Paparella: Volume I: Basic Sciences and Related Principles

Section 8: General Medical Principles

Chapter 35: Hematology

The purpose of this chapter is to present information about hematologic disorders that may be of practical value to the otolaryngologist. The presentation is divided into four main sections, namely, disorders of hemostasis, disorders of red blood cells, disorders of leukocytes and lymph nodes, and blood transfusion reaction.

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Hemostasis and Hemostatic Disorders

Normal hemostasis may be defined as a complex set of biophysiological reactions that, in health, maintain the fluidity of the blood within the vascular space while sparing the body undue hemorrhage or thrombosis. The blood coagulation system, blood platelets, and less well-defined vascular tissue factors are the important effects of hemostasis.

Vascular integrity is usually maintained, despite repeated stress and trauma, because of the inherent strength of the blood vessels and the connective tissues that surround them. In the event of severe injury or disruption of a blood vessel, the endothelial lining of the damaged vessel is interrupted and the underlying collagen is exposed. Because of the biophysical alteration at the injury site, within seconds, platelets begin to adhere to the exposed collagen, where they undergo a series of physical and biochemical changes that lead to the development of an impermeable platelet plug.

At the same time that the platelet plug is forming, the coagulation system is activated. Hageman factor, or factor XII, the initial step in the intrinsic cascade, is activated by exposure to collagen. The extrinsic cascade is activated by the local escape of tissue substances into the milieu of the injury site. In turn, each activated factor activates the next factor in its cascade. Platelet phospholipids (platelet factor III) as well as calcium are also important in some of the interactions. The end-point of each coagulation pathway is the conversion of fibrinogen to fibrin. Along the way, fibrin stabilizing factor, or factor XIII, is activated by thrombin. This substance catalyzes the appropriate crosslinking of the newly formed fibrin. The stable fibrin is deposited in and around the platelet plug, and bleeding is prevented.

Clinical Approach to Patients with Abnormal Bleeding

The clinical evaluation of each patient with a suspected hemorrhagic disorder must include a complete medical history and physical examination whenever possible. Clues that suggest the existence of a specific hemorrhagic disorder are sometimes found by a careful review of the medical history. A lifelong tendency toward hemorrhage suggests a congenital or familial coagulation disorder such as factor VIII or factor IX deficiency or, rarely, a congenital platelet problem. Patients with a history of blood transfusions for postoperative hemorrhage, such as that following tonsillectomy or dental extractions, should be suspected of having disordered hemostasis. The history of acute or recurrent purpura needs to be

pursued. A drug history is extremely important, since many drugs may cause allergic purpura or thrombocytopenia. Recurrent nasal hemorrhage in an adult suggests hereditary hemorrhagic telangiectasia (HHT). Patients with chronic disorders such as connective tissue disease, leukemia, liver disease, and far advanced renal disease often exhibit abnormal bleeding. For example, small telangiectatic lesions of the face, oral and nasal mucous membranes, and finger tips are diagnostic of HHT; perifollicular skin hemorrhage suggests scurvy; and hemarthrosis in the absence of trauma suggests hemophilia. Further evaluation requires using a set of simple laboratory tests that, in most cases, adequately screen for abnormalities of hemostasis (Table 1).

Table 1. Laboratory Screening Evaluation of Hemostasis

Platelets:
      Platelet count
      Examination of stained peripheral blood film
      Bleeding time

Coagulation system:
      Activated partial thromboplastin time (APTT)
      Prothrombin time (PT)
      Plasma fibrinogen.

A platelet count, an examination of a well-prepared, well-stained peripheral blood film, and a determination of the bleeding time are the commonly ordered platelet screening tests. Normal platelet counts in adults and children are approximately 250,000/cu mm with a considerable range. Estimates of the numbers of circulating platelets, as made by examining a stained peripheral blood film, should correlate reasonably well with platelet counts. Striking discrepancies should be rechecked in the laboratory. Using the Ivy technique, or the modified Ivy technique (template bleeding time), the normal bleeding time is 5 ± 2 minutes. These tests begin to lengthen in patients with thrombocytopenia when the platelet count drops below 100,000/cu mm. They are also prolonged in patients with platelet dysfunction, including von Willebrand's disease, in whom platelet counts are often normal or even elevated.

The activated partial thromboplastin time (APTT), the prothrombin time (PT) and a quantitative fibrinogen determination are the tests most commonly used when screening a patient for a suspected coagulation disorder. Great care must be exercised when obtaining blood to be used in the coagulation tests. Minor contamination of the sample with tissue juices, as may occur with a traumatic venipuncture, may activate the coagulation pathways, accelerate or shorten the various tests, and result in misleading laboratory data.

The APTT is used to screen intrinsic coagulation. The PT remains the standard screening test of the extrinsic coagulation system. The foregoing tests measure the coagulation system qualitatively. The fibrinogen determination is a quantitative test that is reported in milligrams per deciliter.

In most instances in which the screening profiles of platelets and blood coagulation are normal, as reported by a reliable laboratory, the patient is not at risk for a major hemorrhagic diathesis. When significant abnormalities are noted in the screening profiles,

further tests are necessary to more accurately define the problems, including special tests of platelet function and qualitative measurement of one or more of the coagulation factors. These latter tests may require several hours or even days to complete.

Even modest abnormalities in the screening profile, such as a bleeding time of 10 minutes or a 5-second prolongation of the APTT or PT, may suggest clinically important problems in patients with a prior history of unexplained bleeding, such as von Willebrand's disease, minimal hemophilia, mild thrombocytopenia, platelet dysfunction, or carrier status for hemophilia. Clarification of the abnormal data prior to surgery is important.

There is no absolute answer to the surgeon's question: "Which patients should have a screening platelet-coagulation profile prior to surgery?". Certainly all patients with a history of easy bruising, a poorly explained prior hemorrhage requiring transfusion, other underlying disease known to be associated with hemorrhage should be screened. Screening of patients prior to major surgery has become nearly routine.

Hemorrhagic Disorders

Bleeding Secondary to Vascular and Connective Tissue Abnormalities

Most patients classified in this group (Table 2) have no major associated platelet or coagulation disorder.

Table 2. Vascular and Connective Tissue Abnormalities That Lead to Secondary Bleeding

Allergic purpura, Henoch-Schonlein purpura, or anaphylactoid purpura
Drug purpura
Purpura simplex
Autoerythrocyte sensitization
Hereditary hemorrhagic telangiectasia
Connective tissue abnormalities.

Henoch-Schönlein Purpura

The cause of Henoch-Schönlein purpura or the "allergic purpura" syndrome is unknown, but it has a peak incidence in children aged 5 to 6 years. The symptom complex involves a purpuric skin rash and often is associated with arthritis, gastrointestinal problems, and glomerulopathy. The skin lesions are extremely variable but commonly occur as purpuric macules that appear large or small, single or confluent. They often have an urticarial component and may itch. Bullae may form, and necrotic areas may even develop. The lesions occur particularly on the legs and buttocks but may be seen on the upper extremities and trunks as well. Crops of new lesions come and go during the self-limited course of the disease, which is approximately 2 to 6 weeks. Gastrointestinal symptoms occur in 50 per cent of patients, but morbid complications such as massive bleeding or perforation are uncommon. Acute arthritis is common. The arthritis, as well as the gastrointestinal problems, may antecede the skin lesions. Glomerulopathy is said to occur in a high percentage of such patients and may lead to a chronic glomerulonephritis in 5 per cent of these individuals.

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Deposits of IgA and components of complement in biopsy samples of the skin and kidney in these patients suggest an immunologic basis for the disease.

Drug Purpura

A wide variety of drugs may cause a skin rash, which at some point may become purpuric. Hemostasis usually remains normal.

Purpura Simplex

This term is used in describing minor "spontaneous" bruises or purpura that occur in otherwise normal individuals. This phenomenon occurs much more frequently in women than in men. The lesions are usually on the lower extremities. There is no clinical significance, and no therapy needs to be considered.

Autoerythrocyte Sensitization

This rare phenomenon is characterized by the appearance of recurring painful ecchymoses, usually on the extremities and almost exclusively in middle-aged, emotionally unstable women. Its cause is unknown but it has some autoimmune implications. The lesions can be reproduced by the intradermal injection of small amounts of the patient's own whole blood or red cells into previously involved skin, but they are not reproduced by similar injections into the uninvolved skin. There is no specific treatment.

Hereditary Hemorrhagic Telangiectasia

This autosomal dominant disease is well known to all otolaryngologists, since frequently the primary manifestation is recurring, often severe, epistaxis. The characteristic vascular lesions, usually not seen until after puberty, are most commonly distributed in the nasal and oral mucous membranes, lips, face, ears, and tips of the fingers. Gastrointestinal lesions are common. Larger vascular lesions, such as pulmonary or systemic arteriovenous fistulae, or both, occur in some patients. Anatomically, the abnormal vessels show an interrupted endothelial lining, thus explaining their lack of integrity and propensity to bleeding.

Nasal hemorrhage, which is usually more severe in postmenopausal women, is sometimes controlled by local measures, including septal dermoplasty. Iron therapy is often necessary to correct and control the accompanying anemia. Oral contraceptives in the form of a combination of estrogen and progestogens, when given cyclicly in fairly large doses, have been reported to control hemorrhage in refractory patients. Biopsy of involved vessels after therapy with the oral contraceptives shows a resolution of the endothelial lining defect.

Connective Tissue Abnormalities

In several disorders in which connective tissue support of capillaries is abnormal, capillary disruption is excessive and, hence, purpura and hemorrhage are common. Ehlers-Danlos syndrome, a rare hereditary disorder of collagen and elastic tissue in which bleeding is common, is associated with a minor abnormality of platelet function. Scurvy, now a very

rare illness, is primarily a disease of disordered connective tissue, but a recognized abnormality of platelet function may play a role in the severe hemorrhage seen in some patients with this condition. Senile purpura and the purpura of cachexia are not associated with serious bleeding.

Platelet Disorders

Bleeding in patients with thrombocytopenia or with malfunctioning platelets usually occurs in or under the skin or from mucous membranes. Deep soft tissue hematomas or massive gastrointestinal bleeding may develop if the deficiency or defect is severe. Purpura is seen more commonly in the lower extremities, presumably because of an increased tendency for capillary disruption in areas with high hydrostatic pressure. Joint bleeding rarely occurs.

Thrombocytopenia

Thrombocytopenia is a laboratory diagnosis. Assuming they have normal platelet function, patients with platelet counts in the range of 100,000/cu mm have minimal bleeding, even after trauma. Spontaneous bleeding may occur in patients with platelets in the range of 50,000/cu mm. Bleeding is often life threatening at the level of 10,000 platelet/cu mm. Fortunately, central nervous system hemorrhage, even in patients with severe thrombocytopenia, is rare. The evaluation of a thrombocytopenic patient includes an examination of a well-stained peripheral blood film and often a bone marrow examination. The peripheral blood examination confirms thrombocytopenia and, in the presence of abnormal red cells (abnormalities of size and shape) or abnormal white cells, gives clues to the cause of the low platelet count. Similarly, a bone marrow evaluation is always helpful. With this examination, the clinician is able to determine the total marrow cellularity and morphology; the megakaryocyte pool; and the presence or absence of fibrosis, neoplasia, or megaloblastic change that may be due to vitamin B_{12} or fold acid deficiency. Such an evaluation leads to a prompt diagnosis and, in turn, to the prompt institution of therapy. The thrombocytopenic disorders are classified using two distinct pathophysiologic settings - decreased platelet production and increased platelet destruction (Table 3).

Decreased Platelet Production

Hereditary. Several varieties of hereditary thrombocytopenia have been described, and all are rare. Some are associated with multiple hematologic abnormalities, others are associated with abnormalities in nonhematopoietic organ systems. Patients with this condition are usually brought to the attention of physicians at an early age because of purpura.

Drug-Induced. Multiple chemical and physical agents have been reported to cause serious bone marrow suppression with resultant peripheral pancytopenia of varying degrees, including thrombocytopenia (Table 4). In such cases, bone marrow examinations usually exhibit striking hypocellularity.

Despite their judicious and carefully monitored use, chemotherapy agents and ionizing irradiation are the most common inducers of severe bone marrow damage. Withdrawal of the suspected offending agent usually but not always, results in the recovery of the marrow. On

rare occasions, chlorothiazides seem to cause thrombocytopenia by directly affecting bone marrow megakaryocytes; slow recovery is the rule after discontinuation of the drug. Alcohol abuse suppresses bone marrow function.

Table 3. Classification of Platelet Disorders

I. Thrombocytopenia
       A. Decreased platelet production
             1. Hereditary
             2. Drugs
             3. Vitamin B_{12} deficiency or folic acid deficiency
             4. Myelophthisis
             5. Infection
             6. Bone marrow aplasia
       B. Increased platelet destruction or loss
             1. Immune thrombocytopenia
                   a. Idiopathic thrombocytopenic purpura (ITP)
                   b. Drug-induced
                   c. Infections - viral

                   d. Secondary - systemic lupus erythematosus; lymphoma
                   e. Post-transfusion purpura
             2. Nonimmune thrombocytopenia
                   a. Post-transfusion dilutional thrombocytopenia
                   b. Platelet pooling (splenic)
II. Disorders of platelet function
       Hereditary and acquired (including drugs).

Table 4. Myelosuppressive Agents

Ionizing radiation
Chemotherapeutic agents
Benzene
Chloramphenicol
Hydantoin derivatives
Phenylobutazone
Gold compounds
Sulfa derivatives
Phenothiazines.

Megaloblastic Anemia. Megaloblastic states caused by a deficiency of vitamin B_{12} or folic acid are discussed in more detail in the section of anemia. It is sufficient to note here that the presenting features of patients with either of these deficiencies may be purpura or hemorrhage. Platelet production is markedly reduced because of abnormal megakaryocyte metabolism; thrombocytopenia is the common result. Platelet function is also abnormal.

Myelophthisis. In patients with any type of leukemia, lymphoma, metastatic carcinoma, or idiopathic fibrosis of the bone marrow, the normal marrow precursors are forced out of the marrow and are replaced by abnormal elements. The usual result is peripheral pancytopenia with accompanying thrombocytopenia.

Bone Marrow Aplasia. (See section on anemia).

Infections. Patients with severe infections may develop transient thrombocytopenia and neutropenia because of temporary suppression of the bone marrow by the toxic effects of the infecting agent. This is commonly seen in alcoholics. The marrow spontaneously recovers when the infection is controlled and alcohol is withdrawn.

Increased Platelet Destruction or Loss

Immune Thrombocytopenia. Thrombocytopenia may develop as the result of immunologic destruction of platelets in a variety of clinical settings. Many drugs have been implicated as the causative agents in patients with immune thrombocytopenia. In only a few cases have the immunologic abnormalities been studied in detail. Some of the drugs reported to cause immune thrombocytopenia are sulfa derivatives of all kinds, penicillin, phenylbutazone, streptomycin, phenytoin, quinine, quinidine, phenothiazines, and heparin.

In other cases, an invading virus may be the agent that stimulates the development of antiplatelet antibodies. Thrombocytopenia after chickenpox, measles, respiratory viruses, and even infectious mononucleosis has been reported. In the neonate, immune thrombocytopenia may accompany congenital syphilis, toxoplasmosis, cytomegalic inclusion disease, rubella, and disseminated herpes infection.

Immune thrombocytopenia is common also in patients with subacute systemic lupus erythematosus (SLE), lymphoma, and chronic lymphatic leukemia.

Idiopathic immune thrombocytopenia (ITP) is the most likely diagnosis in patients with reduced platelet counts who do not have histories of drug use and toxic exposure who do not have systemic diseases. The stimulus that leads to the development of platelet antibodies in such patients is unknown. In this group, splenomegaly is rare.

Bone marrow studies in patients with all forms of immune platelet deficiency show adequate, if not increased, numbers of megakaryocytes. Platelet antibody tests, although difficult to perform and not readily available in clinical laboratories, are often positive.

The management of patients with immune thrombocytopenia depends on the cause of the condition. Viral-induced platelet deficiencies, particularly in children, are usually self-limited. Occasionally, thrombocytopenia in patients with infectious mononucleosis requires the short-term use of corticosteroids. When drugs are implicated, they should be stopped and, when necessary, replaced with acceptable alternatives.

Idiopathic immune thrombocytopenia, as well as thrombocytopenia associated with SLE or chronic lymphocytic leukemia, is difficult to manage. In most patients, corticosteroids alone or, when necessary, corticosteroids followed by splenectomy successfully reverse the

problem. As a rule, platelet transfusions are of limited value in patients with immune thrombocytopenia. Infused platelets usually are destroyed promptly by the patient's pre-existing platelet antibodies.

Transfusion-induced immune thrombocytopenia is rare and is treated with plasma exchange if the disease is severe and persistent.

Nonimmune Thrombocytopenia. *Post-Transfusion Dilutional Thrombocytopenia.* The correction of severe posthemorrhagic anemia by massive transfusions of stored whole blood may lead to transient thrombocytopenia. The dilution of the patient's plasma with blood that contains only a few viable platelets plus the external loss or utilization of the patient's platelets during the antecedent hemorrhagic event are likely the causal factors that lead to the development of thrombocytopenia. This problem is usually not serious and is self-limited.

Splenic Thrombocytopenia. Splenomegaly for any reason may be associated with significant thrombocytopenia because of sequestration and destruction of platelets in the enlarged spleen. Efforts to relieve the splenomegaly should be instituted promptly, whenever possible, when the thrombocytopenia is severe. Splenectomy is occasionally performed in such situations.

Disorders of Platelet Function

In recent years, the knowledge of the functions of platelets has expanded tremendously. It is now recognized that there is a large group of patients whose hemorrhagic disorders are primarily related to abnormalities of platelet function. In laboratory tests, such patients usually are found to have normal platelet counts and prolonged bleeding times. More sophisticated tests of platelet function, using the platelet aggregometer, are always abnormal. In rare hereditary disorders, confusing terms such as thrombasthenia, thrombopathia, and thrombopathy have been used to name particular platelet function abnormalities. Similarly, acquired disorders are seen in patients with a number of common clinical diseases such as cirrhosis, uremia, and the paraproteinemias and in those with myeloproliferative diseases. In the group with myeloproliferative diseases (which includes patients with polycythemia vera, primary thrombocytosis, myelofibrosis, and chronic granulocytic leukemia), platelet counts may be elevated. In addition, the clinician should be aware that certain drugs adversely affect platelet function, which, in turn, may play a role in clinical hemorrhage, particularly in surgical patients.

Included on the list of drugs reported to induce abnormal platelet function are aspirin (plain or in combination with other drugs)), sulfinpyrazone, phenothiazines, dipyridamole, clofibrate, amitriptyline, carbenicillin, ticarcillin, and most of the nonsteroidal anti-inflammatory agents, including indomethacin, and phenylbutazone.

The wary clinician and surgeon should treat patients with platelet dysfunction cautiously. Whenever possible, drugs that cause abnormal platelet function should not be used during the intraoperative period.

Platelet Transfusions. Platelet transfusions are regularly used in the management of bleeding precipitated by severe thrombocytopenia. Random donor platelet transfusions usually

are successful in raising a platelet count by 10,000/cu mm per platelet pack (bag) (1-hour post-transfusion count) in patients unsensitized to "foreign" platelets, and thus platelet-induced hemorrhage is controlled. Human leukocyte antigen (HLA)-type specific platelets may be tried when random donor platelet transfusions fail. Prophylactic platelet transfusions are used in some patients with reversible thrombocytopenia when platelet counts approach 15,000/cu mm.

Platelet transfusions may be used successfully to control bleeding in some patients with severe platelet function disorders. However, the platelet dysfunction in patients with uremia is not corrected with platelet transfusions.

Coagulation Disorders

Patients with coagulation disorders (Table 5) usually have abnormal results on screening tests of coagulation (see Table 1). These tests begin to show abnormalities when one or more coagulation factors are reduced to 30 per cent of normal activity or less. An exception to the rule is factor XIII (fibrin stabilizing factor) deficiency, in which the results of standard screening tests are normal. Should further analysis of a coagulation defect be required, qualitative assays of specific coagulation factors, which are available in many clinical laboratories, are indicated. Usually, qualitative factor levels of less than 30 per cent of normal must be present before abnormal bleeding becomes a problem.

Table 5. Coagulation Disorders

Congenital
> Hemophilia - factor VIII deficiency
> Christmas disease - factor IX deficiency
> Fibrinogen disorders
> Hageman factor deficiency - factor XII deficiency
> Factor XIII deficiency
> Von Willebrand's disease

Acquired
> Vitamin K deficiency
> Hepatic disease
> Inhibitors of coagulation
> Disseminated intravascular coagulation.

Congenital Coagulation Disorders

Hemophilia (Hemophilia A). Hemophilia A is the most common of the X-linked coagulation disorders. Originally thought to be the result of a quantitative deficiency of factor VIII, it is now known that hemophilia results from a deficiency of a single portion of the factor VIII complex, factor VIII:C. Clinical hemophilia ranges from severe (less than 1 per cent of factor VIII:C activity) to very mild (20 to 40 per cent of factor VIII:C activity). Patients with severe hemophilia have a lifelong history of abnormal episodes of bleeding, which may first require treatment at the time of circumcision. The majority of such patients who require the services of an otolaryngologist are under care of another physician familiar with the disease. A patient with very mild hemophilia and with a negative family and personal history of abnormal bleeding may suffer aggravating or even severe operative and

postoperative hemorrhage unless the defect is recognized and treated appropriately. Patients with mild hemophilia usually show a prolongation of the APTT of only 5 to 10 seconds greater than normal.

In hemophilia, bleeding is controlled or prevented with infusions of factor VIII:C, usually in the form of cryoprecipitate of plasma or commercial lyophilized concentrates of factor VIII. Approximately one unit of factor VIII per kilogram of body weight raises the patient's factor VIII:C level by 2 per cent. When used to treat a particular bleeding episode or when used prior to surgery, factor VIII:C levels of 25 to 100 per cent of normal are required in order to achieve normal hemostasis.

The threat of hepatitis of the non-A, non-B variety following such transfusions is real. For several years, the AIDS virus was transmitted to some hemophiliacs via blood products. The institution of screening for the AIDS virus makes this form of AIDS transmission much less likely and current heat treatment of commercial FVIII products has eliminated the risk of AIDS transmission.

An intravenous infusion of i-deamino-8-D-arginine-vasopressin (DDAVP) a synthetic analogue of antidiuretic hormone, results in a transient rise in all the components of factor VIII. The action of DDAVP is related, in part, to the release of factors VIII:vWF and VIII:AG into the plasma. DDAVP may be used in mild hemophiliacs (> 5 per cent of factor VIII:C activity) and in some patients with von Willebrand's disease in whom a single transient increase in factor VIII is believed to be sufficient to control hemorrhage.

Patients with severe hemophilia now have a near-normal life expectancy with the use of concentrated factor VIII preparations. Major surgery is and has been accomplished in such patients with careful laboratory monitoring and appropriate replacement of factor VIII.

On occasion, female carriers of hemophilia may have factor VIII levels in the range of 25 to 40 per cent of normal. Women with this condition are managed in much the same fashion as men with mild hemophilia.

Christmas Disease (Factor IX Deficiency or Hemophilia B). Patients with Christmas disease represent most of the remainder of patients with congenital hemorrhagic coagulation disorders, yet this illness is less than one-fourth as common as hemophilia A. Varying degrees of severity of illness seen in factor IX deficiency parallel those of factor VIII deficiency. Replacement therapy in factor IX deficiency is more difficult and certainly less predictable than in hemophilia A. Cryoprecipitate of plasma and lyophilized factor VIII preparations contain no factor IX and, therefore, are ineffective in the management of Christmas disease. Fresh whole plasma or lyophilized preparations containing factor IX are effective, however.

Fibrinogen Disorders. Patients with congenital hypofibrinogenemia usually are asymptomatic unless fibrinogen levels are less than 100 mg/dl. Even patients in whom fibrinogen levels are approximately 50 mg/dl have relatively mild bleeding episodes.

Patients with hereditary dysfibrinogenemias, qualitative disorders of fibrinogen, are usually asymptomatic or only mildly symptomatic. Usually, such patients are initially identified by exhibiting a prolonged PT and APTT. Delayed polymerization of the abnormal

fibrin monomer or defective release of fibrinopeptides, or both, prolong these tests.

If necessary, hypofibrinogenemia or dysfibrinogenemia syndromes are managed with an infusion of fibrinogen, preferably in the form of cryoprecipitate of plasma when the preparation is available. The risk of hepatitis increases when lyophilized fibrinogen preparations are used.

Hageman Factor (Factor XII) Deficiency. This is an autosomal recessive disorder that produces no symptoms. The defect, which can be either heterozygous or homozygous, is discovered during routine screening of a patient's coagulation mechanism. In patients with homozygous deficiency, the laboratory reports an alarming prolongation of the APTT. However, hemorrhage is not associated with this disorder, and no therapy is required.

Fibrin Stabilizing Factor (Factor XIII) Deficiency. This is a rare autosomal recessive disease in which laboratory screening tests are normal. The presumptive diagnosis is made by noting dissolution of the patient's clotted blood with 5 molar urea. Normal clots are insoluble in this substance.

Von Willebrand's Disease. Von Willebrand's disease may be defined as an autosomal dominant disease of varying clinical severity that is characterized by a prolonged bleeding time and a reduction in all three of the components of the factor VIII complex.

In addition to a prolonged bleeding time, laboratory screening shows a normal platelet count, a normal prothrombin time, and often a mild prolongation of the APTT. The diagnosis is confirmed by noting abnormalities in the factor VIII complex using sophisticated laboratory tests.

Factor VIII parameters increase in women during pregnancy and when taking oral contraceptives. Such observations suggest that under some circumstances the patient with von Willebrand's disease can be induced to make additional factor VIII complex. Treatment, either prophylactic or therapeutic, is with the use of cryoprecipitate of plasma, fresh whole plasma (rarely) or DDAVP. The usual response to such infusions is a brief shortening of the bleeding time and an elevation of the factor VIII:C level, which may remain elevated for several days. Lyophilized factor VIII preparations available in the US have not produced satisfactory results in patients with von Willebrand's disease since they do not contain von Willebrand factor activity. DDAVP may be used in patients with mild von Willebrand's disease in which a single transient rise of factor VIII complex will control bleeding. (See the section of hemophilia.)

Other Factor Deficiencies. Deficiency syndromes have been reported with each of the other factors previously noted. Clarification of such disorders is available in the texts listed in the reference section.

Acquired Coagulation Disorders

Vitamin K Deficiency. Coagulation factors II (prothrombin), VII, IX, and X, produced in the fibrin, are dependent on vitamin K for the maintenance of their normal blood levels.

Hemorrhagic disease of the newborn, a disease syndrome caused by vitamin K deficiency, is totally preventable with the use of vitamin K_1 in the immediate neonatal period.

Various malabsorptive syndromes, long-term administration o antibiotics, and biliary tract obstruction may lead to vitamin K deficiency and a hemorrhagic state. This is more apt to occur if the nutritional status of the patient is poor. The problem is recognized by noting abnormal screening tests and prolonged APTT and PT, which return to normal 24 hours after the parenteral administration of vitamin K_1.

Patients taking oral anticoagulants (usually warfarin) have an iatrogenic deficiency of vitamin K-dependent coagulation factors (II, VII, IX, X). When necessary, this is also reversed promptly with the use of vitamin K. Occasionally, hemorrhage secondary to vitamin K-dependent factor deficiency is life threatening. This problem is immediately reversed after the transfusion of 2 to 3 units of fresh frozen plasma, followed by vitamin K administration.

"Warfarin eaters" are patients who use warfarin surepetitiously. The vitamin K deficiency syndrome in this group may be severe and recurrent, often associated with abnormal bleeding and always with a negative history of warfarin ingestion. There is no characteristic emotional disorder in these patients, although all are severely disturbed.

Hepatic disease. Patients with advanced hepatic disease, whether it is acute or chronic, may exhibit a wide variety of hemostatic disorders at any given time, including vascular purpura, thrombocytopenia, poor platelet function, and complex coagulopathies. The PT and APTT is usually prolonged with advanced liver disease. Occasionally, such abnormalities are corrected with the administration of vitamin K1 and are, indeed, secondary to vitamin K deficiency. In most cases, however, vitamin K1 is of no value or only partially corrects the defect or defects. Multiple factor deficiencies, including deficiency of factor V and fibrinogen as well as vitamin K-dependent factors, persist after administration of vitamin K and reflect a serious abnormality of liver function. Disseminated intravascular coagulation may also occur. This phenomenon is discussed in detail later.

Coagulation abnormalities in patients with advanced liver disease are often difficult to control, even with the replacement of significant amounts of fresh plasma that contains all normal coagulation factors. Patients with this condition carry unusual risks even for selective surgery. A satisfactory response to replacement therapy prior to an anticipated surgical procedure is an important prognostic observation. The absolute need for replacement therapy prior to surgery is impossible to establish. In general, however, patients with liver disease who have a 2- to 3-second prolongation of the PT require no replacement therapy; those whose PT is prolonged 5 seconds or more usually do require replacement therapy.

Inhibitors of Coagulation. Inhibitors of coagulation are abnormal plasma proteins that interfere with the interactions of the normal coagulation factors and, thus, interfere with the coagulation of blood. These substances, sometimes called circulating anticoagulants, have been shown to have the properties of antibodies capable of inactivating single specific coagulation factors. Inhibitors may occur in a variety of clinical settings; some cause severe hemorrhagic disorders, whereas others are clinically unimportant.

Inhibitors develop in as many as 10 per cent of patients with hemophilia. When an inhibitor is present, infusions of factor VIII act as the antigenic stimulus, which leads to the development of more antibody-inhibitor against factor VIII. The clue to the presence of an inhibitor in a hemophiliac is the patient's unresponsiveness, both laboratory and clinical, to infusions of factor VIII. The presence of an inhibitor is suggested in the laboratory by noting that mixing normal plasma with the patient's plasma in a ratio of 1:1 does not correct the APTT toward a normal level. Such a mixture of normal plasma with a patient's plasma without an inhibitor should yield a near-normal APTT. In such patients, therapy is always difficult and is usually managed by a hematologist. Similar inhibitors may appear in patients with Christmas disease or factor IX deficiency. De novo inhibitors to factor VIII have been reported to occur spontaneously in association with some connective tissue diseases, during and after pregnancy, and in otherwise well, usually elderly patients. Fortunately, the incidence is rare. The associated hemorrhage is difficult to control and may be fatal.

Inhibitors are noted frequently in patients with SLE in whom the inhibitor is usually at the level of the prothrombin-converting substance and in patients with dysglobulinemic states in whom there is inhibition of the action of thrombin. The presence of such mild inhibitors prolongs the APTT and PT by several seconds. Further inhibitor studies, as previously outlined, confirm their presence.

Disseminated Intravascular Coagulation. Following abnormal and excessive activation of the coagulation pathways, excess thrombin is generated. This excess, in turn, leads to accelerated platelet aggregation, utilization of multiple coagulation factors, and activation of the plasminogen-plasmin or fibrinolytic system. This extremely complex set of interactions is referred to as disseminated intravascular coagulation (DIC). Originally described in the field of obstetrics following abruptio placentae, it is now recognized to occur in a variety of clinical settings. These include severe infection, shock, trauma, cancer, severe liver disease, promyelocytic leukemia, mismatched blood transfusion, and other disorders. Occasionally, extreme utilization of coagulation factors and platelets leads to a hemorrhagic diathesis. The fibrin-platelet plugs formed during the process and deposited in the microcirculation usually are not symptomatic.

Confirmation of DIC follows complete laboratory evaluation (Table 6). Implicit in establishing the diagnosis of DIC is an elevation of fibrin split products formed by the action of plasmin on fibrinogen and fibrin. Bleeding in patients with DIC usually does not occur unless one or more of the following laboratory criteria are met:

1. Reduction of fibrinogen below 100 mg/dl.
2. Platelet count below 50.000/cu mm.
3. Reduction of factor VIII or V below 40 per cent of normal.

Most patients with DIC exhibit less severe laboratory abnormalities and do not have abnormal bleeding. In any given patient with DIC, all of the typical abnormalities may not be present.

In a patient with acute fulminant DIC and hemorrhage, the therapeutic effort is directed primarily toward the reversal of the underlying disease. With control of the underlying process, DIC is controlled, and bleeding ceases. In the early hours of management

of DIC with hemorrhage, infusions of plasma, cryoprecipitate of plasma, and platelets are used to control the hemorrhage by bolstering a nearly totally disrupted hemostatic system. Heparin, which acts by interfering with the generation of thrombin and at several other sites in the coagulation cascade, has been used in the management of DIC.

Table 6. Abnormalities in Laboratory Tests Associated With Disseminated Intravascular Coagulation

Test	Value
Fibrinogen	Decreased
Factor VIII, V	Decreased
PT	Prolonged
APTT	Prolonged
Platelets	Decreased
Fibrin split products	Decreased.

The value of such therapy has been questioned but with one major exception. In patients with purpura fulminans, which is an unusually severe form of DIC triggered by some infections, the use of heparin may be efficacious.

Thromboembolic Disorders

It seems appropriate in the section of hemostasis to mention briefly the management of some of the thromboembolic disorders that are seen by the practicing surgeon. Very little is known about the cause or pathogenesis of such disorders except that a vascular endothelial component, blood coagulation factors, and platelets all seem to play a role. Laboratory tests are of little value in predicting which patients will develop vascular thrombosis.

However, some rare thrombosing disorders such as antithrombin III deficiency, protein S deficiency and protein C deficiency can be diagnosed through laboratory tests.

Deep Venous Thrombosis (DVT)

If patients with deep venous thrombosis (DVT) remain untreated, the incidence of pulmonary embolus is approximately 10 per cent and the mortality rate approaches 1 per cent. Successful management of patients with DVT depends on the proper use of the currently available anticoagulants - heparin and warfarin. In only a few patients is such therapy contraindicated: (1) in patients in whom active bleeding exists before or during therapy, (2) in patients with an existing severe hemorrhagic disorder, and (3) in postoperative patients in whom a small hematoma or a bleeding episode would be serious, ie, after brain or spinal cord surgery.

At the time that the diagnosis of DVT is established, heparin therapy is instituted because it has an immediate antithrombotic effect. Doses used should maintain APTT at 1.5 to 2.5 times the normal level. Just after a bolus of intravenous heparin is administered, laboratory values may be extremely prolonged. Therefore, when using intermittent IV heparin, such values are checked immediately before the next dose of heparin is to be given. When

administering heparin through constant infusion, values can be checked at any interval. Administering heparin through constant infusion has become popular because of ease of control and perhaps because of a reduced incidence of hemorrhage.

Warfarin is used during the prophylactic phase of management in patients with DTV. Usually instituted a day or two after heparin is begun, warfarin is generally continued for 10 to 12 weeks following an acute episode of DTV. The initial dose of warfarin varies somewhat, depending on the age and weight of the patient and the determination of the physician. Acceptable doses of warfarin are 15 mg on the first day and 10 mg on the second and third days, depending on the size and nutritional status of the patient. Subsequent doses depend on accurate laboratory monitoring. The goal in using warfarin is to achieve and maintain a PT 1.5 to 2.5 times the normal value reported in seconds. Heparin and warfarin therapy are usually overlapped for 5 to 7 days because of the lag of the antithrombotic effect of warfarin. Heparin may be discontinued after 5 to 7 days only if the PT is in the therapeutic range.

Prophylactic Heparin. Low-dose heparin, or miniheparin, has been used successfully in the prophylaxis of DVT in some surgical and internal medicine settings. The usual dose of heparin is 5000 units, given subcutaneously every 12 hours, beginning prior to surgery and continuing for several days after surgery. Such therapy usually is not monitored by laboratory tests. In some patients, the APTT is significantly prolonged for several hours after each heparin injection. In such instances this pronounced effect of low-dose heparin may contribute to postoperative hemorrhage.

Arterial Thromboembolic Disease

Warfarin anticoagulant has been used successfully in the management of patients with arterial embolic disease when the emboli emanate from a mural thrombus in the heart, as seen in postmyocardial infarction, in patients with dilated cardiomyopathy, and following heart valve replacement.

A number of antiplatelet drugs such as aspirin, dipyridamole, and sulfinpyrazone have been used with some success in reducing episodes of symptomatic illnesses, such as cerebral transient ischemic attacks, that may be related to platelet emboli.

Red Blood Cell Disorders

Normal Red Blood Cell Values

Normal red cell values vary considerably with the age of the patient (Table 7). In adults, values in men are higher than in women. Using sample formulas (Table 8), various estimates can be made of the size (mean corpuscular volume (MCV)), the amount (mean corpuscular hemoglobin (MCH)), and the concentration (mean corpuscular hemoglobin concentration (MCHC)) of hemoglobin of an average red blood cell. Of these indices, only the MCHC and MCV are important to the clinician.

Table 7. Approximate Normal Red Blood Cell Values at Various Ages

Age	RBC (10^6/cu mm)	Hb (gm/dl)	Hct (%)
Cord blood	5.2 +/- 1.0	16.8 +/- 3	55 +/- 10
1 month	4.7 +/- 0.9	14 +/- 3	42 +/- 7
6 mo - 6 yrs	4.6 +/- 0.6	12 +/- 1.5	37 +/- 4
7 - 12 yrs	4.7 +/- 0.5	13 +/- 2	38 +/- 4
Adults			
Men	5.4 +/- 0.8	16 +/- 2	47 +/- 5
Women	4.8 +/- 0.6	14 +/- 2	42 +/- 5

Table 8. Red Blood Cell Indices

MCV = Vol packed cells (ml/1000 ml blood) / RBC (millions/cu mm)
MCH = Hb (gm/1000 ml blood) / RBC (millions/cu mm)
MCHC = Hb (gm/1000 ml blood) / RBC (millions/cu mm)

MCV (cu microns) = 90 +/- 9
MCH (micromicrogm) = 30 +/- 4
MCHC (%) = 34 +/- 2.

Anemia

Anemia may be defined as a condition in which the blood is deficient in red cells or hemoglobin. There are many causes of anemia. Accurate elucidation of the causative factors involved in the development of anemia is imperative in order to ensure prompt and appropriate patient care.

When evaluating a particular patient with anemia, the clinician first notes the morphology of the red blood cells and then pursues the cause and pathogenesis of the anemia within its particular morphological framework (Table 9).

Microcytic-Hypochromic Anemias

Iron Deficiency Anemia. In the adult, the total amount of iron in the body is approximately 4 gm. Of this amount, 2.5 gm is found in hemoglobin, 1 gm in storage iron, and the remainder in myoglobin and other enzyme systems. Usually, 1 mg of iron is lost from the body each day by normal processes; in menstruating women, the amount is 2 mg daily. One or 2 mg are absorbed daily from a dietary supply of 10 to 15 mg of iron, and red blood cell values are maintained. Whenever iron loss outstrips iron absorption, iron deficiency and, ultimately, anemia result. In the adult, nearly all cases of iron deficiency anemia are the result of chronic blood loss. Blood loss may be occult and unrecognized by the patient, such as may occur with gastritis or carcinoma of the cecum. In others, the history of blood loss is obvious. Patients with hereditary hemorrhagic telangiectasia and epistaxis are nearly always anemic at some time during their illness. The symptoms, other than those caused by the bleeding organ, usually are nondiagnostic. In young women, however, the history of friable fingernails and unusual hair loss should arouse suspicion. Pica is sometimes noted. Pallor as well as mucous

membrane atrophy, which is most easily noted on the lateral margins of the tongue, may be evident on physical examination.

Table 9. Morphologic Classification of Anemia

Microcytic-hypochromic: MCV < 80 cu microns   MCHC < 30%
    1. Iron deficiency
    2. Thalassemia
    3. Lead poisoning
    4. Sideroblastic anemias
Macrocytic-normochromic   MCV > 100 cu microns   MCHC 33%
    1. Vitamin deficiency
        a. Vitamin B_{12} deficiency
        b. Folic acid deficiency
    2. Anemia of chronic liver disease
    3. Hypothyroidism
    4. Macrocytosis of the elderly
Normocytic-normochromic   MCV 90 +/- 9 cu microns   MCHC 33%
    1. Acute blood loss
    2. Increased blood destruction (hemolysis)
    3. Decreased blood production:
        a. Anemia of chronic disorders
        b. Anemia of chronic renal disease
        c. Aplasia of marrow
        d. Myelophthisis
        e. Refractory anemia
    4. Pseudoanemia.

The laboratory findings vary somewhat, depending on the degree of the chronic blood loss. Before anemia begins to develop, 25 per cent of total body iron has been lost. Storage iron is completely used in an effort to maintain hemoglobin at a normal rate. If blood loss continues, the red blood cells become microcytic. Later, with severe anemia (5 to 7 gm/dl), the RBC become hypochromic. Reticulocytosis is not prominent in severe, untreated iron deficiency. On occasion, it is necessary to measure the serum iron (SI) level and transferrin or total iron-binding capacity (TIBC) in order to confirm the presence of iron deficiency anemia. Fasting serum iron levels are normally in the range of 100 microgm/dl and may fall to as low as 5 to 10 microgm/dl with severe iron deficiency. Transferrin levels may rise from normal values of approximately 200 microgm/dl to the range of 500 microgm/dl range. Such levels are highly suggestive of iron deficiency. Not infrequently, the iron stores in anemic patients with complex multisystem disease must be evaluated by obtaining an iron stain of a bone marrow sample. Stainable storage iron is not present in the marrow in severe iron deficiency.

There are two main issues in the management of the patient with iron deficiency. First the bleeding site, or sites, must be identified and, if possible, corrected. Second, the anemia must be corrected and iron stores replenished. This is best accomplished using inexpensive oral iron preparations in the form of ferrous sulfate or ferrous gluconate given in the dose of 300 mg, one to three times per day. Therapy is continued for 6 months or longer after the

bleeding has been controlled, in order to correct the body's iron stores. In the event that bleeding continues or recurs, the dose and duration of iron therapy are based on the judgment of the individual physician. In severe cases in which there is recurrent hemorrhage and in cases in which oral iron preparations cannot or will not be used, parenteral preparation of iron dextran are of real value. Hazardous side effects are rare. Such preparations are used either intravenously or intramuscularly.

Thalassemia. Originally described in populations bordering the Mediterranean Sea, thalassemia is now known to have worldwide distribution. A genetic defect, or group of defects, prevents adequate production of either the alpha or beta globin chains of hemoglobin. Microcytic hypochromic anemia results from the deficient production of hemoglobin.

In the heterozygous form of thalassemia, called thalassemia minor, anemia is mild, but microcytosis is usually profound. A typical blood count might be: red blood cells (RBCs), 6.0 million per cu mm; hemoglobin (Hgb) 11 gm/dL; hematocrit, 36; MCV 60; and MCHC 30 per cent. The indices are not unlike those seen with iron deficiency except that severe microcytosis and hypochromia to this degree are seldom seen with iron deficiency until hemoglobin levels are in the range of 5 to 6 gm/dL. Therefore, severe microcytosis with minimal anemia usually indicates thalassemia. Serum iron determinations in such patients are normal, with a normal total iron-binding capacity. Diagnosis is confirmed using a hemoglobin electrophoresis by finding an elevation of either A_2 hemoglobin or fetal hemoglobin. Each of these elements is a minor constituent of normal blood. In beta thalassemia minor there is a genetic reduction in beta chain production, which is partially compensated by increased gamma (HgbF) or delta (HgbA$_2$) chain production. In alpha thalassemia minor, although the anemia and the RBC morphologic findings are similar to beta thalassemia minor, the defect is in alpha chain production and there is no compensatory alternate hemoglobin elevation. Using globin chain synthesis techniques, decreased rates of alpha chain synthesis confirm the diagnosis of alpha thalassemia.

Thalassemia minor is asymptomatic and requires no therapy. Recognition of thalassemia is important to both the physician and the patient in order to prevent overzealous and unnecessary diagnostic and therapeutic maneuvers.

Homozygous thalassemia or thalassemia major, a major hemolytic anemia usually evident at birth, is associated with a poor prognosis.

Lead Poisoning. The anemia of lead poisoning both in the toddler and in the adult is microcytic and hypochromic. Lead interferes with heme synthesis. Usually, an adequate medical history suggests the possibility of lead intoxication. Serum iron levels are normal or elevated in such patients. Elevated blood lead levels confirm the diagnosis.

Iron-Loaded or Sideroblastic Anemia. Varying degrees of microcytosis and hypochromia may exist in this group of uncommon, poorly understood disorders. Macrocytosis and hypochromia are seen in some patients. Serum iron levels are usually elevated. The bone marrow always exhibits abnormal myeloid and erythroid maturation. Florid leukemia may develop in patients with such a condition with the passage of time. Iron stain of bone marrow cells show a ring of stainable iron around the nucleus of some red cell precursors, the so-called ringed sideroblast. Some of these anemias respond to large doses of

pyridoxine (vitamin B_6).

Macrocytic-Normochromic Anemias

Vitamin B_{12} and Folic Acid Deficiency. The vitamin B_{12} and folic acid are both important in nucleoprotein synthesis. The vitamin B_{12} is more important than folic acid in certain central and peripheral nervous system metabolic pathways. Adequate supplies of the vitamin B_{12}, contained in animal foodstuffs, are nearly always present in the American Diet. The vitamin B_{12} is absorbed in the terminal ileum only after combining with "intrinsic factor", a substance elaborated by gastric mucosal cells. Folic acid is found in abundant supply in green leafy vegetables, and dairy products and other vegetable supplement this supply. Folic acid is absorbed in the proximal small intestine.

Dietary or nutritional deficiency of vitamin B_{12} deficiency in the US is rare. Vitamin B_{12} does occur, however, in those with pernicious anemia, a familial disease characterized by an abnormally low production of intrinsic factor. Vitamin B_{12} deficiency also develops following total gastrectomy, removal of terminal ileum, and in various malabsorptive conditions. In contradistinction to vitamin B_{12} deficiency, dietary deficiency of folic acid is quite common and is regularly seen in the alcoholic, in the young pregnant woman with peculiar eating habits, and in those with malnutrition. Malabsorptive syndromes also lead to folic acid deficiency.

Severe anemia and even pancytopenia with a depression of the circulating neutrophils and platelets may develop in either vitamin B_{12} or folic acid deficiency.

In addition to the morphologic changes in peripheral blood (which include macrocytosis of the red cells, hypersegmentation of the nuclei of neutrophils, and giant platelets), bone marrow findings are characteristic. Giant red cell precursors with abnormal nuclei, called megaloblasts, are seen along with similar changes in the neutrophil precursors and megakaryocytes. In the absence of a history of ingestion of chemotherapeutic drugs, which can induce similar changes, these observations strongly suggest the presence of either vitamin B_{12} or folic acid deficiency. Clinical distinction between the two conditions is possible since posterolateral spinal cord degeneration, common in vitamin B_{12} deficiency, is not seen with folic acid deficiency. Final distinction requires measurement of the serum levels of both vitamins. Methylmalonic acid excretion in the urine is elevated only in patients with vitamin B_{12} deficiency. Further evaluation using a Schilling test may be done to confirm the presence of pernicious anemia. In patients with vitamin B_{12} deficiency, replacement therapy is always parenteral and lifelong.

Folic acid deficiency may be corrected by adequate diet alone, although oral and parenteral supplements are frequently used. Such supplementation is discontinued if the precipitating cause of the deficiency is controlled.

Anemia of Chronic Liver Disease. Anemia is almost always seen in patients with advanced liver disease. Commonly, such patients have splenomegaly, are malnourished, and bleed intermittently from the gastrointestinal tract. Thus, the anemia may have several causes. Anemia as the result of liver disease is often macrocytic, is usually accompanied by an elevation of reticulocytes, and is the result of ineffective production as well as some increased

destruction of the red cells. The importance of this condition lies mostly in its recognition and its distinction from other forms of anemia. Treatment is directed toward controlling the underlying liver disease.

Hypothyroidism. Macrocytosis sometimes accompanies untreated hypothyroidism, and the anemia is corrected with treatment of the hypothyroidism. Occasionally, myxedema and pernicious anemia coexist in a patient. In this circumstance, each illness is managed separately.

Macrocytosis of the Elderly. Macrocytosis of red cells with minimal anemia is seen in some elderly patients unaccompanied by a specific organic disease. The cause is uncertain. This condition requires no therapy as long as correctable causes of macrocytosis have been ruled out.

Normocytic-Normochromic Anemias

Acute Blood Loss. Usually, the anemia of acute blood loss is readily diagnosed and follows an over hemorrhagic episode. Immediately after a large hemorrhage, the hematocrit level may remain reasonably normal as the blood volume acutely shrinks. With stabilization and reexpansion of the plasma volume, anemia becomes apparent. The characteristic features of the peripheral blood a day or so following bleeding are anemia and a moderate rise in the reticulocyte count as well as leukocytosis and thrombocytosis. Management may include transfusions of red blood cells or whole blood.

Increased Blood Destruction - Hemolytic Anemia. In the absence of a recent large hemorrhage, anemia associated with a significant elevation of the reticulocyte count in the peripheral blood usually suggests hemolysis or abnormally rapid blood destruction. Hemolysis may exist in the absence of reticulocytosis when there is an associated problem in the production of red blood cells as seen, for example, in pernicious anemia, liver disease, and leukemia.

Hemolytic anemias are classified according to their hereditary or acquired nature (Table 10).

Table 10. Types of Hemolytic Anemia

Hereditary
      Spherocytosis
      Hemoglobinopathies
      Erythrocyte enzyme defects
Acquired
      Immune
            Alloimmune
            Autoantibodies
            Drug-induced
      Nonimmune
            Mechanical
            "Hypersplenism".

Hereditary Hemolytic Anemia

Hereditary Spherocytosis. Hereditary spherocytosis is an autosomal dominant disorder characterized by the presence of spherocytic erythrocytes, or spherocytes in the peripheral blood. A cell membrane defect permits osmotic swelling of the erythrocytes and the development of their spherical shape. Patients with spherocytosis are often asymptomatic, although they may become rapidly symptomatic with alarming degrees of anemia during poorly understood, infrequent hemolytic or aplastic crises. Cholelithiasis, splenomegaly, and minimal jaundice are often present. Except for crisis situations, the anemia is mild ($\pm$ 10 gm/dl Hb) and the reticulocyte count is elevated ($\pm$ 5-10 %). Bilirubin is mostly unconjugated or indirect, and results of the Coombs' test is negative. Spherocytes are noted in varying frequency in a stained peripheral blood film. Spherocytes lyse in a greater percentage than normal erythrocytes in the hypotonic salt solutions used in the osmotic fragility test. Since the basis for the hemolysis is trapping and destruction of the spherocytes in the spleen, it is not surprising that splenectomy is recommended and that it controls the hemolysis in symptomatic patients and in those who have had severe spherocytic crises.

Congenital elliptocytosis is usually an asymptomatic illness requiring no therapy. In this disorder, elliptic erythrocytes circulate in the peripheral blood.

Hemoglobinopathies. A large and ever increasing number of patients with inherited abnormal hemoglobin structure have been described. The abnormality is usually a single amino acid substitution in either the alpha or beta globin chain. Such disorders are referred to as hemoglobinopathies. Most are either rare or unrelated to major clinical illness. Some, however, are of major clinical importance. Approximately 8 per cent of black Americans have heterozygous "sickle cell trait"; approximately 0.25 per cent have homozygous "sickle cell disease". The abnormality is the result of a single amino acid substitution in the beta globin chain. This abnormal hemoglobin tends to polymerize and form tactoids under conditions of lowered pH and decreased oxygen tension and, in turn, distorts the surrounding erythrocyte membrane into the shape of a sickle; hence, the term sickle hemoglobin. Except in unusual circumstances of acidosis or hypoxia, in which sickling can occur and trigger clinical disease, heterozygous sickle cell trait is of no major clinical importance. Patients with this condition are not anemic. Sickled cells are not seen in studies of their peripheral blood films. Recognition is important, however, at the level of genetic counselling. Homozygous sickle cell disease is a violent, lifelong hemolytic process. Multiple, recurring, painful, and destructive thrombotic episodes are clinically apparent in multiple organ systems. Thrombi are produced by sickled erythrocytes, which occlude the microcirculation. The blood count in patients with homozygous sickle cell disease reveals severe anemia, marked reticulocytosis (10-25 per cent), and the presence of sickled erythrocytes in a peripheral blood film. Confirmation of the homozygous or heterozygous state is obtained from hemoglobin electrophoresis. In the heterozygous state, the electrophoresis reveals less than 50 per cent sickle hemoglobin; the remainder is normal A hemoglobin. In the homozygous state, the majority of hemoglobin is S, or sickle, with some elevation of the F, or fetal, hemoglobin.

The treatment of crises, which are usually painful, that occur in the homozygous state is primarily symptomatic and includes using oxygen and intravenous fluids, correcting acidosis when present, and administering pain medication. Transfusions of normal red blood cells, with subsequent dilution of the sickling cells to less than 50 per cent of the total red

cell population, often aborts a crisis situation by inhibiting further microthromboses. Surgery in patients with homozygous disease is achieved successfully if acidosis and hypoxia are prevented during the intraoperative period. Preoperative dilution of the patient's blood with greater than 50 per cent of normal blood significantly reduces morbidity.

Combined inheritance of sickle hemoglobin and either thalassemia minor or C hemoglobin is called S-thalassemia or S-C disease, respectively. Both are clinically important but are uncommon and less severe than homozygous S-S disease. The management is much the same as patients with S-S disease.

Erythrocyte Enzyme Defect. Integrity of the intra-erythrocyte glucolytic pathways and their multiple enzyme systems is important in maintaining normal intracellular redox (oxidation-reduction) potentials. Deficiency of any one of the several glucolytic enzymes leads to altered redox potentials; the formation of an oxidized, unstable hemoglobin; and, ultimately, hemolysis. Although several such enzyme deficiencies have been described in association with hemolysis, by far the most common of these is the spectrum of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Several dozen qualitatively abnormal mutants of G6PD have been described, at least 50 per cent of which are unassociated with clinical disease. In the others, hemolysis may be chronic but usually is acute and is triggered by an oxidative stress, such as severe infection, or by the use of an "oxidant" drug (Table 11).

Table 11. Drugs Leading to G6PD Deficiency Hemolysis

Sulfa derivatives
Sulfones
Nitrofurans
Antimalarials
Analgesics, antipyretics:
      Aspirin, acetophenetidin, aminopyrine, acetanilid
Miscellaneous: isoniazid, probenecid, fava beans, chloramphenicol.

G6PD deficiency, which is genetically X-linked, is found worldwide and is seen with a high frequency in peoples of Mediterranean ancestry. It is said to be present in approximately 10 per cent of black American males. Twenty per cent of black American females are said to be carriers, with 3 per cent of these individuals reacting to oxidant drugs.

Following exposure of an affected individual to an oxidant drug, hemolysis with hemoglobinuria is noted on about the third day. Hemolysis continues for several days, and a loss of one-third of the cell mass is not uncommon. Reticulocytosis is usually brisk, reaching its peak at about the 10th day. In patients with mild deficiency, the hematocrit level begins to rise, even if the offending drug is continued, as the blood is repopulated with younger cells that are more resistant to oxidative change. This process does not occur with severe deficiency. In either case, the drug is usually discontinued and the patient recovers. Enzymatic tests that detect G6PD deficiency are available in the clinical laboratory. These tests should not be done immediately after an episode of hemolysis. A false positive test may be reported just after a hemolytic episode because the most deficient of the older erythrocytes have been destroyed.

Acquired Hemolytic Anemia

Immune Hemolytic Anemia. In these anemias, there is premature red blood cell destruction mediated by antibodies against red cells. The cause of a specific case often is not known but may be related to an underlying disease (lymphoma, systemic lupus erythematosus). The Coombs' test (antiglobulin test) is very useful in the diagnosis of these disorders. A direct Coombs' test detects anti-red blood cell antibody, immunoglobulin-G or immunoglobulin-M, and/or complement that has bound to the patient's red cells in vivo. The indirect Coombs' test detects antierythrocyte antibodies present in the patient's serum that react in vitro with other individuals' red cells.

Alloimmune Hemolytic Anemia. The prototype of alloimmune hemolytic anemia is erythroblastosis fetalis. In this condition, fetal red cells that carry paternal antigens (Rh positive cells) leak across the placenta into the maternal circulation. If the mother is Rh negative, she develops antibodies against these fetal cells. These maternal alloantibodies then cross the placental barrier and react with an antigen present on the fetal red cells, resulting in hemolysis in the fetus. The greatest percentage of such fetal-maternal blood incompatibility is the Rh and the ABO systems. Rh incompatibility is far more serious. For more than two decades it has been standard practice to administer anti-RhIgG to all Rh negative mothers who have delivered an Rh positive infant, usually by 72 hours after birth. More recently, it has become common practice to administer another injection at 28 weeks during a subsequent pregnancy. This passive immunization prevents the formation of Rh antibodies in the event of a future pregnancy with an Rh positive fetus.

Autoimmune Hemolytic Anemia. Most patients with autoimmune hemolytic anemia (AIHA) have a positive direct Coombs' test and many have a positive indirect Coombs' test. As in patients with immune thrombocytopenia, such forms of hemolytic anemia are seen in two separate clinical settings. Primary or idiopathic AIHA is said to exist in patients with no obvious underlying disease or triggering event. Secondary AIHA may exist as part of the clinical spectrum in certain inflammatory, infectious, and neoplastic diseases. In AIHA, the antibodies are usually IgG or IgM, but IgG antibodies are more common. Interaction with complement is frequent. Most IgG antibodies react optimally at 37°C and are referred to as warm antibodies. IgM antibodies react optimally at a lower temperature and are called cold antibodies. In warm antibody disease, the antibody activity is mostly directed against antigens in the Rh system. In cold antibody disease, the antibody response is more variable. In primary cold agglutinin disease and following mycoplasmal pneumonia, antibodies have anti-I specificity. In infectious mononucleosis, they have anti-i specificity, and in paroxysmal cold hemoglobinuria, the antibody is directed against the P antigen. Paroxysmal cold hemoglobinuria, a very rare form of autoimmune hemolytic anemia, is complement mediated, and may be seen as a complication of tertiary syphilis.

The treatment of autoimmune hemolytic disease depends on diagnose. When it is secondary to infection, hemolysis subsides as the infection improves. When there is another underlying disease, it should be treated and, if possible, controlled. Corticosteroids and occasionally immunosuppressive agents are used successfully in reversing hemolysis in both primary and secondary AIHA. Splenectomy occasionally is necessary to control hemolysis in warm antibody disease. Cold antibody disease responds poorly to splenectomy but may respond to the use of alkylating agents such as chlorambucil used in combination with

corticosteroids. Infusions of large doses of immune globulin have been successful in reversing uncontrolled AIHA.

A patient with AIHA presents difficult problems in crossmatching when a transfusion is needed. Sometimes a patient's blood reacts with all available units of banked blood. If necessary, the best crossmatched unit of blood may be used with caution but usually without danger.

Drug-Induced Immune Hemolytic Anemia. Many commonly used drugs induce a positive direct Coombs test and, on rare occasions, immune hemolytic anemia (Table 12). Several distinct immunologic mechanisms are involved in the pathogenesis of immune hemolysis. In most instances, the antibody response in a given patient is not directed against his or her specific naturally occurring red cell antigens and, therefore, may be considered a type of isoantibody. In the hemolysis associated with the use of alpha-methyldopa and L-dopa, however, the antibody exhibits red cell antigen specificity and, therefore, is an autoantibody. In all cases of drug-induced immune hemolysis, the direct Coombs test is positive.

Table 12. Some Drugs Reported to Induce Immune Hemolytic Anemia

Quinine, quinidine
Sulfa derivatives
Isoniazid
Penicillin
Alpha-methyldopa
L-dopa.

Hemolysis subsides when the offending drug is discontinued. This occurs slowly in alpha-methyldopa- and L-dopa-induced hemolysis.

Nonimmune Hemolytic Anemia. A variety of mechanical, physical, and chemical factors may cause hemolytic anemia. For example, patients with valvular heart disease, with or without prosthetic valve replacement, may develop hemolysis secondary to excessive turbulence at the site of the diseased or the replaced valve.

Patients with splenomegaly may exhibit hemolysis, because erythrocytes are trapped and destroyed in the enlarged organ.

Anemia of Decreased Blood Production

Anemia of Chronic Disorders. The anemia of chronic disorders or simple chronic anemia is one of the most common anemias seen by the practicing clinician. The anemia is usually mild, with the hemoglobin in the range of 10 gm/dl. The reticulocyte count is not elevated, and the morphology of the erythrocytes is normal. This type of anemia is seen in chronically ill patients, particularly in those with chronic infections, other inflammatory disease, and neoplasms. The anemia is multifactorial and is primarily the result of decreased erythrocyte production. However, there is usually an element of hemolysis. Care must be taken to evaluate such patients completely not only in order to understand the nature of the

associated disease or diseases but also to avoid ignoring a correctable form of anemia. For instance, serum iron values in patients with this condition are usually low. A bone marrow evaluation using special iron stains may be necessary to distinguish between simple chronic anemia and iron deficiency anemia.

Anemia of Chronic Renal Disease. The majority of patients with advanced renal disease are anemic. In contrast to anemia of other chronic disorders, the anemia of renal failure usually progresses to hemoglobin levels of 5 or 6 gm/dl. Once again, the anemia is caused by many factors. Faulty production of erythropoietin by the diseased kidneys plays a major role. Bleeding, malnutrition, and hemolysis are variably involved. A bone marrow examination is often a necessary and valuable tool used in sorting the various factors involved in the development of the anemic process. On occasion, severe anemia may need to be corrected with transfusion of packed red blood cells. Commercially available erythropoietin, given parenterally, is now being used in some patients to correct anemia associated with renal disease.

Hypoplasia (Aplasia) of the Bone Marrow. Severe bone marrow hypoplasia is accompanied in the peripheral blood by pancytopenia that is often severe. In children, several forms of congenital bone marrow aplasia have been described. In adults, as well as children, however, bone marrow aplasia is usually acquired. In some disorders of this acquired group, causative factors can be identified. In others, the causes are unclear. Rarely, aplasia is seen following viral hepatitis. Radiation therapy and chemotherapeutic agents used in the management of neoplastic disease are common offenders. Many other agents are reported to cause severe marrow injury (see Table 4).

In a patient with pancytopenia, a bone marrow aspirate and closed bone biopsy are necessary to confirm severe marrow dysplasia.

Following removal of the causative agent, many patients improve and recover with appropriate supportive care. In selected patients with irreversible bone marrow aplasia, bone marrow transplantation, using marrow cells from a closely matched sibling, is employed successfully in correcting this disorder. In selected patients, cyclosporin and antithymocyte globuline (ATG) also have been used successfully in the management of marrow aplasia.

Myelophthisis. In patients with advanced leukemia, lymphoma, or other forms of cancer and in those with myeloproliferative syndromes of several types, the normal bone marrow substance is primarily replaced with neoplastic tissue or fibrous tissue, or both. Fibrosis of the marrow is much more obvious in some of the myeloproliferative states. The process of myelophthisis, or wasting, of the normal marrow results in anemia and, frequently, in pancytopenia. The peripheral blood studies in such patients often show nucleated RBCs, early myeloid cells, bizarre platelets, and highly atypical erythrocyte forms including teardrop-shaped cells. Myelophthisis is confirmed using bone marrow aspirate and biopsy.

Refractory Anemia. Primary hematologic diseases of poorly understood causes have been described in which anemia that is minimally responsive to therapy accompanies profound nondiagnostic hyperplasia of the bone marrow. Such cases have been referred to as exhibiting hyperplastic refractory anemia. In some patients, the marrow shows proliferation of red blood cell precursors; in others, red cell precursors are decreased or absent. Some

cases, having bizarre white blood cell precursor activity, represent early and unusual leukemic states. Recently, some of these anemias have been reclassified as myelodysplastic states (see the section on leukocyte disorders).

Therapy is difficult. Fortunately, such conditions are rare.

Pseudoanemia

Hematocrit levels may be reduced during pregnancy and also accompanying congestive heart failure, cirrhosis of the liver, and iatrogenic overhydration of a patient. In such cases, the red blood cell mass may be normal, but plasma volumes are expanded and the peripheral hematocrit and hemoglobin levels are low. The recognition of such states is important in order to prevent the incorrect diagnosis of anemia and overzealous attempts at therapy.

Polycythemic Diseases (Table 13)

Table 13. Polycythemic Diseases

Stress or pseudopolycythemia
Erythrocytosis with increased erythropoietin production
      Hypoxia
            Chronic pulmonary disease
            Cyanotic heart disease
            Abnormal hemoglobin levels with high oxygen affinity
      Various tumors
            Hypernephroma
            Cerebellar hemangioblastoma
Polycythemia vera.

Occasionally, the clinician is confronted with patients whose hemoglobin or hematocrit level, or both, is elevated above the normal limit. In a substantial portion of these patients, the plasma volume is low, the red blood cell mass is normal, and the hematocrit level is "falsely" elevated. Such patients, who are usually tense, overweight, cigarette-smoking young men, are said to have stress or pseudopolycythemia.

In the remaining patients, true erythrocytosis or an expanded red cell mass exists, as determined by using measured values of the red cell mass and plasma volume. Hypoxia, with arterial PO_2 values of less than 60 mm Hg (as may be seen in chronic pulmonary disease or cyanotic heart disease), stimulates the elaboration of erythropoietin, and erythrocytosis develops. The hypoxic stimulus also leads to erythrocytosis in rare patients with inherited abnormal hemoglobins that have high oxygen affinity. Excessive erythropoietin production, which may accompany some hypernephromas or cerebellar hemangioblastomas, for example, also may lead to erythrocytosis. Finally, some of the patients have polycythemia vera, a disease of unknown cause, in which there is uncontrolled erythrocyte production in the absence of the stimulus of erythropoietin.

The complete evaluation and therapy of patients with polycythemia usually is not the responsibility of the otolaryngologic surgeon but usually is accomplished by the patient's

family physician or a consulting hematologist. Hematocrit values that exceed 55 per cent should be evaluated in detail. Whole blood viscosity begins to increase at hematocrit levels greater than 55 per cent and, hence, vascular stasis syndromes begin to appear.

Disorders of Leukocytes and Lymph Nodes

The otolaryngologist is seldom the primary physician for patients with severe leukocyte disorders or for patients with lymphoma (Table 14). On occasion, he or she may be the primary physician contact for such patients whose complaints may include lumps in the throat and neck, nosebleeds, mouth ulcers, and acute or chronic sore throat. Recognition of such disorders leads to appropriate management of the patient.

Table 14. Disorders of Leukocytes, Lymphoma, and Myeloma

Leukocyte disorders:
    Leukemia
        Acute lymphoblastic leukemia (ALL)
        Acute myeloblastic leukemia (AML)
        Chronic lymphocytic leukemia (CLL)
        Chronic myelocytic, chronic myelogenous, chronic granulocytic
        leukemia (CML)
        Hairy cell leukemia
        Myelodysplasia
    Neutropenia
    Infectious mononucleosis
Lymphoma
    Hodgkin's disease
    Non-Hodgkin's lymphoma
Multiple myeloma.

The Leukemias

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) May be seen at any age and is the most common form of leukemia seen in childhood. At the time of diagnosis, most patients are ill with fever, purpura, anemia, adenopathy, and hepatosplenomegaly. The blood count usually confirms anemia and thrombocytopenia. The typical blast cells are seen on examination of the stained peripheral blood and in the bone marrow. The total peripheral white blood count may be elevated 10- to 20-fold but may also fall within the normal range or even below.

Therapy of this disorder has improved tremendously in the past decade or so. Using a rather standard therapeutic approach, at least 50 per cent of children with this condition will survive for 5 years, and many are likely to be cured of the leukemia. In adults, long-term survival is less likely unless bone marrow transplantation is possible.

Acute Myeloblastic Leukemia

Acute myeloblastic leukemia (AML) is relatively common in adults of all ages but represents only about 15 per cent of the cases of leukemia seen during childhood. The clinical presentation of such patients is much the same as with ALL, although lymphadenopathy and hepatosplenomegaly are much less common. Once again, the blood count usually reveals anemia and thrombocytopenia. At the time of presentation, a low or normal white blood count is the rule rather than the exception. Variable numbers of blast cells are seen in the peripheral blood. The bone marrow, however, is usually densely infiltrated with the typical leukemic cells.

Therapy for this disorders has greatly improved. Two decades ago, survival after diagnosis was usually only a few weeks; complete remissions following therapy were rare. Now, using newly available chemotherapeutic agents, approximately 70 per cent of such patients achieve complete remission. In young patients (less than 35 years of age), successful induction followed by consolidation chemotherapy appears to achieve long-term survival in approximately one-third or more of this group. In this group of young patients and in older patients who represent a good risk, bone marrow transplantation has resulted in long-term survival in a significant number of patients. In older patients in whom bone marrow transplantation is not possible, long-term survival following achievement of remission is less common.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is probably the most common form of leukemia in the adult and is rare in children. Usually, CLL is seen in patients over 60 years of age but may be seen in younger patients. Often, patients with this condition are asymptomatic when the disease is diagnosed. Blood counts performed following a routine examination or in the anticipation of surgery often reveal the diagnosis. Patients with CLL often first seek medical attention for enlarged lymph nodes discovered by accident. The white blood cell count in patients with CLL is usually elevated, sometimes to levels of several hundred thousand. The predominant cell, the leukemic cell, in the peripheral blood is the normal-appearing, mature lymphocyte. This same cell is seen infiltrating the bone marrow and involved lymph nodes. Because of the lymphocytic and, hence, immunologic orientation of the illness, complications frequently involve abnormal immunologic phenomena, such as hypogammaglobulinemia and immune hemolytic anemia or thrombocytopenia. Survival after diagnosis usually approaches 10 years. Life expectancy is improved somewhat with therapy.

Chronic Myelocytic Leukemia

Chronic myelocytic leukemia (CML) is seen in all age groups but is most frequently in adults between the ages of 30 and 60 years. Most patients are symptomatic at the time of diagnosis. Splenomegaly, which is sometimes massive, is the rule. The white blood cell count is most often elevated and is usually accompanied by a display of early myeloid precursors in the peripheral blood as well as eosinophils and basophils. The bone marrow is hyperplastic, with the predominant cells being myeloid precursors. In patients with CML, the circulating neutrophils lack the enzyme alkaline phosphatase, as demonstrated using appropriate histochemical stains. In 90 per cent of patients with typical manifestations, there is a

cytogenetic abnormality in the leukemic cells. The long arm of chromosome 22, group G, is translocated most frequently to chromosome 9. The abnormal chromosome 22 is called the Philadelphia chromosome, or Ph[1] chromosome.

Most patients respond favorably to therapy. The drugs of choice are either busulfan or hydroxyurea, given orally. Radioactive phosphorus and splenic irradiation are used in some instances. Despite early favorable responses to therapy in these patients, cures are not achieved and life expectancy without bone marrow transplantation is approximately 4 years. When a suitable donor is available, bone marrow transplantation offers the expectation of long-term survival in 35 to 40 per cent of patients who undergo this procedure.

Hairy Cell Leukemia

Hairy cell leukemia is an uncommon lymphoproliferative disease characterized by the presence of peculiar hairy lymphoid cells (cytoplasmic projections) in the peripheral blood and bone marrow. Patients are usually middle aged and exhibit splenomegaly. Pancytopenia may be present at time of diagnosis. The presence of unusual "hairy" lymphoid cells seen using the phase microscope and the presence in these cells of a tartarate-resistant acid phosphatase strongly suggest the diagnosis. Treatment by splenectomy and, more recently, with the use of interferon prolongs life in most patients. A new drug, 2'-deoxycoformycin (Pentostatin), is also being used successfully in the management of this unusual illness.

Myelodysplasia

The term myelodysplasia is used to encompass several related clinical disorders caused by a stem cell abnormality of the bone marrow. Early in the course of the myelodysplasia, patients are found to have sideroblastic anemia, a condition characterized by mild anemia and the presence in the bone marrow of iron-loaded red cell precursors (ringed sideroblasts). With time, the disease progresses and increasing numbers of myeloid blast cells appear in the marrow. Many patients subsequently develop florid acute myeloblastic leukemia. Treatment is usually symptomatic, including the use of red blood cell transfusions when necessary. Therapy using vitamin B6, androgen steroids, and antileukemia chemotherapy is seldom successful.

Neutropenia

Neutropenia is said to exist when the absolute number of circulating neutrophils falls below 2000/cu mm. As has been previously noted in the discussions of anemia and thrombocytopenia, the mechanisms that permit reductions in any circulating blood cell, including neutrophils, are simply decreased production or increased destruction or loss. The causes of neutropenia are multiple, although the effects of certain drugs are commonly involved. Often, patients with neutropenia require a bone marrow examination to help delineate the causes and mechanisms of the disorder. Although, neutropenia is usually not life threatening until the absolute count falls below 500/cu mm, a thorough diagnostic evaluation is appropriate for most patients.

Infectious Mononucleosis

Infectious mononucleosis is caused by the Epstein-Barr virus (EBV). The disease is common during the teens and early 20s and is rare after age 40. The usual clinical syndrome of fever, sore throat, adenopathy, splenomegaly, and headache is familiar to all physicians. The less common features may cause some confusion in diagnosis, especially if seen early in its course. These include jaundice, arthralgia or arthritis, and skin rash. The diagnosis, often suspected after physical examination, is confirmed by laboratory tests by noting bizarre atypical lymphocytes in the peripheral blood.

Sometimes these cells represent 80 to 90 per cent of the circulating white blood cells. The total white blood cell count is usually modestly elevated. Tests for the presence of heterophile antibody in the blood are usually positive after the first week of the illness. Liver enzyme levels are usually elevated early in the illness because of the accompanying hepatitis. Treatment is usually symptomatic, although in severely ill patients and in those with severe hemolytic anemia (positive Coombs' test) or thrombocytopenia, the cautious use of corticosteroids may reverse the severe toxicity of the illness and its serious complications. Splenic rupture, either spontaneous or following minimal trauma, requires surgical intervention.

The Lymphomas

Hodgkin's Disease (Hodgkin's Lymphoma)

Asymptomatic lymph node enlargement in the cervical and supraclavicular areas is the most common presenting finding in a patient with Hodgkin's disease. A simple biopsy of the involved node, or nodes, yields the microscopic diagnosis. In other patients with mediastinal, intra-abdominal, and extranodal involvement, diagnostic biopsy is more difficult to achieve. There appear to be four distinct microscopic patterns in this neoplastic disease (Table 15), with lymphocyte predominance offering the best prognosis; lymphocyte depletion the worst. The diagnosis of Hodgkin's disease is not established unless the Reed-Sternberg cells is identified in the tissue sections. Each patient with Hodgkin's disease requires a complete staging evaluation in order to determine the extent of the disease present at the time of diagnosis (Table 16). Diagnostic staging procedures are elaborate and usually include the following: a bipedal lymphangiogram, bone marrow biopsies, and chest and abdominal CT scans. Intra-abdominal node biopsies, liver biopsy, and splenectomy may all be performed at the time of a diagnostic exploratory laparotomy. The need for any or all diagnostic studies should be guided by a physician familiar with the management of Hodgkin's disease. At the time of diagnosis, using the staging procedures just mentioned, approximately 50 per cent of patients with Hodgkin's are classified as stage I or II; less than 20 per cent are stage IV.

Radical radiotherapy is possibly curative for patients with stage I, II, and III-A$_1$ disease. With far advanced disease, combination chemotherapy offers hope for a prolonged life with a satisfactory life style. The combined therapy of chemotherapy and radiotherapy is administered to some patients with massive nodal disease.

Table 15. Morphologic Classification of Hodgkin's Disease (Lukes)

Good -----> Poor

Lymphocyte predominance - Nodular Sclerosis - Mixed cellularity - Lymphocyte depletion.

Table 16. Staging of Lymphoma (Ann Arbor Classification)

I	Nodal involvement within one region
IE	Involvement of a single extralymphatic site
	Nodal involvement, two or more lymph node regions, on same side of diaphragm
IIE	Local extralymphatic disease + I or II
III	Nodal disease above and below diaphragm
IIIE	Local extralymphatic disease + III
IIIS	Splenic disease + III
IIIES	E + S + III
IV	Disseminate involvement of one or more extralymphatic organs, with or without lymph node disease.

A or B, when added after the above noted Roman numerals, denotes the absence or presence, respectively, of unexplained fever, night sweats, and significant weight loss.

Non-Hodgkin's Lymphoma

As with Hodgkin's disease, the presenting symptom in non-Hodgkin's lymphoma is usually lymph node enlargement. In contradistinction to Hodgkin's disease, in which stage IV disease is uncommon at the time of presentation, more than 50 per cent of patients with non-Hodgkin's lymphoma have advanced stage IV disease when first diagnosed. Even in patients in whom the disease appears to be localized, such as those who first present with lymphoma in Waldeyer's ring, staging procedures should be followed whenever possible and feasible. Treatment depends on the clinical stage of the disease as well as the cell type involved (Table 17). It is worth noting that extensive combination chemotherapy may be curative in some of the large cell lymphomas. Localized non-Hodgkin's lymphoma is uncommon but may occasionally be cured with radiation therapy. Interferon has been shown of therapeutic value in some patients with lymphoma that has been given a good prognosis.

Table 17. Morphologic Classification of Non-Hodgkin's Lymphoma

Rappaport	Lukes-Collins
	Good -----> Poor
Lymphocytic, well differentiated	Small cell lymphocytic and plasmacytoid lymphocytic
Poorly differentiate lymphocytic	Small cell cleaved, follicular center cell
Mixed lymphocyte-histiocytic	Small & large cell cleaved follicular center cell
Histiocytic	Large cell - cleaved and noncleaved
Poorly differentiated	Immunoblastic
Undifferentiated	Convoluted T cells.

Multiple Myeloma

Typical multiple myeloma and associated lymphocyte-plasma cell dyscrasias are common forms of primary hematopoietic neoplasms. This group of diseases, sometimes called the gammopathies, is seen in older patients who frequently complain of weight loss, fatigue, and bone pain. Signs and symptoms of hyperviscosity of the plasma, including purpura and neurologic disease, may be present in some patients. In others who have amyloidosis, mouth and skin lesions may be symptomatic. Anemia is frequently present. Serum protein levels are usually elevated. Electrophoresis of the serum proteins most often shows a sharp spike of the myeloma M protein. Quantitative determination of the urinary proteins may show components of the myeloma protein called Bence Jones proteins. The bone marrow shows varying degrees of invasion by young, often blastic plasma cells. In patients with Waldenstrom's disease, which is a gammopathy characterized by excessive macroglobulin production and the hyperviscosity syndrome, a lymphocytic-appearing plasma cell is the invading cell. Treatment with alkylating agents and prednisone remarkably prolongs life in more than 60 per cent of patients. Interferon is of some value in some cases.

Blood Transfusion Reactions (Table 18)

Adverse reactions to administered blood or blood products (Table 19) are common and involve serious causes and pathogenetic mechanisms.

Table 18. Types of Blood Transfusion Reactions

Hemolytic
Febrile
Allergic
Infection
Circulatory overload
Metabolic effects
Hemorrhagic manifestations.

Hemolytic Reactions. Bone pain, chest tightness, local pain at the site of transfusion, urticaria, chills, fever, hemoglobinuria, and hemoglobinemia are the usual clinical manifestations of hemolytic transfusion reactions. Most reactions are related to hemolysis of the antigenic donor cell in response to antibody in the recipient's plasma; in the remainder, the reverse is true. If a reaction is suspected, the transfusion is discontinued, and both the donor's and recipient's blood are reexamined for antigen-antibody mismatch.

If blood pressure and urinary output are maintained, serious renal complications usually do not occur. DIC, which sometimes accompanies this disorder, may require therapeutic intervention (see the section on DIC).

Febrile Reactions. This febrile transfusion response is secondary to leukocyte or erythrocyte pyrogens or to bacterial or chemical pyrogens present in the transfusion apparatus. Since this benign response can mimic hemolytic reactions, the transfusion is usually stopped, and the blood from the patient and the donor is restudied, as noted previously. Such reactions, which are especially common in patients who have received multiple previous transfusion,

are usually prevented by administration of washed red blood cells that contain a minimum of the offending leukocyte or platelet pyrogenic antigens, or both. Otherwise, treatment is symptomatic.

Allergic reactions. Urticaria, asthma, facial edema, and fever may occur during a transfusion. The etiology may be related to passive transfer of reaginic substances. Transfusions are discontinued. Antihistamines reverse the problem.

Infection. Fortunately, bacterial contamination of infused blood is rare. The response in the unfortunate recipient is the prompt development of a profound picture of septicemia with fever, chills, hypotension, and bone and abdominal pain. The transfusion is discontinued and cultured, and the patient is managed for septic shock. Screening procedures for viral hepatitis type B as well as screening for the AIDS virus have nearly eliminated the risk of transmission of these diseases from donor to recipient. The incidence of non-A, non-B hepatitis has been reduced with appropriate screening and surrogate testing for the virus.

Screening for cytomegalovirus prevents transfusion of cytomegalovirus-positive blood products into cytomegalovirus-negative recipients who are at high risk of acquiring an infection (immunosuppressed patients).

Circulatory Overload. The typical picture of pulmonary edema may develop in patients who have received transfusion too rapidly or in excessive amounts. Careful monitoring of all patients receiving blood reduces the incidence of this complication.

Metabolic Effects. With transfusion of large numbers of units of stored whole blood, hyperkalemia and hypocalcemia may develop. Plasma potassium concentrations of blood stored over a week may reach levels greater than 15 mEq/l. The potassium is derived from red blood cells. Fresh blood or packed cells should be used in patients in whom hyperkalemia is apt to be a problem, such as in patients with advanced renal failure. Citrate binds calcium, and therefore, hypocalcemia may be seen in patients receiving multiple whole blood transfusions. Administrating 1 gm of calcium gluconate given intravenously following each 5 units or so of blood prevents this complication.

Hemorrhagic Manifestations. Thrombocytopenia, which was discussed earlier, may follow multiple blood transfusions in a given patient. On rare occasions, platelet transfusions are required to correct this hemostatic defect. Serious post-transfusion immune thrombocytopenia is rare.