deep blue granules	Hemolysis, many anemias
Cabot's rings	Red-violet rings, concentric or figure-8	Megaloblastic anemia, hemolysis, postsplenectomy
Elliptocyte (ovalocyte)	Oval to elliptical erythrocytes	Hereditary elliptocytosis, thalassemias, iron deficiency, megaloblastic anemias, myelophthisic anemias
Heinz body	Purple inclusions in supravital preparations	Hereditary enzymopathies, unstable hemoglobins
Howell-Jolley body	Large purple inclusions, usually single, 0.5-1.0 μm	Postsplenectomy, hemolytic anemia, megaloblastic anemia, sideroblastic anemia, myeloproliferative diseases
Pappenheimer body	Small purple granules, in periphery of cell	Sideroblastic anemias, postsplenectomy
Polychromasia	Erythrocytes with blue hue	Reticulocytosis
Rouleaux	Linear stack of cells	Paraproteinemia
Schistocyte	Fragmented cell, often with pointed extremities	Microangiopathic hemolytic anemia, prosthetic valve hemolysis, burns

Table 6 (Continued).

Erythrocyte Abnormality	*Description*[a]	*Associated Conditions*
Sickle cell	Various forms, typically bipolar	Sickling disorders
Spherocyte	Spherical, dense cell with loss of central pallor	Hereditary spherocytosis, immunohemolytic anemia, microangiopathic hemolytic anemia
Spiculated cells		
Burr cell (echinocyte)	Short, evenly spaced projections	Uremia, pyruvate kinase deficiency, gastric diseases
Spur cell (acanthocyte)	Irregular projections	Alcoholic liver disease, postsplenectomy, abeta lipoproteinemia
Stomatocyte	Mouthlike area of central pallor	Hereditary stomatocytosis, alcoholism, obstructive liver disease
Target cell (codocyte)	Targetlike (bullseye) appearance	Thalassemias, obstructive liver disease, hemoglobinopathies (S,C), iron deficiency, postsplenectomy, hereditary lecithin-cholesterol acyl-transferase deficiency
Teardrop cell	Elongated, drop-shaped or pear-shaped cell	Myelophthisic anemias thalassemias

[a]Based on appearance on Romanowsky-stained smears unless otherwise noted.

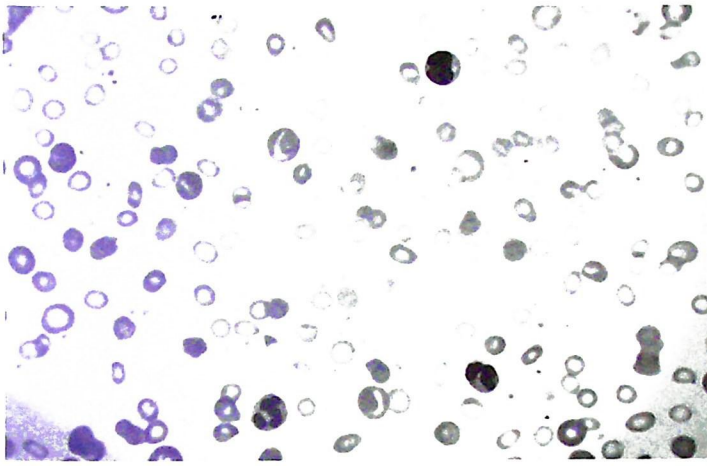

Figure 3 Peripheral blood smear: microcytic, hypochromic anemia due to iron deficiency.

15%. In the anemia of chronic disease, the saturation is also reduced, but a saturation less than 5% favors iron deficiency. In the anemia of chronic disease total iron-binding capacity is reduced. If iron deficiency and the anemia of chronic disease cannot be distinguished, the serum ferritin may be useful. In iron deficiency the ferritin is reduced, whereas in the anemia of chronic disease the ferritin is normal or elevated. Finally, the bone marrow can be evaluated for the presence of iron. In iron deficiency anemia stainable iron is markedly reduced or absent, whereas in the anemia of chronic disease bone marrow iron is increased in amount and is present predominantly in bone marrow macrophages rather than erythroid progenitors.

The sideroblastic anemias and thalassemias present a different picture. In both the serum iron is usually elevated and the saturation of the iron-binding capacity increased. The history and peripheral blood smear often provide invaluable clues to these two diagnoses. Sideroblastic anemia is often idiopathic, particularly in patients who present after age 50 years. However, in some patients sideroblastic anemia is hereditary and in others sideroblastic anemia is associated with an underlying infectious, neoplastic, inflammatory or hematologic disease. Finally, in some patients sideroblastic anemia is due to the ingestion of certain drugs (particulary antituberculous drugs) or alcohol. In the sideroblastic anemias, there are often

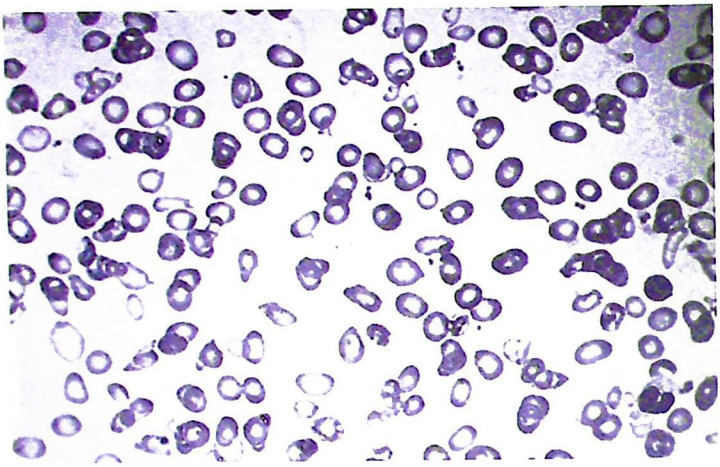

Figure 4 Peripheral blood smear: dimorphic smear in idiopathic sideroblastic anemia.

two populations of erythrocytes ("dimorphic" blood smear): normocytic, normochromic cells and microcytic, hypochromic cells (Fig. 4). A few target cells and mild basophilic stippling may be present and there is often moderate variation of the shape of the cells (poikilocytosis). The bone marrow iron stain in these patients shows the characteristic ringed sideroblasts (Fig. 5), due to mitochondrial iron accumulation.

The thalassemias are hereditary disorders characterized by impaired synthesis of either the alpha (in alpha thalassemias) or beta (beta thalassemias) globin chains. The alpha thalassemias occur most frequently in Oriental populations but are also observed in American blacks and some Middle East populations. Beta thalassemia is common in Mediterranean populations, the Middle East, and Southeast Asia and is occasionally observed in other racial groups. In the thalassemic syndromes, the clinical phenotype can be divided into three categories: (1) thalassemia major with severe anemia evident in infancy; (2) thalassemia intermedia with anemia of lesser severity often without transfusion requirement; and (3) thalassemia minor with mild anemia and no clinical manifestations. Each of these clinical patterns can result from several genotypes. The peripheral blood smear shows target cells and coarse basophilic stippling (Fig. 6). Thalassemia minor is particularly likely to be confused with iron deficiency. In addition to the studies already mentioned, the diagnosis of

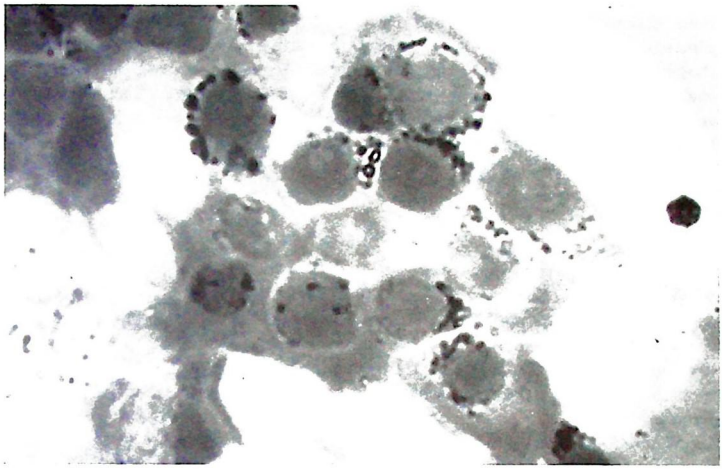

Figure 5 Bone marrow iron stain: ringed sideroblasts.

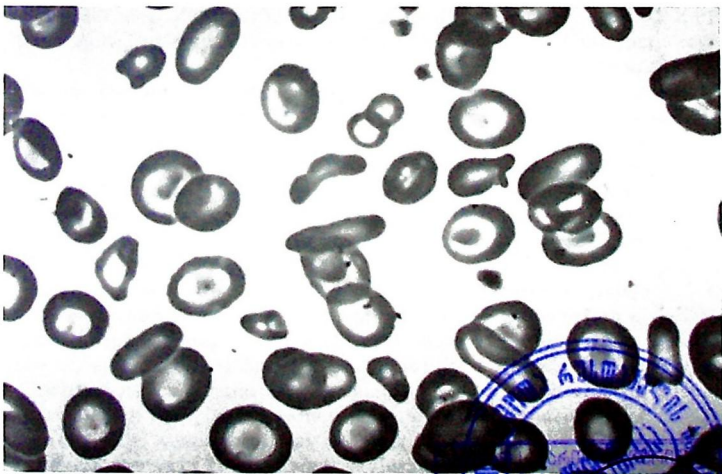

Figure 6 Peripheral blood smear: thalassemia.

beta thalassemia minor is usually confirmed by a hemoglobin electrophoresis demonstrating an increased amount of hemoglobin A_2. In alpha thalassemia minor the hemoglobin electrophoresis is normal and confirmation of the diagnosis requires special investigations. The diagnostic approach to a patient with microcytic, hypochromic anemia is outlined in Figure 7. Table 7 shows the typical changes in iron metabolism that are useful in the differential diagnosis of the microcytic, hypochromic anemias.

Macrocytic Anemias

The macrocytic anemias are due to abnormalities of DNA synthesis (megaloblastic anemias) or to abnormalities of the erythrocyte membrane. Recognizing the presence of macrocytic anemia and determining whether the anemia is megaloblastic or nonmegaloblastic is not difficult, but the specific etiology must be determined to permit appropriate therapy to be given.

When a macrocytic anemia is discovered, the reticulocyte count should be given specific attention. Marked reticulocytosis causes an elevation of mean corpuscular volume. Therefore, a patient with reticulocytosis may have a macrocytic anemia independent of the underlying pathophysiology of the anemia. The mean corpuscular volume determined on an automated counter may be spuriously elevated if the white blood count exceeds 25×10^9/liter. In this case direct calculation of the MCV from the erythrocyte count and hematocrit and direct evaluation of the blood smear should prevent confusion.

Once macrocytosis secondary to an elevated reticulocyte count or artifact are excluded, the history and physical examination may provide some clues to the etiology. A history of excessive alcohol consumption should be sought. Distinction of the two major causes of megaloblastic macrocytosis, folic acid and vitamin B_{12} deficiency is critically important. Poor dietary habits, particularly the omission of green leafy vegetables, may lead to the development of folate deficiency. Vitamin B_{12} deficiency is rarely due to inadequate dietary intake because even when vitamin B_{12} is completely eliminated from the diet, body stores are adequate to prevent a deficiency state for 2 or more years. However, complete elimination of animal products from the diet (vegans) can eventually lead to vitamin B_{12} deficiency. Both folate and B_{12} deficiency can develop when there is increased cell turnover (e.g., hemolytic anemia, myeloproliferative disorders, pregnancy), but folic acid is more likely to be depleted under these conditions. A history of previous gastric resection is an important clue, since this operation can result in deficiency of iron, vitamin B_{12}, or folic acid. Diseases or resection of the small intestine can lead to folic acid

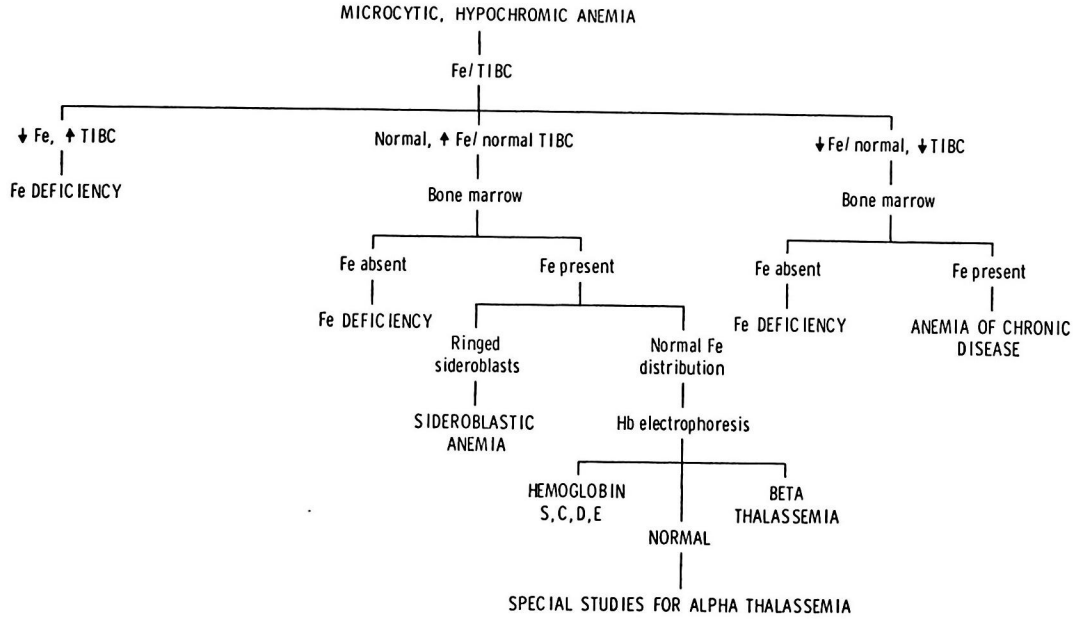

Figure 7 Decision tree for the evaluation of microcytic, hypochromic anemias.

Table 7 **Evaluation of Iron Stores in Anemias**

Condition	*Serum Fe*[a] *(μg/dl)*	*Serum TIBC*[a] *(μg/dl)*	*Saturation (%)*	*Serum Ferritin (μg/dl)*	*Marrow Fe*[b]	
					Sideroblast	*Reticuloendothelial*
Normal	60-150	300-360	20-50	100-300	20-50%	–
Iron deficiency	↓	↑	↓	↓[c]	↓	↓
Chronic disease	↓	↓	↓	nl, ↑[a]	↓	↑
Ineffective erythropoiesis	↑	nl	nl,↑	nl, ↑	nl	nl, ↑
Sideroblastic anemia	↑	nl	↑	↑	↑[d]	↑
Hypoplastic anemia	↑	nl	↑	↑	↓	↑

[a] Abbreviations: Fe, iron; TIBC, total iron-binding capacity; nl, normal
[b] Normally 20-50% of marrow normoblasts contain cytoplasmic iron granules and are called sideroblasts.
[c] Ferritin may be elevated in patients with coexistant inflammatory, neoplastic, or hepatic disease.
[d] Sideroblasts are increased and ringed sideroblasts are present.

or vitamin B_{12} deficiency. Pancreatic insufficiency can result in vitamin B_{12} malabsorption. Pernicious anemia (PA), the most frequent cause of vitamin B_{12} deficiency in the United States, is due to defective production of intrinsic factor by the gastric mucosa. In the absence of intrinsic factor, vitamin B_{12} absorption is severely impaired. PA may be associated with abnormalities of thyroid function and vitiligo that may provide a diagnostic clue. Vitamin B_{12} deficiency is also suggested by the presence of symmetric paresthesias of the hands and feet that may progress to a spastic ataxia (subacute combined system disease). This neurologic syndrome is unique to vitamin B_{12} deficiency and once it is fully developed is usually irreversible. Furthermore, inappropriate administration of folic acid to a patient with vitamin B_{12} deficiency can precipitate or aggravate the neurologic syndrome.

Laboratory evaluation is required to precisely determine the etiology of macrocytic anemias. The serum lactate dehydrogenase (LDH) may be elevated up to 50 times normal in megaloblastic anemias, but not in other macrocytic anemias. The only other cause for LDH elevations of this magnitude is disseminated neoplasia, although hemolytic anemias may cause two- to three-fold elevations. The peripheral blood smear is usually helpful in classifying the macrocytic anemias. Oval macrocytes and neutro-

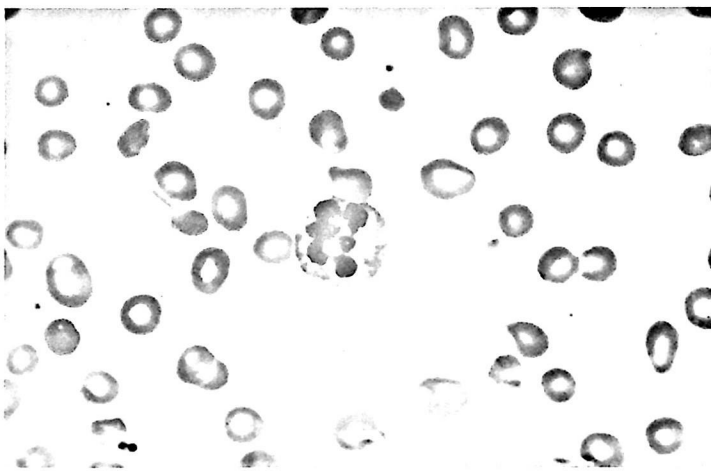

Figure 8 Peripheral blood smear: megaloblastic anemia, hypersegmented neutrophil.

philic hypersegmentation (neutrophils with five or more lobes) (Fig. 8) are characteristic of the megaloblastic anemias but are not a feature of the nonmegaloblastic macrocytic anemias. Furthermore, the megaloblastic anemias are often associated with both leukopenia and thrombocytopenia. The serum vitamin B_{12} level and serum and erythrocyte folate levels should be obtained early in the evaluation. Red cell folate levels are particularly important if the patient has been hospitalized and folic acid deficiency is responsible for the anemia, since an improved diet or administration of folic acid will rapidly raise serum folate levels to normal. Furthermore, the megaloblastic changes in the bone marrow are rapidly (24 to 48 hours) reversed after replacement of either folic acid or vitamin B_{12} in patients deficient in one of these nutrients. If the typical picture of folate or vitamin B_{12} deficiency exists, bone marrow examination is not essential to the diagnosis, and it is not useful in distinguishing vitamin B_{12} and folate deficiency, since bone marrow morphology is identical in these conditions. However, when there is doubt about the diagnosis a bone marrow should be performed prior to administration of folic acid or vitamin B_{12}. The neutrophilic hypersegmentation resolves when the deficiency of folic acid or vitamin B_{12} is corrected but this change reverses more slowly than megaloblastosis, usually requiring one to two weeks.

If the vitamin B_{12} level is subnormal and the serum and red cell folate levels are normal, vitamin B_{12} deficiency is probably responsible for the anemia. When both vitamin B_{12} and folate levels are low, there may be a primary deficiency of one vitamin resulting in malabsorption of the other by the production of megaloblastic changes in the intestinal mucosa. Under these circumstances additional diagnostic studies are necessary. If the serum and red cell folate levels are low and the vitamin B_{12} level normal, folate deficiency is likely. The serum folate level is more labile than erythrocyte folate levels and may become subnormal prior to actual tissue depletion and development of megaloblastic anemia. The red cell folate is considered a more accurate index of tissue folate levels. In the presence of vitamin B_{12} deficiency, folate metabolism may be altered. Vitamin B_{12} is required for the maintenance of cellular folate stores, and in vitamin B_{12} deficiency a redistribution of folate from erythrocytes to the serum may occur, resulting in reduction of red cell folate and increase of serum folate levels (Table 8).

An additional test that may be helpful in distinguishing folate from B_{12} deficiency is urinary methylmalonic acid (MMA) excretion. The conversion of methylmalonic acid to succinic acid requires vitamin B_{12}, and in vitamin B_{12} deficiency an excess of MMA accumulates and is excreted in the urine. Methylmalonic acid excretion is normal in folic acid deficiency.

The studies described to this point must be performed before therapy is instituted, since treatment with the deficient substance alters the test

Table 8 Vitamin B_{12} and Folate Levels in Megaloblastic Anemias

	Serum vitamin B_{12} (pg/ml)	*Folate (μg/liter)*	
		Serum	*Erythrocyte*
Normal	200-900	5-21	150-600
Vitamin B_{12} deficiency	↓	↑	↓
Folate deficiency	normal	↓	↓
B_{12} or folate deficiency with malabsorption	↓	↓	↓

results. Several additional tests can be performed either before or after therapy has been started. Perhaps the most useful of this second group of tests is the gastric analysis. The presence of histamine-fast achlorhydria in a patient with megaloblastic anemia strongly suggests the diagnosis of PA and the absence of achlorhydria excludes the diagnosis of PA. In combination with the presence of circulating antibody to intrinsic factor, which is detected in about two-thirds of patients with PA, achlorhydria is virtually diagnostic of PA. Circulating antibodies to the gastric parietal cell are present in about 90% of PA patients but they are not specific for this diagnosis.

The Schilling test is used to detect vitamin B_{12} malabsorption. This test is often unnecessary in the evaluation of megaloblastic anemias but may be useful in establishing that B_{12} malabsorption exists and determining if the malabsorption is secondary to intrinsic factor deficiency (PA) or an intestinal disorder. The Schilling test is performed by giving a large parenteral loading dose of unlabelled vitamin B_{12}, which saturates tissue and serum binding sites. An oral dose of radioactive B_{12} is given and a 24-hour urine collection obtained. If intestinal vitamin B_{12} absorption is normal, urinary excretion of the labeled vitamin B_{12} will exceed 7% of the administered dose. If the first part of the test is abnormal, the test is repeated but intrinsic factor is given with the oral radioactive vitamin B_{12}. If urinary excretion remains less than 7% intestinal malabsorption is probable; if the urinary excretion now exceeds 7%, intrinsic factor deficiency is probably responsible for the B_{12} malabsorption. The performance of the Schilling test amounts to a therapeutic trial of parenteral vitamin B_{12}, and therefore the blood count and reticulocyte count should be monitored for a response. Since both vitamin B_{12} and folate deficiency can cause malabsorption secondary to "intestinal megaloblastosis" and folic acid deficiency may cause gastric damage and impaired intrinsic factor production, the Schilling test may give misleading results in an untreated patient. Therefore, any patient with an abnormal Schilling

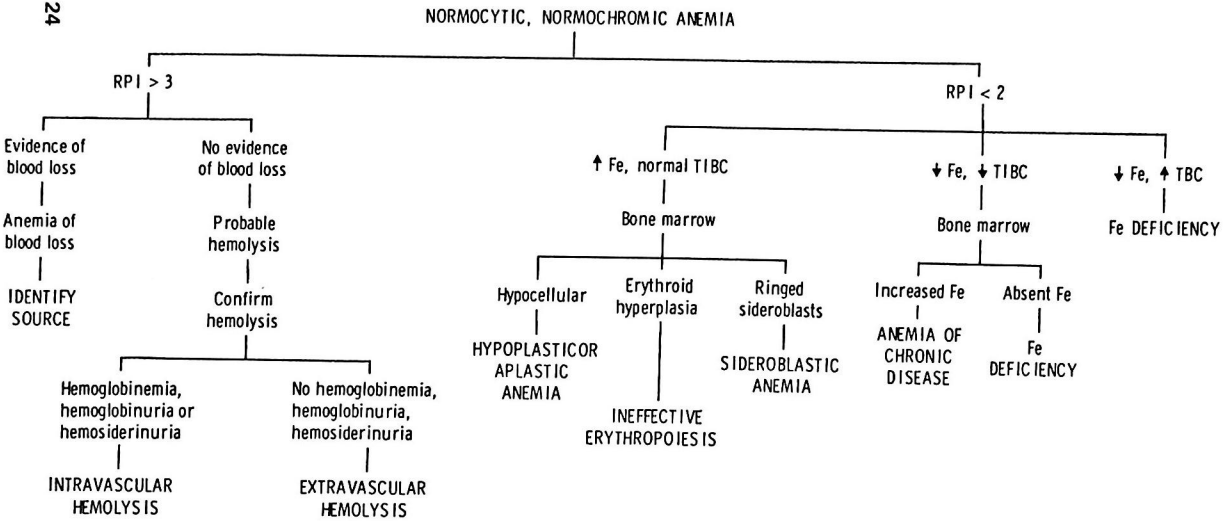

Figure 9 Decision tree for the evaluation of normocytic, normochromic anemias.

test should have the study repeated after several months of therapy, unless the diagnosis is certain by other criteria. Although additional tests are available to assess the megaloblastic anemias, they are rarely needed clinically. The definitive diagnostic test in either folate or B_{12} deficiency is often the therapeutic trial which is discussed in the section on management.

Normocytic Normochromic Anemias

General Approach

Normocytic, normochromic anemias have an extensive differential diagnosis, and these anemias can be the most difficult to ascribe to a specific etiology. The diagnostic approach is outlined in Figure 9. The reticulocyte count and RPI are useful in the preliminary classification of normocytic anemias. If the RPI is above 3 the marrow is responding appropriately to the anemia and acute blood loss or hemolysis is the likely

Table 9 **Laboratory Tests Useful in Establishing the Presence of Hemolysis**

Test	*Comment*
Indirect bilirubin	Elevated in acute hemolysis
Plasma or urine hemoglobin[a]	Elevated transiently in acute hemolysis
Serum haptoglobin	Decreased in acute intravascular hemolysis May be normal or decreased in extravascular hemolysis
Urine hemosiderin[a]	Chronic intravascular hemolysis
Methemalbumin	Present in chronic hemolysis
Urinary urobilinogen	Elevated in hemolysis, ineffective erythropoiesis, liver disease (nonspecific)
Fecal urobilinogen	No longer used
Chromium-51 erythrocyte survival	Usually unnecessary, but may help to diagnose hemolysis in some patients
	Sequestration study may localize sites of destruction
Ferrokinetics (^{59}Fe)	Not generally available, but may be helpful in difficult cases

[a]Elevation indicates an intravascular hemolytic process.

cause. In acute blood loss, the reticulocyte response to bleeding is not detected for 3 to 5 days and may not be optimal for 10 days after bleeding occurs. Therefore, a low RPI in the first few days after bleeding does not exclude blood loss as the etiology of the anemia. The reticulocyte response is also dependent upon the presence of adequate iron stores and the absence of other processes that impair bone marrow function.

In the absence of bleeding, normocytic anemia with an increased RPI suggests a hemolytic process. Studies should be directed at: (1) confirming the presence of accelerated erythrocyte turnover and (2) establishing the etiology of the hemolytic process. Laboratory tests that are useful in establishing the presence of hemolysis are listed in Table 9.

Hemolytic Anemias

When a hemolytic process is diagnosed, certain historical features are helpful in the differential diagnosis. The age of onset may indicate whether the anemia is congential or acquired. The family history may reveal the pattern of inheritance. The ethnic background of the patient should be investigated, since some causes of hemolysis are frequent in certain racial groups. For instance, glucose-6-phosphate dehydrogenase (G6PD) deficiency is common among Mediterranean and African populations and is transmitted as an X-linked trait. Finally, a history of certain diseases or drug ingestion may provide important clues to the etiology of hemolysis.

Evaluation of the peripheral blood smear is often diagnostically helpful in patients with hemolysis (Table 6). The presence of sickled erythrocytes (Fig. 10) is diagnostic of sickle cell anemia or one of its variants. Sickled cells are not observed on routine blood smears in patients with sickle trait.

Hemolytic processes can be further classified by whether the predominant site of hemolysis is extravascular or intravascular (Table 9). The utility of this division is that predominantly intravascular hemolysis occurs in a limited number of conditions (Table 10). The presence of free plasma or urine hemoglobin occurs with acute intravascular hemolysis, whereas urine hemosiderin is usually present in chronic intravascular hemolysis. When there is evidence of intravascular hemolysis diagnostic studies should focus on the conditions in Table 10.

The direct antiglobulin (Coombs') test should be performed early in the evaluation of hemolytic anemias. The direct Coombs' test detects red cell-bound antibody or complement, and in the presence of hemolysis a positive test suggests an antibody mediated pathogenesis. The cold antibody hemolytic anemias (cold agglutinin disease) are usually due to complement-fixing IgM antibodies to erythrocyte membrane antigens and are detected by the presence of the cold agglutinins in the serum (in the presence of hemolysis the titer is usually 5×10^{-2} or greater) and a positive direct antiglobulin test with a specificity for complement. Autoimmune warm-antibody hemolytic anemias cause principally extravascular

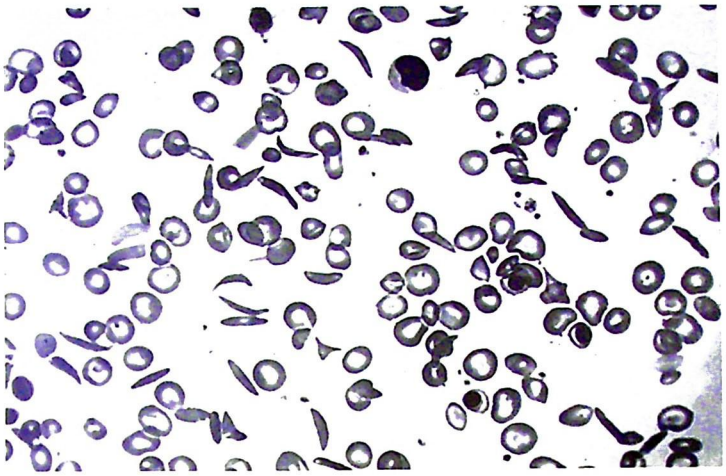

Figure 10 Peripheral blood smear: sickle cell anemia.

hemolysis, but cold antibody hemolytic anemias and alloimmune hemolytic anemias related to transfusion therapy produce intravascular hemolysis.

Alloimmune hemolysis may occur immediately following transfusion, or in some cases up to 2 weeks afterward. Delayed transfusion reactions are due to an anamnestic response causing a rise in antibody titer to an antigen on the transfused cells. The erythrocyte antigens most frequently associated with delayed transfusion reactions are the Kidd, Rh, Duffy, and Kell systems. Immediate reactions are most often due to blood incompatible in the Kell, Duffy, ABO, or Rh systems. The clinical manifestations, diagnosis, and management of transfusion reactions are discussed in Chapter 2.

G6PD deficiency, the most common red cell enzymopathy, affects about 10% of black males. G6PD deficiency is suggested by a family history of affected males and hemolysis occurring after exposure to oxidant drugs. G6PD deficiency can be confirmed by a fluorescent screening test or specific red cell enzyme assay. However, in some variants of G6PD deficiency, newly released erythrocytes (i.e., reticulocytes and young erythrocytes) have normal levels of G6PD and it is only in the aged erythrocytes that G6PD deficiency becomes evident. In this group of G6PD deficient patients erythrocyte G6PD levels may be normal after an acute hemolytic episode because the remaining circulating cells are young.

Table 10 **Conditions Associated with Intravascular Hemolysis**

Condition	*Confirmatory Tests*
Cold antibody hemolytic anemia (cold agglutinin disease)	Direct Coombs, cold agglutinin
Sepsis (Clostridial, *E. coli*)	Blood cultures
Cholera	Stool cultures
Malaria (falciparum)	Blood smears
Warm antibody hemolytic anemia	
ABO-incompatible blood	Repeat cross match
Anti-Kidd (delayed transfusion reaction)	Antibody screen with sensitized erythrocytes
Anti-Kell, Duffy	Antibody screen
G6PD deficiency	Enzyme assay
Physical agents (severe burns)	Blood smear
Traumatic (prosthetic heart valve, cardiac bypass)	Blood smear
Microangiopathic hemolysis	Blood smear
Chemical (snake, spider venoms)	Historical
Paroxysmal nocturnal hemoglobinuria	Sucrose hemolysis, Ham's test
Paroxysmal cold hemoglobinuria	Donath-Landsteiner test

If the diagnosis is strongly suspected but the G6PD level is normal, the test should be repeated in 60 to 90 days. Family studies may also be helpful. Certain oxidant drugs, including acetylsalicylic acid, phenacetin, sulfonamides, primaquine, and nitrofurnatoin, can cause hemolysis. This is particularly likely to occur in patients with an underlying erythrocyte enzymopathy such as G6PD deficiency but occasionally occurs in patients with normal red cells.

Traumatic or microangiopathic hemolytic anemias are suggested by hemolysis occurring in an appropriate clinical setting and confirmed by the blood smear (Fig. 11). Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease of bone marrow stem cells that classically presents with episodes of dark urine (hemoglobinuria) occurring after sleep. The hemolysis in this disease is due to an erythrocyte membrane abnormality that sensitizes these cells to the hemolytic action of complement. This abnormality provides the basis for the screening sucrose hemolysis test and the more definitive acidified serum (Ham's) test. Any patient with an unexplained hemolytic anemia should have a sucrose hemolysis test. Patients with PNH may become iron deficient because of large urinary iron

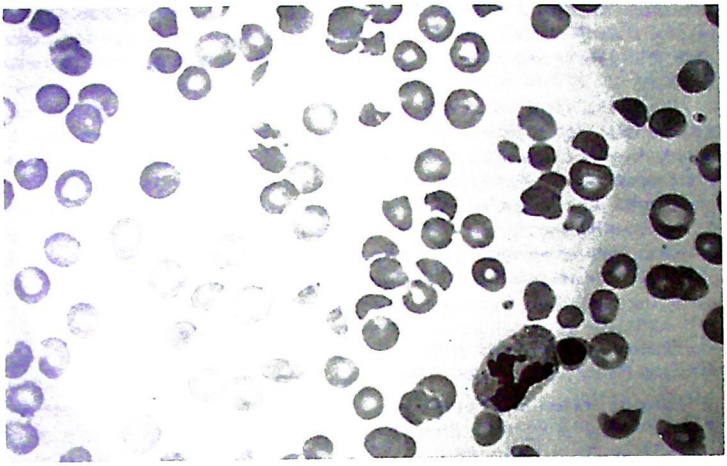

Figure 11 Peripheral blood smear: microangiopathic hemolytic anemia.

losses, and any patient with unexplained iron deficiency should have a sucrose hemolysis test performed. In addition, PNH occasionally presents as recurrent venous thrombosis, and PNH should be excluded in patients with unexplained clotting. Paroxysmal cold hemoglobinuria (PCH) is a rare disorder characterized by acute hemolysis after exposure to cold. This disorder may be idopathic or may occur following viral infections. Before effective antileutic therapy was available, syphillis was the most common etiology. PCH is due to a cold-reacting IgG antibody to an erythrocyte membrane antigen, and this antibody is detected by the Donath-Landsteiner test.

When hemolysis is predominantly extravascular, warm antibody autoimmune hemolytic anemia is frequently the cause. Autoimmune hemolysis can usually be detected by a positive direct antiglobulin test with specificity for IgG and in some cases for complement as well. This process may develop in association with other autoimmune diseases, such as systemic lupus erythematosus, with lymphoma or other lymphoproliferative disorders, or with viral infections. In some patients no underlying disease can be diagnosed. In a small number of patients with autoimmune hemolytic anemia, the direct antiglobulin test is negative. These "Coombs-negative" autoimmune hemolytic anemias are due to hemolytically active antibody present in low concentrations and can be detected using specialized techniques. Several drugs are capable of inducing the production of

antibodies that lead to a hemolytic process. The drugs most frequently involved are penicillin, alpha-methyldopa (Aldomet), L-dopa, and quinidine. The mechanism for the induction of antibody production varies with the drug.

When the cause of hemolysis remains unknown after this evaluation, hemoglobin electrophoresis at alkaline and acid pH should be done to detect hemoglobinopathies or thalassemias and red cell enzyme levels (particularly pyruvate kinase) obtained. In chronically ill, alcoholic, or malnourished patients, a serum phosphate level should be determined, since levels below 1.0 mg/dl are associated with hemolysis. If the etiology of the hemolytic process still remains unknown, it is likely that the cause is obscure. Referral to a hematologist should be made at this time, but in some cases the cause will not be discovered.

Normocytic Anemias with Low Reticulocyte Production

Patients with normocytic, normochromic anemias and an RPI less than 2 have either a hypoproliferative anemia, in which the bone marrow production of erythrocytes is reduced, or ineffective erythropoiesis. Ineffective erythropoiesis is most characteristic of the megaloblastic anemias and thalassemias but refractory anemia with a cellular bone marrow has an element of premature erythrocyte destruction within the bone marrow. In some patients with normocytic anemia and a low reticulocyte production index there is a combination of mild reduction of red cell survival and inability of the bone marrow to compensate by increasing the production of erythrocytes.

As with other types of anemia, clues to the etiology may be derived from the general medical evaluation. The presence of a chronic inflammatory, infectious or neoplastic process suggests the anemia of chronic disease. Anemia of chronic disease is second in frequency to iron-deficiency as a cause of anemia in United States hospital populations. Evidence of hypothyroidism or other endocrinopathies would suggest the anemia of endocrine failure. Mild anemia due to iron-deficiency is often normocytic and normochromic.

The initial laboratory evaluation (Table 5) provides information useful in the differential diagnosis. A reticulocyte count less than 0.5%, and particularly a count of 0.0%, in the presence of anemia suggests aplastic anemia or pure red cell aplasia. A normal creatinine excludes the anemia of renal failure, whereas an elevated creatinine implicates renal failure in the pathogenesis of the anemia. The peripheral blood smear is less helpful than with other types of anemia. However, the presence of nucleated red cells, early granulocytic cells (metamyelocytes, myelocytes) and tear drop erythrocytes suggest either myelofibrosis or infiltration of the bone

marrow (myelophthisic anemia). The anemia of renal failure may be accompanied by burr cells on the blood smear. Although the anemia of chronic disease is usually normocytic and normochromic, in approximately one-quarter of these patients the anemia is characterized by mild microcytosis and hypochromia.

In the anemia of chronic disease, the serum iron and the serum total iron-binding capacity are reduced, and the saturation is usually between 10 and 25%. The reduction in serum iron is less marked than in iron deficiency, and, unlike iron deficiency, the iron-binding capacity is reduced. In the anemia of chronic renal failure the serum iron and iron-binding capacity are usually normal. In aplastic anemia and pure red cell aplasia the serum iron is usually elevated and the saturation of the iron-binding capacity high (in some cases 100%).

Bone marrow examination is frequently required to establish the diagnosis in patients with normocytic anemia and a low RPI. When ineffective erythropoiesis is the pathophysiologic mechanism (refractory anemia) the bone marrow is cellular and shows erythroid hyperplasia, despite the low reticulocyte production index. In refractory anemia the bone marrow may also show megaloblastoid changes and erythroid precursors with two or more nuclei. In aplastic anemia, it may be impossible to aspirate the bone marrow, but the bone marrow biopsy is hypocellular with reduced numbers of all cell lines and in some cases an increased number of lymphocytes and plasma cells. In pure red cell aplasia, there is selective depletion of erythroid progenitors with the other cells lines present in normal quantities. In the anemias of renal failure and endocrine dysfunction the bone marrow usually appears normal but may show mild erythroid hypoplasia. The myelophthisic anemias are characterized by the presence of abnormal cell populations (e.g., tumor cells) or fibrosis in the bone marrow. As with aplastic anemia, the bone marrow may be difficult or impossible to aspirate, and even when aspiration is possible the abnormal cells may not be present. When an aspirate cannot be obtained or when a myelophthisic process is suspected, a biopsy of the bone marrow should be performed. The bone marrow iron stain is often helpful in the differential diagnosis of normocytic anemias. In the anemia of chronic disease bone marrow iron is increased due to accumulation of iron in reticuloendothelial cells (macrophages). This pattern of iron distribution reflects the pathogenesis of the anemia of chronic disease: impaired ability to reutilize reticuloendothelial iron deposits. Since a substantial minority of the patients with this type of anemia are microcytic and hypochromic, the bone marrow iron stain may be invaluable in excluding iron deficiency. In the anemia of renal disease the iron stores will be normal, unless superimposed iron deficiency occurs. In refractory anemia the iron stores are normal or increased.

MANAGEMENT OF THE PATIENT WITH ANEMIA

General Principles

The cardinal rule in managing an anemic patient is to establish a precise diagnosis. In some types of anemia there is no specific therapy except treatment of an underlying disease, whereas in others replacement of a deficient substance will cure the anemia. In a patient with an established cause for anemia, the physician should remain alert to the possibility that superimposed deficiencies may aggravate the anemia (e.g., iron deficiency superimposed on the anemia of chronic renal disease). Recognition of such secondary factors in an anemic patient and appropriate treatment may permit the patient to remain compensated and obviate the need for transfusions.

Exposure of the patient to potential causative agents should be eliminated whenever possible. The possibility of drug-induced blood dyscrasias should be considered, particularly in patients with aplastic or hemolytic anemias. Occasionally, megaloblastic or sideroblastic anemias are caused by drug toxicity.

The need for transfusion of red cells should be determined in each patient. In general, patients with a hemoglobin above 10 g/dl and hematocrit above 0.30 have an adequate oxygen-carrying capacity and do not require transfusion. Some patients with chronic anemias may tolerate a hemoglobin as low as 7.5 g/dl for prolonged periods. This is made possible by a number of adaptive changes, such as reduced affinity of hemoglobin for oxygen (rightward shift of the oxyhemoglobin dissociation curve), increased cardiac output and shunting of blood to vital organs. However, these patients have little reserve capacity and their physical activity is limited. When the hemoglobin is less than 7.0 g/dl, cardiac hyperactivity becomes evident and high output cardiac failure may occur. Cardiac failure and angina pectoris are particularly likely to occur if there is underlying coronary artery disease. If the hemoglobin oxygen saturation is less than 95% due to coexistent pulmonary disease supplemental oxygen should be administered. If overt cardiac failure develops, packed red blood cells should be administered slowly. It is not necessary to raise the hemoglobin to normal levels, and usually a hemoglobin of 8-10 g/dl will suffice. The usual measures for treatment of the heart failure should be employed including strict bed rest.

Empiric therapeutic trials with hematinic agents before the precise diagnosis is established should be avoided except when used to confirm a suspected diagnosis. This is particularly true of folic acid therapy, which may cause progression of the neurologic deficit if the anemia is due to vitamin B_{12} deficiency. Iron deficiency anemia is frequent in menstruating women, and some physicians are in the habit of empircally

treating anemic premenopausal women with iron without pursuing a diagnostic evaluation. This approach is acceptable provided the therapeutic response is monitored and a more thorough evaluation undertaken if no reticulocytosis or improvement in the anemia occurs after 6 weeks of iron therapy. Empiric iron therapy of anemia in males is never justified, since iron deficiency in men is nearly always due to pathologic blood loss.

Specific Measures

The treatment of the most common anemias and some less common anemias for which specific measures are effective will be discussed in this section.

Iron Deficiency

An effort to determine the site of blood loss should always be made when iron deficiency is documented. In males and post-menopausal females evaluation of the gastrointestinal tract by stool guaiac, rectal examination, proctosigmoidoscopy, and contrast radiographic studies is necessary. In premenopausal females the decision to investigate the gastrointestinal tract must be individualized.

Iron is given in the oral form unless there is poor compliance, malabsorption, intolerance of oral iron, or, rarely, when the amount of iron required exceeds that which can be given orally. Enteric-coated or sustained-release tablets should be avoided since they may not permit optimal intestinal absorption. The tablets should contain between 50 and 100 mg of elemental iron in the ferrous form (usually as the sulfate) and a total of 150-200 mg of iron should be given daily. For example, Feosol brand of ferrous sulfate contains 200 mg of anhydrous iron salt and 65 mg of elemental iron. Three tablets daily will provide 195 mg of elemental iron. The tablets should be given before meals to maximize absorption, unless gastrointestinal upset occurs. About 10% of the ingested iron is absorbed, or approximately 20 mg daily. The patient may note an improved sense of well-being within 1 to 2 days, before any objective hematologic improvement. Five to 7 days after iron therapy is started the reticulocyte count increases and becomes maximal by the tenth to fourteenth days, then returns to normal. The hemoglobin begins to increase after the first week of iron therapy but may require 1 to 2 months to reach normal levels. Once the hemoglobin becomes normal, oral iron should be continued for an additional three months to insure repletion of nonhemoglobin iron stores. Ten to 20 percent of patients will have troublesome gastrointestinal side effects, but these can usually be eliminated by initiating treatment with one tablet daily and increasing to full dose over the first week.

When oral iron therapy will not suffice, iron can be given parenterally as iron dextran (Imferon) or iron sorbital-citric acid (Jectofer), both

available in preparations containing 50 mg of elemental iron per milliliter. Iron dextran can be given intramuscularly or intravenously, whereas iron-sorbitol-citric acid is only for intramuscular injection. A convenient formula for calculation of the hemoglobin iron deficit is as follows: deficit (mg of iron) = (normal Hb − patient Hb) X body weight (lbs). For example, a 150-lb man with a hemoglobin of 8 g/dl would require (16 − 8) X 150 = 1,200 mg of iron to correct the anemia. To this amount must be added the deficit in storage iron, which is estimated as 1,000 mg for males and 600 mg for females. Thus, in the example given a dose of 2,200 mg of iron or 44 ml of iron dextran would be required to replete the entire iron deficit. This can be given by daily intramuscular (maximum daily dose 5 ml) or intravenous (maximum daily dose 2 ml) injections. However, iron dextran can be given in a single total dose by infusion intravenously in 1000 ml of saline over two hours. The total dose infusion method is widely used in several countries but has not received FDA approval in the United States. Whenever iron dextran is used, an initial test dose of 0.5 ml should be given by the intramuscular or intravenous route to detect hypersensitive patients. Adverse effects of parenteral iron include staining of the skin from improperly administered intramuscular injections, local thrombophlebitis from intravenous administration, fever, and arthralgias. More severe systemic reactions are uncommon but include hypertension, urticaria and regional or generalized lymphadenopathy. A possible complication of repeated intramuscular injections of iron dextran is the development of sarcomas at the injection sites.

Megaloblastic Anemias

As emphasized previously, a precise etiologic diagnosis should be made in all patients with megaloblastic anemia, preferably before starting therapy. However, if a patient has severe anemia, pancytopenia, bleeding, central nervous system dysfunction, or is otherwise critically ill, therapy with both folic acid 1 mg parenterally daily and vitamin B_{12} 100 μg intramuscularly daily should be started and continued for at least one week or until the patient's clinical condition is sufficiently improved. Before starting therapy blood should be obtained for folate and vitamin B_{12} levels. The vitamin levels will usually indicate which nutrient is deficient and most of the additional diagnostic studies can be performed after therapy has been started.

When vitamin B_{12} deficiency is established treatment should be given as 100 μg intramuscularly daily for two weeks then twice weekly until the hemoglobin is normal. For PA or any irreversible cause of vitamin B_{12} malabsorption, *therapy must be given for life.* Lifetime therapy consists of a 100 μg intramuscular injection monthly after the hemoglobin is normal. Oral vitamin B_{12} or B_{12}-intrinsic factor preparations should be

avoided in the treatment of B_{12} deficiency. If a therapeutic trial of vitamin B_{12} is indicated to confirm the diagnosis, the patient should be placed on a diet deficient in vitamin B_{12} and folic acid and given 1 μg daily of parenteral vitamin B_{12}. If vitamin B_{12} deficiency is the cause of megaloblastosis, reticulocytosis will begin by day three or four and become maximal in approximately one week.

When folic acid deficiency is the cause of anemia, therapy can usually be given orally with 1 mg of folic acid daily. Even when folate deficiency is due to intestinal malabsorption this dosage provides such an excess over the daily folate requirement that adequate amounts are absorbed. If the patient is severely anemic, therapy should initially be given parenterally. A therapeutic trial of folic acid can be given with 100 μg (0.1 mg) daily. The reticulocyte response follows the same course outlined for vitamin B_{12}.

When treating patients with vitamin B_{12} or folic acid, the reticulocyte count should be monitored every other day and the hemoglobin and hematocrit twice weekly until the response is well established. If the response does not follow the expected pattern, the diagnosis should be reconsidered and other factors suppressing the bone marrow should be sought. Iron deficiency commonly occurs along with megaloblastic anemia but may not become evident until after treatment. Some partients develop hypokalemia during treatment with vitamin B_{12} or folate, and serum potassium levels should be monitored.

Blood Loss Anemia

The need for transfusion is determined by the rate and extent of blood loss. Rapid loss of 20% or more of the blood volume often necessitates transfusion, especially if bleeding continues. The initial priority is the restoration of circulating blood volume by infusion of either colloid or crystalloid solutions.

The ability of the bone marrow to respond to blood loss depends largely upon the availability of iron. Even when iron stores are adequate, iron mobilization from storage deposits will only permit erythropoiesis at about three times the basal rate. Supplemental iron will allow erythropoiesis at four to five times the basal level.

Anemia of Chronic Disease

This type of anemia is usually not severe and manifestations of anemia are usually overshadowed by the underlying disease process. There is no effective therapy other than treatment of the underlying disease. If anemia is symptomatic or interfering with the resolution of an acute process (e.g., healing of a surgical wound), transfusion to a hemoglobin of 10 g/dl may be beneficial.

Anemia of Renal Disease

Iron and folic acid deficiency, particularly in patients receiving regular hemodialysis, are commonly present in patients with chronic renal failure and should be treated appropriately. If iron stores are depleted they should be replenished with parenteral iron, and the patient can then be given a maintenance oral iron preparation. Androgens may cause a small increase in hemoglobin and convert some patients from a transfusion-dependent to independent status. Although not yet available, administration of erythropoietin would be an ideal treatment for many patients because deficient production of this hormone plays a major role in the pathogenesis of this anemia.

Hemolytic Anemias

The treatment for this broad spectrum of disorders depends on the precise etiology. All patients with chronic hemolysis should be maintained on daily folic acid 1 mg supplements to prevent folate depletion. Iron supplementation is not indicated unless evidence of iron deficiency develops. Iron deficiency is most likely to occur in patients with continuous intravascular hemolysis such as paroxysmal nocturnal hemoglobinuria or cardiac valve hemolysis.

If the hemolysis is associated with drug ingestion and a negative Coombs' test, G6PD deficiency should be excluded. Whenever hemolysis is associated with a drug, further use of the drug should be avoided. When alpha-methyldopa is responsible for a positive Coombs' test, discontinuation of this drug is not necessary unless hemolytic anemia develops.

Warm antibody autoimmune hemolysis presents a serious problem when the anemia is severe enough to require transfusion. This problem is discussed in Chapter 2. Approximately half of the patients with this type of hemolysis respond to administration of corticosteroids. Prednisone or an equivalent corticosteroid should be given in a dose of at least 60 mg daily. If the patient is acutely ill or there is a concern about gastrointestinal absorption, an intravenous corticosteroid preparation should be given. When the hemoglobin begins to rise, the dosage can be reduced by 5 mg per week until a maintenance dose of 20 mg daily is reached. This dose should be continued for an additional 2 to 3 months then tapered slowly over another 1 to 2 months. Patients should take antacids four times daily while on corticosteroids. The goal of this therapy is maintenance of an adequate red cell mass at a corticosteroid dosage that does not produce unacceptable toxicity. When this cannot be achieved or when a patient is unresponsive to corticosteroids, splenectomy is indicated. Patients initially refractory to steroids may benefit from steroids if they remain anemic after splenectomy. In patients refractory to all of these approaches, more potent immunosuppressive agents such as cyclophosphamide may be useful but should only be employed by an experienced hematologist.

Finally, patients with a positive direct antiglobulin test but no evidence of anemia due to hemolysis, do not require treatment, although they should be monitored carefully.

Cold antibody hemolytic anemias present a different challenge. Maintenance of patient warmth is often effective in reducing symptoms. Corticosteroid therapy is usually ineffective, although a trial is justified by the occasional responses that occur. Splenectomy is usually ineffective. Treatment with cyclophosphamide or other alkylating agents may be effective. Plasmapheresis may be useful in selected patients.

Sickle cell disease presents a number of different management problems. A patient with a painful (infarctive) crisis should be hospitalized, and precipitating causes such as infection should be sought and treated. If infection cannot be excluded, empiric broad-spectrum antibiotic therapy with an agent effective for gram-positive organisms should be given until culture results are available. Hydration with oral or intravenous fluids should be maintained. Oxygen is usually administered but is only of benefit when the hemoglobin saturation is reduced. The patient should be kept warm and adequate analgesia provided. The use of narcotics during an acute attack is justified, but caution must be used in the prescription of addictive drugs for outpatient use. A patient with painful crisis should either have a reticulocyte count or examination of the peripheral blood smear to exclude an aplastic crisis. Painful crises usually resolve in three to seven days with this regimen of supportive care. Transfusion of small amounts of red cells may be helpful in terminating painful crises, but large transfusions should be avoided because of the adverse effect on blood viscosity. A number of experimental approaches have been tried for preventing or treating crises, but none has been clearly shown to be practical and effective. Anticoagulation with heparin is probably indicated when pulmonary infarction is suspected. Although the primary event in this process is in situ thrombosis, activation of the clotting system may play a secondary role.

In hereditary spherocytosis with overt hemolysis or cholelithiasis splenectomy is the treatment of choice and is usually effective. Other hemolytic anemias that may necessitate splenectomy include pyruvate kinase deficiency and hereditary elliptocytosis. Splenectomy is not usually indicated in G6PD deficiency.

Pure Red Cell Aplasia

In one-third or more of these patients a thymoma is found in association with erythroid aplasia. About half of these patients will have a remission after thymectomy, and this operation is indicated when thymic enlargement is detected in a patient with pure red cell aplasia. Thymectomy should not be performed in patients without evidence of thymic enlargement. Corticosteroids and immunosuppressive therapy may

also be effective, and some patients require the addition of one of these agents after thymectomy in order to sustain a remission.

Sideroblastic Anemia

In the secondary types of sideroblastic anemia the only effective therapy is treatment of the underlying disease process or elimination of causative drugs.

In primary (idiopathic) sideroblastic anemias, pyridoxine administered in pharmocologic doses (150-300 mg daily) may produce an occasional response and all patients should have a three month trial. If there is a family history of sideroblastic anemias, the probability that the patient will respond to pyridoxine is greater. About 20% of the patients with acquired idiopathic sideroblastic anemias have megaloblastic changes and macrocytosis, and this group may have some improvement in the anemia with administration of folic acid 1 mg daily. Approximately 7% of the patients with idiopathic sideroblastic anemia eventually develop leukemia, and the hematologic status of these patients should be monitored regularly.

Anemia in Pregnancy

During pregnancy there is an increase in the red cell mass and plasma volume, but because the plasma volume increases relatively more than the red cell mass a dilutional anemia results (physiologic anemia of pregnancy). This anemia becomes apparent toward the end of the first trimester. The hemoglobin in an otherwise normal woman does not decrease below 10g/dl. The dilutional anemia is accompanied by a mild reticulocytosis beginning in the second trimester. The hemoglobin should return to normal levels three to six weeks postpartum.

Iron deficiency is commonly superimposed on the physiologic anemia of pregnancy. Development of iron deficiency can usually be prevented by administration of one ferrous sulfate tablet daily in women without preexisting iron deficiency, but if deficiency exists at the time of pregnancy three tablets daily will be necessary.

Folic acid deficiency also occurs frequently during pregnancy and is most likely to produce overt megaloblastic anemia in the third trimester. This can be prevented by supplementing all pregnant women with at least 100 μg of folic acid daily. Supplementation should continue during the puerperium.

Postgastrectomy Anemia

The etiology of anemia seen after gastric resections in order of decreasing frequency is iron deficiency, vitamin B_{12} deficiency, and folic acid deficiency. In addition, gastrointestinal blood loss must be considered. All

patients should have iron stores assessed at the time of surgery and if evidence of iron deficiency exists iron replacement is given. Oral therapy is usually adequate but if the appropriate response is not observed parenteral therapy is indicated. Serum iron and total iron-binding capacity should be monitored at postoperative follow-up visits. If evidence of vitamin B_{12} deficiency develops, parenteral vitamin B_{12} injections should be given to replenish vitamin B_{12} stores and correct anemia, and then given monthly for life. Evidence for malabsorption due to a blind loop should be sought in patients with vitamin B_{12} or folic acid deficiency since the malabsorption may be amenable to antibiotic therapy or surgical correction.

CASE HISTORY

A 33-year-old man comes to your office with a history of easy fatigability for 3 months, intermittent epigastric distress, and dark stools. He was previously in good health. Physical examination reveals mild epigastric tenderness. The lungs are clear and there is a grade 2/6 systolic murmur along the left sternal border. There is no organomegaly and the rectal examination reveals no masses. Stool guaiac is negative.

Laboratory examinations reveals; Hb 10.5 g/dl, Hct 0.31, WBC 6.5 X 10^9/liter, normal differential, reticulocyte count 2.5%, platelet count 550 X 10^9/liter. MCV 81 fl, MCH 27 pg, MCHC 32 g/dl. Peripheral blood smear shows predominantly normocytic, normochromic red cells with an occasional hypochromic cell and slight polychromasia. The creatinine is 0.7 mg/dl and BUN 15 mg/dl. Serum iron 30, total iron-binding capacity 400.

Questions

1. The anemia in this patient is probably due to
   (a) Acute blood loss
   (b) Malabsorption of folic acid
   (c) Iron deficiency due to chronic blood loss
   (d) Anemia of chronic disease
2. Moderate iron deficiency anemia in adults is often normocytic, normochromic (true or false).
3. Appropriate management of this patient includes
   (a) Immediate bone marrow to confirm iron deficiency
   (b) Tranfusions of packed red blood cells
   (c) Oral iron therapy and investigation of the gastrointestinal tract

Answers

1. c
2. True
3. c.

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2

DENNIS GOLDFINGER

Principles of Blood Transfusion

Blood transfusion has taken on an increasingly important role in the modern practice of medicine. The availability of blood components plays a major part in improving the management of trauma victims and makes the performance of open heart surgery and radical cancer surgery possible. The development of platelet and granulocyte concentrates for providing hematologic support for cancer victims has allowed the institution of potent cytotoxic drug therapy for such patients. The ability to transfuse coagulation factors has revolutionized the management of patients with congenital coagulopathies (e.g., hemophilia). Nevertheless, the transfusion of blood components carries with it many potential risks. Patients may experience adverse reactions to both the cellular and noncellular constituents of blood. A variety of diseases may be transmitted from the donor to the recipient. Infection also may be transmitted to the recipient by contamination of the blood during collection or storage. Finally, the anticoagulants and preservatives, as well as the accumulated products of cellular metabolism and breakdown, may cause undesired effects. Therefore, whenever the decision is made to transfuse a blood component, the relative hazards of the transfusion should be balanced against the possible benefits to the patient. Only when the recipient is clearly in need of transfusion, and the potential value outweighs the risks, should the component be transfused.

PRINCIPLES OF BLOOD TRANSFUSION

Indications for Transfusions

Red Blood Cells

Red blood cell (RBC) transfusion may be required in the treatment of patients with acute blood loss, chronic anemia, or hemolytic anemia. Acute blood loss is encountered most frequently in patients undergoing surgery, in trauma victims, and in patients having gastrointestinal hemorrhage. Since RBC transfusion poses many risks to the patient, it is wise to avoid replacing RBCs in managing acute blood loss, until it is absolutely necessary. Generally, restoration of blood volume is far more important than maintenance of hemoglobin concentration, and volume replacement can be achieved with either crystalloid or colloid solutions, both of which are safer than RBC-containing blood components. Most patients can tolerate losses of 20 percent or more of their blood volume and receive replacement only with nonhemoglobin-containing solutions.

Transfusions of RBCs should be instituted when the patient's hemoglobin concentration reaches dangerously low levels. While it is impossible to define a specific point at which to begin RBC transfusion, acute reductions below 8-9 g/dl usually require administration of RBCs, especially if bleeding has not been controlled. The quantity of RBCs transfused should be only that which restores hemoglobin to a safe concentration (perhaps 10 g/dl), without attempting to achieve "normal" levels.

By limiting the number of units of RBCs transfused, the risk of transfusion-related complications can be minimized.

Transfusion of RBCs to patients with chronic anemia should be reserved for those patients who demonstrate clinical signs and symptoms of hypoxemia. Chronically anemic patients often tolerate hemoglobin concentrations as low as 7.5 g/dl without difficulty. While such patients may complain of tiredness and easy fatigability, these symptoms often are the result of the underlying disease process rather than the anemia.

When managing patients with hemolytic anemia, RBC transfusions should be withheld wherever possible. In acute autoimmune hemolytic anemia, the need for transfusions can be limited by keeping the patient at complete bedrest and administering supplemental oxygen. By avoiding RBC transfusion, the patient will not be exposed to RBC antigens, and future transfusions, if required, can be administered with minimal risk.

Platelets

Platelet transfusions may be used in the treatment of patients with thrombocytopenia or with abnormalities of platelet function. Platelets may be administered prophylactically to severely thrombocytopenic patients, in an attempt to prevent dangerous, spontaneous hemorrhage,

or therapeutically to control existing hemorrhage. Prophylactic transfusions also may be used to prepare thrombocytopenic patients for surgery. While the value of prophylactic transfusion has not been established clearly, it has become common practice to administer platelets, in order to maintain platelet counts in a safe range.

Platelet dysfunction occurs as a congenital or acquired disorder. These syndromes can be associated with a bleeding diathesis. Platelet transfusions may be indicated when bleeding occurs or prophylactically during surgery despite normal quantitative platelet counts in these patients. Von Willebrand's disease is associated with platelet dysfunction, but this is due to deficiency of the plasma factor VIII molecule and the platelets are intrinsically normal. Bleeding in patients with von Willebrand's disease is treated by fresh frozen plasma or cryoprecipitate but platelet transfusions are of no benefit.

Granulocytes

Granulocyte transfusions may be of value when treating established infections in patients with severe granulocytopenia. Prophylactic transfusions to granulocytopenic patients, for the prevention of infection, are of unproven value, and actually may be hazardous. Administration of granulocytes can be considered in the management of established infections in patients with disorders of granulocyte function (e.g., chronic granulomatous disease) although there is a paucity of data supporting the efficacy of transfusions for such patients.

Granulocytopenia is encountered most frequently in patients with aplastic anemia or malignant disorders involving the bone marrow, or as a consequence of chemotherapy for tumors which do not involve the marrow. Granulocyte transfusions should be considered only for those patients with severe granulocytopenia (less than 0.5-1.0 $\times$ 10^9/liter) in whom infection has been proven by culture, or is highly suspect on clinical grounds. Since such patients often respond to antibiotics, even in the face of severe granulocytopenia, treatment usually should be initiated with appropriate antibiotics alone. The addition of granulocyte transfusions, therefore, can be reserved for patients who fail to respond to a 48-hour course of antibiotic therapy.

Plasma and Plasma Derivatives

Transfusions of fresh frozen plasma or concentrated preparations of specific coagulation factors may be useful in the management of patients with coagulation abnormalities. Such disorders may be congenital, resulting from a deficiency of a coagulation factor, or they may occur on an acquired basis. The management of severe congenital coagulopathies (e.g., hemophilia) is a complex problem which should be undertaken only

by specialists in this field. Patients with mild deficiencies of specific coagulation factors, occurring on a congenital basis, may develop clinical complications only when subjected to surgery. The management of these patients also requires consultation with coagulation specialists.

Acquired coagulopathies may be seen as a result of disseminated intravascular coagulation (DIC), severe liver disease, anticoagulant overdose or massive bleeding. Laboratory studies of the coagulation system are essential in the management of patients with acquired coagulation disorders, to determine which of the coagulation factors may be deficient, and to aid in evaluating the patient's response to therapy. The approach to patients with coagulation abnormalities is discussed in Chapter 4.

CHOOSING THE OPTIMAL BLOOD COMPONENTS

General Philosophy of Component Therapy

A commonly held misconception exists that component therapy serves primarily to promote more efficient utilization of donor blood. In fact, an even greater value achieved by transfusing specific blood components relates to a significant increase in the safety and effectiveness of such transfusions. The separation of blood into components results in the production of highly specific fractions in concentrated form. The transfusion recipient, thereby, benefits by receiving greater quantities of the required elements with far less risk of circulatory overload. Moreover, the likelihood of other adverse reactions is minimized by avoiding transfusion of the blood factors which the patient does not need.

Routine separation of blood into multiple components has resulted in widespread availability of a variety of blood products, such as platelets and cryoprecipitates. This not only has increased the efficiency of utilization of donor blood, but has allowed for much more effective management of a variety of patients, such as leukemics and hemophiliacs. Satisfactory treatment of these patients previously had been limited by an inadequate supply of the necessary blood elements for transfusion.

Components for Supplying Red Blood Cells

Components that can be used for providing RBCs include whole blood, packed RBCs, buffy coat-poor RBCs, frozen RBCs, and saline washed RBCs. The choice of the most satisfactory product is based largely on the etiology of the patient's anemia. The single rule of greatest importance is

never to transfuse whole blood to nonbleeding, anemic patients. Such patients generally have normal or expanded blood volumes and may develop circulatory overload and cardiac failure when given whole blood. Patients who are bleeding, on the other hand, can be transfused with whole blood or concentrated RBC preparations. RBC concentrations, however, are totally adequate for treating anemia resulting from acute blood loss, and, often, are preferable to whole blood.

Therapy for patients with active hemorrhage is usually initiated with infusions of crystalloid or colloid solutions to restore blood volume. When anemia becomes sufficiently severe to require RBC replacement, the patient's blood volume already may be near normal. Under these circumstances, RBC transfusions may be accomplished more safely with concentrated RBCs, thereby preventing volume overload. Thus, transfusions with whole blood are mainly of value for patients with continued, active hemorrhage.

Leukocyte-poor RBCs should be utilized for transfusing patients who have suffered febrile, nonhemolytic transfusion reactions. This component may be supplied in the form of buffy coat-poor, frozen or saline washed RBCs. Frozen or saline washed RBCs have the additional attribute of being nearly devoid of plasma, and may be useful for transfusing patients who have suffered other types of transfusion reactions. The value of routine substitution of washed RBCs in place of packed RBCs, as a means of reducing the likelihood of adverse reactions in all patients, is a controversial issue. This decision must rest with the individual physician, as a matter of preference, and with the ability of the blood bank to supply washed RBCs.

Autologous blood can be used to supply the blood needs of patients undergoing elective surgical procedures. Autologous blood avoids many of the hazards of blood transfusion, especially the transmission of hepatitis. Patients scheduled for elective surgical procedures can donate their blood, usually as often as one unit per week. This blood can be stored in the liquid state, for up to five weeks, or as frozen RBCs, for up to three years. Recent studies have demonstrated that donation of blood for autologous transfusion is safe for virtually all patients who are medically fit to undergo elective surgical procedures. Our own studies have shown that blood donations are safe, even for patients with severe coronary artery disease, who are to undergo coronary artery bypass graft surgery.

Components for Supplying Platelets

Two components are available for the transfusion of platelets, namely, platelet concentrates and plateletpheresis concentrates. A platelet concentrate is prepared from a unit of donor blood and contains approximately 80 percent of the platelets present in 1 pint of blood, suspended in ap-

proximately 50 ml of plasma. Plateletpheresis concentrates are harvested from a single donor, using automated plateletpheresis equipment, and contain the number of platelets present in approximately 6 to 10 standard platelet concentrates. Transfusions of fresh whole blood are of no value in supplying platelets to thrombocytopenic patients, since such patients require large numbers of platelets in concentrated form, in order to attain levels adequate for hemostasis. When transfusing patients on a prophylactic basis, a dose of six platelet concentrates, administered 2 to 3 times weekly, usually will suffice to maintain platelet counts above 20×10^9/liter. For patients with active hemorrhage, resulting from surgery or trauma, a dose of 10 platelet concentrates per transfusion is appropriate, in order to attempt to raise the platelet count to greater than 50×10^9/liter. The rate of platelet consumption often is accelerated in this latter group of patients; thus, transfusions may be necessary as often as daily.

Platelet concentrates may be stored in the blood bank, at room temperature, for up to 72 hours. Although platelets stored for 48 to 72 hours retain reasonable hemostatic function, such platelets are most useful for treating patients who are not actively hemorrhaging. When managing patients with dangerous hemorrhagic complications, it may be appropriate to attempt to supply platelet concentrates which are less than 24 hours old.

Transfusions of ABO compatible platelets have been shown to result in greater posttransfusion recovery than seen with platelets collected from ABO incompatible donors. Nevertheless, the observed differences are relatively small, so that ABO incompatible platelets are perfectly acceptable for transfusion. Platelets collected from Rh positive donors survive normally when administered to Rh negative recipients, even if such recipients possess anti-Rh antibodies. The major hazard of Rh incompatible platelet transfusion is the possibility of Rh alloimmunization, because platelet concentrates are contaminated with small numbers of RBCs. This complication is of importance only to women of childbearing years, who may subsequently become pregnant. Therefore, platelets collected from Rh negative donors should be used exclusively in the management of Rh negative females capable of bearing children. It is unnecessary to utilize Rh negative platelet concentrates in the treatment of Rh negative females beyond the childbearing age or of males.

Patients who have received multiple transfusions of blood components may become sensitized to histocompatibility antigens, and be rendered refractory to platelet transfusions, due to rapid immunologic destruction of donor platelets. Such patients often respond much more favorably to transfusions of platelets collected from HLA-compatible donors. HLA-identical or partially matched donors may be found most easily by select-

ing donors from within the patient's family (siblings, parents, children). When close relatives are unavailable, unrelated HLA-matched donors may be used provided the blood bank has available a group of volunteer donors who have been typed for HLA antigens. Unfortunately, transfusions of HLA-matched platelets do not provide satisfactory results in all sensitized patients. In these cases, it is presumed that the patient has developed antibodies to antigens other than those of the HLA system. At the present, no means exist for providing compatible platelets for this group of patients.

Single-donor plateletpheresis concentrates, obtained using automated blood cell separators, may be a superior product for certain patients requiring platelet transfusion. Plateletpheresis concentrates contain the equivalent number of platelets in 6 to 10 standard platelet concentrates, but these are obtained from a single donor. The limited donor exposure is of special value in preventing posttransfusion hepatitis. Limited donor exposure is possible even for patients requiring multiple platelet transfusions over a period of days or weeks, since an individual donor can undergo plateletpheresis as often as every other day. Plateletpheresis also is required when supplying HLA-matched platelets.

Components for Supplying Granulocytes

Currently, the only component suitable for transfusing granulocytes is the granulocyte concentrate collected with automated blood cell separators. Granulocyte concentrates prepared by the technique of filtration leukapheresis (reversible adhesion to nylon-wool fibers) pose an unacceptable risk of recipient transfusion reactions, and probably should not be used. Granulocyte concentrates collected for transfusion to adults should contain at least 1×10^{10} granulocytes, and should be collected within 12 to 24 hours of intended transfusion. Preferably, the ABO group of the donor and the recipient should be identical, and, where this is not possible, the ABO group of the donor's RBCs should be compatible with the recipient's plasma. The use of donors who are matched with the recipient for HLA antigens may improve the recovery and survival of transfused granulocytes, but such donors are often unavailable.

The effectiveness of granulocyte transfusion suffers from the fact that the quantities of granulocytes collected for transfusion are equal only to approximately 10 to 20 percent of the normal daily adult granulocyte production. Furthermore, the intravascular lifespan of a normal granulocyte is approximately 6 hours. Therefore, to be effective, granulocytes must be transfused at least daily. It is essential that adequate antibiotics be administered to all patients receiving granulocytes.

Components for Supplying Coagulation Factors

Cryoprecipitate

Cryoprecipitates prepared from freshly collected plasma contain concentrated amounts of factor VIII (antihemophilic factor), von Willebrand factor, and fibrinogen. Each bag of cryoprecipitate contains approximately 100 factor VIII units, and 200-300 mg of fibrinogen, dissolved in approximately 10 to 15 ml of plasma. Because of the concentration achieved during the production of cryoprecipitates, it is possible to infuse large quantities of factor VIII or fibrinogen without overloading the patient's circulatory system. In fact, the availability of this component has revolutionized the treatment of patients with severe hemophilia and can provide adequate hemostasis under most circumstances. A lyophilized factor VIII concentrate, prepared from pooled plasma, also is useful for the treatment of patients with severe hemophilia A. This material, however, lacks the von Willebrand Factor, so that patients with von Willebrand's disease should be treated with cryoprecipitate rather than lyophilized factor VIII concentrates.

Concentrates of factor VIII and fibrinogen may be useful in the treatment of some patients with acquired coagulopathies. Although patients with DIC frequently develop deficiencies of multiple coagulation factors, it may be beneficial to supply certain factors in concentrated form. In selecting the proper component for transfusion, it is most important to consider the relative danger of each component, particularly the risk of transmitting posttransfusion hepatitis. This consideration is unnecessary for patients with severe hemophilia, since all such patients will receive so many transfusions in their lifetime that exposure to hepatitis is inevitable. In treating patients with mild congenital deficiencies or with acquired coagulopathies, such as DIC, however, exposure to hepatitis may be preventable by avoiding transfusion of components prepared from pooled plasma.

Lyophilized Factor IX (Prothrombin Complex) Concentrate

Commercially prepared concentrates of the vitamin K-dependent factors (factors II, VII, IX and X) are available for transfusion to patients with deficiencies of one or more of these factors. The major use of these preparations is in the treatment of patients with severe hemophilia B (factor IX deficiency). Congenital deficiencies of factors II, VII and X are extremely rare.

Patients with vitamin K deficiency, and those who have received excessive doses of warfarin, will possess inadequate concentrations of

factors II, VII, IX and X. However, lyophilized prothrombin complex concentrates, due to their high hepatitis risk, should not be used in the treatment of such patients. Hemostatic levels of the deficient coagulation factors can be restored within hours by parenteral administration of vitamin K_1. For patients who present with dangerous hemorrhage, hemostasis usually can be achieved quickly by the transfusion of 2 to 4 units (500-1000 ml) of fresh frozen plasma.

Fresh Frozen Plasma

Fresh frozen plasma is the plasma obtained from a single unit of whole blood (approximately 250 ml of plasma) and frozen within six hours of collection of the blood from the donor. This plasma contains normal concentrations of all of the coagulation factors and should be used to treat patients with congenital factor deficiencies for which no concentrated component is available for transfusion (e.g., factor V and factor XI deficiencies). Fresh frozen plasma also may be useful for treating patients with acquired deficiencies of multiple coagulation factors. This latter group includes patients with severe liver disease, DIC, or overdose of warfarin. In addition, fresh frozen plasma frequently is administered to patients who present with excessive hemorrhage and who require multiple blood transfusions. These patients may develop platelet and coagulation factor deficiencies which are attributed to the replacement of shed blood with stored, whole blood and crystalloid or colloid solutions (so-called wash out effect). While it is more likely that the deficiencies seen in these patients result primarily from excessive consumption at bleeding sites, as well as from DIC, treatment with fresh frozen plasma and platelet concentrates, nevertheless, is appropriate.

BLOOD TYPING AND CROSSMATCHING

Alloimmunization to RBC Antigens

A variety of RBC antibodies may be encountered in patients requiring RBC transfusion. In considering the clinical significance of such antibodies, it is useful to divide them into antibodies of the IgM class versus those of the IgG class of immunoglobulins. In general, IgM antibodies are naturally occuring, in that they may be found in patients who, previously, have never been exposed to foreign RBCs. IgG antibodies, on the other hand, tend to be immune in nature and are found only in patients who have been exposed to foreign RBCs, either by prior transfusion or by pregnancy. As a rule, IgM antibodies—with the exception of anti-A and anti-B—are clinically unimportant in that they rarely are capable of causing

hemolytic transfusion reactions. IgG antibodies, conversely, may cause acute or delayed hemolytic transfusion reactions in patients who receive incompatible RBCs. It is imperative, therefore, to identify the specificity of these IgG antibodies and to transfuse sensitized patients only with RBCs that lack the corresponding antigens.

Routinely, the blood bank employs a variety of pretransfusion tests capable of detecting irregular RBC antibodies. If an antibody is present, the specificity of the antibody can be determined, and if the antibody is considered to be clinically significant, antigen-negative units of blood can be selected for transfusion. The processes of antibody identification and selection of specific, compatible units of blood can be time-consuming, and can result in delays of hours, even days, when attempting to transfuse sensitized patients. It is most important, therefore, that physicians caring for sensitized patients notify the blood bank well in advance of anticipated transfusions, in order to avoid undesirable delays in the provision of compatible blood.

Compatibility Testing

The selection of compatible RBCs for transfusion must take into account the patient's ABO group, Rh type and the possible presence of irregular RBC antibodies. Before transfusion, and as a final check for compatibility, the units of RBCs are crossmatched against the patient's serum. The crossmatch serves to detect possible errors which may have been made in ABO grouping of the patient or donor blood, or in the detection of irregular RBC antibodies.

In situations where blood is needed urgently for transfusion, the crossmatch procedure can be abbreviated or totally eliminated. In extreme emergencies, uncrossmatched Group O Rh negative packed RBCs can be transfused with minimal risk. The Group O RBC's are suitable for transfusion to patients of any ABO group. If time permits, it may be possible to determine the patient's ABO group and to supply group-specific, packed RBCs for transfusion. Under these circumstances, an abbreviated crossmatch procedure can be performed. This test assures that no error has been made in ABO grouping of patient or donor blood, but is insufficient for detection of incompatibilities for patients possessing irregular RBC antibodies.

A safe and effective approach for providing compatible RBCs under a variety of clinical circumstances, is as follows: For patients who do not require urgent transfusion, a full battery of pretransfusion testing procedures, including a complete crossmatch, should be performed to provide ABO and Rh compatible blood and to detect alloimmunized patients. When transfusions are more urgent, the patient's ABO group may be determined and group-specific RBCs can be supplied, provided there is

time for an abbreviated crossmatch so as to assure ABO compatibility. Finally, in the case of extreme emergencies, Group O packed RBCs can be transfused in the absence of a crossmatch. When this is necessary, standard pretransfusion testing should begin simultaneously, so that subsequent units of blood, if needed for transfusion, can be supplied more safely. Whenever the decision is made to transfuse blood without crossmatching, or with the use of an abbreviated crossmatch, the risks of a transfusion reaction from an unexpected antibody must be weighed against the risks which would result from delaying transfusion while awaiting the result of routine testing.

Use of the Type and Screen Technique

Numerous studies have demonstrated that a great deal of time, effort, and expense are wasted by the performance of unnecessary crossmatches for patients who never receive blood transfusion. This problem most frequently is encountered in patients undergoing elective surgical procedures, where the surgeon routinely orders two units of blood to be crossmatched prior to surgery. A more efficient and cost-effective means for assuring the blood needs of such patients is by ordering blood typing and antibody screening tests to be performed, but eliminating the order for blood to be crossmatched. For patients with negative antibody screening tests (i.e., patients who do not possess irregular RBC antibodies), blood, if needed, can be provided by the blood bank without delay. Therefore, the patient requiring transfusion is not placed at increased risk, whereas those patients who do not require transfusion are spared the expense of unnecessary crossmatching of blood.

Another situation in which the type and screen approach can reduce unnecessary crossmatching is in assuring the availability of blood for medical patients. A typical example is found in the patient who enters the hospital with GI bleeding, but in whom active hemorrhage has been controlled. Typically, the blood bank is requested to crossmatch and hold 4 to 6 units of blood for such patients, in the event that bleeding should recur. A much better approach is to perform antibody screening procedures every 24 to 48 hours. As long as irregular antibodies are not detected, crossmatching of blood is unnecessary, since blood could be provided on very short notice for these nonsensitized patients. Thus, the patient's blood needs are assured, while wasteful crossmatching is avoided for those patients who do not require additional transfusions.

Whenever type and screen programs are used, it is essential that the blood bank provide notification to physicians of those patients in whom irregular RBC antibodies are detected. For such patients, it will usually be necessary to crossmatch blood in advance of anticipated need, as compatible blood may be difficult to supply in emergencies.

Management of Patients who Possess RBC Antibodies

Patients who have been alloimmunized to RBC antigens are at risk of developing acute or delayed hemolytic reactions following transfusions. The management of these patients includes proper identification of the specificity of the antibodies and provision of RBCs that lack the corresponding antigens. Physicians caring for these patients should anticipate the need for blood as far in advance as possible to allow the blood bank adequate time to obtain compatible units of blood for transfusion. This is especially important for patients with multiple RBC antibodies, for whom the provision of compatible blood can be extremely difficult.

Prevention of Rh Sensitization

Rh-negative patients, who are exposed to Rh-positive RBCs may become immunized to the Rh_0 (D) antigen. Usually, such sensitization can be prevented effectively by the administration of Rh-immune globulin to susceptible individuals. The major clinical circumstance requiring such prophylaxis is following the delivery of an Rh-positive baby by an Rh-negative mother. In addition, Rh-immune globulin should be administered following abortions (therapeutic or spontaneous) occurring in Rh-negative women. The prevention of Rh sensitization in these circumstances can avoid the possibility of serious hemolytic disease of the newborn during subsequent pregnancies.

Rh immunization also may occur as the result of transfusion of Rh-positive RBCs to Rh-negative recipients. This exposure may be due to inadvertent administration of Rh-positive blood to Rh-negative patients, or from transfusion of platelet concentrates collected from Rh-positive donors (since the platelet concentrates contain small numbers of RBCs). Sensitization, under these circumstances, can be prevented by administering Rh-immune globulin following exposure, although the dose of Rh-immune globulin required may be quite large (depending upon the quantity of Rh-positive RBCs which have been transfused). It is reasonable to treat only exposed women who may subsequently bear children, to prevent hemolytic disease of the newborn. Prophylaxis is less important in men, or in women past the childbearing age, since the only consequence of immunization in these latter patients is that they will require that only Rh-negative RBCs be used for future transfusions.

Transfusion of Patients who have Autoimmune Hemolytic Anemia

For patients who are suffering from autoimmune hemolytic anemia, the transfusion of RBCs presents unique difficulties. First, the autoanti-

bodies present in the plasma of such patients may produce incompatible crossmatches in vitro with units of RBCs selected for transfusion. Second, the presence of autoantibodies may mask the presence of alloantibodies which such patients may possess, as a result of prior transfusions or pregnancies. The difficulties encountered in compatibility testing increase the risk of possible hemolytic reactions, if these patients are transfused. These patients should be managed, whenever possible, without the use of RBC transfusions. Transfusions should not be withheld, however, if the patient has a dangerously low hemoglobin concentration, particularly if hemolysis has not been controlled.

The treatment of patients with autoimmune hemolytic anemia ordinarily requires consultation with a hematologist and is discussed in Chapter 1. A careful history should be obtained to determine if the patient has been exposed to RBCs via prior transfusion or pregnancy. Patients who have never been exposed to foreign RBCs have little risk of suffering an acute hemolytic reaction if transfused. The blood bank should perform a detailed serologic investigation aimed at confirming the diagnosis of autoimmune hemolytic anemia and at identifying any alloantibodies which might be present. If compatible blood cannot be found, due to the presence of autoantibodies in the patient's serum, the blood bank should attempt to provide the least incompatible RBCs for transfusion. A variety of sophisticated serologic maneuvers are available which, when performed by experienced immunohematologists, can allow the blood bank to provide RBCs that can be transfused with minimal risk to the patient.

Without doubt, the life span of RBCs transfused to patients with autoimmune hemolytic anemia will be markedly shortened, as the lifespan of the patient's own RBCs is abnormally short. Nevertheless, the posttransfusion survival of transfused RBCs will usually be of sufficient length to raise the patient's hemoglobin concentration to safe levels. Hyperacute, hemolytic transfusion reactions, with their associated clinical complications, rarely are seen when transfusing patients who possess RBC autoantibodies.

ADVERSE REACTIONS TO BLOOD TRANSFUSION

The signs and symptoms of transfusion reactions may include fever, shaking chills, hives, shortness of breath, pain in the back, chest or elsewhere, hypertension, hypotension or shock. Whenever a transfusion reaction is suspected, the most important aspect of therapy is the immediate discontinuation of the transfusion, to minimize the amount of blood infused into the patient. The intravenous line may be kept open with saline solution, while the reaction is being investigated.

The clinical and laboratory evaluation of suspected transfusion reactions is aimed, mainly, at determining whether a hemolytic reaction has

occurred. The workup should proceed quickly, since early diagnosis of acute hemolytic reactions can allow the physician to institute therapy to prevent complications. Furthermore, rapid diagnosis of nonhemolytic, clinically insignificant reactions can avoid unnecessary delays in providing additional blood for transfusion to the patient. Rapid diagnosis of transfusion reactions is achieved most effectively by using a two-part protocol for clinical and laboratory evaluation. The initial phase of the workup is aimed at determining whether or not a hemolytic transfusion reaction has occurred. Since the majority of reactions are nonhemolytic in nature, there usually will be no need for further serologic evaluation. Additional units of RBCs can be provided for transfusion to this group of patients, without dangerous delays. The second, more elaborate phase of the transfusion reaction workup is reserved for those patients in whom the initial studies suggest the possibility of a clinically dangerous reaction.

The initial evaluation of suspected transfusion reactions should include the following:

1. The transfusion should be discontinued immediately, to avoid further transfusion of possibly incompatible RBCs.
2. A rapid clinical evaluation of the patient should be performed by a physician or nurse, to assess the severity of the reaction. Urine output should be monitored. Patients having dangerous reactions usually will have prominent signs and symptoms.
3. A clerical check should be performed at the patient's bedside. It may become apparent immediately that the patient is receiving the wrong unit of blood.
4. Both anticoagulated and nonanticoagulated blood samples should be drawn carefully (to prevent hemolysis) and sent to the blood bank with the empty or partially empty bag of blood.
5. A clerical check should be performed in the blood bank, to determine that the patient has not received the wrong unit of blood.
6. The posttransfusion blood sample should be centrifuged and the plasma examined for the presence of free hemoglobin. Visual examination can detect levels of hemoglobinemia of 25-50 mg/dl. This hemoglobin concentration will be reached following the intravascular lysis of only 5 to 10 ml of RBCs in an average-sized adult.
7. The ABO group of the posttransfusion blood sample and the unit of blood implicated in the reaction should be determined, since the majority of serious hemolytic transfusion reactions are the result of ABO mismatches.
8. A direct antiglobulin (Coombs) test should be performed on the post-reaction blood sample.

These preliminary studies allow the reaction to be categorized as either hemolytic or nonhemolytic in nature. As a rule, nonhemolytic reactions require no further workup. In contrast, if any of the initial studies point to a hemolytic reaction additional studies are necessary. These include measurement of serum bilirubin on the original posttransfusion blood sample as well as one drawn about 6 hours later and a repeat antibody screen and crossmatch.

Reactions to Red Blood Cells

Acute Hemolytic Transfusion Reactions

The acute hemolytic transfusion reaction probably is the most feared complication of blood transfusion. This reaction may result when the recipient possesses antibodies which react with donor RBCs, thereby causing rapid destruction of the transfused RBCs. Most acute hemolytic reactions are due to the transfusion of ABO mismatched blood, although other RBC antibodies are capable of causing equally severe reactions. ABO incompatible transfusions generally result from simple clerical errors which lead to transfusion of the wrong unit of blood to the patient. Meticulous care in the identification of transfusion recipients is the single most important factor in minimizing the risk of acute hemolytic reactions. Consultation with an experienced hematologist is indicated whenever these reactions are suspected.

Whenever an acute hemolytic transfusion reaction is suspected, an attempt should be made, as rapidly as possible, to determine the severity of the reaction. The following factors are of primary importance in diagnosing serious hemolytic reactions.

1. Severe complications rarely occur in patients who receive less than one-half to one full unit of whole blood or packed RBCs.
2. Severe reactions are likely to be accompanied by prominent signs and symptoms. The development of hypotension and shock is an ominous sign.
3. A sample of blood, drawn following the suspected transfusion reaction, will demonstrate visible hemoglobinenemia, whenever there has been significant hemolysis of transfused RBCs.

The serious sequelae that may follow acute hemolytic reactions are hypotension and shock, acute renal failure, due to acute tubular necrosis, and a hemorrhagic diathesis, which may be of life-threatening proportions. It has been demonstrated clearly that the hemorrhagic diathesis results from an episode of DIC causing consumption of the patient's coagulation factors. Hemolytic reactions which produce severe DIC usually have a fatal outcome.

Previously, it had been hypothesized that the acute renal failure following incompatible transfusion resulted from obstruction of the renal tubules by hemoglobin casts. Based upon this concept, therapy with diuretics (especially mannitol) has been recommended. Recent evidence indicates, however, that hemoglobin plays little or no role in the production of renal failure in these patients. Instead, renal failure appears to be due to ischemic damage to the renal tubular epithelium, resulting from generalized hypotension and decreased renal cortical blood flow. These circulatory disturbances are identical to those observed in other forms of shock. Renal tubular ischemia is worsened in those patients developing DIC, as a result of deposition of fibrin thrombi within the microvasculature of the renal cortex.

In light of current knowledge of the pathogenesis of renal failure following acute hemoltyic reactions, therapy with diuretics makes little sense. Instead, vigorous treatment of hypotension, similar to that used in more common forms of shock, should be the most important consideration. Intravenous infusion of fluids, combined with administration of vasoactive drugs such as dopamine, seems to be the soundest approach to therapy. The goal of such therapy should be the restoration of systemic blood pressure and improvement of renal cortical blood flow.

In order to avert the complications of DIC following incompatible transfusion, prophylactic anticoagulation with heparin may be considered. It is likely that anticoagulant therapy is beneficial only if given early, before significant intravascular coagulation has commenced. Since heparin may be contraindicated in many patients who receive incompatible blood (e.g., in postoperative bleeding or trauma), each case must be individualized, with the potential benefits of anticoagulation weighed against the possible risks.

When a serious acute hemolytic transfusion reaction has been confirmed, these steps may be used in treatment:

1. Hypotension should be treated vigorously by intravenous infusion of fluids (colloids or crystalloids).
2. The administration of dopamine should be considered, to combat systemic hypotension and to improve renal cortical blood flow.
3. Prophylactic anticoagulation with heparin may be considered to prevent DIC. If significant DIC has begun, anticoagulation may be of no benefit. Heparin therapy should be continued only as long as the stimulus for DIC is likely to be present (probably not more than 6 to 12 hours).
4. If renal shutdown occurs and cannot be reversed, standard therapy for acute tubular necrosis should be instituted.

Delayed Hemolytic Transfusion Reactions

Delayed hemolytic transfusion reactions occur from a few days to 3 weeks after a transfusion. These reactions occur when the recipient has been previously sensitized to a red cell antigen but has an undetectable antibody level at the time of transfusion. An anamnestic response follows the transfusion and when the antibody titer rises, hemolysis of the transfused red cells occurs. These reactions may be confused with an autoimmune hemolytic anemia, unless the history of recent transfusions is obtained. These reactions are usually mild, although occasionally they may be associated with renal failure.

Reactions Caused by White Blood Cells

Febrile, Nonhemolytic Transfusion Reactions

Fever, often associated with chills, occurring during or shortly after the transfusion, is the most common form of transfusion reaction. These reactions are caused by antibodies to white blood cells and are encountered primarily in multitransfused or multiparous patients. While such reactions are not dangerous in themselves, they can result in significant delays in providing additional blood for transfusion, since they must be differentiated from acute hemolytic transfusion reactions. Therefore, if the recipient of a blood transfusion should develop chills or fever, the transfusion should be stopped immediately, and the reaction promptly investigated to rule out the possibility that a hemolytic reaction has occurred. If appropriate studies reveal that the reaction was nonhemolytic in nature, further transfusions usually can be given without complications, by utilizing leukocyte-poor RBCs.

Noncardiogenic Pulmonary Edema

The development of severe respiratory distress associated with radiologic findings consistent with bilateral pulmonary edema, but without other evidence of heart failure, has been reported as a rare complication of transfusion therapy. These reactions may be extremely severe or fatal. The etiology of the pulmonary edema is not known, but the most prevalent hypothesis is that the reaction is due to leukocyte antibodies—either antibodies possessed by the recipient and directed against transfused leukocytes, or antibodies contained in donor plasma that react with recipient's own white blood cells. While the optimal approach to therapy is unknown, treatment probably should be similar to that used for pulmonary edema resulting from heart failure. Patients who have suffered this

form of transfusion reaction should probably receive leukocyte-poor blood products for future transfusion.

Graft-versus-Host Disease

If immunodeficient patients are transfused with blood products that contain viable lymphocytes, the lymphocytes may engraft and multiply within the recipient. These immunocompetent lymphocytes may react against the foreign tissues of the transfusion recipient, producing the syndrome of graft-versus-host disease (GVH). This syndrome may include fever, skin rash, hepatitis, severe diarrhea, bone marrow suppression, and infection and may be fatal. GVH can be prevented by irradiating all lymphocyte-containing blood components (whole blood, packed RBCs, platelet concentrates and granulocyte concentrates) before transfusion. The administration of 1500-3000 rads renders lymphocytes incapable of replication, and prevents their engraftment in the transfusion recipient.

Until recently, it had been believed that only the most highly immunodeficient patients were in danger of acquiring transfusion-induced GVH. These patients include children with severe combined immunodeficiency, patients receiving bone marrow transplants, and fetuses receiving intrauterine transfusion. Recent evidence, however, indicates that less highly immunosuppressed patients (e.g., patients with acute leukemia and those receiving high-dose chemotherapy for other malignancies) also may be in danger of acquiring GVH from transfusion. If further studies confirm these findings, irradiation of blood products may be recommended as a precaution for increased numbers of patients.

Reactions Caused by Substances in Plasma

Urticarial Transfusion Reactions

Urticarial reactions are common complications of transfusion that result from allergy to one or more substances contained in donor plasma. These reactions are not dangerous and need not be investigated as possible hemolytic reactions, unless the urticaria is associated with fever or chills. In this case, appropriate investigative measures must be undertaken to rule out the occurrence of a hemolytic reaction. Patients who have had urticarial transfusion reactions should be treated with an antihistamine (e.g., Benadryl, 50 mg intramuscularly) before transfusion, or should receive washed or frozen RBCs, which are largely devoid of plasma.

Anaphylactic Transfusion Reactions

Severe anaphylactic reactions, consisting of flushing, dyspnea, wheezing, hypotension, and shock, may be encountered when transfusing

patients who are totally deficient in IgA proteins. These patients may develop anti-IgA antibodies which can react with IgA proteins present in donor plasma. Although IgA deficiency is not a rare disorder (approximately one in 700 normal individuals is totally IgA deficient), anaphylactic transfusion reactions are distinctly uncommon. Patients known to possess IgA antibodies can safely receive only IgA-deficient blood products. RBC transfusions can be administered, using frozen or saline washed RBCs, in which case the IgA proteins have been removed from the RBCs by the washing procedure. If transfusions of plasma or platelets are required, these blood products must be obtained from IgA-deficient donors.

Circulatory Overload

Volume overload, secondary to excessive transfusion of blood components, can be an extremely dangerous complication of transfusion therapy. This complication is encountered most often in elderly patients with poor cardiac reserve, although it may occur in young patients with no history of heart disease. Symptoms may include dyspnea, a feeling of tightness in the chest and headache. The patient's blood pressure may become elevated, and there may be physical and radiographic evidence of frank pulmonary edema. Heart failure, once it occurs, can be irreversible and fatal.

In most instances, circulatory overload is a completely preventable reaction. This is accomplished by avoiding the transfusion of large volumes of blood components to normovolemic patients. While bleeding or hypovolemic patients may receive whole blood transfusions, nonbleeding, anemic patients should receive only packed RBCs. In addition, patients with chronic anemia should never receive more than two-to-three units of RBCs within a 24-hour period. It must be remembered that nonbleeding patients with chronic anemia usually have normal or even expanded blood volumes and cannot tolerate the transfusion of large quantities of blood.

Infectious Complications of Transfusion

Posttransfusion Hepatitis

Posttransfusion hepatitis remains the most frequent, serious complication of blood transfusions. It is difficult to estimate the magnitude of the problem, since the majority of cases are anicteric and subclinical. Recent reports from a number of institutions, however, have demonstrated an alarmingly high rate of hepatitis in carefully followed groups of transfused recipients. In the majority of these studies, between 5% and 10% of patients receiving transfusions developed posttransfusion hepatitis. A signi-

ficant proportion of these patients developed chronic liver disease, as a result of having acquired posttransfusion hepatitis.

Universal testing of all units of donor blood for hepatitis B surface antigen has virtually eliminated hepatitis B as a cause for posttransfusion hepatitis, in this country. The availability of tests to detect hepatitis A infection, also, has made it clear that little or no posttranfusion hepatitis is caused by this virus. Thus, the vast majority of posttransfusion hepatitis now is due to another virus or viruses (so-called non-A, non-B hepatitis).

All blood products are capable of transmitting posttransfusion hepatitis, with the exceptions of albumin, plasma protein fraction, and immune serum globulin. These latter three products have never been implicated in hepatitis transmission, except in circumstances where improper manufacturing practices led to contamination of the final products. The components with the greatest risk of hepatitis transmission are those prepared from pooled plasma. These include factor VIII and factor IX (prothrombin complex) concentrates. While frozen and saline washed RBCs are capable of transmitting hepatitis, evidence suggests that the risk is reduced following frozen or washed RBC transfusion, as compared to transfusion of other RBC products. The decreased risk probably results from removal of hepatitis virus during the extensive washing procedure that these RBC components must undergo.

The value of immune serum globulin for prophylaxis against posttransfusion hepatitis remains an unresolved issue. Several studies have suggested that standard doses of ordinary immune serum globulin preparations are ineffective, but more recent studies have raised pospects that immune serum globulin might offer protection. In addition, a specific hepatitis B immune globulin preparation has been developed, which is of definite value in preventing infection by the hepatitis B virus. Unfortunately, this product will have limited value in preventing posttransfusion hepatitis, because the majority of cases are of the non-A, non-B variety. Until more evidence is accumulated, routine immune serum globulin prophylaxis for transfusion recipients cannot be recommended. Conversely, those rare patients, who have received blood known to be contaminated with hepatitis B virus, should receive prophylaxis with hepatitis B immune globulin.

Cytomegalovirus Infection

Infection with cytomegalovirus has been implicated in the "postperfusion syndrome," an infectious mononucleosis-like condition developing after open heart surgery. More recently, cytomegalovirus infection has been observed in patients with immune-deficiency disorders, including bone marrow transplant recipients and premature infants. Even though such patients frequently receive large numbers of transfusions, it remains

unclear whether transfusions are implicated in the production of this disease. The carrier rate for this virus appears to be very high among normal persons, and, currently, there is no feasible way of screening out and excluding donors who might transmit cytomegalovirus infection. Inasmuch as the virus is carried in peripheral blood leukocytes, it is possible that infection would be less likely using blood components that are leukocyte-poor (e.g., saline washed RBCs).

Malaria

The frequency of malaria in the United States has increased in the past two decades because of the influx of people from Southeast Asia. Well-documented cases of transfusion transmitted malaria have occurred, and this diagnosis should be considered in a patient with unexplained fever and a history of blood transfusion.

Bacterial

Blood may become contaminated with bacterial organisms, usually gram negative, some of which may be capable of proliferation at 4°C. The clinical picture produced by transfusion of contaminated blood is compatible with septicemia—fever, chills, hypotension, and the development of profound shock. If such a reaction is suspected, the transfusion should immediately be stopped and circulatory support measures instituted. The diagnosis may be confirmed by performing a Gram stain on the donor plasma, which should also be cultured. Broad spectrum antibiotics should be administered, but despite aggressive therapy the fatality rate is high in these patients. Fortunately, the frequency of this complication has been markedly reduced by the utilization of sterile, disposable blood bag systems for the collection and processing of blood components.

Other Infections

Rare cases of Epstein-Barr virus transmission by blood transfusion occur. Transmission of syphilis by blood transfusion occurs only with the use of fresh blood and is extremely rare today.

Complications of Massive Transfusions

Massive transfusion is defined as administration of a volume of blood equal to the patient's normal blood volume in a 24-hour period. This situation may produce unique disturbances.

Metabolic

Infusion of large volumes of citrated blood can produce hypocalcemia, which may be associated with electrocardiographic changes and ventricular

fibrillation. Patients receiving such large volumes of blood should have electrocardiographic monitoring and frequent determination of serum calcium, and they may require administration of calcium.

Hyperkalemia can result from administration of a large volume of stored blood and is more likely to occur in patients with impaired renal function or massive tissue injury (e.g., severe trauma).

A massive citrate load can produce acidosis in patients with reduced renal function, but usually citrate is metabolized to bicarbonate and may produce metabolic alkalosis. Lactic acid accumulates in blood during storage, and may worsen existing lactic acidosis in patients following transfusion.

Hemostatic

Dilutional thrombocytopenia may follow massive blood transfusion. Bleeding from this complication is unusual if the platelet count is maintained above 50 x 10^9/ liter by administration of platelet concentrates. Deficiencies of coagulation factors due to dilution may also occur and rarely require replacement with appropriate plasma components. The association of DIC with situations requiring massive transfusion may exacerbate these hemostatic abnormalities.

CASE HISTORY

A 57-year-old man was brought to the emergency room after having fainted. The patient had noticed black, tarry stools for 3 days before this episode. Two years before, he developed a bleeding duodenal ulcer and required transfusions of 5 units of RBCs. The patient was known to be a chronic alcoholic for at least 20 years.

Physical examination revealed the patient to be comfortable while lying in bed; blood pressure and pulse were normal. Orthostatic hypotension and tachycardia could be elicited upon having the patient sit up. The liver was moderately enlarged.

Laboratory studies showed a hemoglobin of 6.8 g/dl and platelet numbers appeared to be adequate on peripheral blood smear. The patient was found to be Group A Rh positive, and antibody screening tests were negative. Four units of Group A Rh positive packed RBCs were crossmatched for the patient and found to be compatible.

Transfusion was initiated with one of the units of packed RBCs, and, after receiving approximately one-half of the unit over a period of 30 minutes, the patient developed shaking chills and fever of 101°F. The transfusion was discontinued and the intravenous line was kept open with an infusion of normal saline.

Questions

1. The patient's chills and fever probably resulted from a febrile, nonhemolytic transfusion reaction. No further evaluation is necessary, and the patient should be treated with acetominophen and the remainder of blood should be infused. True or false?
2. Febrile, nonhemolytic transfusion reactions usually are caused by antibodies to leukocytes and occur most commonly in multitransfused patients. These patients generally can be transfused without complications, by using leukocyte-poor RBCs. True or false?
3. This patient probably has a coagulopathy secondary to chronic liver disease. Therefore, the patient should be given a trial dose of 2 units of fresh frozen plasma to attempt to control his GI bleeding. True or false?

Answers

1. False
2. True
3. False

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3

WILLIAM G. HOCKING

Evaluation and Management of the Patient with Erythrocytosis

CLASSIFICATION OF ERYTHROCYTOSIS

Erythrocytosis is a pathologic state characterized by an elevated red cell mass. Erythrocytosis may result from autonomous proliferation of erythroid progenitors due to an intrinsic cellular defect, epitomized by polycythemia rubra vera (PRV), or from altered erythropoietic regulatory activity (Table 1). Secondary erythrocytosis results from either physiologically appropriate signals to compensate for inadequate tissue oxygenation or from physiologically inappropriate stimulation of erythropoiesis. Erythropoietin secretion is regulated by a poorly defined tissue oxygen sensor believed to be located in the kidney. Tissue oxygen delivery can be compromised by anemia, arterial hypoxemia, increased affinity of hemoglobin for oxygen, or reduced tissue blood flow. With the exception of anemia, each mechanism can result in a compensatory erythrocytosis. Physiologically inappropriate secondary erythrocytosis occurs in two settings: autonomous secretion of erythroid stimulating substances (e.g., erythropoietin, adrenal corticosteroids) by certain neoplasms and local renal ischemia produced by renal mass lesions, hydronephrosis, renal vascular lesions, or after renal transplantation. The regional ischemia is sensed by the renal oxygen sensor and leads to increased erythropoietin secretion and erythrocytosis.

Relative polycythemia, also known as Gaisbock's syndrome, spurious or stress erythrocytosis, is characterized by an elevated hematocrit but normal red cell mass. This syndrome is therefore not an example of true

Table 1 **Erythrocytosis: Classification**

I. Primary: polycythemia rubra vera
II. Secondary
  A. Physiologically appropriate (decreased tissue oxygenation)
    1. High altitude
    2. Chronic lung disease or alveolar hypoventilation
    3. Cardiovascular right to left shunt
    4. High O_2 affinity hemoglobinopathy
    5. Congenitally decreased red cell 2,3-DPG
    6. Carboxyhemoglobinemia
    7. Histiotoxic (e.g., cobalt)
  B. Physiologically inappropriate (normal tissue oxygenation)
    1. Tumors producing erythropoietin or other erythropoietic substances
      (a) Renal cell carcinoma
      (b) Cerebellar hemangioblastoma
      (c) Hepatoma
      (d) Uterine Leiomyoma
      (e) Ovarian carcinoma
      (f) Pheochromocytoma
    2. Renal diseases
      (a) Cysts
      (b) Hydronephrosis
      (c) Bartter's syndrome
      (d) Transplantation
    3. Adrenocortical hypersecretion
III. Relative polycythemia (Gaisbock's syndrome, spurious, or stress erythrocytosis

erythrocytosis. Patients with relative polycythemia are typically middle-aged males, mildly obese and hypertensive. The incidence of thromboembolic disease in these patients approaches 30%. The relationship of this syndrome to smokers' polycythemia is uncertain because many reports of relative polycythemia have not included smoking histories or carboxyhemoglobin levels. It seems likely that in some patients with relative erythrocytosis the elevated hematocrit may be secondary to carboxyhemoglobinemia, which is associated with both a reduction in plasma volume and an increase in red cell mass.

PHYSIOLOGIC EFFECTS OF ERYTHROCYTOSIS

In PRV and physiologically inappropriate secondary erythrocytosis, elevation of the red cell mass is not a compensatory mechanism. However, in physiologically appropriate erythrocytosis, the elevated red cell mass increases oxygen-carrying capacity and systemic oxygen transport to compensate for tissue hypoxia. The increased red cell mass may eliminate the deficit in tissue oxygenation and allow a new equilibrium to be established at a higher hematocrit. However, an excessive rise in red cell mass can impair tissue oxygen delivery as a result of the increasing blood viscosity. Hyperviscosity compromises cardiac output which causes systemic oxygen transport to decrease. The level of red cell mass at which viscosity becomes a limiting factor for oxygen delivery depends upon the total blood volume. In the normovolemic state, systemic oxygen transport is optimal at a hematocrit of 0.40-0.45, whereas in hypervolemia the optimal hematocrit approaches 0.60. Hematocrits in excess of this level impair oxygen delivery even under hypervolemic conditions. Thus a balance exists between the beneficial effects of an increase in hematocrit and the detrimental effects of excessive compensation.

Despite the adverse effects of an excessive rise in hematocrit, some patients with physiologically appropriate secondary erythrocytosis will have hematocrits above 0.70 if untreated. Overcompensation is most frequently observed in patients with cyanotic congenital heart disease or patients with hypoxemia due to pulmonary disease. Patients with an excessive increase in hematocrit may benefit from a reduction in the red cell mass by phlebotomy.

Regional blood flow is reduced in patients with erythrocytosis. Reduction of cerebral blood flow occurs when the hematocrit is in the upper range of normal and is only consistently normalized when the hematocrit is lowered below 0.46. Furthermore, cerebral function is impaired at high hematocrits and improved by reduction to hematocrits at which cerebral blood flow is improved. These factors should be considered in the management of all patients with erythrocytosis.

Diagnosis of Erythrocytosis

An accurate diagnosis must be established in patients with an elevated hematocrit in order to avoid inappropriate therapy. Evaluation requires the measurement of ^{51}chromium red cell mass to establish that true erythrocytosis exists. A hematocrit above 0.60 reliably predicts an elevated red cell mass, but at hematocrits below 0.60 the red cell mass may be normal or even low. Once true erythrocytosis has been confirmed, the

distinction between PRV and secondary erythrocytosis should be made. The criteria that are usually used to establish the diagnosis of PRV were developed by the Polycythemia Vera Study Group (Table 2). In most patients making the diagnosis of PRV requires that the major causes of secondary erythrocytosis are excluded.

In evaluating a patient with erythrocytosis a history of cardiac or pulmonary disease, tobacco smoking, or hematuria should be carefully sought. A family history of erythrocytosis may be an important clue to the etiology. Certain clues to the etiology may be present on physical examination. The presence of obesity suggests the possibility of hypoventilation. A ruddy appearing plethora should be distinguished from cyanosis. The presence of a palpable spleen is particularly important, since splenomegaly occurs in about 75% of patients with PRV but is uncommon with the other causes of erythrocytosis.

The initial laboratory evaluation for a patient with erythrocytosis is outlined in Table 3. An elevated white blood count (greater than 12×10^9/liter) or platelet count (greater than 400×10^9/liter) or basophilia suggest PRV. If the arterial hemoglobin oxygen saturation is below 92%, hypoxemia and tissue hypoxia may underlie the erythrocytosis. If the hypoxemia is due to chronic obstructive pulmonary disease or cyanotic congenital heart disease, other manifestations of the underlying disease processes will usually be evident from the history and physical examination. If alveolar hypoventilation, such as occurs with massive obesity, is responsible for the erythrocytosis, arterial blood obtained during the day in an upright posture may not reveal desaturation. In this circumstance, arterial blood gases obtained while the patient is supine may reveal the hypoxemia.

The leukocyte alkaline phosphatase (LAP) score is a histochemical stain for a neutrophil enzyme. The LAP score is elevated in more than three-quarters of patients with PRV and is usually normal in patients with other causes of erythrocytosis. However, a number of nonspecific stimuli (e.g., fever, infection, inflammation) can cause elevation of the LAP score, so an elevated LAP score is only of confirmatory value in establishing the diagnosis of PRV.

An intravenous pyelogram is indicated to exclude a renal tumor or benign renal lesion in all patients with erythrocytosis. The P_{50} is the partial pressure of oxygen, normally 27.5 mm Hg, at which the hemoglobin becomes 50% saturated (Fig. 1 in Chapter 1). The P_{50} is a measure of the affinity of hemoglobin for oxygen, high affinity indicated by a lower P_{50}. The P_{50} is used to diagnose or exclude a high-affinity hemoglobinopathy as the cause of erythrocytosis.

In erythrocytosis from all causes the bone marrow shows hyperplasia of erythroid cells and often depletion of iron stores. In general,

Table 2 **Criteria for the Diagnosis of Polycythemia Rubra Vera (Polycythemia Vera Study Group)**[a]

Category A	*Category B*
1. Total red cell mass Male ⩾ 36 ml/kg Female ⩾ 32 ml/kg	1. Thrombocytosis (>400X10^9/liter)
2. Arterial oxygen saturation ⩾92%	2. Leukocytosis (>12X10^9/liter)
3. Splenomegaly	3. Increased LAP score
	4. Serum B_{i2} level >900 pg/ml or B_{12} binding capacity >2200 pg/ml

[a]PRV is diagnosed when A1 + A2 + A3 or A1 + A2 and any two from category B are present.

examination of the bone marrow provides no diagnostically helpful data in evaluating a patient with erythrocytosis. However, in PRV the findings of megakaryocytic hyperplasia and an increase in bone marrow reticulin fibers may be confirmatory.

Assays of plasma or urinary erythropoietin may be useful in determining the mechanism of erythrocytosis. Patients with PRV have low or undetectable erythropoietin levels. Patients with hypoxia-induced erythrocytosis usually have elevated erythropoietin levels, whereas patients with tumor-associated erythrocytosis have normal or elevated erythropoietin levels. Although the currently available assay methods for erythropoietin have a number of problems, an erythropoietin radioimmunoassay may soon be available and should improve our ability to accurately measure erythropoietin levels.

Table 3 **Initial Laboratory Evaluation of a Patient with Erythrocytosis**

Complete blood count
Platelet count
Differential white blood count
Arterial blood gases
Leukocyte alkaline phosphatase
Intravenous pyelogram
P_{50}

SPECIFIC SYNDROMES OF ERYTHROCYTOSIS

Polycythemia Rubra Vera (PRV)

PRV is a relatively uncommon disease caused by an intrinsic cellular defect that leads to increased proliferation of erythroid precursors. PRV is one of the myeloproliferative disorders and, like chronic myelogenous leukemia, the abnormal cell population (clone) in PRV is believed to originate from a single cell. The peak age of onset is 50-60 years. Survival in untreated patients averages 1.5 to 3 years, but treatment significantly improves survival.

Clinical Manifestations

PRV is often discovered as an incidental finding, or when one of the major complications of PRV occurs. Weakness is one of the most common complaints. Symptoms related to impaired blood flow to vital organs, particularly the central nervous system, may occur. These symptoms include headache, dizziness, vertigo, tinnitus and visual disturbances. Angina pectoris, intermittent claudication, and venous thromboses may occur. A history of bleeding ranging from easy bruising or epistaxis to severe internal hemorrhage is frequent. Abdominal pain, related either to peptic ulcer of splenomegaly, may occur. Pruritus is one of the most frequent complaints occurring in approximately half of the patients.

Physical examination reveals a ruddy-appearing face. The mucous membranes, conjuctivae, and fundi often appear congested. The spleen is enlarged in three-quarters and the liver in about one-third of the patients. Both systolic and diastolic hypertension are commonly found in patients with PRV.

Laboratory Manifestations

An increased red cell mass is necessary to make the diagnosis. The plasma volume is usually normal, but it may be either increased or decreased. A modest leukocytosis due to increased production of granulocytes occurs in a majority of patients. In some patients a slight "left shift" characterized by the presence of bands, metamyelocytes, and myelocytes in the blood accompanies the granulocytosis. Mild basophilia occurs in about two-thirds of patients. Moderate thrombocytosis (400-800 $\times$ 10^9/liter) is seen in about one-half of patients and occasionally platelet counts over 1000 $\times$ 10^9/liter are observed. The peripheral blood smear is normal early in the disease process, but, as the disease progresses, marked variations in erythrocyte size and morphology may occur along with the presence of nucleated red cells in the peripheral blood.

The bone marrow reveals hyperplasia of the erythroid, granulocytic and megakryocytic series. The marrow iron stores are usually decreased or absent. Some degree of myelofibrosis may be present but detection of this process may require special studies (e.g., reticulin stain) early in the course of the disease. Cytogenetic analysis reveals a distinctive chromosomal abnormality in 15 to 25% of patients at the time of diagnosis.

A number of other laboratory abnormalities may occur in PRV. As already discussed, the LAP score is frequently increased. Hyperuricemia and hyperuricosuria occur in 30% or more of PRV patients. Qualitative abnormalities in platelet function are present in most patients. The serum vitamin B_{12} and B_{12} binding capacity are frequently elevated. The serum iron level is subnormal in about one-third. Occasionally spurious elevations of the serum potassium concentration are noted in patients with thrombocytosis, due to release of potassium from the platelets during clotting.

Complications

The most frequent complications of PRV are thromboembolism, occurring in 15-40% of patients, and hemorrhage, occuring in 20-30%. Thromboses are usually venous and pulmonary embolism may occur. Gout occurs in approximately 10% of patients. Peptic ulcer occurs three to four times more frequently in patients with PRV, and can be accompanied by serious hemorrhage. Long-term complications include the development of acute leukemia or myeloid metaplasia. Acute leukemia develops in less then 1% of patients treated by phlebotomies alone, but in patients receiving radioactive phosphorus (^{32}P) the incidence is at least 6% and in patients treated with alkylating agents the incidence of acute leukemia is about 11%. Acute leukemia in these patients is usually resistant to treatment. Postpolycythemic myeloid metaplasia developed in 3 to 10% of patients with PRV in most series, although the incidence may be close to 100% in patients living long enough. Myeloid metaplasia or spent polycythemia is characterized by progressive enlargement of the liver and spleen and the development of anemia. The white blood count may increase and immature leukocytes, including myeloblasts, as well as nucleated red cells appear in the peripheral blood. This stage of the disease may be confused with chronic granulocytic leukemia.

Management

The principles of treatment for patients with PRV are summarized in Table 4. Since PRV is the only form of erythrocytosis for which myelosuppressive therapy is indicated, it is critical that an accurate diagnosis is made. Therapy must be individualized. The age and sex of the patient, presenting clinical manifestations, and hematologic findings are all important in designing the treatment plan.

Table 4 Principles of Management in PRV

Establish correct diagnosis
Individualize therapy
Rapid reduction of hematocrit by phlebotomy
Maintain hematocrit <0.46
Suppress panmyelosis in patients over 40
Postpone elective surgery until the disease is controlled
Avoid cytotoxic therapy in young patients whenever possible
Treat complications and provide symptomatic care
Avoid severe iron deficiency

All patients should undergo as rapid a reduction in hematocrit by phlebotomy as permitted by the overall clinical status. With normal cardiovascular function phlebotomy of 450 ml can be performed every other day until the hematocrit is less than 0.46. Elderly patients or those with underlying cardiovascular disease should undergo smaller phlebotomies (200-300 ml) twice weekly until the hematocrit is less then 0.46. To prevent hemodynamic instability, the blood removed can be replaced with a crystalloid solution. The hematocrit should be maintained in the 0.42-0.46 range. All elective surgical procedures should be delayed until the hematocrit is normal and other manifestations of PRV are under control. If emergency surgery is necessary, preoperative phlebotomy, with replacement of the volume by crystalloid or colloid, should be done when possible.

In patients with platelet counts over 1000×10^9/liter, extensive extramedullary hematopoiesis leading to discomfort from visceral enlargement, manifestations of hyperuricemeia or uncontrollable pruritus myelosuppressive therapy is indicated. In addition, patients with severe cardiovascular disease in whom frequent phlebotomies would be hazardous and patients requiring more than one 450 ml phlebotomy per month to maintain a normal hematocrit should be treated with myelosuppressive agents. The optimal myelosuppressive therapy remains controversial. In the past chlorambucil was frequently used to suppress the bone marrow, but reported results from the Polycythemia Vera Study Group suggest that ^{32}P is equally effective in controlling the manifestations of PRV and has a lower initial leukemogenic potential. Currently, ^{32}P is recommended rather than an alkylating agent such as chlorambucil, but other approaches are still under investigation. All patients with PRV should be evaluated by a hematologist before deciding on a course of therapy. Myelosuppressive therapy should be avoided in those patients in whom the disease is adequately controlled by phlebotomy alone. It is particularly important

to avoid myelosuppressive therapy in patients under 40, particularly in women of childbearing age, when possible.

Hyperuricemia and its manifestations (acute gouty arthritis, uric acid nephropathy) should be treated with allopurinol (Xyloprim) 300 mg daily. Pruritus may be controlled by cyproheptadine (Periactin), cimetidine (Tagamet) or a combination of these two drugs, but in some patients myelosuppressive therapy is the only effective treatment.

Iron deficiency often complicates PRV, particularly after phlebotomies have been performed. In some cases nonhematologic manifestations of iron deficiency, such as dysphagia, glossitis, nail changes, and generalized weakness, result from iron deficiency. Furthermore, microcytic red blood cells have higher intrinsic viscosity than normocytic erthrocytes. The microcytosis that may occur with iron deficiency is detrimental to tissue oxygen delivery. For these reasons, severe iron deficiency should not be allowed to develop, even though iron deficiency will slow the rate of erythropoiesis. However, iron therapy must be administered with frequent monitoring of the hemoglobin and hematocrit, since rapid and dangerous increases in the red cell mass may occur when supplemental iron is given.

Secondary Erythrocytosis

Smokers' Erythrocytosis

Carboxyhemoglobin is formed when carbon monoxide reversibly binds to the ferrous iron of the hemoglobin molecule. Carbon monoxide has an affinity for heme iron approximately 200 times that of oxygen. Because of this high affinity, carboxyhemoglobin has a biologic half-life of about 4 hours.

Carboxyhemoglobinemia occurs as the result of inhalation of carbon monoxide either from environmental pollutants or tobacco smoke. Carboxyhemoglobinemia has been shown to be an important cause of erythrocytosis in tobacco smokers. Patients with erythrocytosis and a smoking history should have a carboxyhemoglobin determination. If the level is elevated ($\geqslant$4%), carboxyhemoglobinemia may be responsible for the erythrocytosis. The mechanism of erythrocytosis in these patients is at least twofold: (1) carboxyhemoglobin produces a functional anemia, i.e., the hemoglobin bound to carbon monoxide is incapable of transporting oxygen, and (2) the oxyhemoglobin dissociation curve is shifted to the left. The shift of the oxyhemoglobin dissociation curve impairs unloading of oxygen from hemoglobin to the tissues. An important feature of carboxyhemoglobinemia is that the arterial oxyhemoglobin saturation determined from a standard dissociation curve is normal, but this reflects only the hemoglobin available for oxygen-binding. Oxyhemoglobin saturation measured directly is reduced.

High Oxygen Affinity Hemoglobinopathies

Since the first report of a patient with an abnormal hemoglobin and erythrocytosis, more than 20 human hemoglobins with an increased oxygen affinity have been described. The high affinity hemoglobinopathies are the result of genetic point mutations resulting in single amino acid substitutions that either stabilize oxyhemoglobin, destabilize deoxyhemoglobin, or lead to altered binding of 2,3-diphosphoglycerate to hemoglobin. The high affinity hemoglobinopathies are autosomal dominant traits in which the affected patients carry a single gene (homozygosity is probably incompatible with life). The diagnosis is established by measuring the P_{50} (concentration of oxygen at which the hemoglobin is 50% saturated) and, if possible, determining the complete oxyhemoglobin dissociation curve. The P_{50} is usually less than 20 mm Hg in patients with high affinity hemoglobinopathies. Standard hemoglobin electrophoresis will disclose an abnormal band distinct from hemoglobin A in less than half of these hemoglobinopathies and thus cannot be relied on to exclude this cause of erythrocytosis.

Chronic Pulmonary Disease

When patients with chronic obstructive lung disease have hypoxemia, secondary erythrocytosis frequently develops. The elevation of the red cell mass in these patients correlates with the degree of arterial desaturation. However, the plasma volume may be increased so that the hematocrit and hemoglobin concentrations often underestimate the severity of the erythrocytosis. In addition, the hematocrit may be elevated disproportionately to the hemoglobin in these patients because the erythrocyte mean corpuscular volume is often increased whereas the mean corpuscular hemoglobin concentration is reduced.

Cyanotic Congenital Heart Disease

Occasional patients with congenital right to left cardiovascular shunts survive into adulthood without correction of the anatomic lesion. These patients exist in a precarious balance between inadequate oxygen delivery due to venoarterial mixing of blood and hyperviscosity created by the erythrocytosis that is almost universally present in these patients. In some patients adequate oxygen delivery is provided by a hematocrit in the 0.58-0.62 range. In others the hematocrit rises progressively and leads to impaired perfusion of vital tissues. In these patients hematocrits less than 0.55 are also hazardous and may lead to central nervous system dysfunction.

Alveolar Hypoventilation

The alveolar hypoventilation syndrome may be associated with erythrocytosis. Erythrocytosis has been described even in patients who only become hypoxemic during sleep.

High Altitude Erythrocytosis

A well-defined series of physiologic changes occurs in patients transported from sea level to altitudes above 2,000 meters (approximately 6,500 feet). During the first 24 hours, the plasma volume decreases by approximately 20%, causing a relative erythrocytosis. Within a few hours of arriving at high altitude, erythropoietin levels increase and there is evidence of enhanced erythropoietic activity. With prolonged exposure to high altitude, the red cell mass increases. In addition, changes in the oxyhemoglobin dissociation curve occur. Initially, the curve shifts to the left due to respiratory alkalosis, but this is countered by a right shift due to increased erythrocyte 2,3-DPG.

Tumor-Associated Erythrocytosis

Considerable evidence indicates that ectopic erythropoietin secretion occurs in some tumors and circumstantial evidence exists for the production of other erythropoietic substances (e.g., steroids) by some tumors. The tumor most frequently associated with erythrocytosis is renal cell carcinoma which along with other renal tumors accounts for nearly half of all reported cases of paraneoplastic erythrocytosis. Hepatomas, cerebellar hemangioblastomas, uterine leiomyomas and adrenal carcinomas have also been clearly associated with erythrocytosis. The incidence of paraneoplastic erythrocytosis varies with the tumor type: 1-5% in renal cell carcinoma; 5-10% in hepatoma; and 15-20% in cerebellar hemangioblastoma. The red cell mass is variable but may be more than twice normal. A major clinical importance of paraneoplastic erythrocytosis is that it may provide a clue to the presence of a tumor in an early and potentially curable stage. Among the malignant tumors associated with erythrocytosis, renal lesions are most likely to be amenable to cure by early resection.

Management of the Patient with Secondary Erythrocytosis

The general approach to the management of patients with secondary erythrocytosis is outlined in Table 5. Once the cause of the erythrocytosis is established, an effort should be made to eliminate all potential aggravating factors. In some forms of secondary erythrocytosis the red cell mass may be reduced by specific measures. Patients with chronic lung disease may benefit from nocturnal or continuous oxygen therapy.

Table 5 **Principles of Management in Patients with Secondary Erythrocytosis**

Determine the specific etiology
Eliminate aggravating factors when possible (e. g., tobacco, diuretics)
Avoid iron deficiency
Apply specific measures
Consider phlebotomy, but before altering the hematocrit, ask these questions:
(a) Does the elevated hematocrit provide a physiologically important adaptation for this patient?
(b) Is the degree of erythrocytosis detrimental?
Avoid cytotoxic therapy

Patients with the obesity-hypoventilation syndrome are improved by weight reduction. The erythrocytosis associated wih carboxyhemoglobinemia will resolve with abstinence from smoking. Successful surgical removal of erythropoietin-producing tumors or correction of benign renal lesions will usually eliminate the associated erythrocytosis. Patients with an elevated red cell mass due to an anatomic right to left shunt unfortunately are not improved by supplemental oxygen.

In some patients phlebotomy may be indicated, although the precise indications for hematocrit reduction are not established. It is important to recognize that the hematocrit cannot be used as the sole determinant for performing phlebotomy. Two questions should be asked before phlebotomy: (1) Does the elevated hematocrit provide a physiologically important adaptation for this patient?; (2) Is the degree of erythrocytosis detrimental? In patients with physiologically inappropriate erythrocytosis (Table 1) the answer to the first question is "no" and phlebotomy can be performed safely. If elective surgery to remove an erythropoietin-producing tumor or renal abnormality is planned, the hematocrit should be reduced to the 0.42-0.46 range preoperatively. Certainly these patients should not be allowed to maintain a hematocrit above 0.60, since hematocrits at this level are associated with reduced cerebral blood flow and probably with a higher risk of thromboembolic and hemorrhagic complications.

In patients with physiologically appropriate secondary erythrocytosis (Table 1), the answer to the first question is "yes" and phlebotomy must be performed with the recognition that the principal compensatory mechanism for the impaired tissue oxygenation is being altered. The decision to perform phlebotomy is based on the answer to the second

question. Unfortunately, the clinical manifestations of impaired tissue oxygenation due to the effects of blood hyperviscosity and those due to the underlying disease process are often indistinguishable. These symptoms may include lightheadedness, dizziness, headache, tinnitus, and decreased exercise capacity. The question of when to perform phlebotomy is most frequently encountered in patients with chronic obstructive lung disease and cyanotic congenitial heart disease. Systemic oxygen transport declines at a hematocrit above approximately 0.60 and worsening of symptoms related to impaired tissue oxygenation is often observed in these patients when the hematocrit exceeds 0.60. Phlebotomy can produce clinical improvement in these patients. In patients with erythrocytosis secondary to obstructive lung disease objective measurements of cardiopulmonary function have generally shown no change after phlebotomy with the exception of reduced arteriovenous oxygen content difference, reduction in pulmonary artery resistance, and improved hemodynamic function with exercise. Patients with obstructive lung disease and congestive heart failure are the most likely to benefit from phlebotomy. Patients with excessive erythrocytosis due to cyanotic congenital heart disease may have improved cardiac output, decreased arteriovenous oxygen content difference, decreased systemic vascular resistance, increased systemic oxygen transport as well as subjective improvement after phlebotomy. No attempt should be made to reduce the hematocrit to normal in patients with hypoxemia due to pulmonary disease or cyanotic congenital heart disease. In our experience a hematocrit in the 0.55-0.60 range is usually optimal for adults with cyanotic congenital heart disease, but the optimal hematocrit must be determined empirically for each patient. Phlebotomies should be performed with replacement of the volume of blood removed by 0.9% sodium chloride solution in patients with cyanotic heart disease to prevent sudden hemodynamic alterations that are poorly tolerated by these patients. A hematocrit of 0.55-0.60 is not optimal for cerebral blood flow, but higher hematocrits are required in these patients to maintain adequate oxygen carrying capacity. Patients with high oxygen affinity hemoglobinopathies generally require no therapy, but if the hematocrit exceeds 0.60 phlebotomy may be indicated. Cytotoxic therapy is contraindicated in secondary erythrocytosis.

In patients with relative polycythemia an effort should be made to reduce potential aggravating factors. Cessation of smoking may result in return of the elevated hematocrit to normal in some patients. The control of hypertension is particularly important, since the excess mortality in patients with relative polycythemia occurs primarily in those with hypertension, and control of hypertension may result in a reduction of hematocrit. Diuretics may aggravate relative erythrocytosis by reducing the plasma volume, and drugs that act as renin antagonists theoretically

might provide the optimal therapy for these patients. Phlebotomy has generally not been recommended in relative polycythemia, since the red cell mass is not increased. However, recent studies have demonstrated that cerebral blood flow is reduced in proportion to the elevation of hematocrit in patients with relative polycythemia and reduction of the hematocrit by phlebotomy increases cerebral blood flow. Therefore, in those patients with persistently elevated hematocrit after other measures have been employed, isovolemic phlebotomy may be indicated to reduce the hematocrit to 0.42-0.46. However, no data exist regarding the effects of phlebotomy on morbidity or mortality in relative polycythemia.

Patients who have repeated phlebotomies will develop iron deficiency. Since hypochromic erythrocytes have an increased intrinsic viscosity that is translated into a substantial increase in whole blood viscosity, iron deficiency should be avoided.

CASE HISTORY

A 45-year-old man is seen for a routine annual examination. He complains of feeling more tired than usual over the 3 months before his visit. He has noted mild ringing in his ears twice in the past months, but otherwise he has no complaints. Physical examination reveals a mildly obese man with no cyanosis. The blood pressure is 130/90. The lungs are clear and the cardiac exam is normal. There is no hepatosplenomegaly or lymphadenopathy.

Initial laboratory evaluation reveals a Hb 19.3 g/dl, Hct 0.58, white blood count 12,300/μl with 72% segmented neutrophils 2% bands 20% lymphocytes, 3% monocytes and 3% basophils. Platelet count is 450 X 10^3/liter. A screening chemistry profile was normal except for a uric acid of 9.6 mg/dl.

Questions

1. On the basis of this data, the next diagnostic procedure should be

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2. If an elevated red cell mass substantiates the presence of true erythrocytosis, the appropriate diagnostic studies include
   (a) Liver scan
   (b) Bone marrow aspiration
   (c) Arterial blood gases
   (d) Computerized tomographic scan of the abdomen

3. If the arterial hemoglobin oxygen saturation is greater than 92%, the next series of diagnostic studies should include
   (a) Blood histamine level
   (b) Intravenous pyelogram
   (c) P_{50}
   (d) Leukocyte alkaline phosphatase
4. The diagnosis of PRV is suggested in this patient by
   (a) Basophilia
   (b) Leukocytosis
   (c) Absence of splenomegaly
   (d) Thrombocytosis
5. If a diagnosis of PRV is established in this patient, initial therapy should be
   (a) Chlorambucil 4 to 6 mg daily until the hematocrit is normal
   (b) ^{32}P
   (c) Phlebotomy every other day until the hematocrit is below 0.46
   (d) Antiplatelet drugs

Answers

1. ^{51}CR red cell mass
2. c
3. b,c,d
4. a,b,d
5. c

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4

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Bleeding Disorders

Bleeding disorders are relatively common in clinical practice. The hemorrhagic diathesis may be so mild that it is only unmasked during trauma or surgical operations while in other instances spontaneous, life-threatening hemorrhage dominates the clinical picture. Fortunately, an organized approach to history taking, physical examination, and laboratory evaluation permits a specific diagnosis to be made in nearly all cases. In many cases, proper treatment can ameliorate the bleeding manifestations.

History taking should be directed toward elucidating the duration, severity, and sites of bleeding, the family history, assessment of other relevant medical conditions including drug ingestions, and the value of previous, specific treatments, if any.

The duration of the bleeding tendency and the family history may help distinguish congenital from acquired conditions. Bruising, gingival bleeding, menorrhagia, and prolonged bleeding after cuts, trauma or surgical operations are important clues to the presence of a bleeding tendency, but are diagnostically nonspecific. Petechial hemorrhages, epistaxes, hemarthroses, hematuria, or a history of umbilical stump bleeding in the neonatal period, are more helpful in suggesting a specific diagnosis (vide infra), but no sign is pathognomonic. One should always consider the possibility that bleeding at a specific site is due to a correctable anatomic lesion.

The overall assessment of the clinical setting is important. For example, specific abnormalities of hemostasis are suggested if systemic lupus erythematosus is present, if the patient has taken certain drugs, or if the patient has just had a cardiopulmonary bypass operation. The presence of hepatic or renal insufficiency, or recent aspirin ingestion, are important because they may contribute to abnormal bleeding.

The physical examination is concerned with the severity and sites of bleeding. It is important also to note whether lymphadenopathy, splenic enlargement, or stigmata of liver disease are present. The most important initial laboratory studies in the assessment of a hemorrhagic diathesis are the complete blood count and platelet count; examination of the peripheral blood smear; the bleeding time (in nonthrombocytopenic patients); and the prothrombin, activated partial thromboplastin, and thrombin times. The results of these studies will define the nature of the hemostatic defect and lead the clinician to specific diagnostic tests in the majority of patients.

THROMBOCYTOPENIA

The normal whole blood platelet (thrombocyte) count is 140 to 450 $\times$ 10^9/liter, and thrombocytopenia refers to a platelet count less than 140 $\times$ 10^9/liter. *Pseudothrombocytopenia* refers to a reduced platelet count determined by an automated counter but a normal manual platelet count. Pseudothrombocytopenia occurs when the platelets are excessively large (they are not counted as platelets by the automated counter) or agglutinated. Examination of the peripheral blood smear distinguishes pseudo from true thrombocytopenia. In an area of the smear where the red cells are almost touching, there are normally, on the average, at least 10 dispersed platelets per oil immersion field (1000x magnification).

Bleeding Manifestations

The sole clinical manifestation of thrombocytopenia is a tendency to bleed. Thrombocytopenia may be discovered on routine blood examination or from an investigation of a bleeding tendency. Bleeding may be local or generalized. The skin and mucous membranes are the characteristic general sites of thrombocytopenic bleeding. In the mildest cases, flat, nontender, red spots (petechiae) pinpoint in size are found in dependent areas, especially about the ankles. Petechiae do not blanch on pressure. With increasing severity, petechiae are larger and more widespread, and may coalesce (purpura); there is a tendency to epistaxis and bruising. In severe cases, purpura may involve all parts of the skin surface,

the conjuctivae, mucous membranes of the mouth, and retinas. Intracranial hemorrhage, the most serious complication of severe thromboctyopenic purpura, may occur spontaneously and is often fatal.

In general, spontaneous petechiae, bruising, epistaxes, and menorrhagia occur when the platelet count falls below 50×10^9/liter. A platelet count below 5 to 10×10^9/liter is associated with severe purpura and a high risk of intracranial or other life-threatening hemorrhage. The severity of bleeding for a given level of thrombocytopenia depends on additional factors, such as the cause of thrombocytopenia, the quality of platelet function, and whether other hemostatic defects coexist. For example, there may be relatively little purpura despite marked thrombocytopenia in chronic idiopathic thrombocytopenic purpura, because large, young platelets may function exceptionally well in this disorder. If the cause of thrombocytopenia is disseminated intravascular coagulation, the combination of multiple coagulation defects, altered platelet function, and thrombocytopenia may result in a bleeding tendency more severe than would be expected from thrombocytopenia alone.

Petechial and purpuric bleeding in other nonplatelet disorders (e.g., senile purpura, Cushing's disease, psychogenic purpura, petechiae in atrophic skin) may mimic that due to platelet disorders and requires differentiation.

Platelet Kinetics and Survival

Platelets are demarcated from bone marrow megakaryocytes, enter the circulation, and gradually become senescent, surviving 9 to 10 days if not consumed beforehand performing hemostatic duties. In pathologic disorders of enhanced platelet destruction, platelet production increases (increased platelet turnover), and the bone marrow shows normal to increased numbers of megakaryocytes. Normally only about 10-15% of circulating platelets are larger than 2.5 micron in diameter (normal red cells are about 7 micron). When platelet turnover is increased, large platelets (megathrombocytes) may be seen on the peripheral blood smear. Thrombocytopenia can result from accelerated platelet destruction or impaired platelet production. Platelet production can increase up to eight-fold and the platelet count may be normal ($>140{,}000 \times 10^9$/liter) despite a platelet survival as short as 1 to 2 days (compensated thrombocytolytic state). When platelet survival is shorter, thrombocytopenia is the rule. The bone marrow does not contain an immediately mobilizable platelet reserve, and if severe platelet loss or destruction develops abruptly, thrombocytopenia results. Several days are required to achieve maximal platelet production.

Specific Causes of Thrombocytopenia

Thrombocytopenia Due to Platelet Loss

Washout Thrombocytopenia develops during massive exsanguination when red blood cell transfusions and volume expanders are administered without platelet transfusion. Thrombocytopenia may be observed when 6 to 8 units of blood have been transfused and is the rule when 12 units have been given in 24 hours.

Extracorporeal circulation during cardiopulmonary bypass is associated with a 30% to 70% reduction of the platelet count in the immediate operative period due to loss in the bypass circulation. Recovery occurs during the first postoperative week. Although thrombocytopenia may contribute to a postoperative bleeding tendency, other factors that may predispose to bleeding include bypass-related coagulation disturbances, platelet function defects, and preoperative aspirin ingestion.

Thrombocytopenia Due to Drugs

The drugs associated with thrombocytopenia are indicated in Table 1. Immunologically mediated platelet destruction is the cause of thrombocytopenia due to quinine, quinidine, stibophen, and allylisopropylacetylurea (Sedormid), and may be involved in the thrombocytopenia associated with other drugs as well. Thiazide diuretics cause both accelerated destruction and depressed production of platelets. Estrogens and ethanol cause thrombocytopenia by reducing platelet production. The mechanism of drug-associated thrombocytopenia is unknown for many drugs.

The diagnosis of drug-induced thrombocytopenia can be made only by obtaining a thorough history of drug exposures. The time course and severity of thrombocytopenia do not have diagnostic specificity, but recurrent, transient episodes of explosive purpura suggest a drug cause. For most drugs, reliable in vitro tests are not available. Treatment consists of withdrawal of the offending agent, which is usually followed by improvement of the platelet count within 10 days (heroin abuse and gold salts are notable exceptions).

The frequency of purpura due to quinine or quinidine is about one case per 1000 individuals exposed to pharmacologic doses. Prior drug exposure is required. Thrombocytopenia may develop during continuous drug administration, or upon restarting treatment. The onset of purpura may be insidious or abrupt. In fulminant cases, severe purpura, hemorrhagic bullae of the oral mucosa, and gastrointestinal or intracranial hemorrhage may occur. A sensation of warmth or chills may accompany purpura. Ingestion of quinine may be inadvertent, deliberate, or covert. Questioning must include reference to night cramp pills, over-the-counter medications, and bitter drinks (including "bitter lemon," tonic water, and

Table 1 **Drug Causes of Thrombocytopenia**[a]

Analgesics	
Aspirin	Oxyphenbutazone
Indomethacin	Phenylbutazone
(Acetaminophen, Antipyrine, Sodium salicylate, Fenoprofen, Ibuprofen)	
Antimicrobials	
Sulfonamide antibiotics	Isoniazid
Sulfamethoxazole (trimethoprim)	Rifampicin
Chloramphenicol	Paraaminosalicylic acid
Nitrofurantoin	
(Penicillin, Ampicillin, Methicillin, Cephalothin, Lincomycin, Novobiocin, Streptomycin, Pentamidine, Oxytetracycline)	
Sulfonamide derivatives	
Furosemide	Acetazolamide
Chlorthalidone	Diazoxide
Chlorothiazide	Chlorpropamide
Hydrochlorothiazide	Tolbutamide
	Clopamide
Cinchona alkaloids	
Quinine	
Quinidine	
Sedatives, hypnotics, antidepressants, analeptics	
Allylisopropylacetylurea	Carbamazepine
Diphenylhydantoin	Centalun
(Allylisopropylbarbiturate, Butabarbitone, Clonazepam, Diazepam, Paramethadione, Meprobamate, Primidone, Ethyl-phenylhydantoin, Ethyl-allylacetylurea, Thioridazine, Imipramine, Desimipramine, Sodium valproate)	
Chemotherapeutic agents	
Others	
Ethanol	Arsenical antiluetics
Estrogens	Chloroquine
Heroin abuse	Hydroxychloroquine
Heparin	Gold salts
Alpha methyldopa	Mercurial diuretics
Digitoxin	Pertussis vaccine
Stibophen	d-Penicillamine
(Chlorphenirmaine, Antzoline, Disulfiram, Hexopropymate, Iopanoic acid, Prochlorperazine, Propylthiouracil, Spironolactone, Cimetidine, Levodopa, topical Podophyllin)	

[a]Parentheses enclose drugs rarely reported to cause thrombocytopenia.

bitter cocktail beverages). Recovery begins within several days of drug discontinuation and is complete by 10 days.

The frequency of thrombocytopenia among patients treated with gold salts is about 1%. Because of slow drug excretion, the course of thrombocytopenia may be prolonged for months after drug therapy is discontinued. Dimercaprol may shorten the duration of thrombocytopenia.

Thrombocytopenia is occasionally associated with heparin therapy, and is independent of dose and route of administration. It resolves within a few days after discontinuing the drug.

Thrombocytopenia with Schistocytosis

The finding of schistocytosis (microangiopathic hemolysis) on the peripheral blood smear associated with thrombocytopenia limits the number of diagnostic considerations.

Thrombotic thrombocytopenic purpura (TTP) is a serious disorder of unknown etiology. The characteristic pathologic feature is the widespread distribution of microvascular hyaline thromobotic lesions. It is probable that TTP is the common clinical expression resulting from a number of triggering events.

Virtually all patients have thrombocytopenia, microangiopathic hemolysis, and transient neurologic symptoms and signs. Abnormalities of mentation, bizarre behavior, stupor and coma, sensory and motor deficits, aphasia, and seizures are frequent. Fever, purpura, jaundice, nonspecific abdominal symptoms, pulmonary infiltrates, and cardiac conduction abnormalities are common. Renal abnormalities including proteinuria, abnormal urine sediment with cells and casts, diminished glomerular filtration rate, and less often oliguria also occur. The syndrome is most common in the third to sixth decades of life, and females are more often affected than males. Most cases have an acute or subacute onset. Chronic, relapsing-remitting cases are much less common. Spontaneous, sustained remission following a fulminant course which has lasted a few weeks to months is not uncommon. The mortality rate in the past was considered to be over 80%, but is probably 50% or less. Death is usually the result of widespread thrombotic lesions or thrombocytopenia, but cardiorespiratory failure, cardiac arrythmias, and gastrointestinal hemorrhage may be contributing factors.

Laboratory studies show findings of microangiopathic hemolysis, including anemia, schistocytosis, reticulocytosis, circulating nucleated red cells, indirect hyperbilirubinemia, elevated serum lactic dehydrogenase, and decreased serum haptoglobin. The direct Coombs' test is almost always negative. Thrombocytopenia is due to accelerated platelet destruction, and the platelet count is often less than 20×10^9/liter.

Neutrophilic leukocytosis is common, and a leukomoid reaction may be observed. The screening coagulation tests are usually normal, but mild abnormalities may be found. The bone marrow shows erythroid and megakaryocytic hyperplasia, and the small vessel hyaline lesions may be observed. The diagnosis of TTP is based on the clinical picture. Blood cultures and serologic studies to exclude systemic lupus erythematosis should be performed in all patients with TTP.

Although new therapeutic approaches to TTP have emerged in the last few years, there is still no uniformly effective therapy. Clinical improvement has been observed following intensive plasma exhange, whole blood exchange, plasmapheresis, or plasma infusion, or with combined glucocorticoid, dextran, and splenectomy. The value of antiplatelet drug therapy is unclear. Although glucocorticoid drugs are generally ineffective, a therapeutic response may occur if the TTP syndrome is related to systemic lupus erythematosus. Heparin is ineffective. The role of splenectomy is not clear. Red cell transfusion is often necessary but platelet transfusion is best avoided if possible. It appears that some cases of TTP may be self-limited and patients may recover without neurologic sequelae. It is therefore of utmost importance that critically ill patients recieve intensive general medical support in the hope that improvement will occur.

Hemolytic-uremic syndrome (HUS) is clinically similar to TTP, with the exception that it occurs most often in infants and children, seldom in adults, and that neurologic signs are rarely observed. Oliguria or anuria is a cardinal clinical feature. Mortality is related to renal failure and hypertension. The etiology is unknown but an immune or toxic etiology has been proposed. A febrile, viral-like illness often precedes the development of HUS. Hyaline lesions are usually limited to the renal microvasculature, although more widespread lesions may occur. Glomerulitis is also observed. It is not clear that glucocorticoid drugs, heparin, fibrinolytic drugs, or antiplatelet drugs are of therapeutic benefit. Dialysis should be instituted early in the course of renal failure. Most patients who survive eventually show improvement of renal function, but permanent renal dysfunction is common.

The triad of thrombocytopenia, schistocytosis, and neurologic signs may occur in conditions other than TTP, and these must be differentiated: toxemia of pregnancy, malignant hypertension, systemic lupus erythematosus (SLE), bacterial sepsis, subacute bacterial endocarditis, nonbacterial thrombotic endocarditis with malignancy, and prosthetic heart valves with systemic embolization. Thrombocytopenia and schistocytosis may also be seen in acute or chronic renal transplant rejection, disseminated intravascular coagulation, primary pulmonary hypertension, and as a result of heparin administration.

Thrombocytopenia with Immune Hemolysis

The association of thrombocytopenic purpura and immune hemolytic anemia is called *Evans' syndrome*. Both platelet and red cell destruction are probably immune-mediated in these patients. Evans' syndrome may be idiopathic, or it may be associated with clinical or serologic evidence of systemic lupus erythematosus, mixed connective tissue disease, or with lymphoma, chronic lymphocytic leukemia, Hodgkin's disease, or quinidine or alpha methyldopa ingestion.

Thrombocytopenia with Infection

Thrombocytopenia, which may be severe, accompanies gram-positive and gram-negative septicemia in about one third of cases, with or without disseminated intravascular coagulation. Increased amounts of platelet-associated IgG are found in more than half of these thrombocytopenic patients, which suggests that platelet destruction may be immune-mediated in many cases. Platelet survival is very short, and therefore, platelet transfusion should be reserved for treatment of uncontrollable bleeding. There is no established role for glucocorticoid or antiplatelet drugs. Heparin is not indicated except perhaps when there is clear evidence of disseminated intravascular coagulation. When septicemia is controlled by antibiotic therapy, several days may elapse before the platelet count improves. Conversely, improvement of the platelet count is considered a favorable prognostic sign for recovery from the episode of sepsis.

A low platelet count may be observed in other bacterial infections including typhoid, diphtheria, and brucellosis. Thrombocytopenia is common in meningococcemia, and the rash characteristic of this infection may mimic the petechial rash of idiopathic thrombocytopenia purpura. A diagnostic error might have disastrous consequences.

Thrombocytopenia may accompany other nonbacterial infections including trypanosomiasis, malaria, tuberculosis, histoplasmosis, Rocky Mountain spotted fever, typhus, mumps, cytomegalovirus infections, varicella, rubella, measles, infectious mononucleosis, influenza, viral hemorrhagic fevers, viral upper respiratory infections, and after measles vaccination. Glucocorticoid therapy (e.g., prednisone 1-2 mg/kg/day) should be given when severe thrombocytopenia follows a suspected viral upper respiratory infection or is associated with infectious mononucleosis.

Posttransfusion Purpura (PTP)

Posttransfusion purpura (PTP) is a distinct, rare clinical entity with a poorly understood pathogenesis. Nearly all cases have occurred in adult women. Approximately 5 to 10 days following transfusion, severe purpura with a platelet count often $<10 \times 10^9$/liter develops. The risk of fatal

intracranial bleeding is relatively high. The disorder is immune-mediated, and nearly all patients lack the platelet-specific antigen $P1^{A1}$, which is found in 98% of the population.

Untreated, the disorder lasts 1½ to 7 weeks. Usually, however, therapeutic intervention is mandatory because of the severity of thrombocytopenia. Intensive plasmapheresis is the preferred therapy; whole blood exchange may be effective, but transfusion reactions may occur. With either of these therapies, recovery may occur within three days. Glucocorticoid drugs are probably of little benefit. Platelet transfusion is ineffective and may cause severe reactions.

Thrombocytopenia and Disorders with Altered Immune Mechanisms

Thrombocytopenia may be associated with autoimmune disorders including systemic lupus erythematosus, rheumatoid arthritis, other collagen-vascular diseases, Hashimoto's thyroiditis, Graves' disease, and myasthenia gravis. Thrombocytopenia also occurs in sarcoidosis, tuberculosis, chronic lymphocytic leukemia, lymphoma, and Hodgkin's disease. These patients may have normal to increased numbers of megakaryocytes in the bone marrow and absence of splenomegaly. Evidence is accumulating which suggests that antiplatelet antibodies may be the cause of thrombocytopenia in many of these patients, and glucocorticoid therapy may be helpful.

Miscellaneous Causes of Thrombocytopenia

Thrombocytopenia may accompany disseminated intravascular coagulation, severe burns, fat embolism, splenic hamartoma, valvular or subvalvular aortic stenosis, acute or chronic renal transplant rejection, anaphylaxis, primary pulmonary hypertension, cyanotic congenital heart disease with erythrocytosis, and cavernous hemangioma.

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is a relatively common disorder that can be classified into two clinical forms. In *acute ITP*, disease onset is acute or subacute, and the condition is limited in duration to a few weeks or months. Occasionally symptoms suggestive of a viral infection a few weeks before onset are reported. The spleen may be minimally enlarged, but usually is not palpable. Purpura may be severe and the mortality rate is about one percent and is related to intracranial bleeding. Eighty percent of childhood ITP cases are of the acute type, but only a small portion of adult cases are.

When thrombocytopenia has lasted more than six months, the patient

usually has *chronic ITP*. A preceding viral syndrome is infrequent. The onset may be abrupt and fulminant, as it can be in acute ITP, or it may be so insidious that the patient is uncertain when the bleeding tendency began. Spontaneous improvement may occur at any time, but the disease tends to be chronic and persistent. Some patients have thrombocytopenia for decades. As in acute ITP, the spleen usually is not palpable. If it is more than minimally enlarged, another diagnosis is suggested. Seventy-five percent of patients are women.

There is a rough correlation between the degree of thrombocytopenia and the severity of the bleeding tendency. However, some patients have a relatively mild disorder despite the fact that the platelet count may be very low, whereas other patients with modest thrombocytopenia (50-100 $\times 10^9$/liter) may have more severe bleeding than would be expected. An acquired, antibody-induced platelet function abnormality may be responsible for the bleeding in the latter group.

Laboratory findings are diagnostically nonspecific. Anemia may accompany acute blood loss; iron-deficiency anemia may accompany ITP if there is insidious blood loss. The white blood cell count is usually normal. The peripheral blood smear shows decreased numbers of platelets and large platelet size. Screening coagulation tests are normal. The bone marrow shows normal to increased numbers of of megakaryocytes.

ITP is caused by IgG antiplatelet antibodies, but the origin and nature of the immune alteration remains unknown. Platelets are destroyed by phagocytes, particularly in the spleen and liver. The spleen is not only an important site of antibody synthesis, but it also may provide an optimal milieu for platelet sensitization by antibody and subsequent phagocytosis.

New assays have been developed during the last few years to measure the amount of platelet-associated IgG (PAIgG) on the patient's platelets directly. This test is analagous to the direct antiglobulin (Coombs') tests used in the evaluation of hemolytic anemias. These assays are sensitive, and over 90-95% of ITP patients have elevated PAIgG, although elevated PAIgG is not specific for ITP. There is an inverse relationship between platelet count and the amount of PAIgG, and IgG levels fall when there is improvement in the platelet count. The assays may be particularly useful in suggesting an immune etiology of thrombocytopenia in conditions other than ITP.

The diagnosis of ITP can be made confidently only when other causes of thrombocytopenia have been considered and excluded. From a practical standpoint, the abrupt onset of thrombocytopenia purpura in a previously normal individual is not an uncommon problem, and a tentative diagnosis and treatment plan must be formulated rapidly. A tentative diagnosis of ITP can be made when the history and physical examination do not point to another cause, when decreased numbers of platelets and large platelets are the only abnormal findings on the peripheral blood smear, and when

screening coagulation tests are normal. The bone marrow examination (aspirate and biopsy) is important for exluding other conditions, but therapy for presumed ITP should not be withheld for the sake of a bone marrow examination when purpura is severe and the platelet count is severely depressed.

General management of the acutely and severely thrombocytopenic patient includes hospitalization and rest; avoidance of trauma, intramuscular injections, or aspirin administration; prophylactic treatment of constipation (to avoid Valsalva maneuver), reduction of blood pressure in hypertensive patients, and cough suppression if necessary. Platelet transfusion should be reserved for treatment of hemorrhage. Glucocorticoid therapy (e.g. prednisone 1-2 mg/kg/day) should be started immediately in severe cases. Improvement may occur within a day or so, or may not be evident for several weeks. Once there is improvement, the glucocorticoid dose should be lowered. Some degree of improvement is achieved in over 85% of cases, but unacceptably large doses will be required to maintain control in about half of all patients with chronic ITP, and splenectomy should be considered in these patients. Splenectomy will benefit over 80% of patients and is the preferred therapy in those who do not have a satisfactory response to glucocorticoids. The operation should not be performed as initial therapy in new cases, because improvement with glucocorticoids is often prompt, and the disease may be self-limited. Patients who do not have a complete response to splenectomy often have enough improvement so that no further glucocorticoid treatment is necessary. There are no reliable studies available to predict whether there will be a favorable response to splenectomy. Other immunosuppressive agents (vincristine, azathioprine, cyclophosphamide) are effective in 30% to 60% of cases refractory to glucocorticoid drugs and splenectomy. These drugs should not be used in preference to splenectomy unless surgical operation is inadvisable because of other considerations. Vincristine 1.4 mg/m^2 IV (maximum dose 2 mg) may be effective within several days. The drug should be considered ineffective if there is no response after three doses, given at weekly intervals. Recently, it has been reported that the intravenous infusion of gamma globulin will result in a transient rise in the platelet count in approximately 50% of patients refractory to other therapies. However, this therapy is expensive and should be reserved for use in life-threatening situations. Chronic ITP is often a persistent condition which may have a relatively benign course. Therefore, careful consideration must be given to whether a patient with persistent thrombocytopenia after splenectomy should be treated. Side effects of treatment are often considerable. A mild bleeding tendency may be preferable to long-term treatment.

There are several special considerations regarding ITP in pregnancy. The incidence of spontaneous abortion is increased in these patients. There

is high fetal wastage and increased maternal mortality if spenectomy is attempted during pregnancy. About half of term infants born to thrombocytopenic mothers have neonatal thrombocytopenia which may be associated with intrancranial bleeding, especially if a vaginal delivery is traumatic. Therefore, Caesarian section should be considered if the mother is thrombocytopenic at term. Puerperal bleeding in the thrombocytopenic mother may occur. Prednisone may be used if necessary but other immunosuppressive drugs are contraindicated.

Thrombocytopenia Due to Decreased Production of Platelets

Thrombocytopenia often accompanies generalized bone marrow disorders. The megakaryocyte-platelet lineage may be selectively affected in some patients. Decreased platelet production may be a mechanism of thrombocytopenia in certain viral infections and in severe iron deficiency anemia on rare occasions. Very rarely, thrombocytopenic purpura with an absence of bone-marrow megakaryocytes has been found, either in association with systemic lupus erythematosus or with no underlying disease. A modest oscillation in the platelet count with a frequency of 20 to 40 days occurs in some apparently normal individuals. Rarely, an individual may have marked oscillations, and thrombocytopenic purpura occurs during the platelet count nadir. This cyclic thrombocytopenia is due to periodic failure of platelet production. There may be a relationship to the menstrual cycle, but the condition occurs in both sexes.

PLATELET STRUCTURE AND FUNCTION

Platelets play critical roles in primary hemostasis and coagulation, and in pathologic thrombosis. In addition, platelets participate in other clinical disorders such as arteriosclerosis.

By light microscopy in an unstained blood smear, platelets appear as small refractile bodies, less than one-third the diameter of red cells. On Wright-stained smears they usually have a round shape, display variation in size, and show reddish-purple granular staining. Filamentous cytoplasmic extensions are often seen. By electron microscopy, dense granules are a prominent feature of the interior of platelets and contain most of the platelet ADP and serotonin, and some of the ATP and calcium. They have an important role in platelet function and primary hemostasis. The alpha granules are more numerous and contain β-thromboglobulin, platelet factor 4, and other proteins. It is possible that alpha granules play a role in primary hemostasis.

Platelets, upon stimulation, synthesize prostaglandins and related substances de novo from fatty acids cleaved from membrane phospholipids. Platelets synthesize thromboxane A_2 from arachidonic acid, a reaction catalyzed by the enzyme cyclooxygenase. Thromboxane A_2 is a potent inducer and potentiator of platelet aggregation and secretion. Prostacyclin (PGI_2) is synthesized by endothelium, inhibits platelet aggregation and secretion, and is a vasodilator. Thromboxane A_2 and prostacyclin may be local regulators of platelet-endothelial interaction.

The original stimulus initiates events within the platelet to bring about secretion of dense and alpha granule contents (the platelet release reaction). There are at least two secretory mechanisms: thromboxane A_2-dependent and independent. Thromboxane A_2 synthesis is prevented by prior treatment of platelets with aspirin, indomethacin, and other prostaglandin inhibitors. Thrombin or collagen may cause aggregation and secretion in aspirin-treated platelets, indicating that there is at least one thromboxane-independent secretory mechanism.

During platelet aggregation and secretion, platelet procoagulant activity develops. It remains associated with the platelet, and is made available to the coagulation cascade. Although not completely understood, platelet procoagulant activity is probably crucial to normal hemostasis. Platelets play a role at several stages of the cascade, and appear to be involved with the activation of factors XI, X, and II (prothrombin).

Laboratory Evaluation of Platelet Function

Peripheral Blood Smear

The peripheral blood smear may provide information about the cause of platelet dysfunction. Large platelets suggest accelerated platelet turnover rather than decreased bone marrow production. Decreased platelet granularity indicates either a congenital disorder of platelet granules or the phenomenon of circulating spent (hypofunctional) platelets. Abnormalities in the red cells or leukocytes may provide clues to associated disease states.

Bleeding Time

The Ivy template bleeding time is a useful screening test for platelet defects. Errors may result from improper cuff pressure, a cut over a blood vessel, or disturbance of the wound during the test. Scar may form in patients predisposed to keloid formation. The bleeding time is usually prolonged when the platelet count is $<80 \times 10^9$/liter but may be normal in patients with idiopathic thrombocytopenic purpura with platelet counts below this level. The bleeding time is seldom useful in evaluating

profoundly thrombocytopenic patients, and ecchymoses and petechial hemorrhages may complicate the test.

The bleeding time may be prolonged with a normal platelet count in the congenital and acquired intrinsic platelet defects, after ingestion of aspirin and other nonsteroidal antiinflammatory drugs, and in patients with extrinsic defects, including von Willebrand's syndrome, afibrinogenemia, hemophilia A, factor V deficiency, uremia, multiple myeloma, macroglobulinemia, and disseminated intravascular coagulation.

Limitations of the bleeding time test are recognized: (1) A patient with a history of bleeding tendency but a normal bleeding time may nevertheless have a clinically important bleeding disorder. Further evaluation should be pursued in such patients. (2) The bleeding time may be normal in a patient with a known defect, and a normal result is not a guarantee of normal hemostasis during the hemostatic stresses of trauma, invasive procedures, or surgical operations.

Platelet Procoagulant Activity

Platelet procoagulant activity can be assessed by relatively simple assays. The prothrombin consumption test (serum prothrombin time) assesses the residual procoagulant activity of serum after factor V and fibrinogen, which are depleted during clotting, are replaced. If there is deficient platelet procoagulant activity, then clotting factors remain in serum, and the serum prothrombin time is abnormally short. The addition of a platelet substitute to freshly drawn blood corrects the defect. The test also may be abnormal if there is a coagulation factor deficiency.

Clot Retraction Test

Clot retraction is abnormal in Glanzmann's thrombasthenia or if the platelet count is less than 50×10^9/liter. It is also abnormal in hypofibrinogenemia and when fibrinolysis is enhanced. It is normal in other platelet disorders, and its value as a screening test is therefore quite limited.

Platelet Aggregation Studies

Platelet aggregation studies should be considered when the clinical history or the finding of a prolonged bleeding time in the absence of thrombocytopenia or aspirin ingestion indicates that further evaluation is necessary. The patient should not have ingested aspirin or other drugs affecting platelet function for 10 days. An aggregating agent is added to continuously stirred, platelet-rich plasma, and the rate of aggregation is measured by the change in optical density. The aggregation response to ADP or epinephrine is biphasic. Normal and abnormal platelet aggregation patterns are shown in Figure 1.

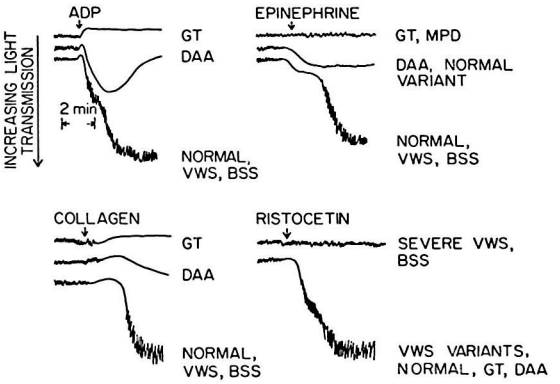

Figure 1 Patterns of normal and abnormal platelet aggregation responses during aggregometry. GT, Glanzmann's thrombasthenia; DAA, defective aggregation augmentation; VWS, von Willebrand's syndrome; MPD, myeloproliferative disorders; BSS, Bernard-Soulier syndrome.

QUALITATIVE PLATELET DISORDERS

Congenital and Familial Platelet Function Disorders

The congenital and familial intrinsic platelet disorders are rare and may be manifested in defects of platelet adhesion, primary aggregation, aggregation augmentation and the release reaction, or procoagulant activity. Some disorders may result in thrombocytopenia with abnormalities of platelet production or survival, or in abnormal platelet size or morphology. Abnormalities of other hematopoietic cell lines or systems may coexist.

There are several well-defined platelet function disorders. *Glanzmann's thrombasthenia* is characterized by an absent first-wave aggregation response to ADP, and a platelet membrane glycoprotein defect. In congenital *dense granule deficiency* (which may be associated with oculocutaneous albinism) and congenital *cyclooxygenase deficiency*, a first-wave aggregation response is seen, but the second wave response (aggregation augmentation) usually is absent. The *Bernard-Soulier syndrome* is characterized by defective platelet adhesion and ristocetin-induced aggluti-

nation and is associated with another platelet membrane glycoprotein defect.

Congenital large platelet syndromes include the Bernard-Soulier syndrome, *May-Hegglin anomaly* (leukopenia, granulocyte Döhle bodies), *macrothrombocytopenia* with deafness and nephritis, and *Mediterranean macrothrombocytopenia*.

Platelet dysfunction or a prolonged bleeding time has been associated with other congenital defects, including Ehlers-Danlos syndrome (type IV), and cyanotic congenital heart disease with erythrocytosis. There is a bleeding tendency in osteogenesis imperfecta, pseudoxanthoma elasticum, the Marfan syndrome, and hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) due to vascular or connective tissue defects.

Acquired Platelet Dysfunction

Myeloproliferative Disorders

Hemostatic abnormalities are characteristic of essential thrombocythemia, polycythemia vera, myelofibrosis with myeloid metaplasia, and chronic granulocytic leukemia. The bleeding tendency may be manifest in bruising, menorrhagia, mucous membrane bleeding, and gastrointestinal hemorrhage. Thrombotic events are less common but may be serious. Cerebral transient ischemic attacks, amaurosis fugax, stroke, digital ischemia, arterial and venous thrombosis, pulmonary embolism, mesenteric thrombosis, and priapism may occur. The correlation between the risk of these complications and the platelet count is poor. The bleeding time is often prolonged in patients with myeloproliferative disorders, but a normal bleeding time is no assurance that a hemorrhagic tendency does not exist. Platelet aggregation responses to epinephrine, ADP, and collagen may be subnormal and the primary epinephrine response may be absent. Some patients show spontaneous platelet aggregation, or have platelets which are hyperresponsive to exogenous ADP, and manifest clinical thrombotic complications. There may be reduced granule content, and ultrastructural abnormalities are common. Aspirin therapy may be effective for digital ischemia.

Acquired Granule Defects

Acquired deficiency of the granule contents (storage pool ADP) occurs in diverse conditions, including myeloproliferative disorders, acute leukemia, lymphoproliferative disorders, hairy cell leukemia, idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), disseminated intravascular coagulation (DIC), valvular heart disease, after cardiopulmonary bypass operations, and following mithramycin administration. It is possible that recirculation of spent platelets, which have been induced to undergo the release reaction, may occur in some of these conditions.

DIC. Circulating monoclonal proteins may interfere with normal platelet function in multiple myeloma and Waldenstrom's macroglobulinemia. A number of platelet defects have been observed in uremia, liver disease, hypothyroidism, and megaloblastic anemias.

Drug-induced Platelet Dysfunction

Aspirin irreversibly inhibits platelet cyclooxygenase resulting in complete inhibition of thromboxane A_2 formation. Following a single aspirin dose, cyclooxygenase activity of circulating platelets begins to reappear 1 or 2 days later and becomes normal over 10 days as senescent platelets are replaced by newly formed platelets that contain the active enzyme. The dose of aspirin necessary to maintain continuous platelet cyclooxygenase inhibition may be 160 mg daily or less. Prostacyclin synthesis, a process dependent on endothelial cyclooxygenase, is also variably inhibited by aspirin. After aspirin ingestion, there may be prolongation of the bleeding time or the bleeding time may remain within the normal range. A normal bleeding time following aspirin ingestion cannot be considered an indication that there will not be excessive bleeding during a surgical operation.

The mechanism of action of dipyridamole is not clearly established, although inhibition of cyclic AMP phosphodiesterase may be involved. Sulfinpyrazone may act by influencing prostaglandin metabolism, or by exerting a protective effect on the endothelium. Dipyridamole and sulfinpyrazone do not prolong the bleeding time or produce abnormalities in routine platelet aggregation studies.

Other nonsteroidal antiinflammatory drugs (e.g., indomethacin, phenylbutazone, ibuprofen, triclopidine, sulindac) cause clinically significant, reversible inhibition of platelet function. Dextran interferes with platelet adhesiveness. Mithramycin administration may be accompanied by a hemorrhagic tendency and defective platelet function. Numerous other drugs (e.g., phenothiazines, antihistamines, local and general anesthetics, nitroprusside, carbenicillin, ethanol) may interfere with platelet function, although these defects are not usually clinically significant.

Therapeutic Approach to Platelet Function Disorders

The therapeutic approach to disorders of platelet function is influenced by the urgency of the clinical situation and the cause of the platelet defect.

Platelet transfusion therapy for hemorrhage is of greatest value when the platelet function defect is intrinsic, and when neither alteration nor enhanced destruction of transfused platelets is anticipated. Platelet transfusions are less effective when the platelet function defect is extrinsic

(e.g., uremia or paraproteinemia) or when accelerated loss of transfused platelets is expected (e.g., isoimmunization from previous transfusions, hypersplenism, disseminated intravascular coagulation, bacterial sepsis).

Complications of platelet transfusion include anaphylactic reactions, isoimmunization, and hepatitis. Platelet transfusions are expensive. Hence, transfusion is best reserved for serious bleeding and for prophylaxis in major surgical operations. Some patients with congenital platelet disorders can be successfully managed during dental operations with topical hemostatic agents and a systemic fibrinolytic inhibitor (e.g., epsilon aminocaproic acid).

MISCELLANEOUS CAUSES OF PURPURA

Purpuric lesions are associated with Henoch-Schönlein vasculitis, scurvy, amyloidosis, hypergammaglobulinemia, cryoglobulinemia, cryofibrinogenemia, acute viral, bacterial and rickettsial infections, subacute bacterial endocarditis, and Kaposi's sarcoma. Petechiae may be observed in the lower extremities of patients with chronic venous stasis and occasionally in normal people, especially at sites of mechanical trauma. Petechiae are likely to occur over the upper trunk, face, and in the conjunctivae following extreme Valsalva maneuvers or violent coughing.

Autoerythrocyte sensitization is a clinical syndrome that occurs during the teen years through the fourth decade. About 95% of affected patients are females. Inflammatory, purpuric lesions over 1 cm in diameter (and which may be very large) occur most frequently on the extremities, but may occur anywhere on the body surface. The appearance of the lesions may be preceded or be accompanied by malaise, chilliness, myalgias, nausea, or headaches. There may be a history of syncope, headaches, paresthesias, paresis, ocular symptoms, other neurologic symptoms, emotional lability, or symptoms referable to chest or abdomen; there is often a history of previous surgical operations. Lesions in some patients may be self-induced. There is no consistently effective therapy and conservative management is recommended.

BLOOD COAGULATION DISORDERS

Over a dozen plasma proteins have been described which participate in coagulation and hemostasis. Some have procoagulant function by which they enhance the rate of formation of cross-linked fibrin. Plasminogen is the precursor to plasmin, the most important fibrinolytic enzyme. Some inhibitory proteins, such as antithrombin III and α_2-plasmin inhibitor,

are important physiologic inhibitors of activated procoagulants and plasmin, respectively. Blood coagulation reactions comprise a finely balanced system which under normal circumstances permits local hemostasis in the face of vascular injury, while retarding thrombosis when it would be unnecessary or deleterious.

Laboratory Evaluation of Coagulation

Activated Partial Thromboplastin Time

Activated partial thromboplastin time (APTT) is a test of the intrinsic and common coagulation pathways (Fig. 2). The APTT is a modification of the whole blood clotting time; the latter is insensitive and inaccurate in the detection of clotting factor deficiencies because of variable surface activation by glass and variability of platelet contribution to clotting. The APTT is performed by recalcification of citrated platelet-poor plasma which has been maximally surface-activated (e.g., by kaolin or celite), and to which a phospholipid platelet substitute has been added. The APTT does not test for factor VII or XIII.

Prothrombin Time

Prothrombin time (PT) is a test of the extrinsic and common pathways. When a tissue extract (e.g., from brain) and calcium are added to citrated plasma, factor VII is activated, and clotting proceeds via participation of factors X, V, II, and fibrinogen (Fig. 2). The PT also does not

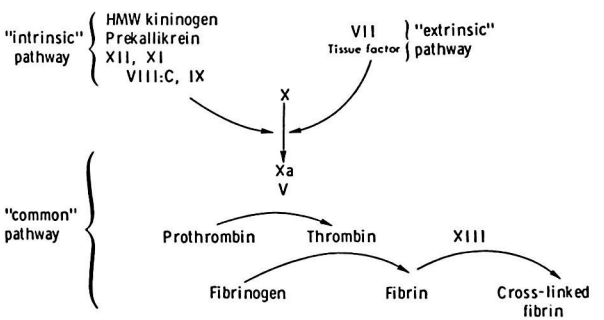

Figure 2 Coagulation cascade. Factor X is activated (to Xa) by "intrinsic" or "extrinsic" pathways. Factors X, V, II, and fibrinogen comprise the "common" pathway leading to fibrin formation. Calcium ions and platelet phospholipid are important cofactors.

test for factor XIII, nor does it test for prekallikren (Fletcher factor), high molecular weight kininogen (Fitzgerald factor), factor XII, XI, IX, or VIII:C, which are tested by the APTT.

Thrombin Time

Thrombin time (TT) is a test of the last step in fibrin formation. Preformed thrombin is added to plasma and the clotting time noted. The test is abnormal when certain antithrombins are present (e.g., heparin, fibrinogen or fibrin degradation products) or when there is marked hypofibrinogenemia or dysfibrinogenemia.

Factor XIII Screening Test

A plasma clot is incubated in 5M urea. If factor XIII is absent, cross-linked fibrin is not formed and the clot dissolves.

Reptilase Time

Reptilase is a thrombin-like snake venom which converts fibrinogen to fibrin. The reptilase time is not affected by heparin and is prolonged in hypo- and dysfibrinogenemia and by elevated levels of fibrinogen/fibrin degradation products.

Stypven Time

Stypven is a snake venom which activates factor X directly; it causes clotting with participation of factors V, II, and fibrinogen. The Stypven time is normal in factor VII deficiency.

Protamine Paracoagulation Test

Soluble complexes of fibrin monomer, fibrinogen, and fibrin degradation products in plasma precipitate upon addition of protamine. When the test is performed properly to eliminate false positive results, a positive test indicates intravascular coagulation.

Serum Fibrinogen-Fibrin Degradation Products (FDP)

A precipitation test using latex particles coated with antiserum to fibrinogen fragments is most commonly used. Positive results are helpful in the diagnosis of intravascular clotting and fibrinolysis.

Coagulation Factor Assays

The most common method is a modification of the APTT or PT, in which the capacity of the test plasma to correct the clotting time of congenitally deficient plasma is compared to that of normal plasma. The most frequently used test for estimating fibrinogen is a thrombin time modification, in which concentrated thrombin is used.

Inherited Disorders of Blood Coagulation

General Features

An inherited disorder of blood coagulation is suspected when the patient has a long-standing hemorrhagic tendency, especially if there is a history of abnormal bleeding in family members. In mild cases spontaneous bleeding may not occur and the deficiency is discovered following surgical bleeding or abnormal coagulation screening tests.

Common bleeding manifestations in the congenital deficiency diseases are ecchymoses, surgical and traumatic bleeding, and menorrhagia in females. With the exception of hemophilia A and B, which are inherited as X-linked recessive traits, these deficiency states show autosomal inheritance.

Von Willebrand Syndrome

Von Willebrand syndrome (VWS) is the most common congenital bleeding disorder. VWS encompasses a spectrum of disorders of the factor VIII molecule. Acquired forms have been described in patients with collagen-vascular and lymphoproliferative diseases. The spectrum of clinical severity is broad, ranging from a severe disorder beginning early in life with recurring life-threatening hemorrhages to a very mild disorder in which abnormal bleeding does not occur except during trauma, childbirth, or surgery. Easy bruising is common, and petechiae or purpura may be noted. Mucous membrane bleeding including epistaxes, upper gastrointestinal bleeding, and menorrhagia may be prominent. Upper gastrointestinal bleeding is often not associated with a specific identifiable lesion in the VWS, and bleeding may occur from multiple sites.

Hemophilia

Factor VIII:C deficiency (hemophilia A) and factor IX deficiency (hemophilia B, *Christmas disease*) are relatively common. These two disorders are clinically indistinguishable, with hemarthrosis the cardinal clinical manifestation. The most commonly involved joints are the knees, ankles, and elbows. Recurrent hemarthroses lead to debilitating hemophilic arthropathy, characterized by progressive synovial and cartilagenous abnormalities, periarticular osteopenia, loss of joint motion, contractures, and muscle atrophy. Other forms of skin and soft tissue bleeding include ecchymoses, intramuscular hematomas, and pharyngeal hematomas (with the risk of asphyxiation). Ilio-psoas hematoma may develop and, if on the right side, may mimic acute appendicitis. An intramuscular or periosteal hematoma may, over weeks to months, behave like a tumor (hence the name pseudotumor) and result in the destruction of muscle, nerves, and bone, with the secondary risk of infection and loss of limb. Hematuria may occur in the absence of a structural urinary tract lesion. In contrast

to VWS, gastrointestinal hemorrhage is often associated with duodenal ulcer. Intracranial hemorrhage is usually preceded by trauma, but may not occur for several days following the injury. A female hemophilia carrier may manifest abnormal bleeding during trauma or surgery.

Other Hereditary Coagulation Disorders

Most patients with factor XI deficiency are of Ashkenazic Jewish ancestry among whom the incidence of homozygous factor XI deficiency is about 1 in 600. Despite severe factor deficiency, the bleeding disorder may be mild, but surgical bleeding is common.

Deficiencies of factor XII (Hageman factor), prekallikrein (Fletcher factor), and high molecular weight kininogen (Fitzgerald factor) are usually not associated with a bleeding tendency. Several patients with homozygous factor XII deficiency have been described who have a mild bleeding disorder. These factor deficiencies are very rare.

Congenital deficiencies of other clotting factors are rare. These include congenital absence of factor VII, X, V, prothrombin, or fibrinogen. Severe deficiency states are characterized by ecchymoses, menorrhagia and surgical bleeding. Hemarthroses may be observed, but they are uncommon. Congenital absence of factor XIII is associated with umbilical bleeding in the neonate, delayed wound healing, delayed bleeding after surgical operation, ecchymoses, pseudotumor formation, intracranial bleeding, and spontaneous abortions.

Qualitative abnormalities of clotting factors have been described. All of these are rare, and most have been described only in individual kindreds. Qualitative abnormalities of fibrinogen (the dysfibrinoginemias) are the most common. Ecchymoses, menorrhagia and surgical and traumatic bleeding have been noted. In some families, the dysfibrinogenemia appears to be associated with a thrombotic tendency.

Laboratory Diagnosis. The laboratory diagnosis of coagulation abnormalities is summarized in Table 2.

In severe von Willebrand's syndrome abnormal test results are obtained for the Ivy bleeding time, ristocetin-induced platelet aggregation in platelet-rich plasma, the APTT and factor VIII:C, although none of these abnormalities is specific for the VWS and test results may be normal in mild forms of the disease. In fact, patients with the VWS may have normal studies even during clinical bleeding. The assays for factor VIII:antigen and the factor VIII:ristocetin cofactor (RCoF) are more specific for VWS, and they have special diagnostic importance in patients with a bleeding history and normal or equivocal screening tests. The factor VIII:antigen assay measures the amount of protein in test plasma which reacts with rabbit antihuman factor VIII antibody. The factor VIII:ristocetin co-factor assay (RCoF) measures the capacity of the test plasma to

Table 2 **Screening and Special Tests for Diagnosis of Coagulation Disorders**

Deficiency or State	*APTT*	*PT*	*TT*	*Other*
Fletcher	↑	nl	nl	APTT shortens with prolonged activation
XII, XI, Fitzgerald				
IX, VIII:C	↑	nl	nl	
VII	nl	↑	nl	Stypven time normal
X, V, or II	↑	↑	nl	
VWS	nl to ↑	nl	nl	Factor VIII-antigen, ristocetin cofactor, crossed immunoelectrophoresis, and bleeding time
Vitamin K deficient states	nl to ↑	↑ to ↑↑	nl	½ nl plasma corrects
Heparin therapy	↑↑	↑	↑↑↑	Potamine sulfate corrects TT. Reptilase time nl
DIC	nl to ↑	nl to ↑	nl to ↑↑	Fibrinogen ↓, nl, or ↑ Protamine paracoagulation test + ; FDP +; ½ nl plasma partly corrects
Hypofibrinogenemia	↑	↑	↑	½ nl plasma corrects Fibrinogen assay
Dysfibrinogenemia	nl to ↑	nl to ↑	↑ to ↑↑	Reptilase time ↑
XIII	nl	nl	nl	5 M urea soluble clot

Table 3 **Coagulation Factor Deficiencies**

Deficiency	*Minimum Hemostatic Level*	*Half Life in vivo*	*Preferred Sources*[a]
XI	10-20%	10-80 hours	FFP
IX	15-25%	12-40 hours	FFP, 9
VIII	25-30%	10-14 hours	Cryo, 8
VWF	?	?	Cryo
VII	5-10%	4-6 hours	FFP, 9
X	10-20%	24-72 hours	FFP, 9
V	15-25%	12-36 hours	FFP
II	20-40%	4 days	FFP, 9
Fibrinogen	75-100 mg/dl	4 days	FFP, Cryo
XIII	5%	10 days	FFP

[a]FFP, fresh frozen plasma; Cryo, cryoprecipitate; 8, factor VIII concentrate; 9, factor IX concentrate.

support ristocetin-induced aggregation of washed, normal platelets. Crossed plasma immunoelectrophoresis using the rabbit antihuman factor VIII antibody detects factor VIII species with abnormal electrophoretic mobility. One or more of these assays is almost always abnormal when a patient has clinical bleeding due to the VWS. In some cases, test results may be equivocal during remissions from bleeding or during pregnancy. Although VWS patients often demonstrate a concomitant decrease of factor VIII:C, antigen, and RCoF activity, many combinations of these abnormalities are recognized. By contrast, the patient with hemophilia A has only a marked decrease of factor VIII:C. The female hemophilia carrier shows values of factor VIII:C approximately half of the factor VIII: antigen value.

Treatment. Indications for hospitalization in the patient with a congenital bleeding disorder include symptoms or signs suggestive of intracranial bleeding, gastrointestinal hemorrhage, oropharangeal hematoma, or intramuscular hematoma. The patient with hemarthroses or ecchymoses can usually be managed without hospitalization.

Although guidelines exist for the expected recovery of the missing clotting factor and its expected half-life in vivo, after factor replacement, each patient must be assessed individually. Patients with hemophilia A should be assessed periodically for the possible development of an anti-factor VIII inhibitor. Patients with congenital coagulation factor

deficiencies should be advised against taking aspirin-containing medications.

Patients with congenital coagulation disorders should be managed with the guidance of an experienced hematologist, and the details of replacement therapy will not be reviewed. The biologic half-life, minimum level necessary to achieve hemostasis, and sources of the coagulation factors are shown in Table 3.

Acquired Disorders of Blood Coagulation

Vitamin K Deficiency States

Vitamin K is required for γ-carboxylation of glutamic acid residues of factors II, VII, IX and X. Deficiency of vitamin K results in a deficiency of functional vitamin K dependent factors and a hemorrhagic disorder.

Causes of Vitamin K Factor Deficiency States. Vitamin K is obtained from the diet and from intestinal bacteria. It is a fat-soluble vitamin and requires bile salts and a normal intestinal mucosa for absorption. During the first 3 to 5 days of life, the neonate may have severe deficiency with *hemorrhagic disease of the newborn*. After the neonatal period, the deficiency state may occur because of dietary vitamin K deficiency (starvation), or malabsorption (biliary obstruction, diffuse bowel disease, protracted diarrhea, excessive mineral oil use). A frequent setting for the development of vitamin K deficiency is the patient with poor dietary intake who is simultaneously receiving broad spectrum antibiotics, which alter intestinal bacterial flora. Hepatic disorders may lead to reduced synthesis of vitamin K dependent clotting factors.

The oral anticoagulants, among which warfarin is the most commonly used, interfere competitively with the action of vitamin K. The margin of safety in the use of warfarin is narrow. Warfarin therapy is initiated with 10-12 mg daily and loading doses are contraindicated. Excessive anticoagulation is most likely to develop during the first months of treatment until proper dosage is established. Warfarin therapy is monitored by the PT and the dosage adjusted to maintain the PT 1½ to 2 times normal. Many drugs have the capacity to potentiate or inhibit the action of oral anticoagulants, and errors in anticoagulation therapy may result from drug interactions (Table 4). The simultaneous use of warfarin and other drugs which may potentiate or inhibit its effect is not absolutely contraindicated, but it is incumbent upon the physician to monitor the PT and to make appropriate adjustements in warfarin dose. The patient must be carefully advised not to alter the dosage of interacting drugs (or to allow a supply to become exhausted). Patients must avoid unprescribed aspirin-containing medications. When a drug has only recently become available for therapeutic use, there may be little knowledge available about the po-

Table 4 **Some Important Drug-Warfarin Interactions**

Drugs that potentiate warfarin action
Antiinflammatory drugs: aspirin, indomethacin, phenylbutazone
Acid sulfonamides (e.g., sulfisoxazole), chloramphenicol, broad spectrum antibiotics
Androgens
Alpha-methyldopa
d-thyroxine
Quinidine
Clofibrate
Cimetidine
Metronidazole, disulfiram
Sulfonylurea drugs (tolbutamide)
Diphenylhydantoin
Cholestyramine
Chlorpromazine
Imipramine
Drugs that inhibit warfarin action
Barbiturates, ethchlorvynol, glutethimide
Estrogens
Rifampin, griseofulvin

tential for a warfarin interaction. If such a drug is used, it is wise to monitor therapy closely until stability is assured. Patients who have liver dysfunction may become excessively anticoagulated while taking warfarin if liver function further declines. For example, the anticoagulated patient with congestive cardiomyopathy may become excessively anticoagulated if hepatic congestion results from a decline in cardiac status.

Clinical Manifestations. The sole manifestation of vitamin K deficiency is a bleeding tendency. Ecchymoses and hematuria are common, there may be oozing from IV sites, bleeding from the gastrointestinal tract and mucous membranes, and intracranial hemorrhage may occur in severe cases. In mild cases, gastrointestinal bleeding is not usual and the presence of an underlying lesion should be suspected when this type of bleeding occurs. Unusual sites for hemorrhage during anticoagulant therapy include the retroperitoneum, bowel wall, the adrenal glands, and the ovaries (corpus luteum).

Laboratory Diagnosis. PT is the most sensitive laboratory test for the diagnosis of depletion of the vitamin K clotting factors. The APTT is less sensitive and the TT is normal. In the mildest cases, the PT is a few

seconds prolonged, and the APTT is normal. In severe cases both the PT and APTT are markedly prolonged. The diagnosis of the vitamin K deficiency state can be made if there is a normal thrombin time, and if there is complete, or near complete, correction of the abnormal PT by mixing the patient's plasma with an equal volume of normal plasma. Correction of the PT after vitamin K administration is diagnostic.

Treatment. The vitamin K deficiency state is treated with vitamin K_1, which may be given by oral, subcutaneous, intramuscular, or intravenous routes. Parenteral administration is necessary in malabsorption states and when bleeding is evident. Oral or subcutaneous administration is desirable when possible to avoid the risk of intramuscular hematoma or anaphylactic reaction to intravenous administration. If liver disease is present, there may be no shortening of the PT after vitamin K administration, or the response may only be partial and delayed for 1 to 4 days.

The minimum effective dose of vitamin K_1 (e.g., Aquamephyton) is quite variable. As little as 1 to 2 mg may be adequate to shorten the PT in the modestly overanticoagulated patient taking warfarin, without reversing the anticoagulated state and rendering the patient temporarily refractory to warfarin effect. If it is necessary to completely reverse the anticoagulated state, 10 to 20 mg Aquamephyton is usually sufficient, but as much as 50 mg rarely may be needed. Hemorrhagic disease of the newborn is preventable by the administration of Aquamephyton 1 to 2 mg intramuscularly. In the adult, Aquamephyton 10 to 20 mg is usually sufficient to treat vitamin K deficiency not related to oral anticoagulants. Five milligrams biweekly will usually protect the patient who is not eating against the development of factor deficiency.

If serious bleeding is present, the deficiency state is immediately reversible by the infusion of a volume of plasma equal to 30 to 40% of the patient's estimated intravascular plasma volume. (Average estimated plasma volume is 45 ml/kg.) Since the therapeutic effect of administered or newly synthesized factor VII is limited by its half-life of 6 hours, and the half-life of warfarin is 30 to 60 hours, vitamin K or plasma must be administered frequently (at least twice daily) to maintain hemostasis after massive warfarin overdose, until the warfarin is catabolized.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a syndrome in which several events occur: (1) coagulation factors and platelets are consumed; (2) clots may form in large vessels with fibrin deposition in small vessles; (3) activation of the fibrinolytic system lyses the fibrin laid down in clots and small blood vessels and may degrade plasma fibrinogen. There is virtually always a recognizable underlying cause (Table 5).

Table 5 **Causes of Disseminated Intravascular Coagulation (DIC)**

Shock
Bacterial sepsis
Obstetric complications
Toxemia
Placental abruption
Retained dead fetus
Retained placental fragments
Amniotic fluid embolism
Puerperal sepsis
Hypertonic saline abortion
Liver failure
Vasculitis
Rickettsial and viral diseases
Purpura fulminans
Collagen-vascular and immune-complex diseases
Malignancy
Especially prostate, lung, pancreas, adenocarcinomas of the gastrointestinal tract, and acute leukemia (especially acute promyelocytic leukemia)
Brain tissue destruction
Cardiopulmonary bypass
Ruptured or dissecting aortic aneurysm
Acute antigen-antibody reactions
Drugs
Anaphylaxis
Hemolytic transfusion reaction
Massive hemolysis
Some venemous snake bites
Activated prothrombin complex concentrates
Kasabach-Merritt syndrome (cavernous hemangioma)
Leveen (peritoneo-jugular) shunt

Pathophysiology of DIC. The precise nature of the initial clotting disturbance in most of the clinical conditions listed in table 5 is not known. The liberation of thromboplastins and endothelial damage are possible initiating events. The generation of fibrin polymer and aggregation of platelets may result in clinically evident thrombosis in DIC. A tendency

to bleed is a more common clinical manifestation, and is due to the consumption and depletion of platelets, clotting factors, fibrinogen, and generation of fibrin(ogen) degradation products which inhibit fibrin clot formation.

Clinical Manifestations. The most common manifestation is bleeding, frequently in the form of ecchymoses, oozing from intravenous punctures or mucosal hemorrhage. If there is clinically significant microvascular clotting, schistocytosis (fragmented, circulating red blood cells) with intravascular hemolysis is commonly associated. The presence of schistocytosis correlates with the presence of end-organ ischemia. Acrocyanosis with infarction of digits and the tip of the nose may be observed. Oliguria and central nervous system dysfunction may develop. It may be difficult to determine with certainty if these latter disturbances are due to DIC per se or to the underlying disease process. Arterial and venous thromboembolic disease and nonbacterial thrombotic endocarditis (the Trousseau syndrome) are associated with malignancy.

Laboratory Diagnosis. Usually one or more of the screening coagulation tests (PT, APTT, or TT) are abnormal. Occasionally, cases of DIC with clinical bleeding or thrombosis are associated with normal screening test values. The presence of hypofibrinogenemia (if it cannot be attributed to advanced liver disease) supports the diagnostic impression of DIC, although it need not be present to make this diagnosis. The presence of serum fibrinogen/fibrin degradation products and a positive protamine paracoagulation test provide strong support for the diagnosis of DIC. Thrombocytopenia is detected in most patients during the course of their illness. Virtually any combination of abnormalities may be observed, but the tests may need to be repeated over time to substantiate the presence of DIC. There is no single diagnostic test for DIC.

Principles of Management. The most important therapy of DIC is the aggressive management of the underlying disease, including the prompt treatment of shock and acidosis when these are present. The DIC process should be considered severe if there is bleeding, large vessel thrombosis, evidence of microvascular fibrin deposition (fragmented red blood cells on the peripheral smear), or if there is marked hypofibrinogenemia or thrombocytopenia.

Therapy for DIC per se may be unnecessary if the coagulation disturbance is mild and if it is expected that treatment of the underlying condition will be successful within a few hours. If bleeding is associated with marked depletion of clotting factors (e.g., PT and APTT $> 2 \times$ normal or fibrinogen <75 mg/dl) or thrombocytopenia (e.g., $< 50 \times 10^9$/liter), replacement therapy should be considered. Fresh-frozen plasma contains all clotting factors. An initial dose should be about 10 ml/kg. If severe hypofibrinogenemia exists, cryoprecipitate can be used as a source

of fibrinogen. Each bag of cryoprecipitate contains about 250 mg fibrinogen and can raise the plasma fibrinogen level about 10 mg/dl. Platelet concentrates can be used for severe thrombocytopenia. The effect of replacement infusions is short-lived if rapid consumption is continuing.

Considerable controversy persists regarding the usefulness of heparin therapy in DIC. Heparin may reduce the risk of thrombosis while it aggravates the bleeding tendency. Before using heparin to treat a patient with DIC, the physician should consider the following: (1) Can the underlying condition be controlled promptly so that the risks from DIC per se will spontaneously decrease; (2) Is there an anatomical lesion from which serious bleeding might occur if heparin were administered (e.g., peptic ulcer, recent cerebral infarct). Large vessel thrombosis and microvascular thrombosis with end organ ischemia and schistocytosis are indications to consider heparin therapy. Patients with acute promyelocytic leukemia undergoing remission induction have a very high incidence of DIC and usually require heparin therapy. Heparin therapy may also be useful early in the course of a major hemolytic transfusion reaction, in the Kasabach-Merritt syndrome (giant cavernous hemangioma), and in envenomations by some snakes (not rattlesnakes), and in amniotic fluid embolism. Heparin is not indicated for DIC associated with placental abruption, aortic aneurysms, hemorrhagic shock, or after surgery with cardiopulmonary bypass. Consultation by a hematologist should be obtained to assist in the management of patients with DIC.

Inhibitors of Coagulation

An inhibitor of coagulation may be discovered as the result of an evaluation of a bleeding disorder, or because of investigation of an abnormal coagulation test result. Inhibitors are either antibodies or in patients with multiple myeloma or Waldenström's macroglobulinemia the paraprotein may act as an inhibitor. Inhibitors against almost all of the known blood coagulation factors have been described.

Clinical Manifestations. Certain coagulation factor inhibitors are strongly associated with a bleeding tendency. Antibodies to the procoagulant activity of factor VIII may develop in several clinical settings: (1) in the multiply-transfused patient with Hemophilia A; (2) in association with other conditions characterized by alterations of the immune system, such as systemic lupus erythematosis (SLE); (3) in women within several months after term of pregnancy; or (4) without known cause. Patients with other severe congenital factor deficiencies may develop antibodies against the missing factor, thereby aggravating the bleeding diathesis and making transfusion therapy difficult. Antibodies against prothrombin (factor II) in systemic lupus erythematosis can be associated with a bleeding diathesis. Isoniazid therapy has been associated with an antibody

to factor XIII and a marked bleeding tendency. Acquired von Willebrand's syndrome associated with SLE or lymphoproliferative diseases is due to an inhibitor of the von Willebrand activity of factor VIII.

Inhibitors of clotting in the laboratory are not always associated with a bleeding tendency. An asymptomatic inhibitor may be found during routine laboratory screening, with no recognizable underlying condition. Approximately 5 to 10% of patients with SLE have a prolonged APTT and a circulating inhibitor of blood coagulation. Some of these patients have no bleeding tendency, and thrombotic events may occur despite the presence of an inhibitor. The most common inhibitor in these patients is the *lupus anticoagulant*. The lupus anticoagulant also occurs in patients with no clinical or serologic evidence of lupus, but who may have other collagen-vascular disorders, infection, or who may have no apparent underlying disease. Most of these patients have no bleeding tendency. Inhibitors may develop during phenothiazine treatment.

Laboratory Diagnosis. An inhibitor of coagulation is associated with prolongation of one or more of the screening coagulation tests (PT, APTT, TT). An antibody against factor XIII is associated with normal screening clotting tests but with clot instability in 5M urea. The presence of a circulating inhibitor is suspected if mixing normal plasma with the patient plasma does not correct the abnormal clotting test. The inhibitor activity may not be evident immediately after mixing of the plasma, but inhibition may become evident after 2 to 3 hours of incubation. Specific factor assay leads to identification of the factor against which the inhibitor is directed.

The presence of the lupus anticoagulant is suspected when there is an inhibitor of the APTT, in some cases associated with a prolonged PT. The lupus anticoagulant may be revealed by a positive tissue thromboplastin inhibition test (TTI), a modification of the PT.

Management. If an anticoagulant is associated with SLE, the activity of the inhibitor usually declines during glucocorticoid therapy. The presence of an asymptomatic coagulation inhibitor does not require treatment. If isoniazid therapy is associated with an antifactor XIII antibody, the drug must be discontinued. In cases of a bleeding diathesis associated with anti-factor VIII antibodies, the use of glucocorticoid or immunosuppressive therapy is seldom successful. If therapy with cryoprecipitate or factor VIII concentrates has failed to stop a bleeding episode, activated prothrombin complex concentrates may be successful. Plasmapheresis may be of value when a monoclonal protein is associated with abnormal bleeding.

Liver Disease

The pathogenesis of the coagulopathy associated with liver disease is complex, and the severity tends to correlate with the degree of hepatocellular dysfunction. Hepatocellular failure or cirrhosis result in decreased

clotting factor synthesis and, occasionally, enhanced fibrinolysis. Factor VIII levels are notably unaffected unless DIC is occurring. Fibrinogen levels are usually normal until liver disease is far advanced, or unless DIC or fibrinolysis develop. Bile salt deficiency may lead to malabsorption of vitamin K and aggravate vitamin K-dependent factor deficiencies. Dysfibrinogenemia may be associated with hepatocellular carcinoma. Thrombocytopenia is common and may be due to portal hypertension with hypersplenism, immune mechanisms, or DIC. Platelet function may be abnormal. DIC is relatively uncommon in liver disease but is suggested by a strongly positive protamine paracoagulation test. Intercurrent bacterial infection may exacerbate the coagulopathy of liver disease. Patients with preexisting hemostatic defects are likely to have severe bleeding when the coagulopathy associated with liver disease develops. Hemorrhage requiring massive transfusion of red blood cells without adequate replacement of plasma and platelets may superimpose the additional problem of washout coagulopathy. Patients with relatively minor abnormalities in coagulation tests or platelet count may nevertheless have severe bleeding during surgical operation. Thrombotic complications are rare.

Assessment of hemostatic funtion in patients with liver disease should include the prothrombin time, plasma fibrinogen, and platelet count. The thrombin time, protamine test, and bleeding time may be of additional value in some patients.

Patients with bleeding complications or requiring surgery usually require treatment to correct the hemostatic defects. Fresh frozen plasma, cryoprecipitate, and platelet transfusion can be used, depending on the precise defect. Vitamin K_1 10 mg parenterally can be given. Although heparin can improve finbrinogen survival in liver disease and attentuate DIC, heparin will likely add to the bleeding tendency and should in most instances be avoided.

CASE HISTORY 1

A 35-year-old man has had 1 week of fever, sweats, increasing confusion, and bruising. He had two teeth extracted 4 weeks before, and subsequently developed maxillary sinusitis treated successfully by drainage and dicloxacillin. Examination now is remarkable for fever (38.6°C), agitation and confusion, mild icterus, petechiae and bruises, a grade II/VI mid to late systolic murmur with a late systolic click at the apex, and minimal splenomegaly. Initial laboratory studies show Hbg 7.8 g/dl, reticulocyte count 9%, WBC 18.8 X 10^9/l (92% granulocytes, 4% monocytes, 4% lymphocytes), platelet count 38 X 10^9/l, prothrombin time 11.6 sec (control 12.0 sec), serum bilirubin 3.7 mg/dl (conjugated 1.0 mg/dl); urinanalysis shows 2+ proteinuria and microscopic hematuria.

Questions

1. Which of the following investigations should be pursued *immediately* to help define the hematologic and medical problems? (more than one answer may be correct)
   (a) Examination of periphral blood smear
   (b) Direct Coombs' test
   (c) Echocardiogram
   (d) Blood Cultures
   (e) Serum antinuclear antibodies
   (f) Renal biopsy
   (g) Liver-spleen scan
   (h) Bone marrow aspirate/biopsy
2. Which is the most reasonable initial emergency treatment pending results of the above investigations?
   (a) Red cell and platelet transfusions
   (b) Whole blood exchange transfusion
   (c) A penicillin-type drug plus an aminoglycoside
   (d) Prednisone

Answers

1. a,b,d,e
2. c

CASE HISTORY 2

A 62-year-old woman has had intermitent colicky right upper quadrant pains for 3 weeks. She is alert and presents with jaundice, acholic stools, and mild hepatomegaly. She develops a hematoma at an antecubital venipuncture site. Lab tests show Hgb 13.0 g/dl, WBC 4.8 $\times$ 10^9/l, platelet count 320 $\times$ 10^9/l, PT 20.4 sec (control 11.8 sec), activated PTT 44.8 sec (control 35.5 sec), serum bilirubin 15 mg/dl, SGPT 75 U/L (normal 5 to 45), serum alkaline phosphatase 485 U/L (normal 30-110).

Questions

1. The most likely explanation for the bleeding tendency is
   (a) Hepatic insufficiency
   (b) Vitamin K deficiency due to malabsorption

(c) Disseminated intravascular coagulation
(d) Circulating anticoagulant

2. Which additional test would most likely help confirm your impression?
(a) Factor VIII:C
(b) Fibrinogen level
(c) PT on a 50-50 mix of patient plus normal plasma
(d) Serum fibrinogen/fibrin degradation products

Answers

1. b
2. c

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5

MARY TERRITO

Approach to the Patient with Frequent Infections

The factors involved in the response to microbial challenge are complex. The virulence and infectivity of an organism are, for the most part, related to its ability to overcome the multiple defense mechanisms of the body. Some organisms, such as those that cause the common cold, have a high incidence of infectivity and overcome the early defenses of most normal individuals. Other organisms, such as pneumocystis or aspergillus, are usually easily contained and nonpathogenic to man, except in situations where the normal defense mechanisms of the body are compromised, and then they may induce severe and even fatal infections; these are referred to as opportunistic infections. When a patient presents with frequent, severe, or unusual infections, consideration should be given to possible abnormalities of their defense systems.

The defense mechanisms of the host can be divided into four major categories: phagocytic cells, the lymphoid system, serum factors, and epithelial or mucosal barriers (Table 1). There are many interrelationships among these four groups all operating to protect the host against the intruding organism; however, different components of the host defense system predominate in protection against specific types of infections. An understanding of host defense mechanisms is important in deciding the approach to, and therapy for, patients with frequent or opportunistic infections.

Table 1 **Host Defense Mechanisms**

Phagocytic cells
Neutrophils
Monocyte-macrophage system
Lymphoid system
T-lymphocytes
B-lymphocytes and plasma cells
Serum factors
Antibodies
Complement
Miscellaneous factors
Epithelial and mucosal barriers
Skin
Gastrointestinal
Urogenital
Respiratory

HOST DEFENSE MECHANISMS

Phagocytes

The principal phagocytic cells of man are the neutrophils, and the mononuclear phagocytes (monocytes and macrophages). Phagocytic cells serve primary roles in the host defense system—the neutrophils being the major cellular defense against pyogenic infectious agents (such as Staphylococcus, Escherichia coli and Candida albicans), and the mononuclear phagocytes serving to control facultative intracellular parasites (such as tuberculosis, listeria, and many fungi). The phagocytic cells are produced in the bone marrow, arising from a common precursor stem cell which, after a series of developmental stages, gives rise to the mature neutrophil or macrophage. In order to control infections, phagocytic cells undergo a complex series of activities including chemotaxis (directed migration of the cells to the infective focus), phagocytosis (ingestion of the organism), and microbial killing and digestion. Some of the means by which microbial killing is accomplished include the effects of active enzymes contained within the lysosomal granules of the cells, acidification of the environment of the organism, and by the production of active oxygen metabolites (e.g., hydrogen peroxide, superoxide).

Lymphocytes

Lymphocytes are another important cellular component of the host defense system. The lymphocyte precursors arise in the bone marrow. As the cells mature, they become modified into either T lymphocytes (after conditioning by the thymus) or B lymphocytes (after conditioning by the bone marrow or fetal liver). The T lymphocytes function in cell-mediated immunity and as such are important in the control of many viral and fungal infections. The B lymphocyte and its mature progeny, the plasma cell, are the source of antibody production. Throughout the body, lymphocytes are organized into various lymphoid tissues ranging from loose collections of lymphocytes, as seen in the tracheal mucosa, to the complex anatomical organizations seen in the lymph nodes and spleen.

Serum Factors

Soluble serum factors play important roles in host defense. Antibodies are produced by B lymphocytes. Antibody can damage organisms directly, coat (*opsonize*) organisms to allow for rapid ingestion by phagocytic cells, or activate T cells to become cytotoxic. A complex system of proteins makes up the complement system. Various complement factors are active in different stages of host defense by acting as opsonic agents (C3b), chemotactic agents (C5a) to recruit phagocytic cells into the inflammatory focus, or by directly lysing certain organisms (C6, C7, C8, C9). Many other plasma components such as the coagulation proteins, the kinin system, and other chemotactic factors are also involved in host defense.

Physical Barriers

The body has cetain physical barriers which are important in protection against microbial invasion; these include the skin and mucosal surfaces. In addition to the purely physical aspects of these barriers, the acid environment of the skin, stomach, and vaginal mucosa, the chemical mediators in the mucus of these systems, and the cleansing and filtering properties of the ciliary and propulsion networks are all important aspects of host defense.

Causes of Recurrent Infections

Recurrent or opportunistic infections can occur when a defect exists in any aspect of the host defense system (Table 2). Patients may have defects in the cellular or serum components of their defense system, as a primary disorder or secondary to another disease process. Patients with these prob-

Table 2 **Causes of Recurrent or Opportunistic Infections**

I. Phagocytic cell abnormalities
  A. Neutropenia
    1. Congenital
    2. Acquired
      (a) Primary
        Idiopathic
        Antibody-mediated
      (b) Secondary
        Drugs
        Radiation
        Marrow infiltration
        Infections
        Autoimmune diseases
        Hypersplenism
  B. Neutrophil dysfunction
    1. Primary intrinsic
      Chronic granulomatous disease
      Chediak-Higashi syndrome
      Job's syndrome
      Myeloperoxidase deficiency
    2. Secondary
      Immunoglobulin deficiencies
      Complement deficiencies
      Diabetes
      Sickle cell disease
      Cancer
      Corticosteroids
II. Lymphocyte abnormalities
  A. T-cell deficiencies
    Lymphomas
    Di George syndrome
  B. B-cell deficiencies
    Agammaglobulinemia
    Myeloma
    Lymphomas
  C. Combined immunodeficiency syndromes
    SCID
    Ataxia telangiectasia

Table 2 (Continued).

	Wiskott-Aldrich
	Common variable
	Secondary (lymphoproliferative, autoimmune, drugs)
III.	Miscellaneous systemic disorders
A.	Post-splenectomy
B.	Complement deficiencies
C.	Multiple factors
	Neoplasia
	Diabetes
	Hematologic disorders
	Collagen vascular diseases
	Infections
	Drugs
IV.	Local problems
A.	Foreign body nidus
B.	Perfusion abnormality
C.	Abnormal skin barrier
D.	Abnormal drainage

lems are referred to as compromised hosts. Recurrent infections also can be seen in patients whose systemic defenses are normal but in whom local physical abnormalities exist.

PHAGOCYTIC CELL ABNORMALITIES

Clinical abnormalities of neutrophils most commonly occur because of a quantitative decrease in the total available circulating neutrophils. This situation is referred to as neutropenia, granulocytopenia, or agranulocytosis. Dysfunction of neutrophils also can occur, but this is less common.

Neutropenia

Neutrophils arise from progenitor stem cells in the bone marrow which give rise to the myeloblast, promyelocyte, and myelocyte, all of which are

capable of dividing, and comprise the mitotic pool of cells. The cells then undergo further differentiation and maturation through the metamyelocyte, band, and neutrophil stages, remaining within the bone marrow as the maturation and storage pool. The mature neutrophils are then released into the peripheral blood where they may circulate freely (circulating pool) or they may temporarily sequester along vessel walls and in small blood vessels (marginal pool). The cells leave the circulation within 6 to 8 hours and migrate into the tissues or inflammatory foci where they function in the acute inflammatory process, then die within 1 to 2 days.

The absolute number of circulating neutrophils is calculated as a product of the total leukocyte count and the percentage of neutrophils in the leukocyte differential count. The clinical manifestations of neutropenia vary with the magnitude of the reduction in neutrophil numbers and the neutrophil reserves. Symptoms rarely manifest when the neutrophil counts exceed 1×10^9/liter. The risk of infection is moderately increased when the neutrophil count is between 0.5 and 1×10^9/liter, and below 0.5×10^9/liter the risk is greatly increased.

Frequent sites of infections are the lung, oropharynx, nasopharynx, genitourinary tract, and blood (septicemia). Gram-negative bacteria, especially pseudomonas, E. coli, and klebsiella, are the common infectious agents, but staphylococcus, other gram-positive agents, Candida, aspergillus, and other fungi, also can be seen. Neutrophils are responsible for many of the clinical findings in infection. If a patient is severely neutropenic, he may not be able to mount an adequate inflammatory response, and many of the classic signs of infection (e.g., abscess, pulmonary infiltrate, sputum production, urinary or CSF leukocytosis, or peritoneal signs) may be diminished or absent.

Neutropenia rarely occurs on a congenital basis. Acquired primary neutropenias occur in idiopathic aplastic anemia, where all marrow components are reduced, or as an isolated neutropenia. *Cyclic neutropenia* is a situation in which low neutrophil counts develop in a cyclic manner every 21-30 days; infections frequently accompany the fall in counts. Some patients have chronic low grade or intermittent neutropenia with neutrophil counts falling below 1.5×10^9/liter. These patients experience recurrent skin abscesses or other usually non-life-threatening infections. They commonly develop malaise, fatigue, and weakness coincident with the nadir of the neutropenia, not necessarily associated with fever or demonstrable infection. The pathogenesis of neutropenia in most of the primary disorders is unknown, and these patients probably represent a heterogenous group of disorders.

Acquired secondary neutropenias occur by several different mechanisms: (1) exposure to myelosuppressive drugs or toxins; (2) radiation exposure; (3) infiltration of the bone marrow (myelophthisic process); and (4) increased destruction or sequestration of granulocytes.

The drugs most frequently associated with neutropenia are the cancer chemotherapy drugs that produce myelosuppression in a dose-dependent manner. Other drugs associated with neutropenia by a non-dose-dependent, idiosyncratic mechanism include phenothiazines, chloramphenicol, thiouracil derivatives, methimazole (Tapazole), penicillins, sulfonamides, phenylbutazone (Butazolidin), and the anticonvulsants. Increased destruction occurs in hypersplenism and in some autoimmune disorders.

The therapy of the neutropenic patient depends on the severity of the neutropenia. In patients with agranulocytosis (less than 0.5×10^9/liter) infections are frequently severe, progressive, and may be rapidly fatal. Because of this, infected agranulocytic patients should be carefully and extensively cultured for bacterial and fungal agents and then immediately begun on a broad spectrum antibiotic regimen. The antibiotics can later be tailored to comply with the culture results.

Normal neutrophil counts vary widely among individuals, and in the same individual in different settings. There is also ample evidence that there are differences among various ethnic or racial groups. This is well demonstrated in the American black population, where neutrophil counts in the general population are frequently below 2×10^9/liter and may be below 0.5×10^9/liter. Similar low normal netrophil counts have been described in black Africans, West Indians, and Yeminite Jews. Sporadic cases also occur in other groups. The hallmark of these chronic benign neutropenias is that they occur in the asymptomatic individual and in the absence of other disorders which secondarily may lead to neutropenia. The finding of neutropenia in and of itself is not necessarily pathologic; however, the finding of neutropenia in a patient with recurrent infections usually implies that the neutropenia is in some way operative in the development of the infections.

Neutrophil Functional Defects

Qualitative abnormalities in neutrophil and monocyte-macrophage function impair host defenses despite the maintenance of adequate numbers of phagocytes. Defects can occur in any aspect of phagocytic cell function such that abnormalities of phagocytosis, cell migration, or microbial killing, for example, can lead to impaired host defense and recurrent infection. Primary intrinsic defects of neutrophil function are uncommon, but detailed studies of patients with these disorders have increased our understanding of neutrophil physiology. *Chronic granulomatous disease* of childhood is a disorder mainly occuring in males characterized by susceptibility to infection manifest from early childhood. The increased susceptibility to infection is linked to a severe defect in the ability of the patient's neutrophils to kill ingested bacteria. Chemotaxis and phagocytosis are intact. The microbicidal defect is due to abnormal

postphagocytic oxygen metabolism with reduced production of the reactive oxygen products, hydrogen peroxide and superoxide.

Job's syndrome is manifested by recurrent cold staphylococcal abscesses usually appearing in early childhood, classically in red haired, fair-skinned girls, and associated with hyperextensible joints and atopic dermatitis, although many variants occur. These patients have defective chemotaxis and high levels of serum immunoglobulin E. This syndrome is probably one of a spectrum of disorders characterized by (1) severe or recurrent infections, (2) hyperimmunoglobulin E, (3) defective neutrophil chemotaxis, and (4) manifestations of allergic disease.

The neutrophil enzyme myeloperoxidase accounts for the green color of pus. This enzyme reduces hydrogen peroxide, and in the presence of intracellular halide produces a substance lethal for many species of microorganisms. Neutrophil *myeloperoxidase deficiency* leads to impaired ability to kill certain classes of microorganisms and may be associated with decreased resistance to candida infections, but clinically the syndrome is frequently benign.

Another intrinsic leukocyte defect is the *Chediak-Higashi syndrome*. This is a congenital, autosomal recessive disorder characterized by partial albinism, increased susceptibility to infection, and ultimately widespread lymphoma-like tissue infiltration. Abnormal giant lysosomes are found in many tissues, including the circulating neutrophils of affected patients. The abnormal structure of the neutrophil granules and abnormal degranulation and locomotion account for the defect in microbicidal activity in Chediak-Higashi syndrome.

Functional defects of neutrophils caused by extrinsic or environmental factors are manifested as abnormalities of chemotaxis or phagocytosis. Causes of such defects include abnormalities of the immunoglobulin or complement systems, abnormal electrolyte environment, and drugs and toxins that interact with the leukocyte surface, energy metabolism, or locomotive mechanisms. The common acquired abnormalities of immunoglobulin production are associated with malignant disorders of the lymphoreticular system, such as chronic lymphocytic leukemia and multiple myeloma or with immunosuppressive drug administration. Deficient immunoglobulin production may result in inadequate opsonization of encapsulated organisms that predisposes these patients to pneumococcal infections. Chemotactic and opsonic abnormalities are found in patients with deficiencies of C5 or C3, respectively. The sera of patients with sickle cell anemia are reported to have reduced opsonic activity for pneumococci. Such patients may fail to trigger fully the alternate pathway of complement activiation. This abnormality, combined with the functional asplenia of sicle cell anemia patients, may underlie their enhanced susceptibility to pneumococcal sepsis and meningitis.

A variety of defects of leukocyte locomotion and chemotaxis have been described. Many of these probably are related to abnormalities of the complement system or to serum chemotactic inhibitors. Others probably result from intrinsic abnormalities of the leukocyte cytoskeletal system necessary for locomotion. Leukocyte movement may be impaired in environments of extremely high osmolarity as in the renal medulla in diabetes mellitus.

Pharmacologic doses of corticosteroids are one of the most common causes of an acquired defect in neutrophil function. Other acquired leukocyte microbicidal defects include those found in acute and chronic myeloproliferative disorders and in burn patients. The mechanisms of these defects are unknown and probably vary from patient to patient. Bacterial toxins and severe hypophosphatemia have also been implicated in the production of neutrophil functional abnormalities.

Therapy of the neutrophil dysfunction syndrome usually consists of appropriate antimicrobial drugs. Granulocyte transfusions have been used, but are of unproven benefit.

Monocyte-macrophage Functional Defects

The cells of the mononuclear phagocyte system are derived from bone marrow precursors. The earliest recognizable cell of this series is the monoblast, which progresses to the promonocyte in the marrow and then to the monocyte, which then passes into the circulation where it remains for 6 to 10 hours. Monocytes migrate into the tissues where they develop into macrophages. Macrophages develop special features related to the organs in which they reside. These cells provide the Kupfer cells of the liver, the macrophages lining the sinusoids of the spleen and lymph nodes, and the alveolar and other tissue macrophages forming what is frequently referred to as the reticuloendothelial system. The monocyte-macrophage system serves many important functions. It is the major scavenger of the body for dead or damaged tissue. Monocytes and macrophages have complex interactions with lymphocytes in both humoral and cell-mediated immune responses. The monocyte-macrophage system is also the major cellular defense against facultative intracellular parasites such as tuberculosis and coccidioidomycosis. Macrophages form the epithelioid cells and giant cells observed in granulomatous reactions.

Defective mononuclear phagocyte function has been described in a variety of inherited and acquired disorders. As with neutrophils, deficiencies of immunoglobulins or complement factors lead to defects in monocyte phagocytosis and chemotaxis. Although the major clinical problems in patients with chronic granulomatous disease (CGD), myelo-

peroxidase deficiency, and Chediak-Higashi disease relate to neutrophil dysfunction as described in the preceding section, monocytes from these patients have dysfunctions similar to the neutrophils

Defects of monocyte migration have been described in some patients with the syndrome of chronic mucocutaneous candidiasis, in Chediak-Higashi disease, transiently in some viral infections, and in many patients with various types of cancer. In addition, inhibitors of monocyte chemotaxis have been identified in the serum of some cancer patients. Monocyte migration is depressed following extensive burns and after corticosteroid administration. Defective monocyte microbicidal activity has been described in some patients with lymphoma and myelomonocytic leukemia.

Studies using human alveolar macrophages have disclosed many differences between cells obtained from cigarette smokers and nonsmokers. Morphologically, smoker alveolar macrophages contain a large number of dense smoker inclusion particles. Smoker macrophages have an increased content of certain lysosomal and microsomal enzymes and an increased glucose metabolism. Alveolar macrophages recovered from patients with pulmonary alveolar proteinosis exhibit morphologic and functional evidence of cellular damage. The macrophages from these patients contain giant lipid inclusions and show impaired adherence, chemotaxis, and microbial killing. These defects may explain the increased frequency of opportunistic pulmonary infection in alveolar proteinosis.

In addition to these documented macrophage dysfunction syndromes, defective mononuclear phagocyte function is thought to occur in many other disorders. Patients who fail to control intracellular parasitic infection could be suspected of having defective mononuclear cell function. Thus, patients with lepromatous leprosy, miliary tuberculosis, and disseminated fungal infections may have macrophage dysfunction. In these disorders, however, intrinsic or acquired defects have been inferred, but not proven.

LYMPHOCYTE FUNCTIONAL DISORDERS

T-lymphocytes primarily are responsible for cell-mediated immune reactions, and as such govern delayed hypersensitivity, rejection of foreign grafts, autoimmunity, and play an important role in resistance to certain pathogens such as viruses and fungi. T-lymphocytes play an active role in regulating many aspects of the host defense system through helper and suppressor activities, and through the production of soluble mediators known as lymphokines (e.g., interferon). The B-lymphocytes are responsible for antibody production and antibody-mediated immunity.

T-lymphocyte Disorders

Di George syndrome is a congenital disorder in which there is an abscence or hypoplasia of the thymus and parathyroid glands due to maldevelopment of the third and fourth pharyngeal pouches. Characteristic facies, cardiac malformations, and neonatal tetany also are part of the syndrome. Moderate to severe decreases in T-lymphocytes are seen. These children are prone to viral and fungal infections. Fetal thymus transplantation has led to improvement in some patients.

Dysfunction of T-lymphocytes occurs in some patients with Hodgkin's disease and other lymphoproliferative disorders, in autoimmune disease, and transiently following some viral infections. A severe, prolonged T-lymphocyte dysfunction (*acquired immunodeficiency syndrome*) has recently been recognized in homosexuals and is associated with cytomegalovirus and multiple opportunistic infections as well as a high incidence of Kaposi's Sarcoma.

B-lymphocyte Disorders

Bruton-type infantile agammaglobulinemia is a sex-linked recessive disorder in which B-lymphocytes and plasma cells are lacking and the patient is unable to produce significant quantities of antibodies. The disease usually is manifested during the first year of life.

Acquired agammaglobulinemia or hypogammaglobulinemia can occur in children or adults and is usually an idiopathic process. These patients have a B-lymphocyte dysfunction and are unable to produce normal quantities of immunoglobulins. Defective immunoglobulin production also can occur secondarily in the lymphoproliferative diseases. Multiple myeloma is a neoplastic disorder of plasma cells usually associated with high serum levels of a monoclonal immunoglobulin. The production of normal immunoglobulins in these patients is frequently defective, so that a state of functional hypogammaglobulinemia exists despite high serum levels of globulins.

Patients with these B-lymphocyte and plasma cell disorders are highly susceptible to infections with organisms such as hemophilus and pneumococcus. These organisms have thick capsules and require opsonization (coating) by immunoglobulin in order to be recognized and killed by phagocytic cells.

Combined Immunodeficiencies

Combined T- and B-cell dysfunction can be seen in a variety of clinical settings. A congenital group of disorders known as *severe combined*

immunodeficiency (SCID) occurs in which both cell-mediated and antibody-mediated immunity are markedly impaired. These occur as either x-linked recessive, autosomal recessive, or sporadic cases. The disease in some instances is related to disturbances in purine or pyrimidine metabolism with enzyme deficiencies of adenosine deaminase or purine nucleoside phosphorylase. Patients with SCID manifest profound lymphopenia with reduction or absence of both T and B lymphocytes, absence of cutaneous delayed hypersensitivity, and agammaglobulinemia. Recurrent episodes of infection with bacteria, fungi, and viruses begin within the first few months of life. Pneumocystis carinii, varicella, and rubeola infections are common. Progressive and fatal disease may occur following immunization with vaccinia or BCG. Failure to thrive, diarrhea, and dermatitis are also common. Bone marrow transplantation from a histocompatible sibling donor has been used successfully to treat some of these patients. Fetal liver or fetal thymus transplants also have been tried. Enzyme replacement therapy has also been attempted in patients with known deficiencies.

Ataxia telangiectasia is a familial disorder characterized by cerebellar ataxia, oculocutaneous tenangiectasia, and recurrent sinopulmonary infections. The patients exhibit absence of immunoglobulin A, occasionally increased immunoglobulin E, low levels and dysfunction of T-cells, and impaired cutaneous hypersensitivity.

The *Wiskott-Aldrich syndrome* is a sex-linked recessive immunodeficiency characterized by eczema, thrombocytopenia, recurrent infections, inability to form antibodies to polysaccharide antigens and depressed cell-mediated immunity.

Many primary immunodeficiency diseases do not fit well into one of the specific disease entities noted above and are referred to as *common variable immunodeficiencies*. These patients have variable T- or B-lymphocyte functional deficiencies and their clinical findings reflect the degree and type of dysfunction.

OTHER DISORDERS

Postsplenectomy State

The spleen is an efficient organ for clearing microorganisms and exposing them to phagocytic cells and immune mediators. Persons who have their spleen removed at a young age (less than six years, possibly less than 12 years) have an increased susceptibility to infections. Patients who have their spleen removed for hematologic or immunologic disorders (e.g., thalassemia, Hodgkin's disease) also have an increased risk of infection. Patients with sickle cell disease develop functional asplenia. Whether

splenectomy increases the infectious tendency in otherwise normal adults is still debated, but if it does, the increase in risk is minimal.

Postsplenectomy patients tend to have infections with heavily encapsulated organisms, primarily pneumococcus, but also hemophilus and meningococcus. Infections in these patients have a tendency to progress rapidly to fulminant septicemia and may be lethal unless treated early.

Combined Factors

Certain underlying diseases may have multiple factors contributing to an increased susceptibility to infections. Patients with neoplastic or collagen vascular diseases may have combinations of T-cell, B-cell, and phagocytic cell dysfunctions. Patients with diabetes can have impaired phagocyte and lymphocyte function, as well as poor blood flow which impairs local defenses.

Drug therapy also can be a factor contributing to an increased problem with infections. As mentioned previously many drugs can cause neutropenia, and some also can induce functional disorders of the host defense system. Corticosteroids, for example, can cause lymphopenia and inhibit T-cell, B-cell and phagocyte function; colchicine can inhibit phagocyte activity; and cyclophosphamide can cause cytopenias and inhibit lymphocyte function.

An infection may cause or contribute to abnormalities that impair host defense. Some viral infections, for example, suppress T-cell function and also can produce neutropenia. These abnormalities may lead to secondary bacterial infections.

LOCAL PROBLEMS

A variety of local problems can impair the normal microbial clearing mechanisms. The presence of foreign bodies within the tissues can establish a nidus of infection which may be difficult for the host defense system to eradicate, unless the foreign body is removed. Whenever recurrent or persistant infections occur in patients who have cardiac valvular prostheses, vascular access catheters, intrauterine devices, Foley catheters, or other types of foreign objects, the foreign body must be suspect as the source of infection and strong consideration should be given to removal of the object.

Since the circulation provides access of immunocompetent cells to an infected site and also is the vehicle for antibiotic delivery, poor perfusion of an area causes difficulties in eradication of infections from the area. The

problems with treating leg ulcers seen in sickle cell and other hemolytic anemias and the foot infections seen in diabetes relate in part, to vascular insufficiency.

Disruption of normal epithelial barriers leads to exposure to many organisms that would normally be physically excluded. The increased incidence of sepsis and other infections in patients with extensive burns, exfoliative dermatitis, severe gastrointestinal disease, and decubitus ulcers is, in part, related to a breakdown in the protection of the intact skin or mucosal barriers.

Local problems leading to impaired drainage or clearing of certain tissues can occur. The normal mucosal clearance systems of the respiratory tract are impaired in patients with cystic fibrosis and chronic lung disease. Urine flow is impeded in patients with obstructive lesions in the urinary tract. In these situations, pathogens can more easily become established in the tissues and cause infection.

INABILITY TO ERADICATE INFECTION

Whenever a site of infection is not totally eradicated, it can serve as a constant source for recurrent local or distant infections. Some of the mechanisms by which persistent infections occur have been discussed. Additional mechanisms include the use of suboptimal antibiotic therapy or the development of resistant microorganisms. Whenever repeated infections occur, an effort should be made to determine if the infections are due to relapse of an inadequately treated infection or recurrence due to reinfection.

EVALUATION OF PATIENTS WITH FREQUENT OR OPPORTUNISTIC INFECTIONS

In patients with frequent infection, the type of organism involved may provide a clue to the underlying defect (Table 3). Infections with agents such as Staphylococcus aureus, pseudomonas, E. coli, or other pyogenic bacteria should alert one to possible neutrophil abnormalities. Pneumococcus or hemophilus infections suggest hypogammaglobulinemia or an asplenic state. Viral, fungal, or P carinii infections suggest the possibility of T-cell or macrophage abnormalities. Deficiency of the late components of complement (C6-9) has been associated with recurrent Neisseria (meningococcal and gonococcal) infections. When infections repeatedly occur in a specific area of the body, local problems of blood flow, drainage, or foreign body should be considered. The presence of other diseases (e.g., systemic lupus erythematosus, sickle cell anemia) should be considered in patients with recurrent infections.

A complete blood count (CBC) with differential is indicated in all patients with frequent infections. Neutropenia, lymphopenia, and leukemia can be diagnosed by this simple test. In addition, information

Table 3 **Evaluation of the Patient with Frequent Infections**

- Type of infection
  - Pyogenic (staphylococcus, pseudomonas) → → → consider PMN or complement disorder
  - Heavily encapsulated organisms (pneumococcus) → → → consider antibody or B-cell disorder, or asplenia
  - Viral, pneumocystis, fungal → → → consider T-cell or macrophage disorder
- Site
  - Multiple sites or systemic process → → → consider problem in general host defense
  - Specific local site → → → consider local blood flow or drainage problem, or foreign body
- Look for other underlying diseases
  - Neoplastic
  - Endocrine
  - Collagen vascular
  - Hematologic
- Specific tests[a]
  - Initial screening tests
    - Complete blood count
    - Quantitative immunoglobulin levels
    - Recall skin testing
  - Special tests
    - Quantitation of T- and B-lymphocytes
    - Bone marrow
    - Complement levels
    - Isohemagglutinin levels
    - Phagocyte function studies

[a]Screening test are performed in the initial evaluation, special tests are performed as indicated by the nature of the infections and the results of the initial evaluation.

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Look for other underlying diseases
Neoplastic
Endocrine
Collagen vascular
Hematologic
Specific tests[a]
Initial screening tests
Complete blood count
Quantitative immunoglobulin levels
Recall skin testing
Special tests
Quantitation of T- and B-lymphocytes
Bone marrow
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Phagocyte function studies

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systemic lupus erythematosus, sickle cell anemia) should be considered in patients with recurrent infections.

A complete blood count (CBC) with differential is indicated in all patients with frequent infections. Neutropenia, lymphopenia, and leukemia can be diagnosed by this simple test. In addition, information

regarding the neutrophil response to bacterial infections or the presence of atypical lymphocytes in viral disorders may be obtained.

A bone marrow examination is indicated in patients with neutropenia to distinguish between failure of neutrophil production within the bone marrow and accelerated peripheral blood neutrophil catabolism.

Neutrophil functional assays are not readily available in most hospitals. Specialized laboratories can evaluate a battery of neutrophil functions including chemotaxis, phagocytosis, microbial killing, lysosomal content, and the production of reactive oxygen products. Similar assays can be performed on monocytes. Serum can be analyzed for chemotactic, opsonic, and microbicidal activities.

B-lymphocytes can be enumerated by surface immunoglobulins, Fc receptors, and complement receptors. Serum antibody should be evaluated by obtaining quantitative immunoglobulin levels (IgG, IgM, IgA). Abnormal serum proteins, such as monoclonal paraproteins, can be detected by immunoelectrophoresis. Antibody production also can be evaluated by measuring isohemagglutinin titer and the antibody response to active immunization with diphtheria vaccines. T-lymphocytes can be enumerated by determining the number of cells that form Rosettes with sheep red cells or that react with specific T-cell antibodies. T-cell function can be assessed by response to the mitogen phytohemagglutinin (PHA). Delayed cutaneous sensitivity to a battery of skin test antigens can be used as an in vivo indicator of T-cell function. Many additional lymphocyte studies can be performed to evaluate various lymphocyte subpopulations and other lymphocyte functional activities such as lymphokine production and cytotoxicity, but specialized laboratories are usually required.

Specific serum complement levels can be obtained in most clinical laboratories and should be considered in patients with mucocutaneous infection, phagocyte dysfunctions, or recurrent Neisseria infections.

THERAPY OF PATIENTS WITH FREQUENT OR OPPORTUNISTIC INFECTIONS

The treatment of patients with repeated or opportunistic infections depends on the pathophysiology of the underlying disorder (Table 4). With each febrile episode the patient must be carefully examined and microbial cultures and antibiotic sensitivity studies carried out in order to select the appropriate antibiotic agents. Underlying systemic illnesses should be treated whenever possible. Efforts should be made to correct contributing local factors. *In patients with defective cellular immunity, immunization with live virus vaccines is contraindicated.*

Primary neutropenias are rarely amenable to therapy. Corticosteroids occasionally cause temporary improvement, and lithium carbonate, which may increase the neutrophil count, has been reported to be beneficial in a few cases. Bone marrow transplantation is the treatment of choice in severe aplastic anemia patients in whom a histocompatible sibling donor is available. Drug or toxin exposure should be sought and discontinued if present. White cell transfusions may be beneficial in some infected patients, but in general, leukocyte transfusions are of limited use.

Gammaglobulin injection can be given on a routine basis (every three to four weeks) in patients with severe agammaglobulinemia or hypogammaglobulinemia. Pneumococcal vaccination should be given to patients prophylactically before splenectomy. It also can be given to other patients with recurrent pneumococcal infections; however, it may not be effective in patients with impaired immune responses. Pneumococcal vaccination should not be given routinely to women in the childbearing years because of a risk in inducing antibodies with hemagglutinin activity. Hyperimmuneglobulin can be used in specific circumstances (i.e., zoster immunoglobulin for varicella exposure). In patients with complement deficiencies, transfusion of fresh frozen plasma may be effective. Fetal

Table 4 Therapy of Patients with Recurrent Infections

General
Appropriate antimicrobial agents
Local therapy
Specific
Neutropenia
Discontinue drug or toxic exposure
Consider steroids, lithium, leukocyte transfusions
Consider bone marrow transplant
Complement abnormalities
Fresh frozen plasma
Antibody abnormalities
Gammaglobulin injections
SCID and Di George syndrome
Administer only *irradiated* blood products
Consider bone marrow or thymus transplantation
Frozen irradiated red cells for ADA deficiency
Never give live virus vaccines

thymic transplantations have been used in patients with Di George syndrome, and bone marrow transplantation has been used in some SCID patients. Irradiated frozen red cells have been used as a source of enzyme replacement in SCID patients due to adenosine deaminase deficiency. It is important to note that blood products that are to be given to patients with severe abnormalitites of cell-mediated immunity should first be irradiated in order to avoid the development of graft-vs.-host reactions mediated by transfused lymphocytes.

CASE HISTORY

A 50 year-old man presents with fever, left-sided pleuritic chest pain, and a purulent cough. The chest x-ray shows a left lower lobe infiltrate, and sputum gram stain and cultures demonstrate many *Streptococcus pneumoniae*. His records show that he has had two other episodes of pneumococcal pneumonia in the past 6 months, each time occurring in a different location in his lungs. He also complains that for the past year he has had low back pain, which has been getting worse in the last few months.

Question

1. What kind of host defense problems would you be considering in this man with recurrent pneumococcal infections?

Answer

1. A possible B-cell or immunoglobulin abnormality. In this age group and with the additional history of bone pain, multiple myeloma must be considered.

Laboratory evaluation was as follows: Hg; 10.0 g/dl; Hct: 0.30; WBC: 4×10^9/l (70% PMN, 25% lymphs, 4% monos, 1% eos); serum prot.: 10.3 g/dl (alb. 3.4, glob. 6.6). Serum protein electrophoresis showed hypergammaglobulinemia with a monoclonal spike. Quantitative immunoglobulins showed an increased IgG of 4,000 mg/dl (nl 600-1400), a decreased IgM of 10 mg/dl (nl 50-250), and a normal IgA of 125 mg/dl (nl 121-563). A bone marrow showed markedly increased plasma cells (65%), many of which were abnormal. X-ray films showed multiple punched-out lesions in the spine, ribs, skull, and pelvis. This picture is consistent with multiple myeloma.

Question

2. How would you treat this patient?

Answer

2. (a) Pencillin for his acute infection.
   (b) Treat the myeloma with chemotherapy (see Chapter 10).
   (c) The role of gammaglobulin injections in this setting is uncertain, but they could be tried if recurrent pneumococcal infections continued in the face of myeloma therapy.
   (d) The role of pneumococcal vaccination in patients with impaired immune responses is also unclear (since they may not respond to the vaccination), but vaccination should be given.

Six months later this same patient returns. He has fevers, chills, marked malaise, and is aching all over. He has been receiving chemotherapy with Alkeran, 2 mg daily, and has been on prednisone, 100 mg for the past four days.

Question

3. What problems would you now be considering?

Answer

3. (a) May be a repeat pneumococcal infection still related to decreased immunoglobulin levels.
   (b) Must consider possibility of neutropenia, which could be related to his chemotherapy or myeloma progression.
   (c) Prednisone inhibits neutrophil and lymphocyte function and and compromises his defense systems.

Laboratory evaluation disclosed the following: Hg: 8.2 g/dl; Hct: 0.25; WBC: 1.2×10^9/l (20% PMN, 65% lymphs, 15% monos); platelets: 57×10^9/l. Bone marrow showed a markedly decreased cellularity (20%) in all cell lines. Plasma cells slightly increased (10%). Serum protein 8.5 g/dl (alb. 4.0, glob. 4.5). Blood culture was positive for pseudomonas.

Questions

4. What is the most likely cause of his present infection?
5. What would you do now?

Answers

4. Neutropenia secondary to chemotherapy.

5. Treat with combination antibiotics for pseudomonas coverage (e.g., gentamicin, carbenicillin). The chemotherapy and prednisone should be withheld until infection clears and blood counts normalize. The myeloma appears to be responding so the chemotherapy should be resumed when his WBC normalizes, but at a lower dose and with frequent monitoring to avoid another episode of marrow suppression.

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6

RICHARD CHAMPLIN

Acute Leukemia

The acute leukemias are a heterogeneous group of neoplasms arising from malignant transformation of hematopoietic cells. The clinical manifestations of the leukemias are due to suppression of normal hematopoiesis, infiltration of the malignant cells into tissues, and the metabolic effects of the malignancy. Acute leukemia can be divided into two main forms: acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML). This division is based on morphologic, cytochemical, and immunologic differences in the malignant cells and has profound implications for prognosis and treatment.

Etiology

In most patients, the etiology of acute leukemia is unknown. Hereditary factors play a role in some cases. There is a high incidence of concordance among identical twins if leukemia develops in the first year of life. Families with an excessive incidence of leukemias and other malignancies have been identified. Acute leukemia occurs with an increased frequency in a variety of congenital disorders, such as Down's syndrome, Bloom's syndrome, Kleinfelter's syndrome, and Fanconi's anemia.

Environmental factors are also important in the etiology of acute leukemias. Excessive radiation exposure is associated with increased incidence of both ALL and AML. Exposure to chemical carcinogens such as benzene has been associated with the development of AML. Viruses,

especially C-type RNA viruses, have been implicated in the pathogenesis of acute leukemias in nonhuman primates. There is, as yet, no direct evidence for a viral etiology of acute leukemia in man.

The incidence of acute leukemia is approximately 7 per 100,000 people per year. Acute lymphoblastic leukemia is generally a disease of children and young adults, whereas AML occurs at all ages. There have been several epidemiologic reports of case clustering of acute leukemia within communities and even in successive occupants of the same house. The bulk of evidence, however, indicates that leukemia is not a contagious disease. The incidence is not increased among close contacts, such as marital partners or in the offspring of women who develop leukemia during pregnancy.

Pathophysiology

Acute leukemia is characterized by proliferation of myeloid or lymphoid blast cells. The leukemic cells arise following malignant transformation of a single hematopoietic or lymphoid progenitor, followed by replication and expansion of the transformed clone. There is an apparent arrest in maturation of the leukemic cells at the myeloblast or promyelocyte stage in AML and the lymphoblast stage in ALL. Leukemic cells accumulate primarily due to a defect in the normal process of differentiation to normal mature cells. The leukemic cells infiltrate the bone marrow and cause suppression of normal hematopoiesis resulting in pancytopenia. Leukemic cells enter the peripheral blood and may infiltrate into other tissues such as lymph nodes, spleen, skin, viscera, and the central nervous system.

The pathophysiology of the bone marrow failure in acute leukemia is complex. Anemia is present in more than 90% of patients and results at least in part from physical replacement of the normal erythroid precursors by leukemic cells. Erythropoietin production is normal but the number of erythroid stem cells is reduced. Granulocytopenia and thrombocytopenia probably result from a reduced number of bone marrow precursors. Other mechanisms may also contribute to the bone marrow failure. Humoral factors derived from the leukemic cells that suppress the growth of normal hematopoietic cells have been described. Alternatively, leukemic cells may interfere with the function of the bone marrow microenvironment or supporting structure.

In AML, many of the residual mature cells produced by the bone marrow are derived from the malignant leukemic clone. These cells may not function normally, and clinically significant qualitative abnormalities of granulocytes, erythrocytes, and platelets may result.

Clinical Features

AML and ALL share many clinical features. These are summarized in Table 1. If untreated, acute leukemia is rapidly lethal, with a median survival of only three months.

The initial symptoms of acute leukemia are generally present for less than three months. Patients may complain of manifestations of anemia such as pallor, easy fatigability, and dyspnea with mild exertion. Nausea, vomiting, and weight loss may be present.

Bleeding is a major problem in patients with acute leukemia and may be related to both thrombocytopenia and coagulation abnormalities. Most patients with acute leukemia present with severe thrombocytopenia. Megakaryocytes may be involved in the leukemic process, resulting in abnormal platelet production and function. Petechiae and easy bruisability are commonly present. Spontaneous hemorrhage becomes increasingly common with platelet counts less than 20×10^9/liter and may occur from gingiva, mucous membranes, or visceral sites. Hypofibrinogenemia and circulating anticoagulants may also occur.

Table 1 **Findings at Diagnosis of Acute Leukemia**

	Acute Lymphoblastic Leukemia, % of Patients	*Acute Myeloblastic Leukemia, % of Patients*
Symptoms		
Fatigue	90	90
Fever	70	50
Infection	20	30
Purpura or hemorrhage	50	60
Bone or joint pain	75	25
Weight loss	66	50
Physical findings		
Hepatomegaly	75	50
Splenomegaly	70	60
Lymphadenopathy	75	40
Sternal tenderness	70	65
Petechiae or ecchymoses	50	50
Retinal hemorrhage	10	10
Extramedullary involvement (lung, heart, testis, GI, kidney, CNS)	5	10

Infection is a common complication of acute leukemia. The incidence of infection is inversely related to the level of circulating neutrophils and becomes a major risk in patients with granulocyte counts less than 0.5×10^9/liter. Neutrophils derived from leukemic progenitors may function abnormally, futher compromising host defenses. Common infections in patients with acute leukemia include gingivitis, stomatitis, cellulitis, perirectal abscess, pneumonia, urinary tract infection, and septicemia. Gram-negative bacteria and candida species are the most frequent pathogens.

Hepatomegaly, splenomegaly, or lymph node enlargement due to leukemic infiltration are present in approximately one-half to three-fourths of patients with ALL and a minority of patients with AML at the time of diagnosis. An anterior mediastinal mass is usually present in patients with the T-cell variant of ALL, but this is a rare manifestation in other forms of ALL or in AML. Acute leukemia may infiltrate other tissues such as the skin, lung, eye, nasopharynx, or kidneys. Soft tissue masses of leukemic cells, "chloromas," may occur. Testicular involvement is particularly common in ALL and is a frequent site of leukemic relapse.

Symptoms related to the expanding malignant cell mass such as bone pain and sternal tenderness occur in approximately half of patients with acute leukemia; osteolytic lesions may occur. Joint pains are frequent in patients with acute leukemia and may mimic the presentation of rheumatic fever or rheumatoid arthritis. These findings are associated with leukemic infiltration of the synovia or adjacent bone.

Renal abnormalities may develop from leukemic infiltration, ureteral obstruction by uric acid stones or enlarged lymph nodes, urate nephropathy, or from infectious or hemorrhagic complications. Gastrointestinal symptoms of early satiety, distension, and obstipation may result from organomegaly or from leukemic infiltration of the bowel.

The leukemic cells may infiltrate through the meninges into the subarachnoid space causing leukemic meningitis. The brain or spinal cord parenchyma may also be involved. Neurologic involvement can only rarely be demonstrated at the time of diagnosis, but the central nervous system is a frequent site of relapse, particularly in patients with ALL presenting with white blood counts $>100 \times 10^9$/liter. The first symptoms of leukemic meningitis are usually headache and nausea. Papilledema, cranial nerve palsies, seizures, and altered mentation develop with disease progression and increased intracranial pressure. Patients presenting with these symptoms should be evaluated with computerized axial tomography (CAT) of the brain to exclude intracranial hemorrhage or a mass lesion such as a chloroma. If a mass lesion is not present, a lumbar puncture should then be performed to exclude leukemic meningitis or infection. With leukemic meningitis, the CSF pressure is typically increased and pleo-

cytosis is present. Cytocentrifuge preparations of cerebral spinal fluid characteristically reveal leukemic blast cells, the CSF protein is increased, and the glucose reduced. If circulating blasts are present in the peripheral blood at the time of lumbar puncture, there is a risk of introducing leukemic cells into the cerebral spinal fluid and intrathecal chemotherapy with methotroxate or cytosine arabinoside should be administered.

Laboratory Features

Patients may present with either pancytopenia without circulating blasts or marked leukocytosis. Leukostasis due to intravascular clumping of blast cells may occur and becomes increasingly common with white blood counts $>100 \times 10^9$/liter. These aggregates of blast cells may compromise the microvasculature and lead to hypoperfusion of vital tissues, most commonly lung and brain.

Anemia is typically present with hemoglobin values approximately 10 g/dl at the time of diagnosis. The erythrocytes are generally normochromic/normocytic or macrocytic. The pathogenesis of anemia involves several factors, including decreased production and increased destruction of red blood cells. Most patients with acute leukemia have thrombocytopenia. Qualitative platelet abnormalities are frequently present as well. These patients' platelets may respond abnormally to aggregating agents in vitro, and the template bleeding time is often prolonged out of proportion to the degree of thrombocytopenia.

Patients with acute leukemia may have metabolic abnormalities. Hyponatremia and hypokalemia are frequently present. Hyperuricemia is common due to accelerated turnover of cells. Lactic acidosis may occur rarely in patients with a large burden of leukemic cells. Massive tumor lysis may occur with antileukemic treatment resulting in severe hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, which may lead to acute renal failure. In order to prevent this complication patients should receive allopurinol and intravenous fluids to induce a brisk urine output before receiving chemotherapy.

Diagnosis

The diagnosis of acute leukemia requires the demonstration of leukemic cells in the bone marrow, peripheral blood, or extramedullary tissues. The bone marrow is typically hypercellular with a monomorphic infiltration of leukemic blasts and a marked reduction in normal bone marrow elements. It is critical to distinguish AML from ALL since these two diseases differ markedly in natural history, prognosis, and response to various therapeutic agents. The diagnostic features of each disease will be

discussed separately. Cytochemical characteristics may help to distinguish these two diseases as summarized in Table 2.

Treatment: General Considerations

The treatment for acute leukemia is based on the quantitative characteristics of the malignancy and the principle of fractional cell kill for chemotherapeutic agents. The growth of the leukemic cell population follows a Gompertzian growth curve with near exponential growth at lower cell mass and progressive slowing of the growth rate at high leukemic cell burdens. As shown in Figure 1, the leukemic mass is usually between from 10^{11} to 10^{12} cells or 100 to 1,000 g of tumor at the time of diagnosis. Chemotherapeutic agents produce a fractional cell kill; that is, a fixed fraction of tumor cells is killed with each course of treatment. Most chemotherapeutic agents employed for acute leukemias are capable of a 3 to 4 log kill, resulting in the elimination of 99.9 to 99.99% of the leukemic population. When the leukemic cell mass is reduced below 10^9 cells, leukemia cells can no longer be detected in the blood or bone marrow and the patient is in remission. If no further treatment is given, however, the residual leukemic cells will proliferate leading to relapse. Additional systemic treatment is necessary for patients in remission to further reduce the leukemic cell mass and, ideally, to eradicate the leukemia.

The treatment regimen is divided into several phases. *Remission induction chemotherapy* is the most critical phase. Intensive systemic chemotherapy is administered with the goals of reducing the leukemic cell mass to produce a clinical remission and restoring normal hematopoiesis. After remission is achieved, additional systemic chemotherapy is given to further reduce the leukemic cell mass. It may not be necessary to completely eradicate the leukemia with chemotherapy, since the immune system may be able to eliminate a small burden of residual leukemic cells. Intensive chemotherapy administered immediately following remission induction is referred to as *consolidation treatment*. Lower dose chemotherapy that is generally continued over several years is referred to as *maintenance treatment*. Intensive chemotherapy given six months to several years after remission induction is termed *late intensification*. Another aspect of treatment involves local chemotherapy or radiation to common sites of relapse such as the central nervous system. The value of these forms of treatment for ALL and AML will be discussed separately.

The supportive care of patients with pancytopenia is a critical aspect of the treatment of leukemia. This involves appropriate administration of blood products and management of infections.

It is generally possible to maintain adequate levels of hemoglobin with transfusions of packed red blood cells. Adequate numbers of circulating

Table 2 **Characteristic Cytochemical Reactions in Acute Leukemia**[a]

	Terminal deoxynucleotidal Transferase	*PAS*	*Sudan Black or Peroxidase*	*Napthol ASD Choracetate Esterase*	*Nonspecific Esterase (Lipase)*
ALL	++	− to ++	−	−	−
AML					
M1 undifferentiated	−	−	±	±	±
M2M3 myeloblastic and promyelocytic	−	−	++	+ to ++	
M4 myelomonocytic	−	− to +	+ to ++	++	++
M5 monocytic	−	− to +	+/−	+	++
M6 erythroleukemia	−	+ to ++	−	−	−

[a] −, negative; ±, weakly positive; +, moderately positive; ++, strongly positive.

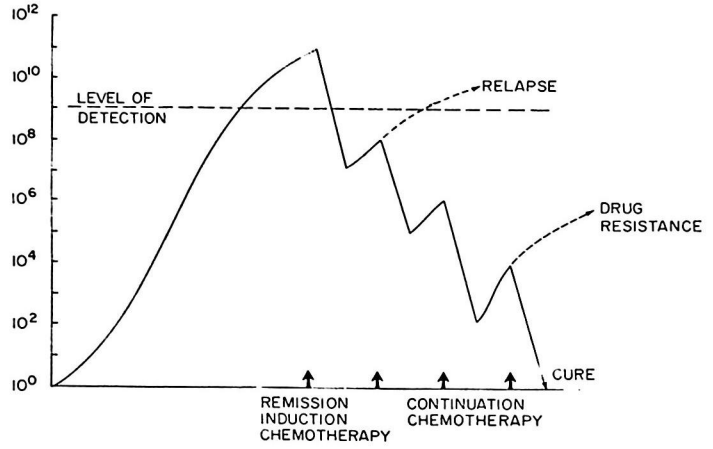

Figure 1 Quantitative considerations in the treatment of acute leukemia. Acute leukemia remains subclinical until the total number of leukemic cells exceeds approximately 10^9. If the leukemic cell burden is reduced below 10^9 with induction chemotherapy, leukemia cannot be detected morphologically and the patient appears in remission. Without further treatment, the leukemic cells proliferate leading to clinical relapse. With further effective continuation (consolidation or maintenance) chemotherapy leukemic cell numbers are further reduced leading to cure. If the leukemia becomes resistant to the chemotherapy employed, regrowth occurs ultimately leading to relapse.

platelets can be initially attained in most patients by transfusions of platelets from unselected (random) donors. Most transfused patients eventually develop antiplatelet antibodies which shorten platelet survival and render the patient unresponsive to further platelet transfusions. The time required for patients to become sensitized and develop antiplatelet antibodies is highly variable. Sensitization may be delayed by the use of platelets obtained from single donors by plateletpheresis rather than transfusing platelet concentrates which are pooled from multiple donors. Patients who fail to respond to transfusions of random donor platelets may respond to platelets from single donors. Indications for the use of platelet transfusions must be individualized. Important variables include the presence of bleeding, infection, splenomegaly, disseminated intravascular coagulation (DIC), and the patient's previous response to platelet transfusions. The

risk of spontaneous hemorrhage is directly related to the degree of thrombocytopenia, and it is generally advisable to maintain the platelet count above 20 X 10^9/liter. A frequently neglected intervention is the administration of anovulatory agents to minimize uterine bleeding in menstruating women with thrombocytopenia.

The role of granulocyte transfusions in the management of granulocytopenic patients remains controversial despite extensive clinical trials. Granulocytes have been administered *therapeutically* in patients with overt infections or *prophylactically* to prevent infections. Patients with granulocyte counts $<0.5 \times 10^9$/liter and documented infections, such as septicemia, pneumonia, perirectal abcess, and cellulitis, have been reported to benefit from *therapeutic* granulocyte transfusions. This is particularly true of patients who fail to respond to appropriate broad spectrum antibiotics. In contrast, no benefit in survival has been demonstrated in patients receiving granulocytes for undocumented infections or for fever alone. *Prophylactic* granulocyte transfusions have decreased the incidence of septicemia in several small series of granulocytopenic patients, but other infections were not effected and overall survival was not improved.

The prevention and treatment of infections is of critical importance in the management of patients with acute leukemia. Most infections in granulocytopenic patients are acquired from the endogenous microbial flora of the skin and gastrointestinal tract. A variety of measures has been evaluated to decrease the incidence of these infections, ranging from oral nonabsorbable antibiotics and reverse isolation to total decontamination in laminar air flow units. Recently oral co-trimoxazole has been proposed for this purpose as well. Although the development of bacterial and fungal infection may be delayed, the efficacy of these modalities in patients with acute leukemia has not been definitively established.

Granulocytopenic patients who develop fever or infections require an intensive diagnostic and therapeutic approach. Fever generally implies a bacterial, fungal, or viral infection. Gram-negative sepsis is common in this setting and may be rapidly fatal. Granulocytopenic patients with unexpected fever or overt infections should be promptly hospitalized and treated for a presumed bacterial infection until a definitive diagnosis is established. A broad spectrum combination of antibiotics, such as an aminoglycoside and a semisynthetic penicillin, should be initially employed and modified when the results of bacteriologic and fungal cultures are available. Patients who respond to antibiotics should receive a full 10- to 14-day course. Systemic candidiasis, aspergillosis, and other fungal infections are also common in granulocytopenic patients and should be suspected in patients who fail to respond to antibiotics. Definitive diagnosis may be difficult, and a therapeutic trial of amphotericin B is often indicated. Surveillance cultures of the skin, nasopharynx, throat, and stool may be useful in identifying patients at high risk of fungal infections.

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children and ranks ninth in adults. The diagnosis of ALL requires demonstratation of excessive numbers of lymphoblasts in bone marrow, peripheral blood, or extramedullary tissues. Leukemic cells in ALL often stain positively with PAS and generally contain substantial amounts of the enzyme terminal deoxynucleotidal transferase (TdT), which can be quantitated biochemically or detected by immunofluorescence. ALL is classified by morphologic criteria into three subtypes in the French-American-British classification. L1 lymphoblasts are a homogeneous population of small blast cells with a thin rim of pale blue agranular cytoplasm and are typically present in childhood leukemia. Most adults present with the L2 variant, in which the lymphoblasts are heterogeneous in size. In the L3 form, the lymphoblasts are homogeneous, with the cytologic appearance of Burkitt's lymphoma, that is, deeply basophilic often with vacuolated cytoplasm.

ALL can be identified and classified on the basis of surface membrane characteristics related to the stage of lymphoid differentiation. Three major subtypes have been identifed. The most common variant is the *null cell* type, in which the cells do not express markers of either T or B cells. This variant comprises approximately 70% of ALL patients. The null cell lymphoblasts generally express a cell surface antigen designated as the common ALL (CALL) antigen. Approximately 20% of cases of ALL have characteristics of mature T cells in which the lymphoblasts form spontaneous rosettes with sheep erythrocytes and display cell surface antigens characteristic of thymic-derived lymphocytes. Patients with T cell ALL are typically male, in the adolescent or young adult age group, and characteristically present with a mediastinal mass and very high white blood counts. In B-cell ALL, the malignant cells exhibit surface membrane immunoglobulin. This variant accounts for less than 5% of lymphoblastic leukemias.

Prognosis in ALL

The two factors that most affect prognosis are age and the white blood cell count at diagnosis. Patients between the ages of three and seven years with white blood counts $<10 \times 10^9$/liter have the best prognosis, with 50 to 80% long-term survival and probable cure with current treatment. Older patients and those with higher white blood counts have a worse prognosis. Less than 20% of adults with ALL are long-term survivors. Males have a worse prognosis than females, due in part to the problem of testicular relapse. T- and B-cell variants of ALL have a poorer prognosis than common null cell leukemia.

Approximately one-half of the patients with ALL will have karyotypic abnormalities with aneuploidy, pseudodiploidy, or hyperdiploidy. Approximately 10% of patients with the clinical diagnosis of ALL will possess the Philadelphia (Ph^1) chromosome, an abnormality typical of chronic myelogenous leukemia. These patients have a poor prognosis.

Treatment of ALL

The treatment of childhood ALL is one of the major successes in modern oncology. Twenty years ago this disease was uniformly fatal and had a median survival of three months. With current therapy, more than half of "good prognosis" groups of childhood ALL now achieve long-term remissions and probable cure. The standard therapy of ALL consists of three phases. Remission induction chemotherapy is followed by central nervous system treatment to prevent relapse of the leukemia in this sanctuary. The third phase is continuation (maintenance) chemotherapy to eradicate residual leukemia.

The goal of remission induction chemotherapy is to eliminate all clinical signs and morphologic evidence of leukemia as well as restoring normal bone marrow function. The intensity of treatment is important, since the duration of remission will be longer if the leukemic cell burden is reduced to the smallest possible fraction. The criteria for complete remission are well established: (1) less than 5% lymphoblasts in the bone marrow, (2) absence of leukemic cells in the peripheral blood and normal peripheral blood counts, and (3) absence of physical findings attributable to extramedullary involvement with ALL.

The combination of vincristine and prednisone induces complete remissions in over 80% of untreated children with ALL. Remission rates exceed 90% if L-asparaginase or daunorubicin are added to the regimen. In addition, the median duration of remission and the proportion of long-term survivors are increased by addition of either of these drugs to vincristine and prednisone. Inclusion of a fourth drug in the regimen does not significantly improve the remission rate or duration and clearly increases the toxicity of treatment. Accordingly, a three-drug combination of vincristine, prednisone, and either L-asparaginase or daunorubicin is recommended. Complete remission is generally achieved within four weeks, with less than 20% of patients showing persistent leukemia in the bone marrow at that time. Some patients with persistent leukemia benefit from two to four additional weeks of treatment with the same or alternate drugs. Failure to achieve remission can be primarily attributed to the development of drug resistance, severe infection, or CNS leukemia.

Once effective remission induction treatment became available, the problems of CNS recurrence became a major obstacle to the control of ALL. Leukemic meningitis was the initial site of relapse in up to two-

thirds of patients who did not receive prophylactic CNS treatment. The rationale for such treatment is based on the hypothesis that circulating leukemic cells infiltrate into the perivascular arachnoid and cerebrospinal fluid early in the course of the disease. Since the drugs used in remission induction chemotherapy for ALL penetrate poorly into the cerebrospinal fluid, these leukemic cells are sheltered from the effects of systemic chemotherapy. Over the ensuing months the leukemic cells may proliferate, giving rise to overt leukemic meningitis. Prophylactic treatment to the central nervous system, instituted immediately after remission induction, has been successful in dramatically reducing the incidence of CNS relapse.

Intrathecal chemotherapy alone is not optimal treatment. Drugs are not evenly distributed throughout the CSF, leaving the intraventricular fluid and perivascular arachoid inadequately exposed to the treatment. Two forms of CNS prophylaxis appear equally effective: cranial-spinal radiation or cranial radiation combined with intrathecal methotrexate. Each treatment reduces the incidence of CNS meningitis from over 40% to less than 10%. Cranial-spinal radiation limits vertebral growth in children and involves radiation to a large portion of the bone marrow compromising tolerance to later chemotherapy. Because of these considerations, most centers employ 2,400 rad whole brain radiation in combination with intrathecal methotrexate 12 mg × 5 doses over two weeks.

Continuation (Maintenance) Chemotherapy

As discussed above, further systemic treatment is required for patients in remission to prevent or delay leukemic relapse. The optimal approach to continuation therapy involves administration of combination chemotherapy given in doses approaching maximum tolerance. The drugs that are effective in inducing remission in ALL have not been useful as maintenance chemotherapy. Currently the combination of 6-mercaptopurine and methotrexate is the most frequently employed maintenance regimen for ALL.

Immunotherapy with administration of nonspecific adjuvants such as BCG ± allogeneic leukemic cells have been evaluated in an attempt to induce immune-mediated cytotoxicity against residual leukemic cells present during remission. Initial studies reported improved duration of remission and survival. Unfortunately, subsequent studies in which patients were carefully stratified according to prognostic factors have not shown any benefit to this approach.

The optimal duration of maintenance chemotherapy is unknown. With

current CNS treatment and maintenance chemotherapy, many patients can discontinue chemotherapy after two to three years and remain in long-term remission. It is prudent to perform a blind testicular biopsy in male patients before discontinuing maintenance chemotherapy, since up to 10% of patients will have occult leukemia present on biopsy. It is currently unknown whether maintenance therapy given for more than three years would further reduce the likelihood of relapse. Since there is currently no method to reliably detect small numbers of residual leukemic cells, there is no objective means to determine when therapy can be safely stopped.

Patients having a poor prognosis with conventional treatment can be identified on the basis of age (adolescents and adults), white blood count ($>50 \times 10^9$/liter), T-cell type, CNS or extramedullary involvement, or failure to achieve a complete remission after four weeks of induction therapy. These patients readily develop drug resistance ultimately leading to the failure of conventional treatment.

Remission rates and survival in adults patients with ALL (>15 years old) are significantly less than for children with the same disease. Remission induction rates are generally between 50 to 80% following treatment with vincristine, prednisone, and L-asparagenase or daunorubicin, and median duration of remission is 10 to 12 months with standard maintenance chemotherapy. Gee and co-workers treated adults and children with a more intensive, multiple-drug chemotherapy program (L-2 protocol) and achieved 78% and 99% remission rates, respectively. Median remission duration for adult patients was two years and a median survival of 33 months. This protocol is highly toxic, however, and has not gained widespread application. Analysis of therapeutic results with current programs reveals that the majority of high risk ALL patients will relapse within one to two years. Certainly new and better chemotherapy programs are required.

Treatment of Recurrent Disease

Leukemia may recur either in the bone marrow or in extramedullary sites. Patients who relapse while receiving maintenance therapy have a very poor prognosis with little possibility for a long-term second remission. Combination chemotherapy with a three- or four-drug regimen including vincristine, prednisone, plus L-asparaginase and/or daunorubicin results in second remission in 50 to 75% of these patients. Remission duration, however, is invariably brief, and subsequent relapse is inevitable. Patients who relapse after discontinuaton of maintenance therapy have a better prognosis. Second remission can be induced in about 90% of these patients. Although most patients will relapse again, a small number will

achieve long-term survival. These patients should have CNS prophylaxis repeated to prevent recurrent disease at this extramedullary site.

Several centers are currently evaluating the use of very high-dose chemoradiotherapy with bone marrow transplantation from an HLA identical sibling donor in high-risk patients with ALL. Preliminary results indicate that one-third to one-half of ALL patients in a second or later remission may be long-term disease-free survivors. This is an intensive form of treatment, associated with a high rate of treatment-related morbidity and mortality. Although there remains a substantial incidence of leukemic relapse following this treatment, bone marrow transplantation is the only form of treatment capable of inducing sustained remissions in this group of patients. Similar programs of high-dose chemoradiotherapy with bone marrow transplantation are currently being evaluated in high-risk patients in first remission.

Treatment of Extramedullary Leukemia

Meningeal leukemia is the most common site of extramedullary relapse. This is primarily seen in patients who did not receive CNS prophylaxis but occurs in about 10% of patients who received prophylactic CNS treatment. Cranial radiation with intrathecal methotrexate alone or in combination with cytosine arabinoside is the standard therapy for CNS leukemia. The dosage commonly used is methotrexate 12 mg and cytosine arabinoside 30 mg given twice per week for six doses. Since the volume of cerebrospinal fluid is relatively fixed after seven years of age, the dose of chemotherapy is not adjusted to body surface area. If leukemic cells persist in the spinal fluid, additional doses are given until spinal fluid samples are free of leukemic cells. Local recurrence of meningeal leukemia is almost inevitable. Median symptom-free interval for successful treatment of CNS leukemia is only about 90 days. Early recurrence tends to be more frequent in patients with high spinal fluid blast counts. Because of this high recurrence rate, maintenance intrathecal therapy given every four to six weeks is recommended.

Testicular relapse has also increased in frequency as patients with ALL survive for longer periods of time. The proclivity for ALL to relapse in the testis is poorly understood. Unlike the CNS, there is no blood-testis barrier to the penetration of chemotherapy. It has been hypothesized that local stromal or immunologic factors may play a role. Testicular relapse may occur during or after cessation of maintenance therapy. The treatment of choice is irradiation of the affected testicle. Bilateral irradiation is probably not indicated, particularly for patients with unilateral involvement confirmed by biopsy. Relapse in the bone marrow and other sites is frequently seen following testicular relapse, justifying the

additional administration of systemic reinduction chemotherapy following testicular radiation.

Complications of Therapy

Chemotherapy-induced myelosuppression and immunosuppression are inevitable side effects of the treatment for ALL. The chemotherapy directed toward the leukemic lymphoblasts also affects normal T and B lymphocytes, resulting in lymphocytopenia. Peripheral blood B cells generally recover to normal levels within three months after treatment is discontinued, but T-cell numbers may remain depressed for up to one year. Infectious complications may occur. Granulomatous infections or pneumocystis carinii pneumonia frequently occur while patients are in remission.

Growth is somewhat retarded during the administration of chemotherapy. Catch-up growth is the rule once therapy is discontinued and most children attain normal height and weight. Oral mucositis, hepatotoxicity, and gastrointestinal tract ulceration may occur in patients receiving methotrexate and 6-mercaptopurine. Sterility may result from treatment with most chemotherapeutic agents and irradiation.

Cranial or craniospinal irradiation has been associated with multiple side effects, including somnolence and low-grade fever. Furthermore, ventricular dilation and interference with brain growth have also been reported. Intrathecal chemotherapy with methotrexate and/or ara-C may result in fever, headaches, vomiting, or meningismus. Chemical arachnoiditis and transient encephalopathy may occur. Rare patients have developed convulsions, dementia, transient paralysis or transverse myelitis. The effect of therapy on neurologic development has become increasingly important as more children achieve long-term, disease free survival. Initial results indicate modest impairment in several neurophysiologic parameters. Further studies are, however, required to evaluate this very important aspect in the treatment of ALL.

Summary of Current Results in ALL

Considerable progress has been made in the treatment of childhood ALL. Complete remissions are achieved in more than 70% of cases using combination chemotherapy. The concept of the CNS as a sanctuary site for leukemic cells is now well recognized. Effective central nervous system prophylaxis has substantially reduced the incidence of CNS recurrence. Maintenance therapy, using combination chemotherapy such as methotrexate and 6-mercaptopurine, prolongs remission duration and results in a median remission duration of 4½ to 5 years in good prognostic groups.

A substantial proportion of these children may actually be cured. Less than 10% of patients who remain in remission for 5 years will suffer later recurrence.

ACUTE MYELOGENOUS LEUKEMIA

The diagnosis of acute myelogenous leukemia requires demonstration of excessive numbers of immature myeloid cells in bone marrow, peripheral blood, or extramedullary tissues. The leukemic cells undergo only limited myeloid differentiation, and a maturation arrest is apparent at the level of the myeloblast or promyelocyte. Several morphologic and cytochemical characteristics distinguish AML from ALL, as shown in Table 2. Myeloblasts are generally larger than lymphoblasts, and they have a lower nuclear:cytoplasmic ratio, discreet nuclear chromatin, and often multiple nucleoli. The presence of Auer rods (abnormal primary granules; see Fig. 2) in the cytoplasm of leukemic cells is pathognomonic of AML. Approximately 10% of patients with AML have these distinctive inclusions. Mature bilobed neutrophils may be present, and dysplastic changes may be prominent in residual granulocytic, erythroid, and megakaryocytic cells. Histochemical stains for myeloperoxidase, α-napthyl-AS-D-chloracetate esterase, nonspecific esterase (lipase), and sudan black are helpful in distinguishing AML from ALL. These stains may be negative, however, in leukemias of undifferentiated cells.

In the FAB classification acute myelogenous leukemia is divided into six groups on the basis of the degree of differentiation and maturation of the predominant cell type: Acute leukemia with minimal myeloid differentiation (M1); AML with differentiation (M2); AML with hypergranular promyelocytes (M3); AML with both granulocytic and monocytic features, myelomonocytic leukemia (M4); monocytic leukemia (M5); and erythroleukemia (M6).

Prognostic Factors in AML

Age, performance status, morphologic diagnosis, LDH level, pretreatment white blood cell and platelet counts, and the presence of splenomegaly, fever, infection, or hemorrhage have been reported to have prognostic importance. The impact of each of these variables on the prognosis is controversial.

Age was previously reported as a significant prognostic factor; elderly patients were much less likely to achieve complete remission. Many hematologists were reluctant to administer intensive chemotherapy to patients older than age 60 and chose low-dose oral treatment with agents such as 6-mercaptopurine given with palliative intent. However, several

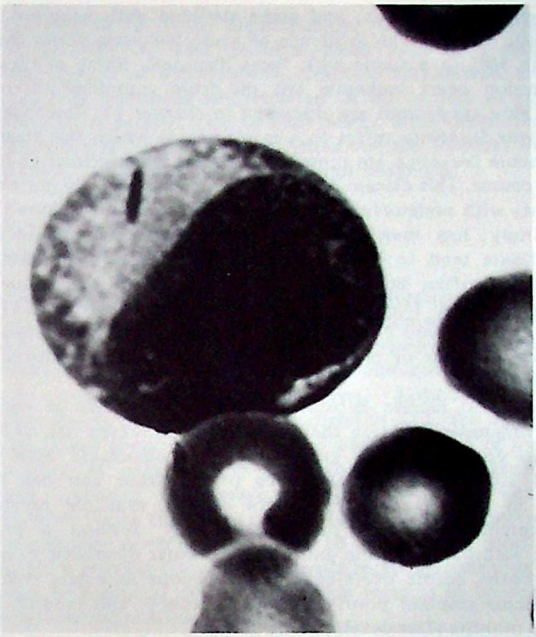

Figure 2 Leukemic cell in acute myelogenous leukemia; note Auer rod.

recent trials have shown no relation between age and remission rate in patients receiving modern intensive regimens. Since the major factor influencing survival is the achievement of complete remission, intensive chemotherapy should be administered to most elderly patients.

The morphologic cell type is of limited prognostic value. Acute progranulocytic leukemia (M3) is associated with disseminated intravascular coagulation, and fatal CNS hemorrhage is a common complication during remission induction chemotherapy for this type of leukemia.

Patients who develop acute leukemia following a previous preleukemic syndrome and those with acute leukemia following cytotoxic chemotherapy have a poor prognosis. The *preleukemic* or *myelodysplastic syndromes* are a heterogeneous group of disorders. The nomenclature describing these disorders is confusing and poorly standardized. Included under this heading are refractory anemia with excessive blasts, chronic

myelomonocytic leukemia, and some patients with acquired idiopathic sideroblastic anemia. The incidence of acute leukemia varies from 10% to more than 50% in patients with these disorders. Many of these patients never develop overt leukemia but die from complications of marrow failure. These syndromes are discussed in chapter 11. *Smouldering acute myelogenous leukemia* refers to a syndrome in which the diagnostic features of acute leukemia are present, but the disease follows an indolent or subacute course. This disease also tends to occur in elderly patients.

Patients with preleukemia or smouldering leukemia respond poorly to chemotherapy; less than 20% of patients achieve complete remission. These patients tend to have prolonged bone marrow aplasia following treatment and often succumb to complications of pancytopenia. Most authors recommend that chemotherapy be withheld until overt leukemia develops. Patients who develop acute leukemia after a preexisting myeloproliferative disorder or paroxysmal nocturnal hemoglobinuria also have a poor prognosis.

Patients who receive cytotoxic chemotherapy with or without concomitant extensive radiation therapy have an increased risk of developing AML. This complication is most commonly associated with prolonged treatment with alkylating agents or procarbazine and has been seen primarily in patients with Hodgkin's disease, multiple myeloma, and ovarian carcinoma. These patients typically develop a preleukemic syndrome with pancytopenia and a hypercellular dysplastic bone marrow several months before overt acute myelogenous leukemia is recognized. These patients respond poorly to chemotherapy, and median survival is only three months after development of AML.

Treatment of AML

The immediate goal in the treatment of AML is to induce a complete hematologic remission. Complete remission is defined as having less than 5% myeloblasts in the bone marrow, absence of myeloblasts in the peripheral blood, normal peripheral blood counts, and resolution of extramedullary involvement.

The drugs active in AML have little therapeutic margin for leukemic cells over normal bone marrow cells. Induction of severe myelosuppression is necessary in order to achieve a complete remission. The two most active drugs are cytosine arabinoside (Ara-C) and daunorubicin. Cytosine arabinoside is a pyrimidine analogue that acts by competitive inhibition of DNA polymerase. Complete response rates of 20 to 40% have been reported with Ara-C given as a single agent. The combination of Ara-C and 6-thioguanine results in a somewhat higher remission rate. Daunorubicin is a cell cycle phase nonspecific agent that acts by intercalating

between the strands of DNA. Daunorubicin produces complete remissions in 30 to 50% of AML patients when used as a single agent. Using a combination of daunorubicin, cytosine arabinoside, and 6-thioguanine, complete responses are reported in 60 to 86% of patients. If residual leukemia is present two to four weeks after chemotherapy, the treatment is repeated up to a total of three courses. Patients who fail to enter remission with this approach have a poor prognosis.

Consolidation, Maintenance, and Intensification Treatments

The quantitative considerations for the treatment of AML are discussed above. Patients morphologically in complete remission may harbor as many as 10^9 viable leukemic cells. Treatment to eradicate the residual leukemia present after remission induction chemothrapy is required to obtain long-term remissions. Although continuation chemotherapy has been shown to be beneficial in ALL, the data in AML is controversial. Many centers have evaluated administration of one to three intensive cycles of consolidation chemotherapy using agents such as daunorubicin, cytosine arabinoside, 6-thioguanine, and 5-azacytidine. Median remission varies from nine months to two years in most series, and five-year disease-free survival ranges from 10 to 25%. The results of these studies suggest a possible benefit for patients receiving consolidation treatment relative to historical controls, but this remains to be confirmed in prospectively controlled clinical trials.

Although uncontrolled studies suggest maintenance therapy improved remission duration, two recent prospective controlled studies reported no benefit for patients receiving maintenance treatment. Late intensification therapy is designed to eradicate residual leukemia. In a recent series, 55% of patients relapsed within one year of intensification, a fraction similar to the expected frequency of relapse in unmaintained patients.

Treatment of Relapsed AML

Most patients who achieve complete remission will ultimately relapse. Reinduction with daunorubicin-cytosine arabinoside combinations is generally unsuccessful, and only 25% of patients achieve second remissions. A large number of drugs have been evaluated alone and in combination in these patients, but results have been disappointing; complete remission rates are uniformly less than 25%. Recently a new agent AMSA (4"-9-acridinylamino-methanesulfon-*m*-anisidide) has been reported to induce complete remission in 28% of patients with relapsed or resistant AML. The duration of second remissions is uniformly brief with

any of these regimens, and median survival is three to six months. Almost all patients will die from a complication of their leukemia.

Central Nervous System Leukemia in AML

With an increasing number of patients entering remission, the incidence of CNS leukemia appears to be increasing. Autopsy studies indicate a 6 to 21% prevalence of meningeal leukemia, and a 10% incidence of clinical involvement has been reported. Cranial irradiation, intrathecal methotrexate, or intrathecal Ara-C are effective in preventing and treating meningeal leukemia. Unfortunately, with available treatment median remission duration has not been prolonged by CNS prophylaxis. This may not be a biologically important leukemic sanctuary in patients with AML, and most centers do not employ routine CNS prophylaxis at this time. Patients who develop meningeal leukemia are treated with cranial radiation (2,400 rad) and intrathecal Ara-C and/or methotrexate. The treatment regimen and potential complications are similar to that described for ALL.

Immunotherapy

The role of immunotherapy is a highly controversial area in the treatment of AML. Immunotherapy has been reported to be capable of suppressing small numbers of tumor cells (10^3-10^5) in experimental animals. As such, it would not be expected to have a role in remission induction treatment, but may be useful to prevent leukemic relapse from a small number of leukemic cells remaining after induction treatment. Unfortunately, clinical trials with immune potentiating agents such as BCG, corynbacterium parvum, or levamisole with or without killed leukemia cells have not shown any benefit in prolonging the duration of remission. There is no convincing data to support the use of currently available immunotherapy in patients with AML.

Bone Marrow Transplantation

Reports from several centers indicate a 10 to 15% five-year disease-free survival in patients with refractory AML who receive very high-dose chemoradiotherapy and allogeneic bone marrow transplantation from an HLA identical sibling. Although only a small proportion of patients benefit, this compares favorably to results obtained with other forms of treatment. These survival figures have been substantially improved when bone marrow transplantation is performed during remission. In patients

transplanted during first remission, the actuarial leukemic relapse rate is less than 15% at four years posttransplant and the overall survival is 50 to 60%. Bone marrow transplantation is an intensive and potentially toxic form of treatment associated with 30 to 50% mortality within one year of transplantation due to infection, graft-versus-host disease, and/or interstitial pneumonitis. Pediatric patients may have better survival than adults, and patients over 45 years of age generally fail to survive the procedure. Bone marrow transplantation appears to offer the best chance for long-term control of AML and should be considered in young patients who have an HLA-identical sibling.

Summary and Future Directions in AML

The last 10 years have witnessed the development of effective induction chemotherapy capable of inducing remission in 65 to 80% of patients and long-term survival in 20%. In the next decade, the focus must be toward measures to prolong the duration of remission as well as developing more effective induction treatment for poor-risk groups. Consolidation treatment with intensive chemotherapy or high-dose chemoradiotherapy and bone marrow transplantation must be evaluated for effect on remission duration and survival. The role of immunotherapy in maintaining remission must be clarified.

Sensitive techniques to detect residual leukemia during morphologic complete remission must be developed to help guide the intensity and duration of treatment. New and effective drugs must be developed with selectivity toward leukemic cells to allow effective treatment yet spare the host from morbidity and mortaltiy attendant to the currently available agents.

CASE HISTORY

A 26 year-old man complains of weakness, diffuse aching bone pain, and easy bruising for one month. He presents to the emergency room with fever and epistaxis for 24 hours. Physical examination reveals a pale young man who appears toxic. Vital signs: temperature 39.4°C, pulse 140, respiration 28, blood pressure 80/50, weight 70 kg. Skin: multiple petechiae over lower extremities, conjuctiva, and buccal mucosa. HEENT, fresh retinal hemorrhages present bilaterally; lymph nodes, nonpalpable; chest-cardiac exam, normal; abdomen-liver, palpable at right costal margin; spleen tip, palpable 1 cm below left costal margin. Rectal exam, nontender stools guaiac 4+ positive. Extremities are normal without edema. Neurologic exam: alert, well oriented, normal mental status, no focal signs. Skeletal exam, mild sternal tenderness. Laboratory, WBC 16 X 10^9/liter,

Hb, 10.2 g/dl; Hct, 0.32; platelet count, 16 X 10^9/liter, differential, 20 segs, 6 bands, 54 lymphocytes, 18 monocytes, 2 eosinophils, 2 nucleated red cells; electrolytes, normal; red cell morphology, macrocytosis; BUN, 21; creatinine, 0.8 mg/dl; urinalysis, normal; chest radiograph and electrocardiogram, normal.

A bone marrow aspirate is performed which reveals a hypercellular marrow with hypergranular promyelocytes comprising more than 80% of the cells. There is a maturation arrest with very few mature granulocytes, erythroid precursors, or megakaryocytes.

Coagulation studies reveal PT, 14.8 sec (control 11.5 sec); PTT, 54 sec (control 32 sec): fibrin degradation products, positive 1:32 dilution; protamine sulfate test, positive.

Question

1. Which of the following laboratory studies should be ordered? (More than one answer may be correct.)
   (a) Blood culture
   (b) Urine culture
   (c) Bleeding time
   (d) Bone marrow - Terminal deoxynucleotidal transferase assay
   (e) Liver spleen scan
   (f) Leukocyte alkaline phosphatase
   (g) Coombs' test
2. Immediate treatment should inlclude
   (a) Intravenous fluids
   (b) Carbenicillin and gentamicin intravenously
   (c) Aspirin for fever
   (d) Blood transfusion 2 units whole blood
   (e) Platelet transfusion 10 units
3. The patient probably has which of the following problems?
   (a) Acute lymphoblastic leukemia
   (b) Aplastic anemia
   (c) Acute monocytic leukemia
   (d) Acute promyelocytic leukemia
4. Which of the following features contribute to disseminated intravascular coagulation in this patient?
   (a) Incompatible blood transfusion
   (b) Sepsis

(c) Thromboplastic material released from leukemic cells
(d) Gastrointestinal bleeding

5. Proper treatment would include which of the following?
   (a) Allopurinol
   (b) Daunorubicin, cytosine arabinoside, and 6-thioguanine chemotherapy
   (c) L-asparaginase vincristine and prednisone chemotherapy
   (d) Heparin
   (e) Amphotericin B

Answers

1. a and b are necessary to determine the nature of the fever and presumed infection.
   c, d, e, f, g, these tests are unnecessary
2. a and b are necessary to treat presumed bacterial infection.
   e platelet transfusion is indicated because of thrombocytopenia and a clear bleeding diathesis due to probable bone marrow failure and DIC.
   c aspirin interferes with platelet function and is contraindicated.
   d blood transfusion is not indicated.
3. d is correct.
4. b and c. DIC is characteristic of acute promyelocytic leukemia.
5. a, b, and d are correct.
   c is appropriate treatment for acute lymphoblastic leukemia.
   e amphotericin B is not indicated.

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7

H. PHILLIP KOEFFLER

Chronic Myeloproliferative Diseases

CHRONIC MYELOPROLIFERATIVE DISEASES

Agnogenic myeloid metaplasia (AMM), chronic myelogenous leukemia (CML), and polycythemia rubra vera (PRV) are the three most frequently encountered myeloproliferative diseases. This chapter discusses AMM and CML and a less frequent myeloproliferative disorder, idiopathic thrombocythemia (IT). PRV is discussed in Chapter 3. Each of the myeloproliferative diseases represents a clonal proliferation of hematopoietic stem cells. Evidence suggests that the granulocytes, monocytes, eosinophils, red cells, and platelets are involved in the abnormal clone at the time the myeloproliferative disease is diagnosed. All of the myeloproliferative diseases have varying degrees of marrow fibrosis. The fibroblasts are not descended from the abnormal clone although the fibroblasts are responsible for the excessive deposition of collagen.

Agnogenic Myeloid Metaplasia

Agnogenic myeloid metaplasia is also known as idiopathic myelofibrosis with myeloid metaplasia. The disease is characterized by marrow fibrosis and clonal expansion of hematopoietic cells in organs outside the bone marrow.

Clinical Features

Agnogenic myeloid metaplasia is a relatively rare disease that affects 0.2 to 2 patients per 100,000 people. The disease occurs most frequently in Caucasians and is rare in Asians and blacks. Most patients are approximately 60 years of age at diagnosis. The disorder is not hereditary and has an equal incidence in both sexes.

Many patients are asymptomatic at the time of diagnosis, and the disease is suspected because of an enlarged spleen or unexplained anemia. The most frequent symptoms at diagnosis are left upper abdominal fullness or early satiety secondary to an enlarged spleen, and malaise and dyspnea secondary to anemia. Other less frequent presenting symptoms include thrombosis or abnormal bruising (or bleeding) secondary to quantitative or qualitative platelet abnormalities and gouty arthritis or uric acid nephropathy or stones secondary to increased production of uric acid.

The major physical findings at diagnosis are listed in Table 1. Almost all patients have an enlarged spleen at diagnosis. Several investigators have estimated that the spleen size increases in AMM patients 1 centimeter below the left costal margin per year, and, therefore, the duration of disease can be correlated with the degree of splenomegaly. However, large variations in splenic growth among patients can occur. Hepatomegaly is present in 70% of the patients at diagnosis, and the enlargement continues for the duration of the disease. The liver is not enlarged without splenomegaly. The patient may develop petechiae and ecchymoses because of abnormal platelet number or function. Hearing can be impaired because of otosclerosis. Gouty arthritis is occasionally present at diagnosis.

Table 1 **Agnogenic Myeloid Metaplasia—Signs at Diagnosis**

Splenomegaly	100%
Hepatomegaly	70
Petechiae or ecchymoses	25
Deafness	5
Gouty arthritis or renal colic	5
Fever	5

SOURCE: Adapted from Ward H, Block M: The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with the myeloproliferative syndrome. *Medicine* 50:357-420, 1971.

Laboratory Findings

The predominant laboratory changes at diagnosis of AMM are summarized in Table 2. The patient is usually anemic with a hemoglobin level of about 10 g/dl. Nucleated red cells are almost always found on the blood smear. Red blood cell (RBC) indices are usually normochromic and normocytic. Anemia is caused by multiple factors, including expanded plasma volume, ineffective erythropoiesis in both the marrow and extramedullary sites, pooling in an enlarged spleen, and decreased RBC survival. White blood cell (WBC) counts are highly variable, with approximately 10-20% of the patients with low counts, 25% with normal counts, and 50% with a leukocytosis. Patients with elevated counts usually have WBC of 10-20 $\times$ 10^9/liter. Occasionally, the WBC count can reach 50-100 $\times$ 10^9/liter. The leukocyte count usually does not change with progress of disease. Often, immature neutrophils are seen in the peripheral blood. Metamyelocytes and myelocytes are most frequently encountered, but blasts occasionally are seen. The presence of immature leukocytes and erythrocytes in the peripheral blood is known as leukoerythoblastosis. Patients with AMM often have mild eosinophilia and basophilia. The leukocyte alkaline phosphatase (LAP) is usually normal or high, as compared to a low LAP in CML.

The platelet count is quite variable at diagnosis. About 40% of the patients have an elevated level and occasionally the concentration is greater than 1,000 $\times$ 10^9/liter. High platelet counts can cause thromboembolic complications. Thrombocytopenia often develops during the late

Table 2 **Agnogenic Myeloid Metaplasia—Laboratory Findings at Diagnosis**

Red blood cells
Hemoglobin: 10 g/dl
Nucleated and teardrop-shaped red cells in blood: 100%
White blood cells
Variable level: mean 12 $\times$ 10^9/liter
Immature forms in blood: 100%
Platelet Count
Low: 20%
Normal: 40%
High: 40%
Bone marrow fibrosis: 100%
Chromosomal abnormality : 40%
Bone roentgenograms
Osteosclerosis: 40%

stage of disease. The platelets vary in size, and many are very large with abnormal granule formation. The platelets frequently do not function normally.

The bone marrow aspirate often has no spicules, and the marrow biopsy specimen shows varying degrees of fibrosis. Hematopoietic bone marrow cellularity ranges from hyperplasia to hypoplasia. The marrow has an abundance of megakaryocytes, and some evidence suggests that these cells may produce a growth factor that stimulates proliferation of fibroblasts. Approximately 40% of AMM patients have a chromosomal abnormality in their hematopoietic cells, but a specific nonrandom chromosomal change has not yet been identified.

Patients frequently have hyperuricemia as a result of the large turnover of purine metabolites from the expanded hematopoiesis. Approximately 10% of the patients develop gouty arthritis or uric acid renal stones during the course of their disease if their serum uric acid production is not controlled.

Osteosclerosis is seen radiographically in 30-70% of the patients. Osteosclerosis is symmetrical in distribution primarily in the axial skeleton and appears radiographically either as increased bone density or as a ground-glass appearance. Bones distal to the elbow and knee are rarely affected. A generalized increase in bone density gives the ribs a very prominent appearance described as a "jail-bar" pattern. Osteosclerosis can cause otosclerosis, resulting in hearing loss.

Extramedullary hematopoiesis is most prominent in the spleen and liver. The lymph nodes usually are not enlarged, but at autopsy they often show active hematopoiesis. Widespread extramedullary hematopoiesis is often present at the end stage of the disease and may occur in abdominal and subcutaneous nodules and pleural and peritoneal involvement, which often produces pleural effusions and ascites. Occasionally, myeloid metaplasia behaves invasively, causing such complications as compression of the spinal cord, ureter, large or small bowel, or blood vessels.

About 5% of the patients develop portal hypertension with esophageal varices and ascites. Occasionally, the cause for the portal hypertension is obvious, such as postsinusoidal obstruction due to hepatic vein thrombosis (Budd-Chiari syndrome) or presinusoidal obstruction due to thrombosis of the portal or splenic veins. Often, the mechanism of portal hypertension is not clear, but possibly the combination of increased blood flow through the portal vein draining the massively enlarged spleen and mild intrahepatic obstruction secondary to hepatic myeloid metaplasia combine to elevate portal pressures.

Differential Diagnosis

The differential diagnosis of AMM is summarized in Table 3. Benzene, irradiation or Thorotrast exposure can cause marrow fibrosis with

Table 3 **Agnogenic Myeloid Metaplasia—Differential Diagnosis**

Toxic bone marrow damage
Benzene, ionizing irradiation, Thorotrast exposure
Infections
Tuberculosis, chronic fungal disease, syphilis
Neoplasms
Breast, prostate, lymphoma, etc.
Bone replacement
Osteopetrosis
Other myeloproliferative diseases
Polycythemia rubra vera, chronic myelogenous leukemia, idiopathic thrombocythemia
Acute myelosclerosis

occasional extramedullary hematopoiesis. Tuberculosis, chronic fungal disease, and syphilis, rarely, can mimic AMM, but the infection is usually chronic, widespread, and easily diagnosed. A variety of neoplasms can invade the marrow and cause marrow fibrosis. Usually the tumor is widely metastatic and easily diagnosed. Occasionally, however, the marrow biopsy specimen will show fibrosis and no obvious tumor. The peripheral blood can have leukoerythroblastosis and teardrop-shaped red cells. Splenomegaly can occur but usually is not as great as in patients with AMM.

Chronic myelogenous leukemia and AMM might be confused early in the course of both diseases. The confusion should not persist. In CML, the LAP is low; in AMM, the LAP is typically normal or high. Only cells from patients with CML contain the Ph^1 chromosome. The WBC counts continue to rise during the progression of CML while they remain stable in AMM. Red cells are teardrop shaped in AMM but not in CML unless the CML marrow becomes markedly fibrotic.

The late (spent or burnt-out) phase of PRV is marked by anemia, thrombocytopenia, myelofibrosis, leukoerythroblastosis, and splenomegaly (*postpolycythemic myeloid metaplasia*). Without the prior history of erythrocytosis, polycythemia rubra vera may be indistinguishable from AMM.

The relationship between IT and AMM is difficult to evaluate. Both diseases have many similarities, and differences are often quantitative rather than qualitative. A patient with IT usually has platelet counts of greater than 1 million, mild anemia, leukocytosis, splenomegaly, and a frequent history of thrombohemorrhagic problems. The marrow often has

mild fibrosis. The IT patients have frequent episodes of thrombosis or hemorrhage.

Acute myelosclerosis is a disease that is rapidly fatal, as contrasted with the chronicity of AMM. Acute myelosclerosis is characterized by pancytopenia, a fibrotic bone marrow with both hyperplasia and increased immaturity of the cells of all three hematopoietic cell lines. Megakaryocytes are particularly prevalent in the marrow. The red cells in the peripheral blood are decreased in number but have no anisocytosis or poikilocytosis as typically seen in AMM. Myeloblasts often are present in the peripheral blood. Splenic enlargement is absent in acute myelosclerosis. The disease is usually refractory to all forms of therapy, including chemotherapy and the patient often dies within 1 to 1½ years.

Therapy

Conservative, supportive management is the therapy of choice for AMM. Treatment does not significantly prolong survival but can decrease morbidity. Thrombocytosis should be treated if the patient has thrombosis or hemorrhage. Occasionally anemia responds to androgen therapy, and an incapacitating spleen should be removed. Leukocytosis rarely, if ever, requires therapy.

Androgen. Androgens should be tried when the patient has severe anemia. A 30-40% response rate is expected. Patients with a normal karyotype may respond to androgens better than patients with a chromosomal abnormality. A variety of androgens are effective, including oxymethalone in an oral, daily dose of 2-4 mg/kg, or several intramuscular agents, like nandrolone decanoate given at a dose of 3 mg/kg per week or testosterone enanthate, 400-600 mg per week. A 3 to 6 month trial of the androgen should be given before considering the patient a failure. Side effects of androgens include hirsutism, fluid retention, increased libido, and with oral administration hepatic dysfunction may occur.

Pyridoxine. Pyridoxine hydrochloride given orally 250 mg per day has been reported to elevate the RBC counts. In one study, approximately 50% of patients receiving the drug responded within 3 months with a rise in the Hb level of at least 3 g/dl. These results have not been confirmed, but a trial of pyridoxine is warranted in severely anemic patients because the drug is not toxic.

Splenectomy. The removal of the spleen may be beneficial. Previously, clinicians felt that splenectomy might remove the only active site of hematopoiesis. This does not appear to be true. The specific indications for splenectomy are not clearly defined, but the procedure should be considered for the following:

1. Severe and persistent left upper abdominal discomfort or early satiety from a massive spleen

2. Severe anemia or thrombocytopenia from sequestration of red cells or platelets in an enlarged spleen
3. Portal vein hypertension with esophageal varices secondary to high blood flow through the portal vein

The morbidity and mortality rate of splenectomy is high when the surgeon is inexperienced, the patient is elderly, or the spleen is massive or adherent to the peritoneum. The morbidity of the procedure can approach 25%, especially including hemorrhage and infection. Platelet counts over 1 million occasionally occur immediately postoperatively and can lead to thrombosis and hemorrhage. For an experienced surgeon, the immediate postoperative mortality rate can be 6-10%.

Hematologists may perform ^{59}Fe ferrokinetic and ^{51}Cr sequestration studies before surgery to evaluate marrow production and splenic sequestration of erythrocytes. However, the studies are difficult to interpret and rarely alter the decision to perform a splenectomy. Rapid enlargement of the liver may occur after splenectomy. This usually does not pose a problem but occasionally can produce pressure symptoms, anemia, and/or thrombocytopenia. Splenectomy does not increase the length of survival but can increase the platelet and erythrocyte counts, decrease portal hypertension, and relieve abdominal discomfort.

Chemotherapy. Chemotherapy is considered when the platelet count is greater than $1{,}000 \times 10^9$/liter or when the spleen is massively enlarged in a patient who is not a candidate for splenectomy. The platelet count usually falls slowly over a period of several weeks to a month after the initiation of chemotherapy. Chemotherapy reduces the spleen size, but this response usually only lasts several months. Usually, an alkylating agent, such as busulfan, cyclophosphamide, or chlorambucil is used. Low doses of the alkylating agent should be used because occasional patients are very sensitive to the drug and develop severe cytopenias. A dose of 2-4 mg per day of busulfan is probably the maximum amount of drug the patient should receive, and weekly blood counts should be performed.

Splenic Irradiation. Splenic irradiation has very few indications. The clinician might consider irradiation if surgery or chemotherapy cannot be used to treat a patient with massive symptomatic splenomegaly. The spleen may decrease in size after irradiation, but this effect usually lasts only several months. The spleen should be irradiated with low doses over a prolonged period of time because patients are occasionally very sensitive to irradiation and can develop severe cytopenias.

Hyperuricemia should be controlled with allopurinol. Glucocorticoids have no proven role in management of AMM.

Survival

Five years usually elapse between the development and the diagnosis

of AMM. After diagnosis, the patient usually survives 4 to 5 years. Therapy does not affect survival but can improve the quality of life. At the time of diagnosis a patient who has no symptoms, anemia, thrombocytopenia, or hepatomegaly has a better prognosis than the patient who is either symptomatic, anemic, thrombocytopenic, or has an enlarged liver. The poor prognosis patients probably are diagnosed later in the progression of the disease rather than having a more fulminant disease. Agnogenic myeloid metaplasia is a chronic, progressive disorder, and many patients die of infection, atherosclerotic heart disease, or bleeding. Approximately, 5-10% of patients develop AML. It is not clear if the leukemia is secondary to the effects of irradiation, or alkylating agents, or represents a predisposition for AML to develop in patients with AMM.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is an acquired, clonal disorder involving the hematopoietic stem cell and is associated with a prominent expansion of the granulocyte compartment. The etiology of this disease is unknown, although there is an increased incidence following exposure to ionizing radiation. Chronic myelogenous leukemia can develop at any age, but the incidence increases steadily throughout life. CML constitutes about 15-20% of all adult leukemias.

Clinical Features and Laboratory Diagnosis

Patients with CML frequently present with malaise, fever, night sweats, weight loss, abdominal fullness, and, occasionally, easy bruising or bleeding. The diagnosis of CML is generally established with ease because of the frequent findings of splenomegaly; leukocytosis with absolute increases in the numbers of basophils and eosinophils; low leukocyte alkaline phosphatase level; and the presence of the Ph^1 chromosome in the majority of the hematopoietic cells.

At the time of diagnosis, the leukocyte count is often near 200×10^9/liter, the platelet count is about 400×10^9/liter, and the hemoglobin concentration is near 10 g/dl. A direct relationship between the leukocyte count and the percentage of immature granulocytes in the peripheral blood is usually present at diagnosis. A 50-60 day cyclic oscillation of the leukocyte and platelet counts occurs in a small proportion of patients.

The bone marrow in CML shows granulocytic and often megakaryocytic hyperplasia with orderly granulocyte maturation, eosinophilia, and basophilia. Marrow myelofibrosis occurs in 30-40% of patients during the course of the disease. The cause of marrow fibrosis is not known. Most studies indicate that the fibroblasts are not part of the malignant (Ph^1-positive) clone.

The diagnosis of CML is aided by two laboratory tests: cytogenetic analysis of the hematopoietic cells and determination of the level of leukocyte alkaline phosphatase. The Ph^1 chromosome is detectable in about 90% of patients with the clinical picture of CML. The Ph^1 chromosome generally is defined as a balanced translocation from the long arm of chromosome no. 22 to the long arm of chromosome no. 9 (22q−, 9q+). About 10% of patients with CML lack the Ph^1 chromosome. These patients are usually older, have a lower leukocyte count, respond poorly to therapy, and have a shorter survival than patients with the Ph^1 chromosome. *Juvenile CML* is a Ph^1-negative form of the disease, which has its peak incidence at age 1 to 2 years. The patients usually have a marked elevation of fetal hemoglobin. The response to therapy is poor, and survival from the time of diagnosis is generally less than 1 year in juvenile CML.

Leukocyte alkaline phosphatase is decreased or absent in the neutrophils of patients with CML at the time of diagnosis. LAP can rise to normal or high levels with infection, inflammation, secondary malignant disease, peripheral-blood remission as a consequence of chemotherapy, or the onset of blast crisis.

Within a mean of 3 years after diagnosis, the relatively benign chronic phase gives way to either an accelerated period of disease or a phase known as blast crisis. The definition of blast crisis is not precise, but this stage is characterized by increasing numbers of blasts in the peripheral blood and bone marrow, by progressive anemia and thombocytopenia, and by a lack of response to therapy. During blast crisis extramedullary myeloblast tumors can develop, especially in bone, lymph nodes, or skin.

Many patients go through a period of malaise, fever, increasing splenomegaly, progressive anemia, basophilia, thrombocytosis, and leukocytosis before blast crisis. This phase, known as the accelerated phase, may be characterized by all the clinical manifestations of blast crisis without an

Table 4 Chronic Myelogenous Leukemia—Features of Accelerated Phase

Malaise
Fever
Lymphadenopathy
Increasing splenomegaly
Progressive anemia
Increasing basophilia, leukocytosis, or thrombocytosis
Elevation of leukocyte alkaline phosphatase
New karyotypic abnormality

increase in the percentage of blast cells in the blood and bone marrow. Manifestations that may herald the onset of the accelerated phase are listed in Table 4. In about 80% of cases, additional chromosomal abnormalities occur in the Ph^1-postive hematopoietic cells as blast crisis develops. The most frequent chromosomal alterations found during this period are double Ph^1, trisomy 8, and isochromosome 17.

Chemotherapy During Chronic Phases of CML

The usual objective of treatment in the chronic phase of CML is to maintain the patient in a symptom-free condition without incurring complications of therapy. Since the symptoms of the disease parallel the peripheral-blood granulocyte count, therapy usually should be designed to maintain the peripheral blood WBC count below 50×10^9/liter.

Many drugs are active in the chronic phase of CML, and these agents yield partial or complete peripheral blood remissions in approximately 75% of patients. Remission is loosely defined as regression of organomegaly and return of the WBC count to nearly normal levels. The decrease in the number of circulating granulocytes is a good indication of the therapeutic effect. As a rule, only rare immature cells are seen in the blood when the leukocyte count is reduced to normal. With treatment, anemia is frequently corrected, and thrombocytosis is controlled. The spleen size usually decreases, parallel with the decrease in the WBC count. The low level of leukocyte alkaline phosphatase occasionally will rise to normal with remission. Although the peripheral blood reverts to normal with therapy, the bone marrow continues to show granulocytic hyperplasia, and the Philadelphia (Ph^1) chromosome is present in dividing marrow cells. Therefore, a true hematologic remission is not achieved.

Survival does not appear to be affected if maintenance therapy is used or if drug treatment is not reinstituted until the leukocyte count has risen to about 50×10^9/liter. Patients who receive intermittent therapy can generally have repeated peripheral blood remissions, and in these patients the disease does not become refractory to therapy until it enters the accelerated or blast phase. Maintenance therapy requires more frequent patient visits to monitor the WBC and platelet counts and to adjust the dosage of drugs.

Busulfan (Myleran) is the alkylating agent most frequently used. The WBC count usually begins to fall 2 to 3 weeks after the initiation of busulfan. Once the leukocyte count begins to decrease, it falls exponentially. Because of the unpredictability of the response to busulfan, the drug should be discontinued when the white cell count is about 20×10^9/liter, since the leukocytes can continue to decrease for as long as 1 month after the cessation of therapy.

Hydroxyurea, an inhibitor of DNA synthesis, has an advantage over other drugs because it can rapidly lower the WBC and platelet counts in CML. Daily maintenance therapy is necessary, however, because leukocyte counts begin to rise almost as soon as the drug is discontinued. Control of CML can also be achieved with mercaptopurine or thioguanine.

Pregnancy does not appear to have an adverse effect on the course of CML. However, 10-20% of pregnant women with CML deliver prematurely, with resulting fetal mortality. Single-agent chemotherapy can be given with relative safety after the first trimester of pregnancy.

Splenic Irradiation

Before the era of chemotherapy, splenic irradiation was used extensively to treat CML. The dose of radiation given varies widely but is generally in the range of 600 to 1,000 rads, delivered in daily fractions of 25 to 200 rads. Radiation treatment controls the leukocytosis and splenomegaly. The duration of control is variable but is usually several months. The spleen eventually becomes totally refractory to this mode of therapy. Splenic irradiation is inferior to busulfan as the sole therapy for CML. Splenic irradiation has been temporarily effective in a few patients in whom the disease has entered an accelerated phase and has become refractory to chemotherapy.

Splenectomy

The indications for splenectomy are not clearly defined. When splenomegaly cannot be controlled with chemotherapy or irradiation, splenectomy may be effective in alleviating abdominal discomfort and decreasing thrombocytopenia and transfusion requirements.

The operative mortality rate is generally less than 3% when splenectomy is performed by an experienced surgeon. A high operative mortality rate occurs in older patients, in patients with the blastic phase of the disease, and in patients with splenic infarcts leading to extensive adhesions. Deaths after splenectomy usually are due to bleeding, infection, complications of anesthesia, and thromboembolism.

Other Treatments

Radioactive phosphorus (^{32}P) is taken up by dividing marrow cells, and it ultimately localizes to bone, where it kills hematopoietic progenitors and thereby lowers the white-cell count. This form of therapy is often useful in older patients and in those who cannot be seen at regular intervals. The ^{32}P may also be given in conjuction with other modes of therapy.

Several investigators have attempted to control the chronic phase of CML by removing peripheral white cells with intensive leukapheresis. Although the reported results are variable, the white-cell count usually

can be reduced only for short periods of time. The spleen will occasionally decrease in size, but the bone marrow does not revert to normal. The technique of leukapheresis is time-consuming and expensive, and red cells and platelets are lost during the procedure. Leukapheresis does not have an advantage over conventional therapy.

Another form of treatment is extracorporeal irradiation of the blood. An arteriovenous shunt permits peripheral blood cells to flow through a radiation source. This procedure is inconvenient for the patient, and it only temporarily lowers granulocyte counts.

Aggressive Chemotherapy and Bone Marrow Transplantation During the Chronic Phase of CML

Recently, investigators have treated patients in the chronic phase of CML with aggressive chemotherapy in the hope of eradicating the leukemic clone. Usually the patients receive the same or more aggressive therapy than used for patients with AML. Overall results with aggressive chemotherapy in the chronic phase of the disease thus far have been disappointing and should be considered experimental.

Bone marrow transplantation allows administration of high doses of antileukemic therapy without lethal hematologic toxicity. Patients with *blastic CML* have received marrow grafts from HLA-identical siblings and from identical twins. Survival has been poor; incomplete engraftment and recurrent leukemia have been major problems. Because the leukemic cells appeared resistant to vigorous chemoradiotherapy in the blastic phase, investigators have attempted transplantation during the chronic phase of CML. Preliminary results in patients with *chronic-phase CML* who received marrow cells from genetically identical twins have been encouraging with most patients free of disease from 1 to 4 years. The results showed that the Ph^1-positive leukemic clone could be eradicated and that the marrow of the patients with chronic-phase CML could be repopulated by normal hematopoietic stem cells. Initial experience in patients with chronic-phase CML who have received marrow transplants from HLA-identical siblings has been encouraging. Several trials are now in progress in which patients with CML in the chronic phase receive marrow transplants from HLA-matched siblings for a comparison of the increased short-term mortality related to transplantation versus the possibility of long-term benefit or cure.

Chemotherapy During Blast Crisis of CML

Chemotherapeutic regimens that are useful in the treatment of AML have been tried in patients with CML in blast crisis, but these programs are

not very effective. Death usually occurs in 2 to 3 months. For a complete remission of AML with the potential for prolonging survival, chemotherapy must be given until bone marrow aplasia occurs. If the cells in the blast crisis of CML appear to be myeloblastic, chemotherapy is usually given to the point of marrow aplasia. The time required for marrow regeneration is variable, and many patients die during this period because of infection or hemorrhage. Experience with aggressive chemotherapy and twin bone marrow transplantation in blastic transformation has provided ample evidence that inducing remissions is considerably more difficult in CML blast crisis than in AML.

A subset of patients with CML in blast crisis who have lymphoblastoid transformation are more sensitive to chemotherapy. About 30% of patients have blast cells with lymphoid characteristics, including the presence of a unique enzyme, terminal deoxynucleotidyl transferase (TdT), that can be detected by biochemical or immunofluorescent techniques. About 50% of these patients with lymphoid blast crisis will respond to chemotherapy.

The therapy for lymphoid blast crisis is vincristine sulfate, 2 mg given intravenously each weak, prednisone, 60 mg per square meter of body-surface are given daily by mouth and usually either daunorubicin or L-asparaginase. At least two to three courses of therapy should be given before the patient's disease is judged refractory to this therapy. It is possible that patients with lymphoid blast crisis represent a special group whose disease is more apt to respond to a variety of chemotherapeutic regimens including hydroxyurea, mercaptopurine, and cytarabine.

As Table 5 shows, approximately 30% of patients will have a partial or complete clearing of leukemic blast cells when treated with a variety of chemotherapeutic regimens with a median survival of 27 weeks. Usually, when patients are no longer responsive to a chemotherapeutic regimen that includes vincristine and prednisone, they are refractory to other chemotherapeutic agents.

The best approach to remission maintenance in CML blast crisis is not known. In patients with lymphoid blast cells, oral methotrexate or hydroxyurea may be effective, and monthly doses of vincristine with or without prednisone appear helpful for prolonging remission.

With increasing survival in blast crisis, meningeal leukemia has become more frequent. In one series, meningeal leukemia developed in over 40% of the patients who had complete remissions. Treatment of meningeal involvement includes intrathecal injections of cytarabine or methotrexate twice weekly. Intrathecal chemotherapy is continued until spinal fluid is clear of leukemic cells; maintenance therapy is given weekly, then twice monthly, and, finally, monthly. Cranial irradiation (2,400 rads) should be given, especially when cranial nerve deficits are present. The role of

Table 5 **Treatment for Blast Crisis of Chronic Myelogenous Leukemia**

Regimen	*No. of Patients*[a]	*Complete Remission (%)*[b]	*Partial Remission (%)*[c]	*Median Survival in Blast Crisis (wk)*	*Median Survival with Treatment Responses (wk)*
Prednisone, vincristine, methotrexate, and mercaptopurine	13	8	15	–	29
Prednisone and vincristine	73	23	11	20	27
Cytarabine and carmustine		6	11	5	–
Cytarabine, carmustine, prednisone, and vincristine	39	3	10	8	–
TRAMPCO[d]	19	42	47	–	29
Hydroxyurea, mercaptopurine, corticosteroids, and vincristine	202	12	22	12	30
Multiple regimens	59	15	19	8	22
Mean	452	14	17	10	27

SOURCE: Reproduced with the permission of Koeffler HP, Golde DW, and the *New England Journal of Medicine*: Chronic myelogenous leukemia—New concepts. *N Engl J Med* 304:1201-1209, 1269-1274, 1981.

[a] Patients' blast cells had myeloid or lymphoid features.

[b] Complete remission is defined as a blast count of less than 5% in bone marrow and normal peripheral blood white counts.

[c] Partial remission is defined as a less than complete decrease in the blood and marrow blast counts.

[d] TRAMPCO consists of thioguanine, daunorubicin, cytarabine, methotrexate, prednisone, cyclophosphamide, vincristine, and L-asparaginase.

prophylactic central nervous system therapy has not been defined.

Some patients have an abrupt onset of blastic transformation of CML with a rapidly rising white cell count. Cerebral or pulmonary vascular leukostasis can occur when the blast count exceeds 100×10^9/liter. These potentially fatal complications require rapid reduction of the blast count. A daily dose of either hydroxyurea or cytarabine may be effective. The patient should be well hydrated, the urine should be alkalinized, and allopurinol should be administered to prevent uric acid nephropathy.

Survival

Median survival in patients with CML is from 36 to 44 months (Table 6). Effective chemotherapy produces hematologic and clinical benefit and may prolong survival. Patients who are treated with busulfan or a comparable drug have a mortality rate of 5-10% during the first year after diagnosis. The mortality rate increases during the second year, and thereafter it is approximately 26% per year. With good management, most patients with CML are free of symptoms until the blastic phase. The median survival in blast crisis is usually 2 months with resistant disease and averages 8 to 12 months if a remission is achieved.

Idiopathic Thrombocythemia

Idiopathic thrombocythemia (IT) has a variety of names, including

Table 6 **Treatment of Chronic Myelogenous Leukemia**

Regimen	*No. of Patients*	*Mean Survival*[a] *MO*
No therapy	52	31
Splenic irradiation	54	28
^{32}P	118	22
Busulfan	78	41
Hydroxyurea	53	45
Dibromomannitol	73	43
Melphalan	33	29
Aggressive therapy	62	65

SOURCE: Reproduced with the permission of Koeffler HP, Golde DW, and the *New England Journal of Medicine*: Chronic myelogenous leukemia—New concepts. *N Engl J Med* 304:1201-1209, 1269-1274, 1981.

[a]Survival is estimated from the time of diagnosis or the beginning of therapy.

essential, hemorrhagic, or primary thrombocythemia. The disease is marked by abnormal proliferation of megakaryocytes.

Clinical Features

The disease is often diagnosed at 50 to 60 years of age and affects both sexes equally. Recurrent hemorrhages and thrombosis occur in most patients with IT. The gastrointestinal tract is the major site of hemorrhage, but bleeding can occur from the urinary tract, subcutaneously (ecchymoses), and excessive bleeding can occur at surgery. Almost any vessel can develop a thrombosis including the splenic vessels causing splenic infarction or portal hypertension, cerebral vessels producing cerebral infarction, leg vessels resulting in gangrene or thrombophlebitis, and penile vessels causing priapism. Approximately 50% of the patients with IT have splenomegaly. The most prominent laboratory finding in patients with the disease is a markedly elevated peripheral blood platelet count, usually greater than $1{,}000 \times 10^9$/liter. The platelets often have a number of qualitative defects. The bone marrow has an abundance of megakaryocytes and, occasionally, increased fibrosis. The patient generally has a leukocytosis of about 20×10^9/liter. The peripheral blood contains bands, metamyelocytes, and rare myelocytes. Anemia is often present, and iron deficiency is frequently present as a result of bleeding. Levels of LAP and uric acid usually are elevated.

Differential Diagnosis

Reactive thrombocytosis is usually temporary, asymptomatic, and responds to treatment of the underlying disorder. Platelet counts usually are not above $1{,}000 \times 10^9$/liter. Frequent causes of reactive thrombocytosis include inflammatory diseases, neoplasia, iron-deficiency anemia, postsplenectomy, and conditions associated with accelerated erythropoiesis like various hemolytic anemias and following acute blood loss.

Idiopathic thrombocythemia is marked by platelet counts greater than $1{,}000 \times 10^9$/liter. The thrombocytosis persists for many months or years and usually only decreases with therapy. The disease is marked by hemorrhage, thrombosis, splenomegaly, and morphologic or functional abnormalities of platelets.

Differentiation between patients with PRV and IT can be difficult except that PRV patients usually have a prominent elevation of the red cell volume.

Treatment

The patient may present with symptoms from a markedly elevated number of blood platelets, such as transient cerebral ischemic attacks, thrombosis, or bleeding. Rapid lowering of the platelet count in symp-

tomatic patients is essential. Peripheral blood plateletpheresis is probably the most effective means to rapidly lower platelet levels. Although formal proof is lacking, clinical experience suggests that the lowering of the platelet count can improve the function of the platelets. More lasting but slower acting therapies are ^{32}P-phosphate or chemotherapy. Management with ^{32}P-phosphate has been used for many years and has very few side effects. Alkylating agents, such as melphalan, chlorambucil, or busulfan, have often been used. These drugs can be given intermittently or the patient can receive a maintenance dose after the platelet count is in the normal range. Preliminary results suggest that daily doses of aspirin and dipyridamole may help prevent thrombosis. The role of prophylactic anticoagulants, such as heparin and coumarin, is not clear. Splenectomy often results in an uncontrollable rise in the platelet count and can result in fatal hemorrhage of thrombosis. Splenectomy is contraindicated in IT.

CASE HISTORY

A 51 year-old man was referred for evaluation of chronic myelogenous leukemia. The disease was diagnosed 38 months ago. At that time the patient had mild splenomegaly, a WBC count of 200×10^9/liter, a LAP score of 2, and his hematopoietic cells contained the Ph^1 chromosome. The patient's disease was controlled with busulfan. Recently, the patient has felt weak, has lost 10 pounds, and, occasionally, has a low grade fever. On physical examination, the patient is found to have enlarged lymph nodes in his neck, axilla, and groin. This is a new finding. His spleen is tender and has rapidly enlarged to 10 cm below the left costal margin, midclavicular line.

The results of laboratory tests revealed that his WBC count is 155×10^9/liter with 25% blasts. The blast cells appear lymphoid with scant cytoplasm and one to two nucleoli per nucleus. The cells are negative for myeloperoxidase, Sudan black, AS-D chloroacetate esterase, and α-napthyl butyrate esterase but are rich in TdT. His hematocrit is 0.25, and his platelet count is 200×10^9/liter. Karyotypic examination reveals that almost all the hematopoietic cells contain both the Ph^1 chromosome and trisomy 8.

Questions

1. The patient has
   (a) Chronic phase of CML
   (b) Blast crises of CML
   (c) An infection
   (d) Acute myelogenous leukemia

2. The therapy of choice
   (a) Busulphan
   (b) 6-Thioguanine, cytarbine, and daunorubicin
   (c) Folate
   (d) Vincristine and prednisone

Discussion

The patient has evolved into the blast crisis of CML. He has developed malaise, fever, enlarging lymph nodes and spleen, elevation of the WBC count which is refractory to busulphan, numerous blast cells in the peripheral blood, and anemia. The Ph^1-positive blast cells have a new karyotypic abnormality. Approximately 80% of patients develop a second karyotypic abnormality when they enter blast crisis. The blast crisis of the patient is lymphoid because the cells appear lymphoid, are not positive with myeloid specific stains and are TdT positive. Nearly 50% of patients with lymphoid blast crisis will respond to vincristine and prednisone. Those patients who respond to therapy will survive approximately 27 weeks.

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8

JEROME E. GROOPMAN

Disorders of Lymphocytes

Lymphocytes are mononuclear leukocytes that function as effectors and regulatory cells for the immune system. Lymphocytes can be classified into two broad groups: T lymphocytes, which are involved in cellular immune responses and regulation of immune reactions, and B lymphocytes, which are involved in humoral immune responses. Human T and B lymphocytes are derived from precursor cells in the bone marrow. The T-lymphocyte progenitors leave the bone marrow and migrate to the thymus, where they develop some of the functional and cell surface characteristics of mature T-cells. These processed lymphocytes then leave the thymus and migrate to the T-cell-dependent areas of peripheral lymphoid tissues (the paracortical areas of lymph nodes and the periarteriolar sheath of the spleen). The mature T lymphocytes enter a pool of long-lived lymphocytes that recirculate from blood to lymph and are believed to be important in maintenance of immunologic memory. B cells develop from precursor cells in the bone marrow and migrate to peripheral lymphoid tissues. After exposure to antigen, B cells differentiate into plasma cells that produce specific antibody. Long-lived "memory" B cells recirculate from blood to lymph and are involved in the anamnestic response to antigen. Mature B cells are predominantly found in the primary follicles and germinal centers of the lymph nodes and spleen.

Lymphocyte subpopulations can be defined by determination of surface marker characteristics (Table 1). The T-cell phenotype is characterized by the formation of rosettes with sheep erythrocytes and the presence of cell-surface antigens that can be detected by specific anti-

Table 1 Characteristics of T and B Lymphocytes

	B Lymphocytes	*T Lymphocytes*
Prevalence in blood (% of total lymphocytes)	5-20%	70%
Surface immunoglobulin	+	−
Fc receptor	+	±
Complement receptor	+	−
Sheep RBC rosette	−	+
Antibody production	+	−
Cell-mediated immunity	−	+

bodies. In addition, subpopulations of T lymphocytes are defined by recently recognized cell-surface antigens. The B-cell phenotype is characterized by the presence of immunoglobulin on the cell surface, a receptor for the third component of complement (C3), and a receptor for the Fc portion of the immunoglobulin molecule. These studies are now widely available and may be useful in the classification of certain immunologic or lymphoproliferative disorders. Normally, approximately 70% of human peripheral blood lymphocytes are T cells, 20% are B cells, and the remaining 10% are called null cells since they do not express the surface markers associated with the T or B lymphocytes. There is considerable variation in the morphology of circulating normal lymphocytes in man. Cell diameter may vary from 7-10 μm; the nuclear chromatin may appear dense and clumped (mature) or have an immature fine reticular appearance and contain a nucleolus. Normal lymphocytes manifest great differences in cytoplasmic color, ranging from pale blue or slate grey to a deep, rich blue color. Some lymphocytes may contain up to six to eight round, azurophilic granules. The nucleus may be perfectly round or slightly indented, and the nuclear to cytoplasmic ratio varies.

LYMPHOCYTOSIS

Relative lymphocytosis refers to an increased percentage of circulating lymphocytes without an absolute increase in lymphocyte number. Absolute lymphocytosis indicates the total number of peripheral blood lymphocytes is increased. The total leukocyte count may be decreased, normal, or increased in absolute lymphocytosis. Some conditions may be accompanied by marked lymphocytosis and leukocytosis, including infectious mononucleosis, toxoplasmosis, cytomegalovirus infections,

Table 2 Nonmalignant Causes of Lymphocytosis

Viral infection
Infectious mononucleosis, cytomegalovirus
Bacterial infection
Pertussis, brucella, tuberculosis
Protozoan infection
Toxoplasmosis, amebiasis
Hypersensitivity reactions
Sulfa, phenytoins
Acute infectious lymphocytosis
Autoimmune disorders

Bordetella pertussis infection, and the lymphocytic leukemias. The normal peripheral blood lymphocyte count varies with age. Absolute lymphocytosis is defined as a peripheral blood lymphocyte count above 9×10^9/liter in infants and young children, 7×10^9/liter in older children, and 4×10^9/liter in adults.

Benign Lymphocytosis

The causes of an absolute lymphocytosis in nonmalignant conditions are shown in Table 2.

Infectious Mononucleosis

Infectious mononucleosis is one of the most frequently recognized causes of benign lymphocytosis. This disease is an acute illness most frequently affecting older children and adults, but occasionally occurring in older patients. It is caused by the Epstein-Barr virus (EBV), a member of the herpes family.

EBV infects B lymphocytes, but the "atypical" lymphocytes that are seen in the peripheral blood are reactive T cells. Atypical lymphocytes are larger than normal lymphocytes and have lobulated, indented, or horseshoe-shaped nuclei that may be eccentrically placed in the cell. The nuclear chromatin is dense, and nucleoli may be present. The abundant cytoplasm of the atypical lymphocyte is often vacuolated, foamy, and basophilic. In normal blood, up to 10% of lymphocytes may appear atypical. Infectious mononucleosis does not occur in persons with previous EBV infection who possess antibody directed against the virus. Thus, presence of antibody correlates well with resistance to infectious mono-

nucleosis infection. High antibody titers against EBV may be found in other disorders, notably Burkitt's lymphoma, Hodgkin's disease, sarcoidosis, and systemic lupus erythematosus. However, the etiologic role of EBV in these other diseases is uncertain.

Epstein-Barr virus is found in the throats of 85% of patients with acute infectious mononucleosis, and virus excretion may persist for over 1 year after the illness. The disease is transmitted by close person-to-person contact by means of saliva. Among close contacts of an infected patient the attack rate is approximately 10%. The incubation period is 30 to 50 days. The estimated incidence of infectious mononucleosis in the general population is about 50 per 100,000, or approximately 100,000 cases per year in the United States. Serologic evidence of prior infection without history of clinical disease is common and probably reflects mild or subclinical infectious mononucleosis. EBV infection is acquired earlier in life in developing countries and in the poorer socioeconomic groups of affluent countries. There is no clear temporal variation in the incidence of the disease, although among college populations the disorder is more frequent in October and from January to April. There have been no epidemics of infectious mononucleosis, although localized outbreaks, such as in a school or hospital, have been recorded.

In patients with infectious mononucleosis the classic triad of fever, cervical adenopathy, and sore throat occurs in more than 80% of cases. Early symptoms, such as headache, malaise, fever, puffy eyes, anorexia, and loss of taste for cigarettes, may precede the development of sore throat and lymph node enlargement. The onset of symptoms is usually gradual. The headache (mainly retro-orbital), photophobia, nausea, and vomiting probably result from a low-grade viral encephalitis. Generally, there are wide daily temperature fluctuations up to 104°F with a peak occurring in the early evening and with a morning remission. An erratic and fluctuating fever course may extend over a period of 2 to 3 weeks. Remission of fever for several days followed by recurrence of fever is unusual in uncomplicated infectious mononucleosis and should suggest a bacterial superinfection, such as streptococcal pharyngitis. Lymphadenopathy is most prominent in the cervical region, although occasionally axillary and inguinal nodes enlarge. The nodes may be mildly tender but are not fluctuant, hard, or fixed. Occipital lymphadenopathy is rare in EBV infections and suggests rubella infection. The lymphadenopathy of infectious mononucleosis usually disappears over the course of a month. Sore throat is generally severe, and dysphagia may occur. There is lymphoid hyperplasia with redness and edema of the tonsils, and in approximately one-third of cases an exudate is present. Such a picture may be readily misdiagnosed as a streptococcal pharyngitis. Whitish, discrete, and pasty superficial lesions that tend to harden and fall off may

be noted on the tonsils. An adherent greenish grey exudate that becomes a confluent membrane and subsequently ulcerates may occur. Rarely, this results in occlusion of the upper airway. Petechiae on the palate occur in approximately one-quarter of the cases near the end of the first week of illness, and in the appropriate setting this finding is highly suggestive of infectious mononucleosis. The petechiae are red, sharply circumscribed, punctate lesions usually located at the border of the soft and hard palates.

Splenomegaly is present in at least one-half of the cases, and the spleen may be tender. Aggressive palpation of the spleen should be avoided, as this may precipitate rupture of the organ. The occurrence of splenic rupture is marked by the sudden onset of pain in the left upper quadrant associated with weakness, syncope, and tachycardia. Splenic rupture is most likely to occur during the third week of illness, and surgical intervention with splenectomy is required when this complication occurs. Enlargement of the spleen is greater in the second and third weeks of the illness. The liver is often tender, and hepatomegaly is demonstrable in about 10% of the cases. Jaundice occurs in approximately 5% of infectious mono mononucleosis patients and is generally mild and uncomplicated. Older patients appear to be predisposed to infectious mononucleosis hepatitis, and this diagnosis should be considered in patients with hepatitis and no evidence for hepatitis A or B infection. The transient maculopapular rash of mononucleosis occurs in approximately 5-10% of patients and is especially common after the administration of ampicillin. Neurologic manifestations, aside from the viral encephalitis, are also rare but include ascending paralysis (Guillain-Barré), an acute cerebellar syndrome, aseptic meningitis, and a radicular neuritis. Atypical lymphocytes may be present in the spinal fluid. Cardiopulmonary manifestations are rare, although both pneumonitis and myocarditis have been reported.

The principal hematologic abnormalities are a lymphocytosis and monocytosis, usually exceeding 50% of the circulating WBC. Atypical lymphocytes account for at least 10% of the circulating leukocytes. The leukocyte count rises during the second week of the illness with counts generally between 10 and 20 $\times$ 10^9/liter. Rarely, patients with infectious mononucleosis may have counts from 30-80 $\times$ 10^9/liter. The absolute lymphocyte count usually exceeds 4.5 $\times$ 10^9/liter, and atypical lymphocytes exceed 1 $\times$ 10^9/liter. Thrombocytopenia and hemolytic anemia are uncommon complications. The hemolytic anemia is associated with a positive direct Coombs test and the presence of cold agglutinins with anti-i specificity.

The most widely used test for diagnosis of infectious mononucleosis is the detection of heterophile antibody in the serum. Agglutination of sheep or horse red blood cells by the patient's serum after the serum has been absorbed with guinea pig erythrocytes is the usual manner in which the

heterophile antibody is determined. The commonly used "monospot test" is a sensitive slide agglutination test using horse erythrocytes and differential absorptions to distinguish other serum antibodies. Over 95% of typical cases of infectious mononucleosis are heterophile antibody positive if followed for a sufficient period of time, although some patients are heterophile negative during the first days of their illness. A titer of 1:40 or greater is considered diagnostic of infectious mononucleosis infection, and a rise in titer indicates recent infection. The absolute titer does not directly correlate with the severity of illness, but mild cases tend to show lower, delayed, or even absent heterophile antibody titers. In addition, heterophile antibody titers have been reported during other viral infections, as well as in serum sickness, lymphomas, and some leukemias, so that a positive heterophile is not diagnostic by itself of infectious mononucleosis. The diagnosis of infectious mononucleosis requires the appropriate clinical, hematologic, and serologic findings.

Specific antibodies against EBV can also be detected. The presence of specific EBV antibody is essential for diagnosis of mononucleosis in heterophile-negative cases. When confronted with a patient having clinical and hematologic features suggestive of infectious mononucleosis but with a negative heterophile test, the tests for antibody directed against cytomegalovirus, rubella, adenovirus, and toxoplasmosis should be done to exclude these diseases. In addition, the patient's serum should be screened for antibody directed against the Epstein-Barr viral capsid antigen.

The morphologic changes in lymph nodes and spleen during the course of infectious mononucleosis are highly variable. There is marked proliferation of B lymphocytes, and even the bone marrow may show a marked increase in lymphocyte number. Biopsy of lymph nodes is not encouraged during the initial workup of a patient with lymphadenopathy and fever if the diagnosis is likely to be infectious mononucleosis. The lymph node pathology during the acute phase of the illness is often very difficult to interpret.

There is no specific therapy for EBV infection. Administration of antibiotics or gamma globulin has no role in the prevention or treatment of the uncomplicated illness. Isolation is not necessary because of the low infectivity in adults. Irrigation with saline is useful for membranous tonsilitis. Patients with significant splenomegaly should avoid straining at stool, heavy lifting, and abdominal trauma that might cause splenic rupture. Corticosteroids may be indicated when severe and potentially fatal complications arise, including (1) central nervous system involvement with impairment of respiratory function; (2) upper airway obstruction, which may require intubation, emergency tonsillectomy, or tracheotomy; or (3) thrombocytopenic purpura with hemorrhage or severe hemolytic anemia. Antibiotics are indicated for superimposed bacterial infection.

Toxoplasmosis

The clinical presentation of *Toxoplasma gondii* infection depends upon the age of the patient and the extent of infection. Immunocompromised adults have recently been recognized as particularly susceptible hosts to this organism. Disseminated toxoplasmosis in the adults presents as dysfunction of the central nervous system, heart, or lungs. Chorioretinitis may be evident as well. An infectious mononucleosis-like syndrome caused by toxoplasmosis is characterized by fever, lymphadenopathy, and atypical lymphocytosis. This syndrome is distinguished from infectious mononucleosis by a negative heterophile antibody, absence of upper respiratory tract symptoms, and the lack of splenomegaly. The diagnosis is made by demonstrating a fourfold rise in titer by indirect immunofluorescence or hemagglutination tests.

Cytomegalovirus

Infection with this virus produces different clinical syndromes according to the age and immunocompetence of the host. Adult immunosuppressed patients may have diffuse pulmonary involvement, commonly in association with *Pneumocystis carinii* infection. Virus may be cultured from urine, buffy coat, or sputum. Corticosteroid therapy, or the development of impaired humoral immunity (hypogammaglobulinemia), appears to predispose particularly to cytomegalovirus (CMV) infection. A syndrome that closely resembles infectious mononucleosis may result from CMV infection: fever, splenomegaly, mild elevation of liver function tests, and atypical lymphocytosis. Occasionally, patients develop a transient rubelliform rash, but pharyngitis is not part of this syndrome. The heterophil test is negative. Diagnosis is made by rising antibody titers to cytomegalovirus or culture of the virus from urine. This syndrome has recently been recognized to follow blood transfusions from donors who presumably carried circulating virus. Despite the presence of complement-fixing antibodies, a patient may continue to harbor cytomegalovirus in his leukocytes, as well as be susceptible to reinfection.

Pertussis

The syndrome of whooping cough caused by *Bordetella petussis* infection in children can result in marked elevations of the absolute lymphocyte count. Usual levels are 15-30 $\times$ 10^9/liter, but counts as high as 50-60 $\times$ 10^9/liter have been reported. The lymphocytes are usually not atypical, and the marked lymphocytosis generally occurs in the first 3 weeks of the illness. The diagnosis should be suspected in an infant with paroxysmal cough, low-grade fever, and lack of significant physical findings. The diagnosis is confirmed by culture of the organism from the

nasopharynx. Pertussis may be confused with acute lymphoblastic leukemia, but the absence of other hematologic abnormalities in pertussis is a helpful differential feature.

Acute Infectious Lymphocytosis

This is a poorly defined syndrome observed in children, teenagers, and young adults. Most of the affected individuals are asymptomatic or have mild diarrhea. The disorder is detected by finding an elevated white cell count in the patient and close contacts. There is a striking elevation of the lymphocyte count averaging 20-30 $\times$ 10^9/liter although levels of nearly 100 $\times$ 10^9/liter have been reported. Circulating lymphocytes are not atypical. The lymphocytosis resolves over a 3 week period, often in association with a transient eosinophilia. No single etiologic agent has been identified in these epidemics, but it is likely that this syndrome results from a variety of enteric viral infections.

Miscellaneous Causes

A mild elevation in the lymphocyte count may be seen in a variety of viral infections, such as measles, mumps, chicken pox, and infectious hepatitis. Certain bacterial infections, such as brucellosis, as well as rickettsial diseases may cause a mild lymphocytosis. Inflammatory diseases, such as ulcerative colitis, are often accompanied by a moderate increase in circulating atypical lymphocytes. Immune thrombocytopenic purpura and autoimmune hemolytic anemia may be associated with lymphocytosis. Both Graves' disease and primary adrenal insufficiency (Addison's disease) are often associated with lymphocytosis. Lymphocytosis occasionally accompanies hypersensitivity reactions to naturally occurring antigens or the sulfa drugs and the phenytoin derivatives.

Malignant Lymphoproliferative Disorders

The causes of neoplastic lymphocytosis are outlined in Table 3. Hodgkin's disease and the non-Hodgkin's lymphomas are discussed in Chapter 9, plasma cell dyscrasias in Chapter 10, and acute lymphocytic leukemias in Chapter 6. The lymphoproliferative disorders are a heterogeneous group of diseases, each resulting from the neoplastic transformation of a normal lymphocyte counterpart in the spectrum of lymphocyte maturation. These diseases have unique clinicopathologic features, but there is also overlap between diseases.

B-Cell Chronic Lymphocytic Leukemia

This is the most common type of leukemia in the Western world. Chronic lymphocytic leukemia (CLL) is generally an indolent disorder that

Table 3 Neoplastic Causes of Lymphocytosis

Chronic lymphocytic leukemia
Non-Hodgkin's lymphomas
Plasma cell dyscrasias
Prolymphocytic leukemia
Hairy cell leukemia
Mycosis fungoides - Sézary syndrome
Acute lymphoblastic leukemia

affects patients over 40 years old. Approximately 95% of the cases of CLL are due to an abnormal proliferation of B-lymphocytes. Typical presenting features include fatigue, malaise, reduced exercise tolerance, and abdominal discomfort due to enlarged organs. The disease is often discovered in an asymptomatic patient during a routine evaluation. Lymphadenopathy and splenomegaly are usually present. As the disease progresses, there may be infiltration of the neoplastic lymphocytes into liver, skin, and, occasionally, the lung and gastrointestinal tract. Skin involvement in patients with CLL may include lymphocytic infiltration of the skin, erythroderma, and exfoliative dermatitis. The erythroderma must be distinguished from Sézary syndrome, which is a chronic pigmented exfoliative erythroderma due to a T-cell cutaneous lymphoma. CLL involving the skin can usually be distinguished from the Sézary syndrome by the histologic appearance of the skin lesions.

Diagnosis of CLL is based on a persistent increase in the number of small mature appearing (well-differentiated) lymphocytes in the blood. This population of neoplastic lymphocytes is monotonous in appearance although morphology may vary greatly among patients. The absolute lymphocyte count ordinarily ranges between 10 and 150 $\times$ 10^9/liter, and there is relatively little fluctuation in the total leukocyte count. The granulocyte, platelet, and erythrocyte counts may be reduced as a result of bone marrow replacement by neoplastic lymphocytes, hypersplenism, or, less commonly, autoimmune hemolytic anemia or immune thrombocytopenia. Hypogammaglobulinemia occurs in all stages of CLL but is more likely to occur as the disease progresses. Hypogammaglobulinemia, particularly when accompanied by granulocytopenia, predisposes the patient to a variety of infections. Less commonly, a monoclonal paraprotein, usually of the IgM variety, may be present in CLL.

The diagnosis of CLL is also suggested by the presence of generalized lymphadenopathy or splenomegaly in association with a persistent absolute lymphocytosis. In an asymptomatic patient without enlargement

of lymph nodes or spleen and a mild lymphocytosis the diagnosis is more difficult. The benign causes of lymphocytosis should be considered. When available, determination of the surface marker phenotype, particularly surface membrane immunoglobulin, may be helpful. Diffuse infiltration of the bone marrow or of enlarged lymph nodes by small lymphocytes is a typical feature. Establishing the diagnosis of CLL is rarely an emergency in an asymptomatic patient, so that repeated observations over the course of months are preferable to an aggressive and invasive diagnostic approach. When anemia, thrombocytopenia, organ infiltration, or recurrent infections are present, there is more urgency to establishing the diagnosis in order to initiate treatment. A useful clinical staging system for CLL is outlined in Table 4.

The dictum *primum no nocere* should be followed in managing patients with CLL. Many patients require no therapy and may be followed for years without specific treatment. Aggressive use of irradiation or chemotherapeutic agents affecting the bone marrow may have a disastrous effect in patients with chronic lymphocytic leukemia. The indications for starting chemotherapy are (1) thrombocytopenia; (2) granulocypenia due to either bone marrow infiltration or splenomegaly; (3) organ dysfunction or discomfort due to lymphadenopathy, particularly in critical areas,

Table 4 **Staging and Prognosis of CLL**

Stage		*Median Survival (months)*
0	Absolute lymphocytosis $>10 \times 10^9$/liter and 40% or more lymphocytes in bone marrow	>150
I	Absolute lymphocytosis + lymphadenopathy	100
II	Absolute lymphocytosis + enlarged liver or spleen or both; adenopathy may or may not be present	70
III	Absolute lymphocytosis + anemia; Hgb <11 g/dl; lymphadenopathy and/or organomegaly may or may not be present	20
IV	Absolute lymphocytosis + thrombocytopenia (platelets $<100 \times 10^9$/dl); lymphadenopathy and/or organomegaly may or may not be present	20

SOURCE: Rai KR, Sawitsky A, Cronkite EP, et al: Clinical staging of chronic lymphocytic leukemia. *Blood* 46:219-234, 1975.

such as the porta hepatis and retroperitoneum; (4) autoimmune hemolytic anemia; and (5) general symptoms, such as increasing fatigue, anorexia, or weight loss, that are believed to be caused by the CLL. Hypogammaglobulinemia is usually not improved by treatment of CLL. The treatment for CLL consists of continuous or intermittent administration of an alkylating agent, usually chlorambucil (Leukeran). Patients with autoimmune manifestations may require prednisone as well. Prognosis is best correlated with stage (Table 4).

T-Cell Chronic Lymphocytic Leukemia

This variant of CLL has only recently been recognized, and it is believed to account for about 5% of all cases of CLL in the United States. Patients with T-CLL may be younger than 40 years of age and have moderate splenomegaly, minimal or no lymphadenopathy, and frequent skin involvement. Mediastinal involvement has not been reported. In contrast to typical CLL, the T-cell variant is associated with normal immunoglobulin levels or polyclonal hypergammaglobulinemia. The natural history of T-CLL is variable, and the optimal therapy has not been established.

Prolymphocytic Leukemia

This variant of CLL may be of either B- or T-cell origin and usually occurs in patients over 60 years old. This disease is characterized by massive splenomegaly with minimal or no lymphadenopathy. The lymphocytes are larger than typical CLL lymphocytes and have a prominent nucleolus. In patients with prolymphocytic leukemia the absolute lymphocyte count tends to be extremely high, usually above 200×10^9/liter. Prolymphocytic leukemia is a more aggressive disease than CLL but may respond to combination chemotherapy.

Hairy Cell Leukemia

Hairy cell leukemia, which has also been called leukemic reticuloendotheliosis, is a lymphoproliferative disorder that has generated much interest. Hairy cell leukemia originates most commonly as a monoclonal proliferation of B lymphocytes, although T-cell variants have been described. Hairy cell leukemia affects young and middle-aged adults and generally presents as splenomegaly without lymphadenopathy. The peripheral blood picture is characterized by pancytopenia and lymphocytosis. Hairy cells are lymphocytes with short projections from the cell membrane. These cells contain the isoenzyme V of acid phosphatase, which is characterized by resistance to inhibition by tartrate. This isozyme is not detected in normal lymphocytes and is rarely observed in other diseases, so that cytochemical stains for tartrate-resistant acid phosphatase

are diagnostically very helpful in hairy cell leukemia. Frequently, the bone marrow cannot be aspirated in patients with hairy cell leukemia.

The course of hairy cell leukemia is generally indolent, and splenectomy is the major modality of therapy. Generally, chemotherapy is tolerated poorly in hairy cell leukemia. For this reason it is particularly important to consider this diagnosis in the spectrum of lymphoproliferative disorders. There is an increased incidence of infections in patients with hairy cell leukemia, and this propensity to infections can be exacerbated by steroid therapy. Steroids should be avoided in hairy cell leukemia at all costs.

Mycosis Fungoides and Sézary Syndrome

Mycosis fungoides is a cutaneous lymphoma derived from helper T lymphocytes. It may present cutaneously as a nonspecific dermatitis (premycotic) or as true dermal lymphoma with eczema, psoriasis, limited or generalized plaques, nodular masses, ulcerative lesions, or an exfoliative erythroderma ("red man" syndrome). When this cutaneous lymphoma is accompanied by circulating lymphoma cells, it is called Sézary syndrome. The Sézary cells are generally large with characteristic convoluted cerebriform nuclei.

Lymphadenopathy is common in mycosis fungoides and may be dermatopathic or due to lymphomatous invasion of the node. Visceral involvement of spleen, liver, lung, and bone marrow is frequent in the advanced phase of the disease.

Prognosis is related to stage. The premycotic stage often lasts several years, but median survival after biopsy diagnosis of true cutaneous lymphoma is about 5 years. Poor prognostic features include lymphadenopathy, visceral involvement, and erythroderma. The presence of circulating Sézary cells per se is not a poor prognostic factor.

Topical chemotherapy and electron beam therapy are effective in treating cutaneous disease. Systemic chemotherapy for visceral disease may be useful.

LYMPHOCYTOPENIA

Absolute lymphocytopenia is defined as a lymphocyte count less than 1.5×10^9/liter in adults and less than 3×10^9/liter in children. Lymphocytopenia may result from decreased production, increased destruction, or actual loss of lymphocytes from the body. Failure of lymphocyte production occurs on a genetic basis in association with abnormalities of the thymus or in widespread bone marrow failure associated with aplastic anemia. Increased destruction of lymphocytes is commonly seen in an iatrogenic setting, such as treatments with adrenocorticotrophic hormone

(ACTH) or glucocorticoids, irradiation, and chemotherapy. Loss of lymphocytes from the circulation occurs in thoracic duct drainage and in states of loss of lymphatic fluid from the intestine due to congenital lymphatic abnormalities, such as intestinal lymphangiectasia, or in acquired states, such as Whipple's disease, and increased venous pressure in severe right-sided heart failure. Lymphocytopenia may occur in patients with malignancies, collagen-vascular diseases, and autoimmune disorders.

LYMPHADENOPATHY

Hyperplasia of lymph nodes and spleen accompanies a variety of infectious, immunologic and neoplastic diseases.

Localized Lymphadenopathy

Localized enlargement of lymph nodes suggests an infectious process in the region drained by these nodes or lymphatic spread of a neoplasm. Generalized lymphadenopathy is characteristic of certain systemic infections or lymphoproliferative neoplasms. Acute bacterial infections, particularly with streptococci, are characterized by enlarged, soft, and tender lymph nodes. There may be overlying erythema and edema of the soft tissues in the area of the affected lymph nodes. Suppurative cervical lymphadenitis is characteristic of tuberculosis (scrofula). Acute lymphadenitis in an unusual site, such as the epitrochlear lymph nodes, should suggest other uncommon causes of acute infectious lymphadenopathy, such as rat-bite fever or tularemia. Cat-scratch disease should be suspected in a patient with localized tender lymphadenopathy and a history of contact with cats. Systemic symptoms and, occasionally, fever may be present, but splenomegaly is uncommon.

The lymphadenopathy associated with chronic infections is characterized by firm and often matted lymph nodes. Syphilis, leprosy, fungal infections, and lymphogranuloma venereum can result in such chronic lymph node enlargement. In such instances, excisional biopsy is required for histologic examination and appropriate cultures to differentiate between infectious and malignant lymphadenopathy.

Enlargement of certain groups of lymph nodes may be associated with particular disease processes. Isolated occipital lymphadenopathy suggests scalp infections. Posterior auricular lymphadenopathy is rare in lymphomas and suggests the diagnosis of rubella. Anterior auricular lymph node englargement may occur in lymphoma but is more frequently associated with infections of the periorbital region and conjunctivae. Anterior cervical, submandibular, or submental lymphadenopathy is seen in lymphoma or carcinoma of the head and neck and infections of the oral

cavity or pharynx. Hard, matted lymph nodes in the supraclavicular fossa indicate metastatic deposits from an intra-abdominal or intrathoracic neoplasm. Left supraclavicular lymphadenopathy suggests spread from an upper abdominal process, whereas right supraclavicular adenopathy suggests a mediastinal process. Enlarged axillary lymph nodes are caused by infections of the upper extremity, particularly cat-scratch disease, sporotrichosis, brucellosis, extragenital syphilis, and pyoderma. Axillary lymphadenopathy is not uncommon in Hodgkin's disease and the non-Hodgkin's lymphomas. Epitrochlear lymphadenopathy is frequently observed in manual laborers. Epitrochlear nodes may be enlarged in sarcoidosis and non-Hodgkin's lymphomas.

Inguinal lymphadenopathy is very common in normal adults due to repeated trauma and infections in the lower extremities and perineum. Veneral diseases, including syphillis, chancroid, gonorrhea, mycoplasma, and herpetic urethritis, cause inguinal adenopathy. Rectal, testicular, and ovarian neoplasms can also spread to the inguinal lymph nodes. When a lymph node biopsy is contemplated in a patient with generalized lymphadenopathy, the inguinal lymph nodes should be avoided unless they appear to be the major site of pathology.

Mediastinal or paratracheal lymph node enlargement is seen in tuberculosis, sarcoidosis, fungal infections (such as histoplasmosis and coccidioidomycosis), lymphomas and metastatic tumors. Rarely, infectious mononucleosis may result in mediastinal lymph node enlargement.

Intra-abdominal or retroperitoneal node enlargement generally indicates a neoplastic process, although infectious mesenteric lymphadenopathy can occur. In non-Hodgkin's lymphomas both retroperitoneal and mesenteric lymph nodes are usually enlarged, whereas, in Hodgkin's disease, involvement is usually restricted to the retroperitoneal nodes.

Generalized Lymphadenopathy

Many systemic illnesses produce generalized lymph node enlargement. Generalized lymphadenopathy occurs in infectious mononucleosis, a number of acute viral infections, secondary syphilis, leptospirosis, salmonellosis, typhoid and paratyphoid fever, tularemia, listeriosis, and diphtheria and may be associated with splenomegaly. Protozoan infections, such as toxoplasmosis and amebiasis, may cause generalized lymphadenopathy.

A clinicopathologic syndrome known as *angioimmunoblastic lymphadenopathy* has been recognized in the last decade. There is often a history of hypersensitivity to drugs, particularly those of the sulfa family and phenytoins. These patients present with generalized lymphadenopathy, hepatosplenomegaly, and various immunologic abnormalities, including

hemolytic anemia and dysproteinemia. Pulmonary infiltrates and skin lesions may also occur. The diagnosis of angioimmunoblastic lymphadenopathy is based on the typical clinical syndrome in association with specific histologic findings in the lymph node biopsy. It is important to distinguish this disorder from malignant lymphoma since cytotoxic chemotherapy may be detrimental in angioimmunoblastic lymphadenopathy.

Collagen-vascular disorders, especially rheumatoid arthritis and systemic lupus erythematosus, commonly are associated with generalized lymphadenopathy. Splenomegaly also occurs in these disorders. The clinical manifestations and lymph node histology in patients with collagen-vascular diseases can lead to confusion with the lymphomas, but the clinical features and serologic tests are usually helpful in making this distinction.

Lymphadenopathy, fever, splenomegaly, hepatomegaly, and rash may result from drug reactions, particularly in patients taking anticonvulsant drugs. Generally, upon suspension of drug therapy, the lymphadenopathy and constitutional symptoms resolve, but cases of late development of lymphoma have been reported.

Idiopathic atypical giant lymph node hyperplasia (Castleman's disease) is characterized by mediastinal, paratracheal or cervical lymphadenopathy without a clear infectious, allergic, or neoplastic cause. Such lymphadenopathy is particularly common in young adults, and the disease is generally self-limited. The diagnosis is suggested by the clinical findings and the histologic appearance of lymph nodes, but other causes of lymphadenopathy must be excluded as this is fundamentally a diagnosis of exclusion.

SPLENOMEGALY

A wide variety of infectious, autoimmune, and neoplastic disorders is associated with an increase in the size of the spleen. The spleen is normally not palpable, so that detection of splenic enlargement on physical examination, often confirmed by a liver-spleen scan, may alert the clinician to a particular disease process. The most frequent disorders associated with splenomegaly are (a) collagen vascular: systemic lupus erythematosus and Felty's syndrome, (b) hemolytic anemias, (c) myeloproliferative diseases, (d) lymphoproliferative diseases, (e) infectious diseases, and (f) portal hypertension.

The term primary or idiopathic hypersplenism is a diagnosis of exclusion that is made only after an exhaustive search for an infectious, autoimmune, or neoplastic etiology. Splenectomy may be required for symptomatic cytopenia due to splenic destruction, sequestration of blood elements or both. Careful, long-term follow-up of such patients is required,

as ultimately a lymphoma or collagen-vascular disorder may become apparent.

CASE HISTORY

An 18-year-old, college freshman has noted malaise, anorexia, and night sweats for two weeks. He owns no pets and has no significant travel history or occupational exposure. On physical exam he appears pale but in no acute distress. BP 105/70, P 90 R 18 T 38°C. No rash or petechiae are visible. His sclerae are slightly icteric, tympanic membranes clear, and pharynx injected without exudate. No palatal petechiae are noted. There is diffuse cervical and axillary adenopathy. The nodes are 1½ X 2 cm, movable, firm, and mildly tender. His heart and lungs are unremarkable. There is a tender liver edge palpated 1 cm below the right costal margin, and a tender spleen 3 cm below the left costal margin. His exam is otherwise normal. Laboratory evaluation includes Hgb 10.5 g/dl Hct 0.32, WBC 10.8 X 10^9/liter, segs 20%, bands 1%, lymphs 68%, monos 11%, platelets 160 X 10^9/liter. Peripheral blood smear shows few spherocytes and many atypical lymphocytes. SMA-12 normal except bilirubin 3.0 mg/dl, direct bilirubin 1.0 mg/dl, alkaline phosphatase, SGOT, SGPT, all mildly elevated. Heterophil positive. Cold agglutinins positive 1:128.

Questions

1. The most likely diagnosis is
   (a) Toxoplasmosis
   (b) Acute lymphoblastic leukemia
   (c) Infectious mononucleosis
   (d) Cytomegalovirus infection
2. The jaundice evident in this patient may result from
   (a) Hemolysis
   (b) Hepatitis
   (c) Gilbert's disease
   (d) Any of the above
3. Lymph node biopsy is indicated to make the diagnosis. True or false?
4. Appropriate therapy for this patient includes
   (a) Analgesics, antipyretics
   (b) High-dose steroids
   (c) Vincristine, prednisone, and L-asparaginase

(d) Sulfa and pyrimethamine
(e) Ampicillin

Answers

1. c
2. d
3. False
4. a

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9

GREGORY SARNA

Hodgkin's Disease and Non-Hodgkin's Lymphomas

Hodgkin's disease and the non-Hodgkin's lymphomas share many common features. They have similar modes of presentation, histologic findings, natural history (when untreated), and response to therapy. The lymphomas are important diseases in terms of incidence and prevalence, and they are valuable prototypes of tumors responsive to chemotherapy and to radiation therapy.

Hodgkin's disease and the non-Hodgkin's lymphomas also have important differences. Biologically, these diseases probably arise as malignant transformations of different cell lines. Clinically, they differ subtly as to patterns of disease presentation, prognosis, and current therapeutic approaches. This chapter will discuss both Hodgkin's disease and non-Hodgkin's lymphomas, with an attempt to compare and contrast these diseases when appropriate.

HODGKIN'S DISEASE

Vital Statistics

The estimated incidence of Hodgkin's disease in the United States in 1981 was 7,100 cases (approximately 1% of cancer incidence and one-third of the incidence of non-Hodgkin's lymphomas). The estimated mortality was 1,700 deaths (approximately 0.4% of cancer deaths and one-eighth of the deaths due to non-Hodgkin's lymphomas). Hodgkin's disease is estimated to be the fourth leading cause of cancer mortality in

males 15 to 34 years and the fifth leading cause in females of that age group.

Pathophysiology

Hodgkin's disease is classified as a malignancy because of its tendency to metastasize and to invade, its response to antineoplastic therapy, its probable monoclonality as revealed by studies of chromosome abnormalities, and its ability to grow in experimental systems, such as the brain of "nude" (athymic) mice.

The cell which appears to be malignant is the Reed-Sternberg cell or its precursor cell, the Hodgkin's cell. The Reed-Sternberg cell is a multinucleate (generally binucleate) cell with prominent nucleoli, often seen in a mirror image or "owl's eyes" configuration. This cell appears to be a cell of the macrophage/monocyte line on the basis of in vitro and in vivo phagocytosis, surface membrane characteristics, and staining properties. The possibility that this cell is of lymphoid lineage, however, has not been totally excluded. The Hodgkin's cell is a mononuclear equivalent of the Reed-Sternberg cell.

Hodgkin's disease tends to arise in a lymph node. It commonly spreads first to contiguous lymph nodes, next to distant lymph nodes and the spleen, and then to the liver and other viscera, particularly lung, bone, pleura, and bone marrow. It may invade parenchymal tissue (commonly lung) adjacent to an involved lymph node and, very rarely, may arise in a viscus.

Hodgkin's disease may be associated with (and presumably cause) immunosuppression. This is predominantly but not exclusively manifest as T-cell dysfunction. Immunosuppression may be reflected by cutaneous anergy, lymphopenia (decrease of both B cells and T cells), and impaired in vitro monocyte and T-cell function.

Related to the immunodeficiency of Hodgkin's disease is the increased incidence and severity of infections caused by opportunistic pathogens, including *Herpes zoster, Herpes simplex Listeria, Pneumocystis carinii, Nocardia, Cryptococcus, Aspergillus,* and *Toxoplasma*. The patient who has been splenectomized or has received splenic irradiation, particularly in childhood, is also at increased risk of infections with *Streptococcus pneumoniae, Salmonella,* and *Neisseria meningitidis*.

Etiology and Epidemiology

The factors that cause Hodgkin's disease are not known. Epidemiologic studies have shown occasional time-space clustering of cases and have shown a slightly increased incidence of Hodgkin's disease in high socioeconomic groups. These and other factors are consistent with an infectious

(presumably viral) etiology with a substantial latency period. The putative infectious agent may be common or ubiquitous, with Hodgkin's disease a rare manifestation of infection, the likelihood of which is influenced by multiple factors, including age of exposure (early exposure being protective). While such an hypothesis has appeal, hard data to support this are lacking and a putative etiologic virus has not been clearly identified.

Histology

Lymph nodes involved with Hodgkin's disease commonly show disruption of normal architecture with a lymphoid or pleomorphic (lymphoid cells, macrophages, eosinophils, plasma cells) infiltrate. Reed-Sternberg cells and Hodgkin's cells are generally seen but may be infrequent.

Hodgkin's disease is commonly subclassified into four histologic types: lymphocytic predominance (10-15%), nodular sclerosis (20-50%), mixed cellularity (20-40%), and lymphocytic depletion (5-15%). Hodgkin's disease of the latter two classes is more likely to be advanced than is disease classed as lymphocytic predominance or nodular sclerosis. For equally advanced disease, however, prognosis is relatively independent of cell type. The diagnosis of nodular sclerosis Hodgkin's disease may be made without Reed-Sternberg cells being seen. The presence of nodules, separated by broad bands of collagen, and of lacunar cells (artifacts of formalin fixation seen as holes with an adjacent Hodgkin's cell) may lead to the diagnosis. Further information regarding these histologic types is found in Table 1.

Table 1 Histologic Subtypes of Hodgkin's Disease

Lymphocyte predominance
Mature lymphocytes with some Hodgkin's and Reed-Sternberg cells; usually in patients <50 years of age with early stage disease
Nodular sclerosis
Broad bands of fibrous tissue divide a lymph node into lymphoid nodules; lacunar cells are seen; most common histology in the 20-30 year-old group; usually mediastinal or supraclavicular involvement
Mixed cellularity
Pleomorphic cellular infiltrate with Reed-Sternberg cells; frequently advanced stage.
Lymphocyte depletion
Transformed lymphocytes, Hodgkin's cells, Reed-Sternberg cells, fibrosis, and necrosis; usually older patients with advanced disease

Clinical Features at Presentation of Disease

Hodgkin's disease usually (≥90%) presents as lymphadenopathy, frequently in supraclavicular or cervical sites. Mediastinal, hilar, axillary, inguinal, and retroperitoneal adenopathy are also often present. Peripheral adenopathy usually is manifest as a palpable or visible swelling that may or may not be painful. Hilar or mediastinal adenopathy may present with cough, dyspnea, superior vena caval obstruction, or pain. Retroperitoneal adenopathy may present with pain, a palpable mass, increased abdominal girth, or lymphedema. In advanced disease, splenomegaly and hepatomegaly may be present. Epitrochlear and popliteal adenopathy are rare but can occur.

Hodgkin's disease may also present with fever, sweats, weight loss, anorexia, weakness, fatigue, and pruritus. Rarely, Hodgkin's disease presents as nephrotic syndrome, hemolytic anemia, immune thrombocytopenic purpura, or alcohol-induced pain.

The age distribution of patients with Hodgkin's disease is bimodal, with the early peak in the 15-30 year range and a later peak in the over-50 years group. There are some differences between the cohorts of younger and older Hodgkin's disease patients. The younger patient is more likely to have mediastinal disease and less likely to have mixed cellularity histology. The younger patient has a better prognosis than an older patient with equivalent disease.

Overall, males are more likely to have Hodgkin's disease than females. However, the incidence of Hodgkin's disease is relatively independent of gender in young adults, and females predominate among the subset of young patients with nodular sclerosis histology.

Diagnosis and Staging

The initial diagnosis of Hodgkin's disease is commonly made by lymph node biopsy. Occasionally, it will be made by pathologic examination of biopsy specimens of other sites, such as liver, spleen, or bone marrow. The presence of Reed-Sternberg cells is nearly diagnostic of Hodgkin's disease. Rarely, however, these cells may be seen in other conditions, such as mononucleosis or a viral illness. Whereas the presence of Reed-Sternberg cells is usually necessary for the diagnosis of Hodgkin's disease, under some circumstances that diagnosis may be reached without such cells being found (see above). The differential diagnosis of Hodgkin's disease is generally the differential diagnosis of lymphadenopathy (see Chapter 8).

In assessing the prognosis and planning the treatment of Hodgkin's disease, it is useful to detemine the extent of disease and classify it by

Table 2 Modified Ann Arbor Staging System

Stage I	Involvement of a single lymph node region (or single extranodal organ [Ie])
Stage II	Involvement of two or more lymph node regions on the same side of diaphragm (or a single extranodal organ plus one or more lymph node group on the same side of the diaphragm [IIe])
Stage III	Involvement of lymph node regions on both sides of the diaphragm (or of a single extranodal organ plus lymph nodes on both sides of the diaphragm [IIIe])
Stage III_1	Stage III disease with infradiaphragmatic disease confined to the upper abdomen (e.g., spleen, splenic hilar nodes, celiac nodes)
Stage III_2	Stage III disease with infradiaphragmatic disease in the lower abdomen (e.g., para-aortic or pelvic nodes); upper abdomen may or may not be involved
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without lymph node involvement

stage. A staging system commonly used is shown in Table 2. It reflects both anatomic extent of disease and symptomatic status. The basic staging scheme is the Ann Arbor classification. A modification of that system is presented here, in which stage III is subdivided into III_1 and III_2 to reflect different patterns of subdiaphragmatic involvement. Useful and recommended noninvasive-staging studies are shown in Table 3. The stage that is assigned on the basis of noninvasive data is called "clinical stage." If a staging laparotomy is performed or if visceral involvement is documented by biopsy, the stage is called "pathologic stage." The question of who should and who should not undergo a staging laparotomy is an evolving issue. The decision is based on an assessment of the chance of surgical findings changing the assigned stage, of the effect of a change in stage on treatment plans, of the risk of a laparotomy, and of the risk of delaying therapy to perform that surgery. One useful approach would be to perform laparotomy in patients of low surgical risk who are in the following categories: (1) clinical stage $IIIA_1$; (2) supradiaphragmatic disease of clinical stage IB or IIB; or (3) supradiaphragmatic disease of clinical stage IA or IIA with either mixed cellularity or lymphocytic depletion histology. A staging laparotomy should include biopsies or representative

Table 3 **Recommended Staging Studies**

	Hodgkin's Disease	*Lymphoma*
Physical exam	+	+
Chest x-ray	+	+
Liver-spleen scan	+	+
Bone scan	+	+
Lymphangiogram	+	Optional
Abdominal computed tomography	Optional	+
Bone marrow aspirate and biopsy	+ in patients otherwise stage III, or with B symptoms, or with hematologic abnormalities	+
Staging laparotomy	+ in patients otherwise stage IB, IIB, or $IIIA_1$; also in patients Stage IA or IIA with left supraclavicular disease or with mixed celluarity or lymphocyte depletion histology	0
Others (gallium scan, abdominal ultrasound, chest tomography, IVP, IVC-gram, liver biopsy)	Optional	Optional

para-aortic and pelvic lymph nodes and of any other suspicious lymph nodes, splenectomy, and liver biopsies (e.g., one wedge and two needle biopsies). An oophoropexy (moving the ovaries out of a likely radiation field) should be considered in a woman of childbearing age. A surgical bone marrow biopsy would be an optional procedure. From pathologically staged series, it appears that the breakdown of Hodgkin's disease by stage at presentation is roughly 10-15% stage I, 40-50% stage II, 25-35% stage III, and 10-15% stage IV.

Course and Treatment

Hodgkin's disease if untreated, is fatal, with a median survival of less than 2 years (patients of all stages) and with 5-year survival less than 10%.

With current therapeutic regimens, median survival (patients of all stages) approaches 15 years. Therapy and prognosis are largely related to stage.

For stage I or II disease, radiation therapy is the treatment of choice. Generally, supradiaphragmatic disease is treated with a "mantle" field of irradiation (cervical, supraclavicular, subclavicular, axillary, hilar, and mediastinal lymph nodes) with or without additional infradiaphragmatic irradiation. Stage I or II infradiaphragmatic disease is generally treated with an inverted Y field (para-aortic, splenic and pelvic nodes) with or without a mantle field. The extent of radiation given will vary with the sites of disease involvement. Doses delivered are usually in the 4,000 to 4,500 rad (40-45 gray) range.

Overall survival and relapse-free survival after radiation therapy would be roughly 90% and 80% respectively for stage I disease, and 80% and 70 respectively for stage II disease. Factors denoting a poorer prognosis within these stages include bulky disease, multiple sites of involvement in Stage II disease, "B" symptoms, age $\geqslant$49 years, and possibly extranodal extension of disease.

For stage III_1A disease, total nodal radiation therapy (mantle and inverted Y) would be the treatment of choice, with roughly 80% survival and 70-80% relapse-free survival beyond 5 years. For stage III_2 A disease, results with radiation are poorer in many institutions, (roughly) 60% survival and 40-50% relapse-free survival); chemotherapy alone or chemotherapy plus irradiation may be preferable. For IIIB disease, radiation therapy results in roughly 40% survival and 30% relapse-free survival beyond 10 years, and chemotherapy alone seems superior. Stage IV disease is not treated effectively by irradiation and should be treated with chemotherapy.

Patients who relapse after treatment with radiation therapy can frequently be treated effectively with chemotherapy, although extensive radiation may impair bone-marrow tolerance of chemotherapy and may make the safe delivery of effective doses difficult.

Multiagent (combination) chemotherapy is superior to sequential single agent chemotherapy as initial chemotherapy for advanced Hodgkin's disease. Combination chemotherapy improves survival, disease-free survival, and cure rates when compared with sequential single agents. The most extensively tested effective combination regimen is MOPP (nitrogen *m*ustard, *o*ncovin, *p*rednisone, and *p*rocarbazine) (Table 4). When used as initial chemotherapeutic treatment for advanced Hodgkin's disease, MOPP produces a 70-80% complete response rate with overall survival roughly 50-60% and overall disease-free survival roughly 40-50% at 10 years. A satisfactory course of treatment would include a minimum of six monthly cycles of MOPP and would extend two cycles beyond the time that a complete remission is achieved. There are some data to suggest that MOPP

Table 4 **The Mopp Regimen**

Regimen Components	*Administration of 28-Day Cycle*															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14.....28		29(1)
M (nitrogen mustard) 6 mg/m^2 IV	x							x								
O (oncovin [vincristine]) 1.4 mg/m^2[a] IV	x							x								x
P (procarbazine) 100 mg/m^2 PO	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
P (prednisone) 40 mg/m^2 PO[b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x

[a] Upper limit of single dose=2 mg.
[b] Given only on the first and fourth cycles.

alternating with another four-drug regimen (ABVD: *a*driamycin, *b*leomycin, *v*elban, *d*acarbazine) or MOPP followed by low-dose adjuvant radiation therapy to previously involved sites may be superior to MOPP alone in preventing relapse. The combining of full dose radiation and full dose chemotherapy for disease that otherwise would be treated with irradiation alone (stages I to IIIA) is not warranted as there is no clear improvement in survival. Both acute and delayed morbidity (particularly the risk of acute leukemia) are increased by the use of combined modality therapy.

Patients treated with MOPP to a compete remission who subsequently relapse are likely to respond again to MOPP if they have been disease-free off chemotherapy for 1 year or more. They are unlikely to respond to that regimen if they have been disease-free 6 months or less. Some of the patients who fail MOPP will respond to ABVD or an alternative non-cross resistant regimen. Responses to secondary chemotherapy are frequently of short duration but are sometimes durable. The optimal approach in MOPP failures is not yet clear.

NON-HODGKIN'S LYMPHOMAS

Vital Statistics

The estimated incidence of non-Hodkin's lymphomas in the United States in 1981 was 23,000 (2.8% of cancer incidence) and the estimated mortality was 13,200 deaths (3.1% of cancer deaths).

Pathophysiology

The non-Hodgkin's lymphomas are malignancies of lymphoid cells. Because Hodgkin's disease is probably of monocyte/macrophage rather than lymphoid origin, it is likely that Hodgkin's disease, biologically, is *not* a lymphoma. Thus, the use of the term "non-Hodgkin's" to modify lymphomas may be unnecessary.

Lymphomas are a heterogeneous group of diseases. As lymphoid cells differentiate from the putative lymphoid stem cell to mature T cells, mature B cells, and plasma cells, malignancy can occur at any point. Malignancy of the primitive lymphoid cells presumably presents as acute lymphoblastic leukemia or as an analogous form of lymphoma, the lymphoblastic lymphoma. Malignancies of the most mature cells encompass such entities as chronic lymphocytic leukemia, diffuse well-differentiated lymphocytic lymphoma, and, perhaps, mycosis fungoides. A number of lymphomas are derived from cells between these extremes of maturation.

A majority of lymphomas are of B-cell origin. B-cells are antibody producing lymphocytes normally found in lymphoid follicles of lymph nodes, spleen, and tonsils, in the medullary cords of lymph nodes, and in the bone marrow or blood. Lymphomas of T-cell origin are derived from thymus-processed lymphocytes active in cell-mediated immunity and normally found in the thymus, paracortical regions of lymph nodes, splenic white pulp, blood, and bone marrow. Rare lymphomas lack evidence of B- or T-cell differentiation and are considered undifferentiated or null cell lymphomas. The truly histiocytic neoplasms (originating from the monocyte/macrophage line) include monocytic leukemia, malignant histiocytosis and, probably, Hodgkin's disease and multifocal eosinophilic granuloma. The term *histiocytic lymphoma*, however, is often broadly used, referring to malignancies of true lymphoid cells that appear similar to histiocytes under light microscopy.

Lymphomas, like Hodgkin's disease, may spread by contiguity to adjacent lymph nodes. The lymphomas are more likely than Hodgkin's disease, however, to disseminate hematogenously or to spread noncontiguously, with "skip areas," through the lymphatic system.

Immunosuppression (cutaneous anergy, hypogammaglobulinemia, lymphopenia, impaired mitogen response) and opportunistic infections may occur with lymphomas but are less prominent than with Hodgkin's disease.

Etiology and Epidemiology

While a specific etiology cannot be determined for most cases of lymphomas, certain contributing factors have been recognized. Viral infection is a clear etiologic factor in a number of experiemental (primarily murine) lymphomas. In man, Burkitt's lymphoma is closely linked to infection with Epstein-Barr virus. Immunodeficiency (e.g., due to congenital immunodeficiency syndromes or due to immunosuppression in renal transplantation), autoimmune disease (particularly Sjögren's syndrome, possibly mediated by decreased suppressor T-cell activity), chronic immunostimulation, drug reactions (e.g., diphenylhydantoin), premalignant lymphoproliferative disorders (α-chain disease, angioimmunoblastic lymphadenopathy), and Kaposi's sarcoma all may predispose to lymphoma. Chromosomal abnormalities have been found in a variety of lymphomas.

Histology

The lymphomatous lymph node, like the lymph node involved with Hodgkin's disease, shows disruption of normal architecture and an

infiltration with mononuclear cells. The lymphomatous infiltration tends to be less pleomorphic than in Hodgkin's disease; it is usually monomorphic or dimorphic. Reed-Sternberg cells are absent. Capsular invasion is common. The cellular infiltrate is composed of cells that look like well-differentiated or poorly-differentiated lymphocytes or cells that look more like histiocytes than lymphocytes.

There are multiple classification systems for lymphomas. Medical literature before the 1960s tended to classify lymphomas as lymphosarcoma, reticulum cell sarcoma, and giant follicular lymphoma. These classes were too broad and too vaguely defined to be useful.

The Rappaport classification scheme (Table 5) now modified from the original to separate lymphoblastic lymphomas from the diffuse poorly-differentiated lymphocytic lymphoma category, is popular, usable, and useful. It classifies lymphomas by nodal architecture (nodular vs. diffuse) and by cellular characteristics (well-differentiated, poorly-differentiated, mixed histocytic and lymphocytic, histiocytic, and undifferentiated). This scheme has prognostic and therapeutic value. In general, the nodular lymphomas (excluding nodular histiocytic) and diffuse, well-differentiated lymphocytic lymphoma comprise a favorable histiology group, characterized by an indolent course, response to gentle therapy, and long survival. The diffuse histologies (excluding diffuse well-differentiatied lymphocytic) and nodular histiocytic disease comprise an unfavorable histology group characterized by an aggressive course, a poor response to gentle therapy but the capacity to respond well to combination chemotherapy, overall poor survival with advanced disease, but the potential for "cure" of some patients.

The Rappaport system, however, does not take advantage of current technologic advances that classify lymphoid cells immunobiologically. Additionally, the Rappaport classification erroneously uses the term histiocytic lymphoma for the large cell lymphoid malignancies. A number of classification schemes classify lymphomas immunologically or relabel and subclassify histiocytic lymphomas. The Lukes-Collins approach is one of the more popular systems. This system categorizes lymphomas as B- and T-cell diseases. Most lymphomas (and all nodular lymphomas by Rappaport criteria) are B-cell tumors. Assigning lymphomas to merely a B-cell or T-cell category, however, is not particularly useful as there is great heterogeneity within each category. The Lukes-Collins system subdivides T- and B-cell lymphomas into clinically meaningful groupings. This and other immunlogic classification schemes are achieved at the cost of increased complexity and perhaps decreased reproducibility and diminished applicability outside of specialized centers. A third system has been sponsored by the National Cancer Institute as a compromise between the Rappaport, Lukes-Collins, and other systems. The ultimate roles of the

Table 5 **The Rappaport Classification System for Lymphomas**

	Well-Differentiated Lymphocytic	*Poorly-Differentiated Lymphocytic*	*Mixed (Histiocytic/Lymphocytic)*	*Histiocytic*	
Nodular	NWDL (F)[a]	NPDL (F)	NM (F)	NH (U)[b]	
Diffuse	DWDL (F)	DPDL (U)	DM (U)	MD (U)	Undifferentiated (U) Lymphoblastic (U) Pleomorphic Burkitt's

[a] Favorable histology
[b] Unfavorable histology

new systems relative to the Rappaport system are yet to be determined. This chapter will primarily use the Rappaport system.

Clinical Features at Presentation of Disease

Lymphomas, like Hodgkin's disease, commonly present with peripheral adenopathy (two-thirds of patients); supraclavicular, cervical, inguinal, and axillary sites are frequently involved. Mediastinal, hilar, and other intrathoracic disease is less common than with Hodgkin's but is not rare. Lymphoblastic lymphoma, however, commonly presents with an anterior mediastinal mass. Primary extranodal disease accounts for roughly 25% of lymphomas at presentation. This is in sharp distinction to Hodgkin's disease in which primary extranodal involvement is uncommon. Common sites of extranodal primary lymphomas include Waldeyer's ring, the gastrointestinal tract, and the skin. Less common are the kidney, bone marrow, thyroid, brain, lung, and testis.

Lymphomas are more likely to be advanced at presentation than Hodgkin's disease, with 80% or more of patients stage III or IV at presentation (50-60% stage IV). Lymphomas like Hodgkin's may present with constitutional symptoms.

Overall, lymphomas are roughly equal in incidence in males and females. Lymphoblastic lymphomas and (pediatric) Burkitt's lymphomas, however, are more common in males. While lymphomas can occur in any age group, peak incidence is in the 40-50-year age group, and nodular lymphomas are less common than diffuse lymphomas in patients older than 60 years. Nodular lymphomas are extremely rare in the pediatric age group.

Diagnosis and Staging

Like Hodgkin's disease, lymphomas are usually diagnosed by lymph node biopsy. However, because lymphomas may present extranodally or disseminate, biopsies of viscera may also lead to the diagnosis. A visceral biopsy does not provide information on nodal architecture, and precise classification by the Rappaport scheme is not possible. When lymph nodes exhibit both nodular and diffuse architecture, the disease tends to behave like nodular disease. Sometimes composite lymphomas (with two different cell types) are seen; these tend to behave like the less favorable cell type present. The differential diagnosis of lymphomas is the same as that of Hodgkin's disease.

For most lymphomas, stage is assigned by the Ann Arbor classification scheme, as for Hodgkin's disease. This system, however, is not particularly

useful for certain lymphomas, such as childhood lymphomas, adult or childhood Burkitt's lymphoma, and mycosis fungoides. A variety of other staging systems has been suggested for those lymphomas, but these will not be discussed here.

Recommended clinical staging studies are similar to those suggested for patients with Hodgkin's disease (Table 3). Abdominal computed tomography, however, is preferable to a lymphangiogram in lymphomas because this technique permits evaluation of mesenteric lymph nodes and abdominal viscera in addition to the para-aortic lymph nodes. These areas are more commonly involved in lymphomas than in Hodgkin's disease. The bone marrow examination has a higher yield in lymphomas than in Hodgkin's disease and is recommended for all staging workups.

Staging laparotomy is rarely necessary in patients with lymphomas because therapeutic decisions can be effectively based on clinical stage. Further, the morbidity of staging laparotomy is, in general, greater in patients with lymphomas than in those with Hodgkin's disease, due to an older median age and higher stage at presentation in patients with lymphomas. In surgically staged series, nodular disease is rarely (<10%) stage I and commonly (>80%) stage III or IV. In diffuse histology disease, approximately 70% of patients are stage III or IV, but stage I disease is of appreciable frequency, reaching as high as 30% for diffuse histiocytic lymphoma.

Course and Treatment

A minority of patients with lymphomas, generally those with favorable histology (see below), have very indolent disease and may survive several years without therapy. In most patients, however, the disease is progressive and fatal in months to years without intervention. Prognosis without treatment varies substantially with histology and stage, but advanced, unfavorable histology lymphomas would generally result in median survival less than 6 months if untreated.

Favorable histology lymphomas, if stage I or II, can be effectively treated with radiation therapy alone, with resultant 50-80% 5-year disease-free survival. Because these tumors may be indolent, however, late relapses are possible and 5-year figures may not accurately reflect cure rates. The curative potential for radiation therapy in early stage disease is not well defined but presumably exists, at least for a subset of patients. While basing therapy on clinical stage means that some patients are being treated with radiation therapy that will not be curative (because occult disease exists outside the radiation ports), those patients generally can be salvaged by subsequent chemotherapy.

Stage III or IV favorable histology disease may be indolent without therapy, but usually symptoms, bulk, or location of disease make therapy

advisable. Single alkylating agent chemotherapy (e.g., chlorambucil) is well tolerated and results in a 70-90% response rate (30-60% complete response) with an overall median survival in the 2 to 7 year range. Combination chemotherapy (e.g., with CVP:*c*yclophosphamide, *v*incristine, and *p*rednisone) yields similar response rates and survival figures. The combination chemotherapy approach may achieve a more rapid response at the expense of increased toxicity; its rapid action is useful in the patient with bulky, symptomatic, or threatening disease. There is no clear benefit to adriamycin containing regimens or other regimens as compared to CVP in treating favorable histology lymphomas. Fractionated total body irradiation is an alternative mode of therapy that has efficacy and morbidity similar to treatment with a single alkylating agent.

While, with any of the above forms of therapy, both survival and disease-free survival in patients with advanced favorable histology lymphoma may be prolonged, population studies show a constant relapse rate regardless of the duration of relapse-free survival. This suggests that therapy is usually palliative rather than curative. One exception to this statement, however, may be nodular mixed lymphoma. There are some data that suggest that treatment of patients with this histology with combination chemotherapy (COPP:*c*yclophosphamide, *o*ncovin, *p*rocarbazine, *p*rednisone) may cure a portion of responding patients. The relative incurability of favorable histology lymphoma is relevant to the decision not to perform staging laparotomies in patients with clinical stage I and II disease; one is probably not compromising survival or curability by delaying systemic therapy until disease in a nonirradiated site becomes apparent.

Stage I or II, unfavorable histology, lymphomas are less successfully treated with radiation therapy alone than are favorable histology lymphomas. In these patients 5-year disease-free survival figures will vary from 20-50%. Either combined modality therapy (combination chemotherapy plus radiation) or chemotherapy alone appears to be superior to radiation therapy alone. Reliable figures for "cure rates" with these approaches are not yet available, however.

Advanced disease of unfavorable histology is best treated by aggressive combination chemotherapy. Adriamycin containing regimens, such as CHOP (cyclophosphamide, *a*driamycin, *o*ncovin, *p*rednisone), produce a 50-80% response rate (40-60% CR) with median survival of 1 to 1½ years (vs. <6 months without therapy) and with long-term disease-free survival in 50-75% of complete remitters. Unfavorable histology disease, thus, may be paradoxically more curable (although with poorer median survival) than favorable histology disease.

Factors reflecting a poor prognosis in patients with an advanced unfavorable histology lymphoma include bulky disease (e.g., >10 cm),

bone-marrow involvement, gastrointestinal tract involvement, hepatic involvement, and histologic subclassification by Lukes-Collins system as T-cell immunoblastic sarcoma or as large, noncleaved cell lymphoma. Lymphomas in patients with diffuse poorly-differentiated lymphocytic histology sometimes behave more like favorable histology disease, and such patients may fare better than patients with diffuse mixed or diffuse histocytic lymphoma.

OTHER LYMPHOMAS

Lymphoblastic lymphoma is a distinct lymphoma with a poor prognosis. This entity is probably on a continuum with acute lymphoblastic leukemia. It is frequently of T-cell origin, and the cells are usually positive for the enzyme terminal deoxynucleotidyl transferase (TdT). It commonly, but not exclusively, presents as a mediastinal mass in a boy, and it frequently involves the meninges and the bone marrow. Lymphoblastic lymphoma is probably best treated as leukemia, with regimens including L-asparaginase or cytosine arabinoside, rather than as an unfavorable histology lymphoma. Also, treating the central nervous system prophylactically with intrathecal chemotherapy and whole-brain irradiation appears to be indicated.

Burkitt's lymphoma is a B-cell malignancy commonly presenting in children. The endemic form is found in the malaria belt of central Africa. The etiology is probably related to past Epstein-Barr viral infection, and the disease usually presents as a facial mass or as an abdominal mass. Burkitt's lymphoma is a rapidly growing tumor that, if treated at an early stage, may be cured by high dose chemotherapy (e.g., cyclophosphamide alone or with other agents). "Tumor lysis syndrome" is a common sequela of effective therapy when a large tumor burden is present. This may be manifest as hyperkalemia, hyperphosphatemia, hypocalcemia with renal and soft-tissue calcification, lactic acidosis, hyperuricemia, and possible shock or death. Vigorous hydration, use of allopurinol, and monitoring of and reacting to metabolic abnormalities should minimize the risk of these complications. American Burkitt's lymphoma is generally similar to the endemic form but differs in some ways. The relationship to Epstein-Barr virus infection is less clear in the American form. The patients are older and are likely to present with abdominal or pelvic disease. Bone marrow and lymph node involvement are more common in the American form. Stage for stage, prognosis is similar. Overall long-term survival for Burkitt's lymphoma is roughly 50%, with 60-80% survival in early disease and 10-40% in advanced disease. Response rates to chemotherapy are high (60-90% complete response rates), but relapse may occur. Although

meningeal spread is common, central nervous system "prophylaxis" is of little benefit. Where bulky abdominal disease is present, surgical debulking appears to improve the prognosis if more than 90% of the tumor can be removed.

CASE HISTORY 1

A 36 year-old man presents with fever to 101°F and cervical adenopathy of 6 week duration. Physical examination shows bilateral firm but mobile cervical and supraclavicular adenopathy with lymph nodes ranging from 0.5-2 cm in size. Physical examination is otherwise normal. Chest radiograph shows bilateral hilar adenopathy. A biopsy specimen of a cervical node shows mixed cellularity Hodgkin's disease.

Question

1. How do you proceed?

Answer

1. The patient's disease should be staged; liver-spleen scan, lymphangiogram, bone scan, and bone marrow aspirate and biopsy should be performed. If clear evidence of Hodgkin's disease is found on lymphangiogram or splenic scan, the patient's disease is (at least) stage IIIB. If any of the other studies are diagnostic of involvement with Hodgkin's, the patient is stage IVB. In either case the patient should be treated with combination chemotherapy. Mild splenomegaly is not sufficient to diagnose involvement with Hodgkin's disease. Massive splenomegaly (>15 cm) with filling defects, however, would be sufficient. If these noninvasive studies are negative, the patient should have a staging laparotomy. The chance of upstaging with laparotomy is substantial considering the histology, B symptoms and left neck involvement. If staging laparotomy is negative, this patient is stage IIB. Therapy would be irradiation alone. If it is positive, therapy would be chemotherapy.

The patient has a positive lymphangiogram but other studies are negative. He is in clinical stage IIIB. He receives six cycles of MOPP and is in a clinical complete remission by cycle number three. He is taken off therapy. Two years later he has a headache and a mild change in affect. Computed tomography of the head shows a single solid lesion in the right

frontal lobe. Spinal tap is normal. Physical examiantion and chest x-ray examination are normal.

Question

2. At this point you should
   (a) Irradiate the brain
   (b) Restart MOPP
   (c) Start ABVD
   (d) Perform a biopsy of the lesion

Answer

2. d—A solitary brain recurrence of Hodgkin's disease, while possible, is unusual. Opportunistic infection (e.g., cryptococcus) and second malignancy must be considered and excluded before starting therapy for Hodgkin's disease.

CASE HISTORY 2

A 50 year-old woman develops lymphadenopathy in cervical, supraclavicular, inguinal, femoral, and axillary sites. Lymph nodes are 1-3 cm, firm, and mobile. She is asymptomatic except for mild discomfort from lymphadenopathy. Physical examination shows splenomegaly (5 cm below the left costal margin) as well as the lymphadenopathy but is otherwise normal. Chest x-ray examination is normal, and a lymph node biopsy specimen shows nodular poorly-differentiated lymphocytic lymphoma. Abdominal computed tomography and liver-spleen scan are normal except for splenomegaly. Hemoglobin is 10 with a corrected reticulocyte count of 4% and a negative Coomb's test. WBC count is 3×10^9/liter with a normal differential. Platelets are 80×10^9/liter. Bone marrow examination shows myeloid and erythroid hyperplasia without evidence of lymphoma.

Question

1. At this point one should
   (a) Do a staging laparotomy
   (b) Treat with total nodal irradiation
   (c) Treat with daily chlorambucil
   (d) Treat with CVP

Answer

1. c or d—The patient does not need a staging laparotomy as clinical stage III disease is apparent and systemic therapy is indicated. Total nodal irradiation, while effective for true stage III disease, is less well tolerated than chlorambucil and is not reasonable unless one has performed a staging laparotomy to confirm pathologic stage as III. Treatment is indicated because of bulk of disease and hypersplenism. Chlorambucil is less likely to cause profound pancytopenia but will take longer to be effective than CVP. Either of these approaches is acceptable.

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10

GARY S. LAZAR

Multiple Myeloma and Other Monoclonal Gammopathies

MONOCLONAL GAMMOPATHIES

The monoclonal gammopathies are a heterogeneous group of benign and malignant disorders characterized by proliferation of a single clone of lymphocytes or plasma cells and the production of a monoclonal (M) protein. Monoclonal proteins (*paraproteins*) consist of one class of heavy polypetide chains and a single type of light chain. They are distinguished from polyclonal immunoglobulins, which consist of one or more heavy chain classes and both κ and λ light chains.

The monoclonal gammopathies can be classified as shown in Table 1. A discussion of these entities will be preceded by a brief discussion of the structure and biologic properties of normal immunoglobulins.

Basic Structure of Immunoglobulins

The five classes of human immunoglobulins share a common basic structure. The immunoglobulin molecule is composed of two identical heavy (H) polypeptide chains, which are designated by Greek letters: γ in IgG, α in IgA, μ in IgM, δ in IgD, and ϵ in IgE, and two identical light (L) polypeptide chains, κ or λ. Interchain disulfide bonds link the H and L chains together (Fig. 1).

Papain exposure splits the immunoglobulin molecule into three fragments. The Fab fragments consist of a complete light chain and the amino-terminal end of the heavy chain and they are capable of antigen

Table 1 **Classification of Monoclonal Gammopathies**

Malignant monoclonal gammopathies
Multiple myeloma
IgG, IgA, IgM, IgD, IgE
Free light chains, κ or λ
Plasma cell leukemia
Nonsecretory myeloma
Solitary plasmacytoma of bone
Extramedullary plasmacytoma, solitary and multiple
Waldenström's macroglobulinemia (IgM)
Heavy chain diseases (HCD)
γ-HCD
α-HCD
μ-HCD
Amyloidosis
Pattern I
Localized
Monoclonal gammopathies of unknown significance
Benign (IgG, IgA, IgD, IgM, and, rarely, free light chains)
Associated with malignant lymphoma
Associated with neoplasms not known to produce monoclonal proteins (breast, colon, biliary, prostate)
Associated with inflammatory and infectious diseases

SOURCE: Modified from Kyle RA, Boyrd ED: *The Monoclonal Gammopathies*. Springfield, Ill, Charles C Thomas, 1976, pp 4-5.

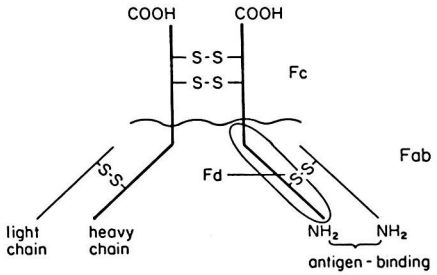

Figure 1 Basic immunoglobulin structure. The curved line indicates the sites of papain cleavage into Fc and Fab fragments. The Fd piece is that part of the heavy chain included in the Fab portion.

binding. The Fc fragment consists of the C-terminal portion of both heavy chains. This fragment has important biologic activities, such as complement fixation, binding to receptors on macrophages and lymphocytes, and transfer across the placenta. The portion of the heavy chain in the Fab fragment is called the Fd piece. Free light chains, when present unassembled, are referred to as Bence Jones proteins. They are named after Henry Bence Jones who described the peculiar thermal properties of these proteins that precipitate on heating to 45-60°C, redissolve on boiling, and reprecipitate on cooling.

Biologic Properties of Normal Immunoglobulins

IgG is the major immunoglobulin class in human serum, and is particularly important in antibody responses to bacterial and viral infections. IgA is the most important secretory immunoglobulin. It is found in high concentration in the respiratory and gastrointestinal tract secretions, where it usually exists as a dimer. In these secretions, it exhibits antibacterial and viral-neutralizing activities. IgM immunoglobulin is restricted primarily to the intravascular space due to its high molecular weight. It is the first immunoglobulin detected after exposure to new antigens (primary antibody response). Some clinically important IgM antibodies are anti-A and anti-B isohemagglutinins, cold agglutinins, rheumatoid factor, and heterophil antibodies. The function of IgD immunoglobulin is unknown, but it has been found on the surface of normal lymphocytes. IgE mediates immediate (type 1) hypersensitivity reactions, such as allergic rhinitis, asthma, and anaphylaxis. IgE binds to basophils and causes histamine release when the cytophilic IgE reacts with antigen.

Relation of Monoclonal Proteins to Normal Immunoglobulins

Monoclonal proteins were once thought to be abnormal in structure. It is now clear that the monoclonal proteins associated with multiple myeloma, Waldenström's macroglobulinemia, and benign monoclonal gammopathy are usually normal immunoglobulins which are produced in excessive quantities. Some monoclonal proteins have been shown to possess antibody activity against defined antigens, such as the bacterial toxin streptolysin O. It is likely that all monoclonal proteins have antigen specificity, but unless the reaction of monoclonal protein (antibody) with the antigen produces a clinical syndrome the specificity is not recognized.

In contrast, some of the monoclonal gammopathies are associated with structurally abnormal monoclonal proteins. The heavy-chain diseases are associated with secretion of a defective heavy chain that has a major

deletion in the Fd region. Most cases of amyloidosis are associated with amyloid fibrils that are unrelated to immunoglobulins. However, in type I (primary) amyloidosis the amyloid deposits are composed of fragments of immunoglobulin light chains.

MULTIPLE MYELOMA

General Comments

Multiple myeloma is a plasma-cell neoplasm. The malignant plasma cell proliferation occurs in the bone marrow and results in clinical manifestations by two mechanisms: alteration of normal bone-marrow function, and production of monoclonal proteins. The M proteins are found in the blood (usually IgG or IgA) or urine (κ or λ light chains). Other common manifestations include lytic bone lesions, renal disease, and abnormalities in normal immunoglobulin synthesis. Approximately 10-15% of patients with multiple myeloma have only light chains present in their urine. This type of myeloma has been called light chain disease (LCD). Rarely, multiple myeloma occurs without a detectable monoclonal protein in the serum or urine (nonsecretory myeloma).

Incidence and Etiology

The National Cancer Institute has estimated that there will be approximately 9600 new cases of multiple myeloma in 1982. Myeloma accounts for about 1% of all malignancies, and 10% of hematologic malignancies. The mean age at diagnosis is 62 years, with an approximately equal incidence in men and women. A higher incidence has been noted in blacks. The etiology is unknown.

Clinical Features

The clinical manifestations of multiple myeloma vary tremendously from patient to patient depending upon the stage of disease, the rate of progression, and the type of monoclonal protein present. As indicated in Table 2, differences exist in clinical features among the three major types of myeloma.

Constitutional symptoms, such as weakness and fatigue, are common; night sweats and weight loss are late symptoms, usually occurring in patients with advanced disease. Fever due to myeloma in the absence of infection is distinctly uncommon. The physical examination is nonspecific. Pallor is common, and bone tenderness or deforminity may be seen. The

Table 2 **Clinical Features at the Time of Diagnosis in 212 Patients with Multiple Myeloma of Different Classes**

Clinical features	*Class*		
	IgG	*IgA*	*Light chains*
No. of patients	112	54	40
Mean serum level of M protein (g/dl)	4.3	2.8	±
Lytic bone lesions (%)	55	65	78
Hypercalcemia (%)	33	59	62
Serum urea >79 mg/dl (%)	16	17	33
Normal immunoglobulins <20% of normal mean (%)	68	30	19
Mean doubling time of M protein (months)	10.1	6.3	3.4
Hospital admissions because of infection[a] (%)	60	33	20
Amyloidosis[b] (%)	0.5	7	10

SOURCE: Modified with permission from Hobbs JR: Immunochemical classes of myelomatosis. *Br J Haematol* 16:599-606, 1969.

[a] In 48 IgG, 21 IgA, and 20 BJ myeloma patients followed up to 3 years.

[b] In 228 IgG, 102 IgA, and 94 BJ myeloma patients.

liver is palpable in approximately 20% patients, but it is rarely greatly enlarged. Lymphadenopathy and splenomegaly are uncommon findings.

Skeletal Disease

Bone pain occurs in more than 70% of patients with multiple myeloma and is the most common feature of the disease at the time of diagnosis. The pain usually involves the back or chest and, less commonly, the extremities. Osteolysis, particularly in hematopoietically active areas of bone marrow, leads to lytic bone lesions and diffuse osteoporosis (Figs. 2 and 3). Skeletal surveys reveal lytic lesions, osteoporosis, or fractures in approximately 80% of patients. The bone lesions are usually lytic with no evidence of osteoblastic activity. Bone scans are less sensitive in detecting myeloma bone lesions. Pathologic fractures can occur with minimal trauma, and this diagnosis must be considered in the presence of localized pain, particularly if the pain is of recent onset. Vertebral body collapse may produce signs of nerve root or spinal cord compression, including

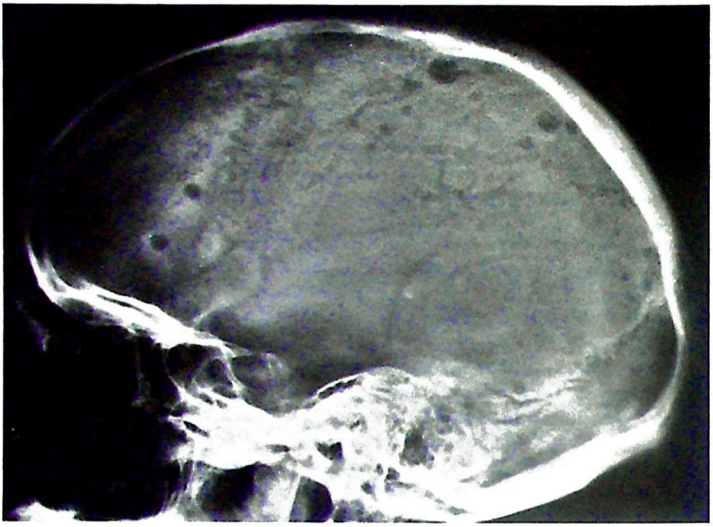

Figure 2 Skull radiograph showing multiple lytic ("punched out") lesions in a patient with multiple myeloma.

paraplegia. Skeletal disease is the greatest cause of debility in many patients.

Infections

Bacterial infections of the upper respiratory tract, lungs, and urinary tract are particularly common in patients with multiple myeloma and are a frequent cause of death. Although gram-positive organisms, particularly *Streptococcus pneumoniae* and *Staphyloccocus aureus* have been the most commonly isolated organisms, the importance of gram-negative organisms has been recently emphasized. Impaired antibody responses, cytotoxic and corticosteroid therapy, and hypogammaglobulinemia are among the important reasons for the propensity to infection in these patients.

Hypercalcemia

Hypercalcemia may develop insidiously in patients with multiple myeloma. In one large study hypercalcemia was present in 30% of patients at the time of diagnosis. Symptoms include anorexia, polyuria, nausea,

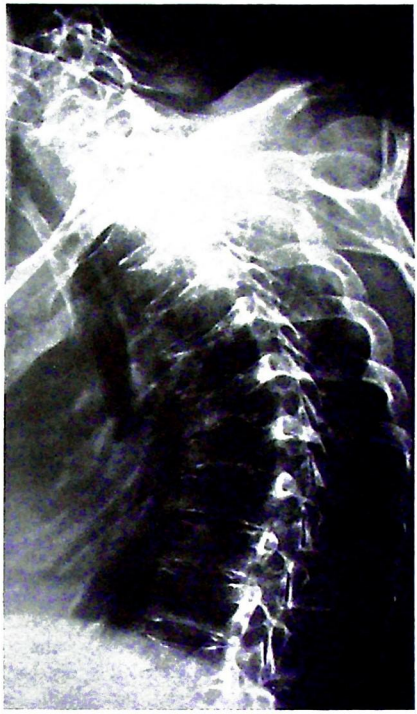

Figure 3 Thoracic spine radiograph showing severe osteoporosis and a compression fracture of T-7 in a patient with multiple myeloma.

vomiting, constipation, weakness, confusion, and coma. The presence of symptoms depends upon the level of calcium in the blood and the rate at which it rises. For instance, the central nervous system effects are more common in patients with an acute rise to levels of only 12-13 mg/dl. Conversely, levels of 15 mg/dl may be accompanied by relatively minor manifestations, if the elevation occurs gradually. Even in the absence of symptoms, however, hypercalcemia should be promptly treated, as it may contribute to kidney damage. The causes of hypercalcemia in multiple myeloma include destructive skeletal lesions, immobilization, and secretion of osteoclast activating factor (OAF) by the myeloma cells.

Renal Disease

Renal failure is an important manifestation of multiple myeloma, and it is associated with shortened survival. Aside from infection, uremia is the most common cause of death. Approximately one-half of patients will have elevated serum creatinine levels at the time of diagnosis. The renal failure may be partially reversible if coexistent hypercalcemia or hyperuricemia are successfully treated.

Renal failure generally correlates with the presence and magnitude of urinary light chain excretion. Other factors that may contribute to the development of renal failure are pyelonephritis, uric acid nephropathy, hypercalcemic nephropathy, infiltration of the kidney by myeloma cells, and amyloidosis. Acute renal failure due to precipation of light chains in the renal tubules may occur after intravenous pyelography or other radiographic contrast studies in patients with multiple myeloma. *Contrast radiographic studies should be avoided when possible in myeloma patients*, but when they are indicated, acute renal failure can be avoided by vigorous hydration of the patient before the procedure. The nephrotic syndrome, when it occurs, usually is associated with coexistent amyloidosis.

Other Manifestations

Amyloidosis may complicate the course of multiple myeloma. It should be suspected in patients with multiple myeloma who develop the nephrotic syndrome, congestive heart failure, macroglossia, or peripheral neuropathy.

Unlike Waldenström's macroglobulinemia, the hyperviscosity syndrome occurs rarely in patients with multiple myeloma. Symptoms, including epistaxis, visual disturbances, neurologic problems, and congestive heart failure, usually occur when the serum viscosity relative to water exceeds 4.0. Patients with IgA myeloma may develop the hyperviscosity syndrome because of the capacity of some IgA proteins to form polymers of high intrinsic viscosity. Cryoglobulinemia and coagulation abnormalities are uncommon manifestations of multiple myeloma.

Myeloma Variants

Several uncommon variants of multiple myeloma exist as distinct clinical syndromes. Solitary plasmacytoma of bone (SPB) presents as a solitary lytic lesion of bone, usually associated with a serum M protein. The plasmacytoma occurs almost exclusively in areas containing normally active hematopoietic tissue (Fig. 4). Despite treatment, SPB usually progresses to generalized multiple myeloma.

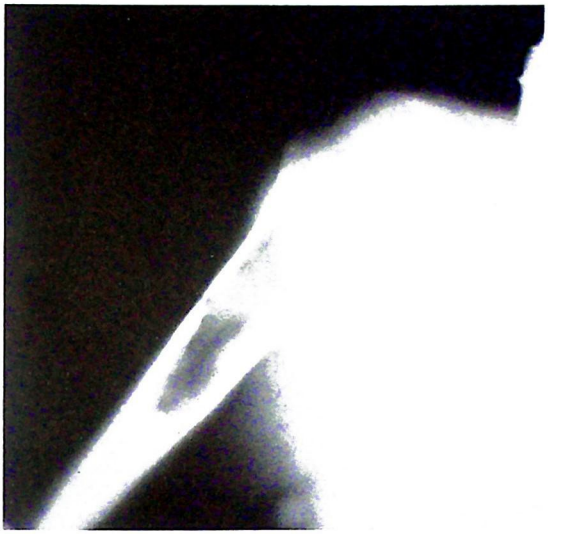

Figure 4 Radiograph of the right humerus showing a lytic lesion in a patient with solitary plasmacytoma of bone. This patient later developed generalized multiple myeloma.

Extramedullary plasmacytoma (EMP) usually arises in the nasopharynx or respiratory tract or, less frequently, in the gastrointestinal tract or lymph nodes (Fig. 5). EMP has a lower propensity for bone marrow dissemination than SPB and is often curable with radiotherapy.

Plasma cell leukemia (PCL) occurs in fewer than 2% of patients with multiple myeloma. It may be diagnosed when the plasma cell count in the peripheral blood is at least 2×10^9/liter. PCL usually occurs in advanced multiple myeloma and has a poor prognosis.

Laboratory Features

Blood

Anemia is present in over 60% of patients with multiple myeloma at the time of diagnosis. The anemia is usually normochromic and normocytic and the reticulocyte count is normal or low. Leukopenia (WBC <4

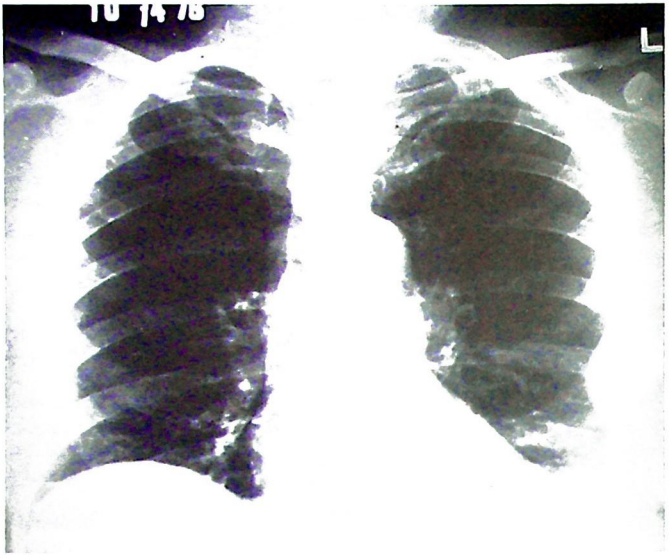

Figure 5 Chest radiograph showing a left pleural density. Biopsy of this mass revealed an extramedullary plasmacytoma.

$\times 10^9$/liter) is relatively uncommon. Thrombocytopenia (platelets $<100 \times 10^9$/liter) and thrombocytosis (platelets $>400 \times 10^9$/liter) occur with equal frequency. Pancytopenia occurs when there is extensive replacement of the bone marrow by plasma cells. A leukoerythroblastic reaction, characterized by the presence of nucleated red blood cells and immature granulocytes in the peripheral blood, may be seen. Plasma cells are seen occasionally in the peripheral blood but rarely exceed 5% of the total leukocyte count.

The Westergren erythrocyte sedimentation rate (ESR) is usually greater than 50 mm/hr due to the presence of the monoclonal protein. The M protein is also responsible for the rouleau formation that is often seen in the peripheral blood smear.

Bone Marrow

The bone marrow examination reveals plasmacytosis of a variable degree. Patients with early disease usually have more than 10% plasma cells. Patients with advanced disease often have more than 30% plasma

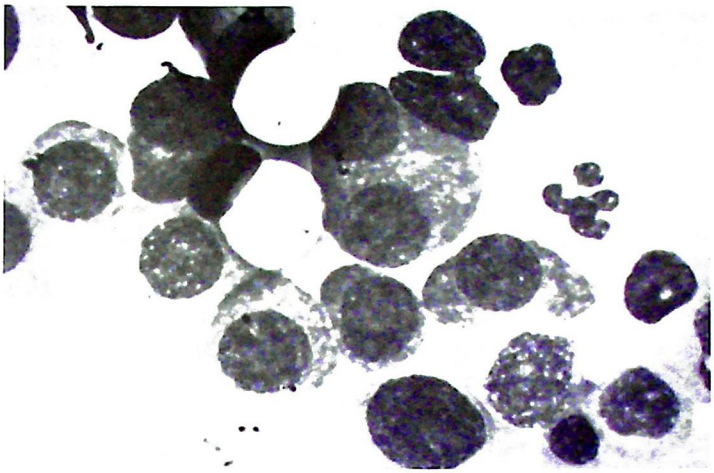

Figure 6 Photomicrograph of the bone marrow in a patient with multiple myeloma. Numerous plasma cells, including a large, binucleate plasma cell with a prominent nucleolus, are present.

cells. However, sampling error makes the percentage of plasma cells an unreliable measure of the extent of disease.

It may be difficult to differentiate neoplastic plasma cells from a benign reactive plasmacytosis. The presence of immature or multinucleated cells, numerous mitotic figures, or large clusters of plasma cells suggests neoplasia (Fig. 6).

Serum and Urine Protein Electrophoresis

Serum protein electrophoresis (SPEP) on cellulose acetate is a useful screening method for detecting the monoclonal proteins because of the wide availability and low cost of this procedure. A tall, narrow band is most commonly seen in the γ region (Fig. 7). Free light chains are rarely detected by SPEP. SPEP reveals hypogammaglobulinemia without a protein spike in fewer than 15% of patients. Serum immunoelectrophoresis (IEP) can be very helpful in such cases (see below). Quantitative immunoglobulins (QIG) should be performed to quantitate the serum immunoglobulins.

Analysis of the urine for abnormal protein is an important diagnotic test. Urinary protein electrophoresis is the preferred method, since the

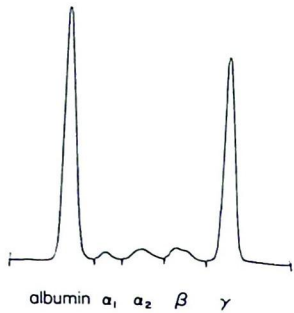

Figure 7 Serum protein electrophoresis in multiple myeloma. The tracing on the left shows a narrow spike in the γ region. The cellulose acetate strip on the right shows a dense, homogeneous band in the γ region.

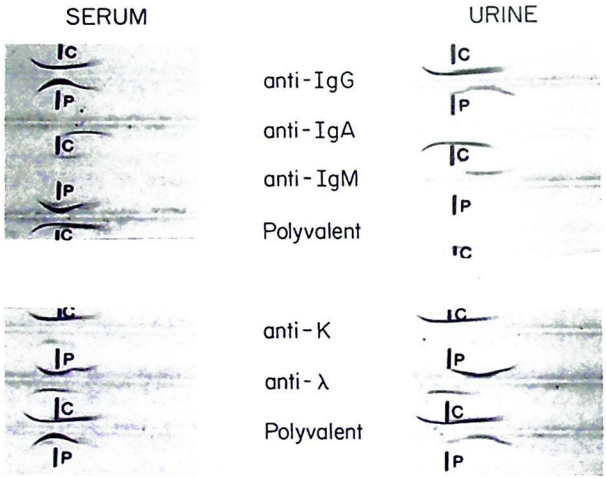

Figure 8 Immunoelectrophoresis of serum and urine from the patient shown in Figure 7. In the serum, an abnormal arc is present adjacent to the anti-IgG well and the anti-λ light chain well. The IgA and IgM arcs are reduced. The urine shows a reaction with anti-λ light chains. The diagnosis is IgG-λ myeloma.

urinary dipsticks rarely give a positive reaction with light chains, and the heat tests for Bence Jones proteinuria are unreliable. Urinary light chains are detected in 75-80% of patients with myeloma by protein electrophoresis.

Immunoelectrophoresis

When a monoclonal protein is detected in the serum or urine, immunoelectrophoresis (IEP) should be performed to identify the heavy chain class (γ, α, μ, δ, ϵ) and light chain type (κ, λ) (Fig. 8). IEP is useful in distinguishing a monoclonal from a polyclonal increase of immunoglobulins. Occasionally, IEP detects a low concentration of monoclonal protein that is not recognized on protein electrophoresis.

In fewer than 1% of patients with multiple myeloma, no abnormal protein can be demonstrated in the serum or urine. The diagnosis of this type of myeloma, which is called nonsecretory myeloma, relies on the presence of the typical clinical features and the bone marrow examination.

Biochemical Abnormalities

Renal failure, with elevation of the serum creatinine and urea nitrogen (BUN) concentrations, is common in multiple myeloma. Hyperuricemia occurs in about one-half of patients. In addition, both proximal and distal renal tubular acidosis have been seen occasionally. A narrowed anion gap is sometimes observed due to retention of bicarbonate and chloride anions to offset the cationic charge of the monoclonal immunoglobulins. Despite extensive bone lesions, the serum alkaline phosphatase level is normal or minimally elevated.

Diagnosis

In patients with lytic bone lesions, more than 30% plasma cells in the bone marrow, and a paraprotein on SPEP the diagnosis of multiple myeloma is usually clear. However, the diagnosis is more difficult in patients with early disease or those in whom the paraprotein is difficult or impossible to detect (i.e., light chain disease or nonsecretory myeloma). Laboratory abnormalities that provide a clue to the diagnosis of myeloma include anemia, hypercalcemia, azotemia, and panhypogammaglobulinemia.

Multiple myeloma must be distinguished from the other monoclonal gammopathies. Benign monoclonal gammopathy (BMG), the most common abnormality of monoclonal proteins, is not associated with lytic bone lesions, renal disease, or depression of normal immunoglobulin levels. The most important criterion in establishing the diagnosis of BMG is stability of the amount of paraprotein with time. The diagnosis of Walden-

ström's macroglobulinemia is easily made in the setting of IgM monoclonal protein, the hyperviscosity syndrome, hepatosplenomegaly, lymphadenopathy, and ocular changes. Although patients have been described with monoclonal IgM paraproteins and typical features of multiple myeloma, these patients are exceptions.

Metastatic carcinoma may be associated with lytic bone lesions, monoclonal gammopathy, and reactive plasmacytosis in the bone marrow. In metastatic carcinoma, tumor cells are usually found in the bone marrow biopsy specimen or a biopsy specimen of a lytic bone lesion.

After the diagnosis of multiple myeloma is made, or if the diagnosis is in question, hematology consultation should be sought. Early diagnosis and treatment are associated with a better response to treatment and improved survival.

Prognosis and Staging

Multiple myeloma is a uniformly fatal disease with a median survival of 2 to 3 years in treated patients. Untreated patients have a median survival time of 12 months. Poor prognostic factors include anemia, elevation of serum creatinine levels, hypercalcemia, high monoclonal protein levels, and extensive bone lesions. These factors tend to be correlated with a high tumor cell mass and have been incorporated into a clinical staging system for multiple myeloma (Table 3).

A poor prognosis is associated with IgA myeloma and with the excretion of λ light chain alone. Patients who rapidly respond to chemotherapy may have a shortened survival compared to those who respond slowly. Infection and renal failure are the most common causes of death.

Treatment

Chemotherapy

Chemotherapy is indicated when the diagnosis of multiple myeloma is confirmed. Patients with a low tumor burden tend to have a higher response rate and improved survival.

Melphalan (L-phenylalanine mustard) (Alkeran) is an alkalating agent that has been widely tested in multiple myeloma. It is most commonly given as a pulse, 0.25 mg/kg per day for 4 days, along with prednisone 60 mg/m^2 per day. Although prednisone is not a useful agent in multiple myeloma by itself, the response rate to melphalan and prednisone is higher than with melphalan alone, and this combination is widely accepted as the standard chemotherapy for myeloma. Continuous therapy with melphalan (2-4 mg/day) can also be used, but this regimen has no advantage to pulse therapy and is more likely to produce prolonged myelosuppression.

Melphalan is excreted by the kidneys. Therefore, dosage adjustments must be made if renal failure is present. The major toxicity associated with melphalan is bone marrow suppression.

Cyclophosphamide (Cytoxan), another alkalating agent, is also effective in multiple myeloma. In untreated patients cyclophosphamide is equal to melphalan in efficacy. Patients who have become resistent to melphalan may respond to cyclophosphamide.

BCNU [2,3 Bis(2-chloroethyl)-1-nitrosourea] and CCNU [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea] are also effective agents in multiple myeloma. Other drugs that may be useful include doxorubicin (Adriamycin), vincristine (Oncovin), and procarbazine (Matulane). Recently, several patients were treated with human leukocyte interferon with encouraging results. No drug combinations have been shown to be superior to melphalan and prednisone.

Supportive

Bone pain is a major problem in patients with multiple myeloma. Immobilization increases demineralization of bone, and, therefore, patients must be encouraged to remain active. Potent analgesics are often necessary to keep patients ambulatory. Local radiotherapy may provide significant relief of bone pain. Fractures of long bones often require fixation with an intramedullary rod and methyl methacrylate, followed by irradiation.

Since bony lesions rarely heal with chemotherapy, other types of therapy have been tried. Sodium fluoride (100 mg/day) and calcium carbonate (4 g/day) have been reported to reduce bone pain and increase bone density in some patients. However, there is some evidence that patients treated with this combination have more brittle bones that are more likely to develop pathologic fractures.

Spinal cord compression from extradural extension of myeloma is usually treated with radiation therapy. Surgical decompression may be necessary if there is a progressive neurologic deficit.

Infection must be promptly treated, after appropriate bacterial cultures are obtained. Broad spectrum antibiotics are often necessary until the results of cultures are available. Special care must be exercised when nephrotoxic antibiotics are given to patients with multiple myeloma who may already have impaired renal function.

Mild elevations of serum calcium levels (up to 1.5 mg/dl greater than normal) with minimal symptoms can be managed initially with increased oral fluid intake of 2 to 4 liters over normal. Oral sodium phosphate, in the form of Fleet Phosphosoda (5 ml t.i.d.) may be added. If this therapy is unsuccessful, or if more severe hypercalcemia is present, the patient should be treated with intravenous fluid hydration. Saline (6-8 liters/day) is preferred, since sodium promotes renal calcium excretion.

Table 3 **Myeloma Staging System**

Criteria	*Measured Myeloma Cell Mass (cells X $10^{12}/m^2$)*	*Estimated Median Survival (months)*
I All of the following:		
Hemoglobin value >10 g/dl		
Serum calcium value normal (<12 mg/dl)		
On x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only	<0.6 (low)	191
Low M-component production rates		
IgG value <5 g/dl		
IgA value <3 g/dl		
Urine light chain M component on electrophoresis <4 g/24 h		
II Fitting neither stage I nor stage III	0.6-1.20 (intermediate)	48

III One or more of the following:		
Hemoglobin value <8.5 g/dl		
Serum calcium value >12 mg/dl		
Advanced lytic bone lesions (scale 3)		
High M-component production rates	>1.20	28
IgG value >7 g/dl	(high)	
IgA value >5 g/dl		
Urine light chain M component on electrophoresis >12 g/24 h		

Subclassification

A

Relatively normal renal function (serum creatinine value <2.0 mg/dl

B

Abnormal renal function (serum creatinine value >2.0 mg/dl

Reprinted with permission from Durie BGM, Salmon SE: A clinical staging system for multiple myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer* 36:842-854, 1975.

Examples: Stage IA: low cell mass with normal renal function; stage IIIB: high cell mass with abnormal function.

The cardiac status must be carefully monitored for signs of congestive heart failure, and intravenous furosemide (40 mg) is usually necessary three to four times per day. The serum electrolytes must be monitored closely, and potassium and magnesium must be repleted. Prednisone is frequently useful in doses of 100 mg/day, which can be added to the saline and furosemide therapy. Intravenous phosphates should be avoided because of the risk of metastatic calcification. Mithramycin is helpful, particularly with moderate to severe hypercalcemia, or when the cardiac status prevents saline diuresis. It is given intravenously in a dose of 25 μg/kg, which may be repeated in 24 hours. Thrombocytopenia may occur as a result of this therapy.

Hyperuricemia may contribute to the development of renal failure and gout. Hyperuricemia should be treated with allopurinol (Xyloprim), and uricosuric agents should be avoided. Hemodialysis has been used in patients with acute renal failure and multiple myeloma, with improvement of renal function noted in some. However, the overall prognosis of the patient must be taken into consideration before employing this approach.

The hyperviscosity syndrome, although rare in multiple myeloma, can usually be managed with plasmapheresis in combination with cytotoxic therapy to reduce the production of monoclonal protein.

WALDENSTRÖM'S MACROGLOBULINEMIA

Waldenström's macroglobulinemia (WM) is a neoplasm of B lymphocyte-plasmacytic cells characterized by the production of large amounts of monoclonal IgM (macroglobulin). In contrast to multiple myeloma, lymphadenopathy, hepatosplenomegaly, and the hyperviscosity syndrome are typical features of Waldenström's macroglobulinemia, while lytic bone lesions are rare. Anemia and bleeding are other common manifestations.

Incidence and Etiology

WM is an uncommon disorder with a mean age at diagnosis of 62 years. About two-thirds of patients are male. The etiology is unknown.

Clinical Features

The disease often develops insidiously. The most common symptoms are fatigue, weakness, bleeding, and weight loss (Table 4). Epistaxis is the most frequent type of bleeding, although gastrointestinal bleeding and

Table 4 **Presenting Symptoms in 227 Patients with Waldenström's Macroglobulinemia**

Symptoms	*Cases (%)*
Fatigue, weakness	44
Bleeding	44
Weight loss	23
Neurologic disturbance	11
Visual disturbance	9
Dyspnea	8
None	6

SOURCE: Modified from McCallister BD, Bayrd ED, Harrison EG Jr, McGuckin WF: Primary macroglobulinemia: Review with a report on 31 cases and notes on the value of continuous chlorambucil therapy. *Am J Med* 43:394-434, 1967.

Table 5 **Physical Findings in 227 Patients with Waldenström's Macroglobulinemia**

Physical Finding	*Cases (%)*
Ocular changes	37
Hepatomegaly	37
Splenomegaly	35
Lymphadenopathy	27
Neurologic problems	16
Petechiae, purpura	15
Congestive heart failure	4
None	10

SOURCE: Modified from McCallister BD, Bayrd ED, Harrison EG Jr, McGuckin WF: Primary macroglobulinemia: Review with a report on 31 cases and notes on the value of continuous chlorambucil therapy. *Am J Med* 43:394-434, 1967.

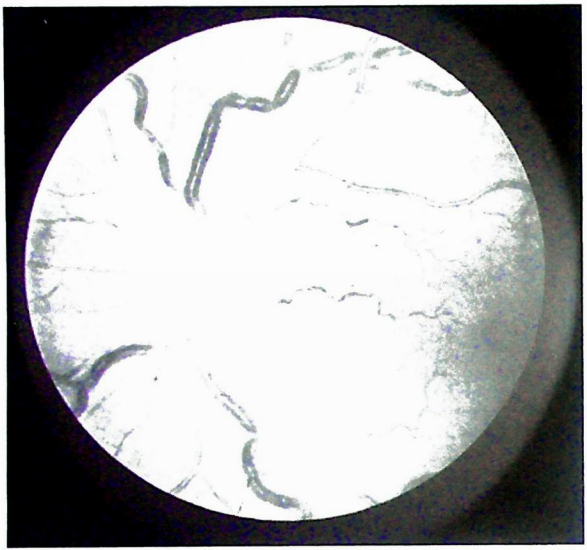

Figure 9 Photograph of the fundus of a patient with Waldenström's macroglobulemia showing dilated, tortuous retinal veins and sausage-like segmentation of some greatly dilated veins.

hemoptysis can occur. Other less common symptoms are dyspnea, Raynaud's phenomenon, and symptoms of infection.

The physical examination reveals hepatosplenomegaly, lymphadenopathy, and a variety of striking ocular changes (Table 5). The funduscopic examination shows dilated, tortuous retinal veins in early disease. With more advanced disease, retinal hemorrhages, microaneurysms, and sausage-like segmentation of dilated retinal veins occur as the result of hyperviscosity (Fig. 9). Neurologic disturbances, including peripheral neuropathy, acute cerebral dysfunction, confusion, and coma, occur with elevated serum viscosity. Congestive heart failure may result from hypervolemia.

Laboratory Features

Normochromic, normocytic anemia is present in about 90% of patients with WM. The etiology of the anemia is multifactorial. An expanded

plasma volume due to elevated levels of IgM causes hemodilution. Shortened red cell survival has been described. The Coombs' test is usually negative. The leukocyte and platelet counts are usually normal. However, abnormal platelet function occurs as a result of coating of platelets with IgM protein. The macroglobulin may impair blood coagulation by inhibition of fibrin-monomer aggregation which can be detected by prolongation of the thrombin time. The erythrocyte sedimentation rate is often greatly elevated.

The serum viscosity relative to water is greater than 4 (normal 1.4 to 1.8) in more than one-third of patients and is proportional to the serum macroglobulin level.

The SPEP reveals a narrow, tall, homogeneous band in the region between β and γ. The IEP show this paraprotein to be IgM (Fig. 10). Approximately 80% of the cases are κ light chain subtype. Bence Jones proteinuria occurs in about one-quarter of patients. In contrast to multiple myeloma, the concentrations of normal immunoglobulin are not depressed.

Bone marrow examination often reveals a characteristic morphology that distinguishes WM from multiple myeloma. The aspirate is often difficult to obtain, and it may be hypocellular. However, the marrow biopsy sections are hypercellular and may be confused with lymphoma or multiple myeloma. The hallmark of WM is the presence of large numbers of plasmacytoid lymphocytes. These cells have morphologic features intermediate between lymphocytes and the mature plasma cell. Occasionally, PAS (periodic acid-Schiff) -staining intracellular globulins are seen in marrow lymphocytes. When seen in the nuclei of these typical plasmacytoid lymphocytes, they are diagnostic of WM.

Skeletal radiographs are useful in distinghishing WM from multiple myeloma. Lytic lesions are extremely rare in WM, although osteoporosis can occur.

Differential Diagnosis

Waldenström's macroglobulinemia is usually easily distinguished from multiple myeloma. WM may be confused, however, with chronic lymphocytic leukemia or malignant lymphoma, both of which may be associated with marcroglobulinemia. The distinction between WM and these entities is sometimes arbitrary. The level of IgM is usually higher (>2 g/dl) in WM and tends to increase over time. Benign monoclonal gammopathy (BMG) of the IgM type is distinguished from WM by the lack of signs of malignancy, the lower levels of monoclonal IgM, and stability of the IgM paraprotein over time. BMG rarely evolves into WM. A referral to a hematologist should be made if WM is suspected.

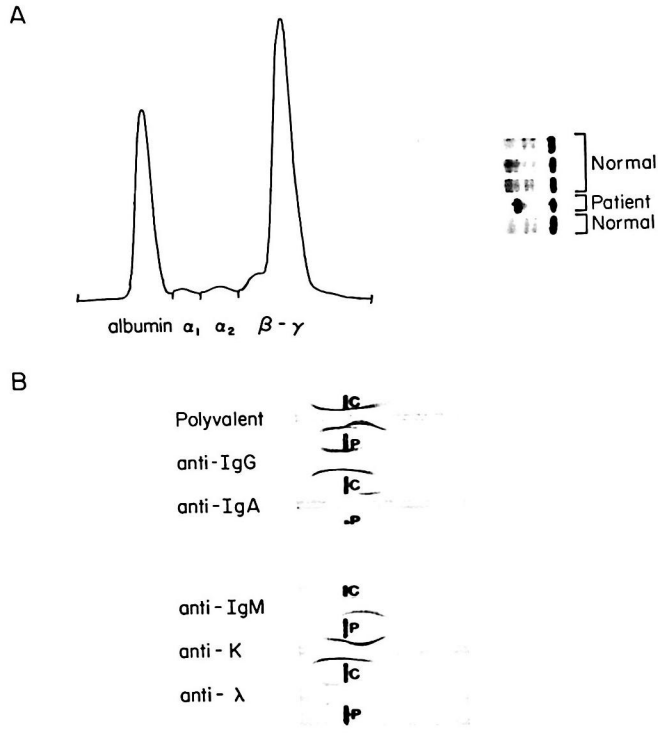

Figure 10 (A) Serum protein electrophoresis showing a spike in the β - γ region and a dense homogeneous band on the cellulose acetate strip. (B) Immunoelectrophoresis of the same serum showing abnormal arcs in the IgM and κ patterns. This patient has Waldenström's macroglobulemia of IgM-κ type.

Course and Treatment

Waldenström's macroglobulinemia is a slowly progressive disease. Patients often live for years after the diagnosis is made. Causes of death include infection, hyperviscosity, and hemorrhage.

Plasmapheresis is the safest and most rapid means of reducing the serum viscosity. This effect is achieved by reducing the serum

concentration of macroglobulin. Plasmapheresis should be employed immediately in patients who present with the hyperviscosity syndrome and should be repeated as needed.

Chlorambucil (Leukeran), an oral alkylating agent, has been the chemotherapeutic agent most often used to control the disease over long periods of time. The most frequent side effect is bone marrow suppression.

HEAVY CHAIN DISEASES

The heavy chain diseases (HCDs) are neoplastic disorders of the lymphoid-plasma cell series in which a structurally abnormal immunoglobulin heavy chain fragment is produced. In most cases, the Fc portion of the molecule is intact, but there is a major deletion in the Fd region (Fig. 1). Light chains are usually not produced by the neoplastic cells. Three types of HCD are recognized. In the proper clinical setting, HCD is diagnosed by the demonstration of a monoclonal protein that reacts with antisera to a heavy chain (α, γ, μ) but does not react with light-chain antisera (κ or λ) on IEP. Because of their rarity and the lack of standardized treatment modalities, patients with these diseases should be referred to a hematologist or oncologist.

γ-HCD

γ-HCD (Franklin's disease) was the first type of HCD to be described. Most patients are elderly, but several patients under 40 years of age have been observed. The clinical features resemble malignant lymphoma more than multiple myeloma. Fever, malaise, hepatosplenomegaly, generalized lymphadenopathy, and anemia are prominent features. Involvement of lymph nodes in Waldeyer's ring may give rise to erythema and edema of the uvula and palate, which is uncommon in other types of lymphoma, but also occurs in patients with infectious mononucleosis.

The abnormal protein can be detected in the urine of more than 50% of patients by IEP. Serum protein electrophoresis often shows a broad-based spike. There is usually marked depression of normal serum immunoglobulin levels.

The pathologic features include tissue infiltration with plasma cells, lymphocytes, and eosinophils. An increase in plasma cells, lymphocytes, and eosinophils can also occur in the bone marrow. There are no diagnostic histopathologic findings, and in some cases the diagnosis of granulomatous diseases or Hodgkin's disease has been erroneously made.

The course of the disease is variable but may be rapidly progressive over a few months. Some patients have survived longer than 5 years. Death is usually due to infection or progressive tumor infiltration. Preferred

treatment has not been established but has included drugs that are active against malignant lymphoma.

α-HCD

α-HCD (mediterranean lymphoma and western lymphoma) is the most common type of heavy chain disease. It occurs most commonly in patients under the age of 50 (in the Mediterranean type), although in the United States older patients may be affected (western type). Lymphoplasmacytic proliferation is prominent in the IgA producing organs, particularly the gastrointestinal tract. The usual presenting manifestations in the Mediterranean type are a severe malabsorption syndrome associated with diarrhea, steatorrhea, weight loss, and hypocalcemia. In contrast, patients with western type often present with bowel obstruction. Abdominal masses and abdominal pain are frequent in both types. Like γ-HCD, hypogammaglobulinemia is common, but Bence Jones proteinuria is not a feature. Remissions of α-HCD may be induced by treatment with antibiotics very early in the course, suggesting that infection plays an etiologic role. Patients with more advanced disease require chemotherapy for maligant lymphoma. Late in the course of this disease, features typical of immunoblastic sarcoma may develop.

μ-HCD

μ-HCD is a rare disorder that is usually associated with chronic lymphocytic leukemia (CLL) of long duration. Unlike CLL, however, enlarged lymph nodes are infrequent, and most patients excrete large amounts of κ light chains in the urine. Vacuolated plasma cells in the bone marrow are a common finding. Treatment is usually directed toward the underlying CLL.

AMYLOIDOSIS

The term amyloidosis encompasses a heterogeneous group of disorders characterized by deposition of a homogeneous, eosinophilic material in various tissues. This material can be demonstrated by staining with Congo red or other metachromatic dyes. Despite the homogeneous appearance of this fibrillar substance among patients with amyloidosis, several different types of amyloid proteins have been biochemically and immunologically defined.

Some forms of amyloidosis are closely related to plasma cell dyscrasias and monoclonal gammopathies. The classification of amyloidosis has

Table 6 **Classification of Amyloidosis**

Type	*Amyloid Protein*	*Distribution of Amyloid Deposits*	*Associated Conditions*	*Clinical Manifestations*	*Relative Frequency (%)*
I (Primary)	AL	Tongue, heart, GI tract, muscles, ligaments, skin (mesenchymal)	Monoclonal gammopathy (usually Bence Jones); overt myeloma or other plasma cell dyscrasias	Cardiac failure, macroglossia, malabsorption, neuropathy, carpal tunnel syndrome, purpura, arthropathy, bleeding	50
II (Secondary)	AA	Liver, spleen, kidney, adrenal (parenchymal)	Chronic infections, rheumatoid arthritis Hodgkin's disease, renal cell carcinoma, FMF	Hepatosplenomegaly, hepatic failure, renal failure, nephrotic syndrome	17
Mixed I and II	Unknown	Mesenchymal or parenchymal sites	Monoclonal gammopathy	Mixed	30
Localized	Variable	Lung, GI tract, eye, endocrine organs	Extramedullary plasmacytoma, endocrine tumors; monoclonal gammopathy in some	Localized tumors	3

SOURCE: Modified from Isobe T, Osserman EF: Patterns of amyloidosis and their association with plasma cell dyscrasia, monoclonal immunoglobulins and Bence-Jones proteins. *N Engl J Med* 290:473-477, 1974.

recently undergone revision as a result of a more thorough understanding of the immunochemistry of the amyloid proteins. A currently acceptable scheme for the classification of amyloidosis is shown in Table 6.

Primary or Myeloma-Related Amyloidosis (Pattern I)

Amyloid fibrils in this type are composed of immunoglobulin light chain fragments and are called amyloid L-chain (AL) protein. The distribution of amyloid infiltration predominantly involves the tongue, heart, kidneys, gastrointestinal tract, and skeletal muscle. Common symptoms include macroglossia, carpal tunnel syndrome, articular manifestations, congestive heart failure, and peripheral neuropathy. Renal involvement may occur but is less common than in secondary amyloidosis. A bleeding tendency is also common due to amyloid infiltration of small blood vessels. The bleeding tendency may be aggravated by concomitantly acquired factor X deficiency, which is due to binding of this factor to amyloid fibrils. The bleeding diathesis most frequently causes cutaneous bleeding, particularly in a periorbital distribution ("raccoon eyes"), although more serious hemorrhage can occur. Deficiency of factor X is suggested by prolongation of the prothrombin time, activated partial thromboplastin time, or both.

Secondary Amyloidosis (Pattern II)

In secondary amyloidosis the amyloid fibrils are composed of amyloid A (AA) protein, which is unrelated to immunoglobulin light chains. Secondary amyloidosis is associated with a variety of chronic diseases, including rheumatoid arthritis, ulcerative colitis, Hodgkin's disease, renal cell carcinoma, familial Mediterranean fever (FMF), leprosy, paraplegia, chronic infections, and other inflammatory conditions.

Secondary amyloid deposits are commonly found in the liver, spleen, kidneys, and adrenals; less commonly, the gastrointestinal tract, heart, or musculoskeletal system is involved. Patients with secondary amyloidosis present with hepatosplenomegaly and renal abnormalitites. Renal vein thrombosis and renal failure are most frequent with this type of amyloidosis. Secondary amyloidosis, and the familial types of amyloidosis usually are not associated with monoclonal proteins, although some forms of localized amyloidosis are.

Diagnosis and Treatment

The diagnosis of all types of amyloidosis rests on biopsy of involved tissue and demonstration of the typical staining with Congo red dye and

birefringence under polarizing light. Rectal or gingival biopsy is sufficient to demonstrate amyloid deposition in the vast majority of patients. Because of the potential for coagulation abnormalities, a prothrombin time and activated partial thromboplastin time are indicated before any biopsy procedure.

Distinguishing amyloidosis from multiple myeloma is essential. A bone marrow aspiration and biopsy are indicated to exclude a systemic plasma cell dyscrasia. Furthermore, the bone marrow may show typical amyloid deposits. Skeletal lesions are not associated with amyloidosis in the absence of myeloma.

Treatment should be directed at the underlying disease. Treatment of primary amyloid in the absence of multiple myeloma or Waldenström's macroglobulinemia has been disappointing and may be hazardous. In secondary amyloidosis, control of the underlying disease process may lead to regression of amyloid deposits.

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Monoclonal gammopathy of undetermined significance refers to the presence of a monoclonal paraprotein in association with one of a heterogenous group of diseases but without evidence of multiple myeloma, Waldenström's macroglobulinemia, or amyloidosis (Table 1). Monoclonal gammopathy of undetermined significance has been described in association with malignant lymphoma, nonreticular neoplasms, chronic inflammatory, infectious, and neurologic diseases, and in association with lipid storage diseases (e.g., Gaucher's disease). However, the commonest type is that which exists without any associated neoplasm and is called benign monoclonal gammopathy (BMG) (Table 7).

Benign Monoclonal Gammopathy

BMG is the most frequent cause of monoclonal paraproteinemia. It occurs in approximately 3% of patients over the age of 70, and the incidence may be as high as 12% in patients over age 80. The mean age at diagnosis is 60 years, with an age range similar to that for multiple myeloma.

The history and physical examination are unrevealing in these patients. The complete blood count is normal, unless some other disease process is present. The erythrocyte sedimentation rate is elevated in the majority of patients. Bone marrow examination, renal function tests, serum calcium and serum albumin are all normal, and no lytic bone lesions are seen.

Serum protein electrophoresis and serum immunoelectrophoresis show monoclonal IgG, IgA, or IgM in most cases. In one large study the level of

Table 7 Diseases Associated with Monoclonal Protein

	Total	
Disease	*No.*	*%*
None	62	26
Cardiac and cerebrovascular	31	13
Inflammatory	26	11
Malignant	16	7
Connective tissue	14	6
Neurologic	15	6
Benign tumor	8	3
Hematologic	9	3.5
Endocrine	9	3.5
Miscellaneous	51	21
Totals	241	100

SOURCE: Reprinted with permission from Kyle RA: Monoclonal gammopathy of undetermined signifance: Natural history in 241 cases. *Am J Med* 64:814-826, 1978.

monoclonal proteins was less than 2.6 g/dl in 96% of cases. The level increased by more than 50% of the initial value over time in only 9% of these patients. Patients with more than 2 g/dl of IgG, 1 g/dl of IgA, or 2 g/dl of IgM monoclonal protein must be suspected of having multiple myeloma or Waldenström's macroglobulinemia. Urine immunoelectrophoresis reveals Bence Jones proteinuria in a minority of patients. Quantitative immunoglobulin determination may reveal depressed levels of normal immunoglobulin in up to one-third of patients. A comparison of the features of BMG and multiple myeloma is shown in Table 8.

About 11% of patients with BMG will eventually develop multiple myeloma, WM or amyloidosis if followed over long periods of time. At present, it is impossible to predict which patients are at risk for developing a malignant monoclonal gammopathy. Therefore, periodic reexamination is necessary. No treatment for BMG is indicated.

Monoclonal Gammopathies Associated with Neoplasia

Monoclonal gammopathy has been reported in association with all histologic types of malignant lymphoma and with Hodgkin's disease. The paraprotein is usually present in low concentrations (<2.0 g/dl) and is most often IgM type.

Table 8 The Relative Frequency of Various Signs in Multiple Myeloma and in Benign Monoclonal Gammopathy

	Myeloma	*Benign Monoclonal Gammopathy*
Bone destruction	++++	–
Plasma cells (bone marrow)		
>20%	++++	–
20-10%	+++	(+)
<10%	+	+++
Atypical	+++	+
Normal	+	+++
Bence Jones protein	(+)+++	(+)
M-component		
>3.0g/dl	++++	?
3.0-2.0g/dl	++	++
2.0-1.0g/dl	+	+++
<1.0g/dl	(+)	(+)+++
Increasing concentration	+++	(+)
γ fraction: normal concentration	+	(+)+++
Serum albumin: normal concentration	+	+++
Erythrocytes: normal number	+	+++

SOURCE: Modified with permission from Waldenström, JG: Benign monoclonal gammopathy, in Williams, WJ (ed): *Hematology*. New York, McGraw-Hill Book Company, 1977, pp 988-991.

Key: ++++ = frequent occurrence; +++ = common; ++ = occasional; + = infrequent; – = extremely rare.

Monoclonal proteins also occur in patients with nonreticular neoplasms, particularly adenocarcinoma of the rectosigmoid, prostate, and breast. The monoclonal protein in these patients is usually of IgG type. The significance of monoclonal gammopathy occurring in these patients is undetermined.

CASE HISTORY

A 79 year-old man was seen for evaluation of severe back pain. The pain began gradually and was not associated with trauma or neurologic

symptoms. The patient denied a history of recent infections, weight loss, or polyuria.

The patient had a history of benign monoclonal gammopathy since 1965. At that time the M-protein level was 1.5 g/dl and was noted to be IgG type. In recent years the level of the M-protein was 2.5 g/dl.

Physical examination revealed bony tenderness over the lumbar spine that impaired ambulation. There was no neurologic deficit. There was no hepatosplenomegaly.

Laboratory studies revealed a normochromic, normocytic anemia,with a hematocrit of 0.34. The Westergren ESR was 51 mm/hr. Serum electrolytes, including serum calcium, were normal. The serum creatinine was 2.0 mg/dl.

X-ray examination of the lumbar spine showed severe osteoporosis and an old compression fracture of L-2. A skull series showed osteoporosis. No lytic lesions were seen.

SPEP revealed a narrow band in the γ-region, which measured 5.4 g/dl. IEP demonstrated an IgG-κ M protein. Urine protein electrophoresis and immunoelectrophoresis were normal. QIG showed marked depression of IgA and IgM and elevated IgG. Bone marrow aspiration and biopsy revealed 50% plasma cells, occasionally occurring in sheets.

The patient was diagnosed as having multiple myeloma. Melphalan and prednisone were started. A course of radiotherapy to the lumbar spine greatly improved the back pain.

Questions

1. BMG may evolve into a malignant monoclonal protein disorder in approximately 11% of patients. True or false?
2. The absence of lytic bone lesions makes the diagnosis of multiple myeloma questionable. True or false?
3. The clinical stage (Table 3) of this patient is _____, which is associated with an intermediate prognosis.

Discussion

This patient had a stable BMG for many years that subsequently evolved into multiple myeloma. In the large series of monoclonal gammopathy of undetermined significance reported by Kyle, about 11% of patients eventually developed multiple myeloma, Waldenström's macroglobulinemia, or amyloidosis. Unfortunately, it is impossible to predict which patients are at risk for developing a malignant monoclonal gammopathy.

Osteoporosis may be the most common radiographic finding in multiple myeloma, although lytic bone lesions are seen frequently. The other common radiographic finding is fractures, particularly in vertebral bodies.

The staging system of Durie and Salmon would place this patient in the intermediate myeloma cell mass category (II) due to the intermediate M-protein levels, the intermediate bone disease, and the normal serum calcium. The serum creatinine of 2.0 mg/dl subclassifies this patient as Stage II_B.

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11

JOHN H. FITCHEN

Pancytopenia and Bone Marrow Failure

Pancytopenia means a reduction in the level of all of the formed elements of the blood, resulting in the combination of anemia, leukopenia, and thrombocytopenia. Pancytopenia occurs in a variety of disorders and may result from the destruction of blood cells in the circulation or from failure of the bone marrow to produce adequate numbers of blood cells. The focus of this chapter will be on the latter circumstance: pancytopenia due to failure of the bone marrow to produce blood cells.

Bone marrow failure resulting in pancytopenia can occur by three basic mechanisms: ineffective hematopoiesis (hypercellular marrow with decreased production), myelophthisis (replaced marrow), and marrow hypoplasia (empty marrow). Although each of these processes reults in pancytopenia, it is crucial to the intelligent management of patients to differentiate among them. It is axiomatic in this regard that accurate diagnosis and effective management of pancytopenia cannot be accomplished without evaluation of bone marrow cellularity and morphology.

Bone marrow failure is not always global and may effect only a single hematopoietic lineage (e.g., agranulcytosis). The general principles that dictate the approach to patients with pancytopenia are applicable to patients with selective bone marrow failure, and only special features of these latter syndromes will be discussed.

CLINICAL MANIFESTATIONS OF PANCYTOPENIA

Irrespective of the mechanisms by which pancytopenia is produced, the clinical manifestations are similar. The symptoms that develop in pancytopenic patients are the result of anemia, leukopenia, and thrombocytopenia. The onset of symptoms is often insidious but may occasionally be acute and fulminant. Patients may complain of weakness, easy fatigability, and exertional dyspnea because of anemia, or the presenting complaint may be related to a bleeding diathesis (purpura, epistaxis) secondary to thrombocytopenia or to the increased susceptibility to infection that results from leukopenia. Because the manifestations attributable to hemorrhage and infection depend on the location of the bleeding and the site and nature of the infectious process, the clinical picture may vary greatly.

The physical findings in pancytopenia are nonspecific. Anemia produces pallor and tachycardia, and thrombocytopenia may result in purpura. However, a careful physical examination is important as it may yield clues to the underlying process. For example, an enlarged spleen suggests the possibility of peripheral destruction of blood cells due to hypersplenism rather than decreased production of blood cells due to marrow failure. The finding of splenomegaly is not conclusive, however, since an enlarged spleen can also occur in disorders that cause bone marrow failure, such as the lymphoproliferative disorders or myelofibrosis with myeloid metaplasia. Other diagnostic clues revealed by the physical examination will be considered in the sections on specific causes of pancytopenia.

Laboratory evaluation of patients with pancytopenia reveals anemia (Hgb <12.0 g/dl), leukopenia (WBC $<4.5 \times 10^9$/liter) with neutropenia (absolute neutrophil count $<2.5 \times 10^9$/liter) and thrombocytopenia (platelet count $<140 \times 10^9$/liter). The reticulocyte count is particularly important as it helps to differentiate between peripheral destruction of red cells and failure of bone marrow production; the reticulocyte count is usually elevated in hypersplenism and other disorders involving peripheral destruction of red cells and normal or reduced in marrow failure syndromes. Bone marrow aspiration and biopsy are always indicated in the evaluation of pancytopenia since accurate diagnosis and intelligent management are impossible without the information gained from this procedure. Physicians sometimes hesitate to perform bone marrow biopsy in patients with severe thrombocytopenia for fear of untoward bleeding at the biopsy site. However, this fear is unwarranted, and bone marrow evaluation should never be postponed or omitted because of a low platelet count; if bleeding does occur, it can almost always be stopped with adequate pressure. Bone marrow evaluation should include needle biopsy

in order to obtain an accurate assessment of marrow cellularity. The bone marrow aspirate smear is very useful for morphologic detail but is unreliable for assessing marrow cellularity. Other laboratory tests in the evaluation of pancytopenia depend upon the findings in the peripheral blood and bone marrow and are directed at determining the underlying cause of the pancytopenia.

PANCYTOPENIA DUE TO INEFFECTIVE HEMATOPOIESIS

Ineffective hematopoiesis refers to situations in which the bone marrow is hypercellular but is defective in generation of mature circulating blood cells.

Causes of Ineffective Hematopoiesis

Ineffective production of blood cells by a hypercellular bone marrow can result from intrinsic abnormalities of the nucleated cells in the bone marrow or from a deficiency of factors essential for normal nuclear maturation. The latter situation occurs in folate and B_{12} deficiency, problems which are discussed in detail in chapter 1. Intrinsic abnormalities of nucleated bone marrow cells occur in a group of idiopathic disorders referred to as the *myelodysplastic syndromes* (MDS). These disorders have in common a defective production of red blood cells that is unresponsive to any treatment. They are, therefore, often referred to collectively as the refractory anemias. Because granulopoiesis and thrombopoiesis may also be abnormal, the term myelodysplastic syndromes is preferable to refractory anemia. In the past, it was believed that acute leukemia ultimately evolved in most of these patients, and the term preleukemia was, therefore, applied to these disorders. However, the incidence of acute leukemia is variable in different subgroups of MDS and the term preleukemia should be used in a retrospective fashion only.

Clinical and Laboratory Features

The myelodysplastic syndromes have been divided into three distinct groups: acquired idiopathic sideroblastic anemia (AISA), refractory anemia with excess blasts (RAEB), and chronic myelomonocytic syndrome (CMMS). All are disorders that occur predominantly in patients over 50 years of age. Physical examination is usually normal or may reveal splenomegaly.

The laboratory manifestations of the myelodysplastic syndromes are summarized in Table 1. Common to all three groups are anemia, reticulo-

Table 1 Laboratory Manifestations of Myelodysplastic Syndromes

	AISA	*RAEB*	*CMMS*
Peripheral Blood			
Hemoglobin	↓	↓	↓
Reticulocytes	↓	↓	↓
White blood count	N or ↓	↓	Variable
PMNs	N or ↓	↓	↓
Monocytes	N	N	↑
Bone Marrow			
Cellularity	↑	↑	↑
Erythroblasts	↑	N or ↓	N or ↓
Dyserythropoiesis	+	+	+
Ringed sideroblasts	++	±	±
Percent myeloblasts	N	↑	↑
Incidence of acute leukemia	10%	25-30%	50%

Key: N = normal; ↓ = decreased; ↑ = increased.

cytopenia, and dyserythropoietic bone marrow morphology. In the peripheral blood, the red cells are normochromic and normocytic, but anisocytosis, poikilocytosis, and basophilic stippling are common. Occasionally, dimorphic populations of hypochromic and normochromic red cells may coexist. Neutropenia is frequent in all three disorders. Polymorphonuclear leukocytes may be morphologically abnormal with decreased granulation of the cytoplasm and a Pelger-Huët anomaly of the nucleus. Monocytosis is common in CMMS, and thrombocytopenia frequently accompanies RAEB and CMMS. A hypercellular bone marrow with dyserythropoietic changes is seen in all three categories. The morphologic abnormalities of erythropoiesis include megaloblastic changes indistinguishable from those seen with folate or B_{12} deficiency, multinucleation, nuclear budding, cytoplasmic vacuolization, and excessive amounts of iron in mitochondria (especially in AISA in which ringed sideroblasts are a uniform feature). Cytogenetic analysis of the bone marrow may reveal aneuploidy and various chromosomal aberrations, but the significance and prognostic value of such abnormalities are controversial.

Diagnosis

The diagnosis of MDS rests upon the findings of refractory anemia and a hypercellular, dyserythropoietic bone marrow, without evidence of folate

or B_{12} deficiency. Distinctive features of AISA, RAEB, and CMMS are outlined in Table 1. AISA has prominent ringed sideroblasts in the bone marrow; RAEB is characterized by increased myeloblasts in the bone marrow; and peripheral blood monocytosis is a distinguishing feature of CMMS. A major problem may be to distinguish RAEB from acute myelogenous leukemia (AML). Serial examinations of the bone marrow will resolve this problem as the percentage of myeloblasts remains relatively stable in RAEB but increases rapidly in AML.

A degree of overlap exists among the three categories of MDS, but it is important to attempt to make a specific diagnosis of AISA, RAEB, or CMMS because the incidence of acute leukemia varies depending upon the category into which the patient fits. AML is relatively infrequent in AISA (about 10%), occurs in 25-30% of pateints with RAEB, and in approximately 50% of patients with CMMS.

The diagnosis of MDS should be entertained in any patient with chronic anemia for which another explanation cannot be found (e.g., iron deficiency, folate deficiency, chronic renal failure). Subtle cases may require referral to a hematologist, and since MDS may evolve into acute leukemia, even typical cases should probably be reviewed by a hematologist for confirmation.

Management

There is no specific therapy for MDS. Folic acid is often given because of the resemblance to megaloblastic anemia, but the drug is not effective in MDS unless true folate deficiency also exists. Androgens have been tried but are rarely effective in raising hemoglobin levels. Occasional responses to corticosteroids have been reported, but because of the side effects of this form of therapy (particularly an increased risk of infection in patients who are already leukopenic), steroids should be reserved for carefully selected patients in whom in vitro marrow culture studies show a likelihood of responsiveness. These studies are available only at major research centers.

Supportive therapy is effective in alleviating symptoms in patients with MDS. Red blood cell transfusions should be given if anemia is symptomatic. Platelet transfusions should be used to manage clinically significant bleeding (major gastrointestinal bleeding or intracranial hemorrhage) but are not usually indicated for purpura. Prompt evaluation of intercurrent infections with appropriate cultures and institution of broad-spectrum antibiotics may be lifesaving.

Chemotherapy is not advisable in MDS, since many patients remain stable for months or years without treatment. Cytotoxic drugs should be withheld until a picture of frank leukemia develops, as some patients treated with aggressive chemotherapy may die of infectious complications

during the period of unusually profound and prolonged marrow aplasia induced by this treatment in MDS.

PANCYTOPENIA DUE TO MYELOPHTHISIC PROCESSES

The term myelophthisis comes from the Greek (myelos: marrow + phthisis: a wasting away), and refers to situations in which the normal hematopoietic elements of the bone marrow are replaced by fibrosis or nonhematopoietic cells. The result is bone marrow failure and pancytopenia.

Causes of Myelophthisis

The causes of myelophthisic bone marrow failure are listed in Table 2. Myelofibrosis can occur in association with any of the myeloproliferative disorders (see chapter 7) but is most commonly seen in agnogenic myeloid metaplasia. It is also seen frequently as a late sequela of polycythemia rubra vera. Infiltration of the marrow space by nonhematopoietic cells occurs in hematologic neoplasia (leukemia, lymphoma, and mulitple myeloma) and metastatic carcinoma from lung, breast, prostate, melanoma, thyroid, kidney, or stomach primaries. Hairy-cell leukemia, a lymphoproliferative disorder discussed more fully in chapter 8, usually presents with pancytopenia due to marrow infiltration and splenomegaly. Rare causes of myelophthisis include replacement of the marrow by fat-laden macrophages in Gaucher's disease or by granulomata in tuberculosis and histoplasmosis.

Clinical and Laboratory Features

The presenting complaints of some patients with pancytopenia due to myelophthisic processes are like those of pancytopenia from any cause; in others, symptoms attributable to the underlying disease may predominate. For example, patients with myelofibrosis and agnogenic myeloid metaplasia often have massive splenomegaly and may present with complaints of abdominal fullness or early satiety. Other examples are enlarged lymph nodes in patients with lymphoma, low back pain due to pathologic vertebral fractures in patients with multiple myeloma, and persistent fever in patients with miliary tuberculosis.

The degree of pancytopenia in patients with myelophthisic disorders depends upon the extent of marrow involvement by the primary process. With early myelofibrosis or carcinoma metastatic to the bone marrow,

Table 2 Causes of Myelophthisic Bone Marrow Failure

Myelofibrosis
Agnogenic myeloid metaplasia
Late ("burnt out") polycythemia rubra vera
Other myeloproliferative disorders
Hematologic neoplasia
Leukemia
Lymphoma
Multiple myeloma
Metastatic carcinoma
Lung cancer
Breast cancer
Prostate cancer
Malignant melanoma
Thyroid cancer
Hypernephroma
Stomach cancer
Other
Gaucher's disease
Disseminated tuberculosis
Histoplasmosis
Sarcoidosis

pancytopenia is often mild, whereas with primary hematologic malignancies, such as leukemia and lymphoma, the reduction of the peripheral blood counts is frequently more pronounced. Marked anisocytosis and poikilocytosis, particularly with teardrop forms, may be prominent findings in patients with extramedullary hematopoiesis. In addition to anemia, leukopenia, and thrombocytopenia, patients with myelophthisic disorders often have laboratory abnormalities that reflect the underlying disease. These findings include a monoclonal protein spike on serum protein electrophoresis and lytic bone lesions in patients with multiple myeloma, an elevated serum acid phosphatase level in patients with carcinoma of the prostate, and miliary infiltrates on the chest roentgenogram in patients with disseminated tuberculosis. These examples are a few of the many laboratory abnormalities that may be encountered in patients with myelophthisic disorders, all of which depend upon the underlying

disease. Clues obtained from the history and physical examination should dictate which tests are appropriate to order.

One laboratory feature of particular importance in patients with myelophthisic disorders deserves special emphasis. This is the finding of immature white blood cells and nucleated red blood cells on the peripheral blood smear. This finding is often noted by hematology laboratory technicians and should prompt review of the slide by the attending physician. The appearance of immature white and red blood cells in the peripheral blood is referred to as a leukoerythroblastic picture. It is believed to result from the early release of bone marrow cells into the circulation because of disruption of the sinusoidal architecture of the bone marrow by the myelophthisic process.

The cellularity and morphology of the bone marrow in myelophthisic disorders depend upon the underlying disease. In myelofibrosis, the marrow is usually hypocellular; special stains reveal a marked increase in reticulin deposition (Fig. 1). In leukemia, lymphoma, and multiple myeloma, the marrow is often hypercellular with a monotonous infiltration of mononuclear cells. In multiple myeloma, malignant plasma cells are characteristically found in clusters. Carcinoma metastic to the bone marrow also frequently appears as clumps or syncytia of large, immature cells. The ability to determine the site of primary tumor based on the morphology of the metastatic cells in the bone marrow generally depends upon the degree of differentiation of the primary tumor. Bone marrow granulomas may be observed in the biopsy, and special stains may demonstrate infectious microorganisms. Gaucher's disease can usually be recognized by the presence of lipid-laden macrophages with the typical appearance of "cigarette paper" cytoplasm.

Diagnosis

Examination of the peripheral blood film and bone marrow are usually sufficient to establish that pancytopenia is due to a myelophthisic process. A leukoerythroblastic picture on the peripheral smear strongly suggests this diagnosis, and the impression is confirmed by the findings in the bone marrow. The diagnosis of pancytopenia due to a myelophthisic process is only a start, however, as it is crucial to determine the nature of the underlying disorder. With some diseases, the diagnosis is readily apparent from examination of the bone marrow (for example, in acute leukemia the marrow is packed with blast cells), but, at times, elucidation of the underlying process may present a major diagnostic challenge. For example, carcinoma metastic to the bone marrow may be missed on the initial bone marrow biopsy since the metastatic cells tend to occur in clumps or islands with a patchy distribution. Therefore, in patients with pancytopenia and a leukoerythroblastic blood picture, if the initial bone marrow examina-

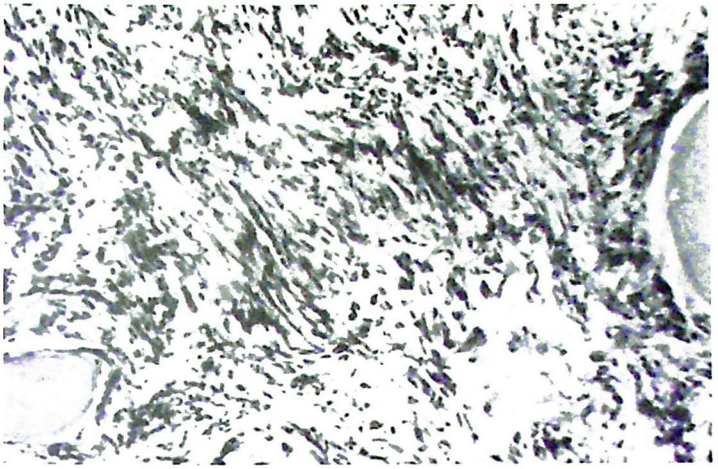

Figure 1 Reticulin stain of bone marrow biopsy showing hypocellularity and marked marrow fibrosis.

tion is unrevealing, bone marrow biopsy should be repeated at another site.

Management

Supportive care with transfusions and prompt treatment of intercurrent infections is indicated in patients with pancytopenia due to myelophthisic processes but should not replace a thorough search for the underlying disorder. Once the primary diagnosis has been established, specific treatment can be instituted, and if the primary disease responds to therapy, the pancytopenia will resolve. Worthy of reemphasis in this regard is the principle that the recognition of a myelophthisic process should prompt an evaluation to determine the underlying etiology.

PANCYTOPENIA DUE TO HYPOPLASTIC BONE MARROW FAILURE (APLASTIC ANEMIA)

The finding of pancytopenia in association with a hypocellular bone marrow has been referred to for decades as aplastic anemia. This term is

misleading because it focuses attention on anemia without mention of leukopenia or thrombocytopenia and because the bone marrow in these patients is rarely totally aplastic. Hypoplastic bone marrow failure is a more descriptive term, but aplastic anemia will be retained in this discussion because of its general usage in the medical literature.

With the exception of acute leukemia, none of the causes of pancytopenia is as dramatic and life threatening as aplastic anemia. In the past, little could be done for these patients. The recent development of bone marrow transplantation has provided a potentially curative treatment for aplastic anemia, and early diagnosis and prompt referral are now of paramount importance.

Causes of Aplastic Anemia

In the majority of patients, no etiology for aplastic anemia can be identified. In some patients, however, a clear relationship exists between an inciting or toxic event and the development of aplasia. An etiologic classification of aplastic anemia is shown in Table 3.

Drug-induced aplastic anemia occurs by several mechanisms. Some drugs are uniformly toxic to the bone marrow and produce marrow failure in a dose-related fashion. Many of the drugs used in cancer chemotherapy have this effect, and it is for this reason that blood counts are closely monitored in patients receiving chemotherapy. Organic solvents, such as benzene, have also been implicated in the etiology of aplastic anemia, although the mechanism by which they produce marrow damage and whether the effect is dose related or idiosyncratic is not clear. A large number of drugs have been reported to cause aplastic anemia in a sporadic or idiosyncratic fashion. In many cases, a definite cause and effect relationship between administration of a drug and the development of

Table 3 Causes of Aplastic Anemia

Drug-induced
Dose-related (e.g., chemotherapy)
Toxic chemical (e.g., benzene)
Idiosyncratic (e.g., chloramphenicol)
Posthepatitic
Other
Infections (tuberculosis, viral)
Paroxysmal nocturnal hemoglobinuria
Idiopathic

aplastic anemia has not been established. Nevertheless, certain classes of drugs are causally associated with aplastic anemia in occasional patients. These drugs are listed in Table 4.

Chloramphenicol is by far the most frequently implicated drug in the causation of idiosyncratic drug-induced aplastic anemia. This antibiotic produces some degree of bone marrow suppression, particularly of the erythroid series, in all patients who receive it, but only a small portion develop irreversible aplastic anemia. At present there is no way to predict which patients will have the severe type of reaction, so the drug must be used only when it is clearly indicated and alternative drugs are not available. Particularly worrisome is the fact that aplastic anemia may develop as long as 6 months after chloramphemicol is discontinued.

In most cases, the etiology of aplastic anemia has no effect on the clinical course of the disease. A notable exception is posthepatitic aplastic anemia; this rare disorder has a particularly grave prognosis. Most cases have occurred in patients with HB_SAg-negative hepatitis, and aplasia usually occurs after the hepatitis has resolved. The occurrence of post-hepatitic aplastic anemia in siblings has been reported, suggesting that there may be a genetic predisposition to this disorders.

Clinical Spectrum

There is considerable variability in the clinical severity of aplastic anemia. Some patients have a rapid downhill course and die of infection or hemorrhage. Others, whose cytopenias are less pronounced, may live for years with moderate pancytopenia and few symptoms. Since early bone marrow transplantation offers effective treatment for aplastic anemia, it is crucial to the management of aplastic anemia to identify those patients whose course will be acute. Although there are no exact criteria to identify

Table 4 **Drugs Clearly Implicated in the Etiology of Idiosyncratic Drug-Induced Aplastic Anemia**

Chloramphenicol
Phenylbutazone (Butazolidin)
Diphenylhydantoin (Dilantin) and mephenytoin (Mesantoin)
Gold compounds
Sulfonamides
Tolbutamide (Orinase)
Prophylthiouracil and methimazole (Tapazole)
Chlorpromazine (Thorazine)

such patients, the prognosis is poorest in patients whose pancytopenia and marrow hypocellularity are the most profound. From this knowledge has emerged the designation severe aplastic anemia which is defined as follows:

Blood: Absolute neutrophil count $<0.5 \times 10^9$/liter
Platelet count $<20 \times 10^9$/liter
Reticulocyte count (corrected) $<1.0\%$

Marrow: Moderate to severe hypocellularity on bone marrow biopsy
Hematopoietic cells comprise $<30\%$ of the remaining cells

Patients who meet these criteria have a median survival of only 3 months when treated with supportive therapy alone.

Less severe forms of the disease are also serious but are compatible with prolonged survival. Thus, patients with aplastic anemia who survive more than 4 months after diagnosis have a 60% chance of living 5 more years and a 40% chance of living 10 more years.

Diagnosis

Patients with aplastic anemia present with complaints similar to those of patients with pancytopenia due to any other cause. Splenomegaly and lymphadenopathy are not usually found. Hepatomegaly and abnormalities of liver function tests may be seen in posthepatitic aplastic anemia, but this syndrome usually occurs after the hepatitis has completely resolved. Serologic tests for viral antigens are almost always negative whether or not the hepatitis is active.

The diagnosis of aplastic anemia is established by bone-marrow *biopsy* which reveals moderate to severe hypocellularity (Fig. 2). Much of the marrow space is occupied by fat. The morphology and maturation of the remaining hematopoietic cells are normal. Because of the decrease in red cell and white cell precursors, plasma cells may be relatively increased, but immature plasma cells are not seen.

Treatment

The treatment of aplastic anemia has been revolutionized by the availability of bone marrow transplantation as a therapeutic option. However, this form of therapy is currently feasible only for patients who have an HLA-identical sibling to serve as bone marrow donor (only about one patient in three). In addition, such aggressive therapy is probably indicated only in patients who meet the criteria for severe aplastic anemia and is poorly tolerated in patients over 40 years of age. Before discussing bone marrow transplantation, it is, therefore, appropriate to review the

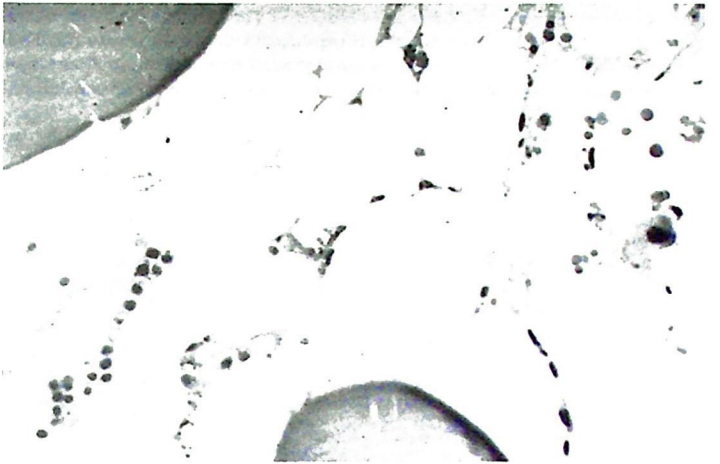

Figure 2 Hematoxylin and eosin stain of bone marrow biopsy showing profound hypocellularity. A small residual island of erythropoiesis is present at the lower left.

other therapeutic options available to the clinician managing a patient with aplastic anemia.

Supportive Care

Red Cell Transfusions

Red blood cell transfusions are the mainstay of supportive care for aplastic anemia in patients whose major symptomatic problem is anemia. Long-term red cell support carries with it the hazards of iron overload and serum hepatitis, but the risks are outweighed by the advantage of maintaining adequate tissue oxygenation. With the advent of bone marrow transplantation, an additional factor must be considered in transfusion therapy; namely, the possibility of sensitizing the recipient to histocompatibility antigens, which are carried by the white cells and platelets contained in red cell transfusions. It is clear in animal systems, and probable in humans, that a single unit of packed red cells may sensitize a potential bone marrow transplant recipient and greatly increase the risk of bone marrow graft rejection. This potential problem must be considered at the time of diagnosis of aplastic anemia even before it is known if an

HLA-identical transplant donor is available. If the clinical situation necessitates red cell transfusion before transplantation can be accomplished, frozen or washed red cells should be employed as they contain fewer white cells and platelets (although they are not completely free of these cellular elements).

Platelet Transfusions

Platelet transfusions are effective in raising platelet counts in severely thrombocytopenic patients with asplastic anemia. They should never be given as a matter of routine, however, since their administration is accompanied by two major problems: (1) sensitization to minor histocompatibility antigens with increased risk of graft rejection if bone marrow transplantation is subsequently performed, and (2) the development of antiplatelet antibodies and refractoriness to future platelet transfusions. The latter problem occurs in the majority of patients with aplastic anemia after only 6 weeks of twice weekly random donor platelet transfusions.

In view of these problems, when should prophylactic platelet transfusions be given? There is no good clinical study correlating platelet count with the incidence of serious (i.e., intracranial or major gastrointestinal) bleeding, but careful studies of fecal blood loss in thrombocytopenic patients have demonstrated that there is no significant increase until the platelet count falls to $5 \times 10^9/l$ or less. Since routine laboratory platelet counts are subject to some error in this low range, it is probably prudent to consider $10 \times 10^9/l$ the level below which prophylactic platelets should be instituted. Of course, if clinically significant bleeding occurs, platelet transfusions should be given to the thrombocytopenic patients with aplastic anemia independent of the actual platelet count.

If the decision is made that platelet transfusions are required, what type of platelets should be employed? Random donor platelets are readily available and initially effective. The development of refractoriness to random donor platelets does not affect the subsequent utility of single donor or HLA-matched platelets. Single donor platelets are obtained by plateletpheresis from healthy volunteers. The increment in platelet count 1 hour after infusion of platelets from individual donors should be measured so that future single donor platelet transfusions may be obtained from the most suitable donors. HLA-matched platelets are often effective in patients refractory to random donor platelets, but the logistical problems of identifying HLA-identical donors are often prohibitive.

Granulocyte Transfusions

The role of granulocyte transfusions in neutropenic patients with serious infections is controversial. With current technology, it is impossible to give granulocytes in sufficient number to produce meaningful incre-

ments in neutrophil count. In addition, the half-life of granulocytes in the circulation is short (about 6 hours), and transfusions must be administered at least daily. At present, then, granulocyte transfusions should be considered only in severely neutropenic patients (absolute neutrophil count $<0.5 \times 10^9$/liter) with documented life-threatening infections who have failed to respond to broad spectrum antibiotic therapy.

Androgens

A great deal has been written about the possible role of androgens in the treatment of aplastic anemia. Although some experts have argued adamantly that androgens are effective, it is clear from several carefully controlled, prospective studies that patients with severe aplastic anemia who are treated with androgens do no better than those given only supportive care. However, there are convincing anecdotes of patients in whom remission from aplastic anemia was clearly androgen dependent: when androgens were discontinued relapse occurred, and when androgens were restarted, remission was once again obtained. These androgen successes appear to occur only in patients with the milder forms of aplasia in which the marrow retains some hematopoietic activity. When androgens do work, clinical improvement often does not occur until after several months of therapy. Therefore, androgens should not be considered a failure until they have been given for at least 6 months. Because the effect of androgens is often delayed, bone marrow transplantation should not be postponed while a trial of androgens is given.

Several androgen preparations are available, all of which are roughly comparable in reported efficacy and incidence of undesirable side effects. Testosterone enanthate is given as weekly intramuscular injections of 3-10 mg/kg. Some authorities have favored nandrolone decanoate (1-1.5 mg/kg per week) since it is reported to have fewer virilizing effects. Oxymetholone is given orally in doses of 2-4 mg/kg daily. In addition to virilization, each of these androgens has been reported to produce occasional serious hepatotoxicity (e.g., cholangiolitic jaundice), although this complication is most frequent with oral preparations. Liver function tests should be monitored frequently during therapy, and androgens should be discontinued if abnormalities occur. The development of hepatocellular carcinoma has also been reported in patients being treated with androgens. Because of these potentially serious side effects, androgens should be reserved for carefully selected patients who are not candidates for bone marrow transplantation, who have evidence of residual islands of hematopoiesis on bone marrow biopsy and whose pancytopenia is severe enough to produce symptoms.

Miscellaneous Approaches

Corticosteroids probably have no role in the treatment of aplastic anemia. Scrutiny of the sporadic reports of so-called steroid-responsive aplastic anemia suggests that successes have occurred in patients with pancytopenia due to ineffective hematopoiesis rather than hypoplastic marrow failure. There is no role for splenectomy in the management of aplastic anemia. Recently, anti-thymocyte globulin (ATG) has been shown to produce remissions in about 50% of patients. The role of ATG requires further study.

Bone Marrow Transplantation

With currently employed techniques, bone marrow transplantation is successful in restoring normal hematopoiesis and effecting long-term survival in approximately 60% of patients with severe aplastic anemia. Survival is improved to 80-90% in patients who have never been transfused before transplantation. Despite these dramatic results, there remain several major problems with bone marrow transplantation in the treatment of aplastic anemia. These include donor availability, restriction to use in younger patients (age less than 40 years), graft-versus-host disease (which occurs in approximately 50% of patients and is fatal in 20%), bone marrow graft rejection (the incidence has been reduced from approximately 30% to less than 10% with newer transplantation techniques), cost (average transplant costs about $60,000), and side effects of immunosuppressive preparation for transplantation (especially interstitial pneumonitis secondary to total body irradiation or viral infection). Even considering these formidable problems, bone marrow transplantation is the therapy of choice in patients who meet the criteria for the severe form of the disease. It is essential that this option be considered early so that transfusion-induced sensitization to histocompatibility antigens can be avoided and the best chances for successful transplantation preserved.

BONE MARROW FAILURE IN SINGLE HEMATOPOIETIC LINEAGES

A detailed discussion of selective failure of the bone marrow is beyond the scope of this chapter. However, a few points are important to mention because of their relevance to treatment.

Pure red cell aplasia is a rare disorder characterized by severe anemia, reticulocytopenia, and a near absence of nucleated red cell precursors in the bone marrow. This syndrome is often associated with immunologic

abnormalities, such as a biologically false-positive VDRL, a positive antinuclear antibody test, a monoclonal serum protein spike. and benign thymoma. The syndrome is important to recognize because it often responds to corticosteroids or immunosuppressive therapy. Any patient with anemia and profound erythroid hypoplasia of the bone marrow should, therefore, be referred to a hematologist for further evaluation and appropriate therapy.

Agranulocytosis refers to selective failure of granulopoiesis in the bone marrow and is characterized by severe neutropenia in the presence of a normal hematocrit and platelet count. This disorder is frequently drug-induced and is associated with many of the same classes of drugs that can cause aplastic anemia. Unlike drug-induced aplastic anemia, however, drug-induced agranulocytosis is usually reversible if the offending drug is discontinued. Therefore, it is critically important that a detailed drug history be obtained from patients who present with isolated granulopoietic failure and that intercurrent infections be aggressively treated in order to support the patient until the white blood count returns to normal.

SUMMARY

Pancytopenia, or reduction of the red cells, white cells, and platelets in the peripheral blood can result from diverse causes. The pathophysiologic mechanisms responsible for the development of paneytopenia include ineffective hematopoiesis, myelophthisic processes, and aplastic anemia. Bone marrow aspiration and biopsy, to determine marrow cellularity and morphology, is essential to distinguish among these various causes of pancytopenia. Careful examination of the bone marrow usually clarifies the cause of pancytopenia, and appropriate management can then be instituted.

CASE HISTORY 1

A 63 year-old man comes to your office complaining of low back pain and fatigue. On physical examination he appears to be in acute pain. He is afebrile. The conjuctivae and mucous membranes are pale. There is no bone tenderness, no adenopathy, and no hepatosplenomegaly. Rectal examination reveals a prominence of the right prostatic lobe and guaiac negative stool. Initial laboratory evaluation yields the following results: hemotocrit, 0.25; hemoglobin, 8.2g/dl; white blood cell count, 2.5×10^9/liter; platelet count, 78×10^9/liter; reticulocyte count, 1.0%. The red blood cell indices are normocytic/normochromic.

Questions

1. Additional tests that would be appropriate to order at this time include (all, some, or none may be correct)
   (a) Differential count on a peripheral blood film
   (b) Roentgenograms of the lumbosacral spine
   (c) Serum acid phosphatase determination
   (d) Serum iron and iron binding capacity
   (e) Serum protein eletrophoresis
2. Analysis of the peripheral blood film reveals occasional myelocytes, metamyelocytes, and nucleated red blood cells. X-ray films of the lumbosacral spine demonstrate osteoblastic lesions of L-3, L-4, and L-5 and the serum acid phosphatase level is elevated. Based on this information, which of the following should be ordered (all, some, or none may be correct)?
   (a) Technecium-99 bone scan
   (b) Liver-spleen scan
   (c) Bone marrow aspiration and biopsy
   (d) Broad spectrum antibiotics
3. The bone marrow aspiriation and biopsy reveal normal cellularity and normal maturation of the red and white cell series. Plasma cells are not increased. Occasional clumps of immature cells are noted. At this point, it would be appropriate to (all, some, or none may be correct)
   (a) Repeat bone marrow biopsy at another site
   (b) Request urologic consultation for biopsy of the right lobe of the the prostate
   (c) Give platelet transfusions
   (d) Order a urine test for free light chains

Comment

The initial presentation of this patient with low back pain and fatigue and the subsequent finding of pancytopenia suggests several possible diagnoses. Most prominent among these are multiple myeloma and metastatic carcinoma. The finding of asymmetric enlargement of the prostate provides a clue favoring metastatic carcinoma as the more likely of these two.

Examination of the peripheral blood film is essential in the evaluation of patients with pancytopenia. In this patient, it revealed immature red and white blood cells; a so-called leukoerythroblastic picture. Because of his complaint of low back pain, x-ray films of the lumbosacral spine were appropriate to search for the osteoblastic lesions that may be seen with

metastatic carcinoma of the prostate or the osteolytic lesions that occur with multiple myeloma. A serum acid phosphatase determination is also appropriate, as this enzyme is usually elevated in patients with metastatic prostate cancer. Serum iron and iron binding capacity are not necessary in the evaluation of the normochromic, normocytic anemia in this patient. The serum protein electrophoresis usually reveals a monoclonal protein spike in patients with multiple myeloma and is an appropriate screening test to rule out this diagnosis.

Once the leukoerythroblastic picture is demonstrated in the peripheral blood, a bone marrow aspiration and biopsy are absolutely indicated. A bone scan is not essential since standard x-ray films have already revealed osteoblastic lesions, but might reveal other sites of bony involvement. A liver-spleen scan is unlikely to provide useful information. Antibiotics are not indicated despite the patient's leukopenia as he is afebrile.

Biopsy of the prostate confirmed the diagnosis of carcinoma of the prostate. The patient was treated with diethylstilbesterol. His pain resolved, and there was gradual improvement of the pancytopenia.

CASE HISTORY 2

A 19 year-old college student comes to the emergency room with fever and a nose bleed that began 3 hours earlier. He states that his gums have bled after brushing his teeth over the past week and that he has noted "red spots" on his legs. He denies taking drugs, prescribed or otherwise, and has had no exposure to solvents. He states that he had hepatitis 3 months ago but that this illness resolved in a few weeks and that his doctor told him his "liver tests" had returned to normal.

Physical examination reveals a blood pressure of 130/60 without orthostatic changes, pulse rate of 110/minute, and oral temperature of 104°F. He is bleeding profusely from the right nostril. The fundi are benign. The pharynx is markedly erythematous. The lungs are clear and the heart normal except for tachycardia. The liver and spleen are not palpable. The stool is guaiac negative. There is a petechial rash in the pretibial areas.

Initial laboratory results are as follows: hematocrit, 0.18; hemoglobin, 5.8 g/dl; white blood cell count, $.6 \times 10^9$/liter; differential count: neutrophils, 20%; lymphocytes, 70%; monocytes, 10%; platelet count, 14×10^9/liter; reticulocyte count, 0.1%; liver function tests, normal; HBsAg, negative.

Questions

1. Immediate management of this patient should include (all, some, or none may be correct)

(a) Platelet transfusions
(b) Red cell transfusions
(c) Granulocyte transfusions
(d) ENT consultation for control of epistaxis
(e) Complete cultures and institution of broad spectrum antibiotics

2. The nasal bleeding is controlled with anterior packs, and antibiotics are started after cultures are obtained. A bone marrow aspiration and biopsy are performed and reveal a markedly hypocellular marrow. What should be done next (all, some, or none may be correct)?
   (a) Contact the patient's siblings and arrange for immediate HLA typing
   (b) Continue to avoid transfusions if clinically feasible.
   (c) Intramuscular injection of nandrolone decanoate 1.5 mg/kg
   (d) Contact a bone marrow transplantation center for early transfer of the patient
   (e) Begin prednisone 60 mg q.d.

Comment

This patient presented with epistaxis, fever, and profound pancytopenia that developed 3 months after an episode of hepatitis. The most likely diagnosis on the basis of this information is posthepatitic aplastic anemia. Because of the grave prognosis of this disorder, the patient should receive a bone marrow transplant if a suitable donor is available. Transfusions should be avoided in this situation, as they increase the risk of bone marrow graft rejection. Local control of the nasal bleeding should be attempted and platelet transfusions withheld unless heavy bleeding persists. Although the patient has severe anemia, red cell transfusions should also be withheld, since he is not hemodynamically compromised. Institution of broad spectrum antibiotics after complete culturing is appropriate and potentially life saving in this profoundly neutropenic patient. Granulocyte transfusions should be considered only if he fails to respond to antibiotics and deteriorates clinically.

Bone marrow biopsy confirmed the diagnosis of severe aplastic anemia in this patient. All efforts at this point should be directed at identifying an HLA-identical sibling and early transfer to a bone marrow transplantation center for definitive treatment. Intramuscular injections are contraindicated in patients with severe thrombocytopenia, and early bone marrow transplanataion should not be postponed while the patient is given trials of androgens or steroids.

Two of the patient's six sibling were found to be HLA identical. His fever resolved with antibiotics, and transfusions were avoided. He was

transferred to a bone marrow transplantation center and underwent bone marrow transplantation from his HLA-identical sister. After a stormy 3-week course complicated by recurrent bleeding and infections, his blood counts began to rise and there was dramatic clinical improvement. He returned to college full-time and was hematologically normal 2 years after bone marrow transplantation.

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