CHAPTER 35

Hematologic Disorders

Hemophilia

Hemophilia, a genetically determined disorder, is characterized by abnormal blood coagulation as a result of functional deficiency of a specific factor, namely factor VIII or IX. Since biblical times the crippling deformities of the musculoskeletal system and death resulting from uncontrolled hemorrhage have been well depicted in the pages of history. Talmudic writings of 200 A.D. state that a child whose siblings had bled excessively after circumcision was excused from the ritual.[53] Queen Victoria of England transmitted the gene through her daughters to the ruling families of Russia, Spain, and Austria.

The term *hemophilia,* coined by Hopff in 1828, means blood loving. Wright is credited with being the first to demonstrate the prolonged clotting time in the disorder.[130] The deficient substance was isolated in 1937 by Patek and Taylor, who named it antihemophilic globulin.[90]

Modern management of hemophilia has reduced the morbidity of the disease remarkably. The development of HIV infections among those receiving blood products has been a major setback. Better treatment of HIV infection and safer methods of factor preparation are reducing the impact of this unfortunate disease complex.[65] Currently, factors VIII and IX are produced with recombinant DNA methods, which avoids the hazards of blood-borne disease.

INCIDENCE

The incidence of hemophilia is estimated to be 1 per 10,000 male births in the United States and 0.8 per 10,000 male births in England.[4,24] A 1998 study estimated the national prevalence at 13,320 cases of hemophilia A and 3,640 cases of hemophilia B, with a U.S. birth prevalence of both A and B of 1 per 5,032 live male births.[112]

CLASSIFICATION AND INHERITANCE

The hemophilias may be subclassified as hemophilia A, hemophilia B, and von Willebrand's disease.

Hemophilia A. Hemophilia A, or classic hemophilia, results from a congenital deficiency in factor VIII (also known as antihemophilic factor, AHF) or antihemophilic globulin (AGH). This type accounts for about 80 percent of cases and is caused by a gene carried on the X chromosome. Current research has identified at least 58 different mutations that result in a deficiency in normally functioning factor VIII protein.[68]

Hemophilia A occurs in males and is transmitted by asymptomatic female carriers. A female could be affected if her mother were a carrier and her father a hemophiliac; this, however, is very rare.

Hemophilia B. Hemophilia B, or Christmas disease, is due to a deficiency in factor IX (plasma thromboplastin component, or Christmas factor). Its clinical manifestations are quite similar to those of classic hemophilia. The hereditary transmission is also by an X-linked recessive gene. As with hemophilia A, many mutations of the gene responsible for factor IX production have been identified.[86,105] Hemophilia B accounts for about 15 percent of the cases of hemophilia.

Von Willebrand's Disease. In this bleeding disorder both factor VIII deficiency and platelet functional abnormality are present. It is inherited as an autosomal dominant trait and occurs in both males and females. The bleeding disorder is relatively mild.

Factor VIII, a glycoprotein with a molecular weight of 2 million daltons, is composed of subunits of about 200,000 daltons molecular weight. All these subunits contain carbohydrates and are held together by disulfide bonds.[52,96] The precoagulant sex-linked hemophilic defect is located on the lighter, protein portion of the glycoprotein, whereas the autosomal dominant von Willebrand's defect is related to the larger molecular weight carbohydrate moiety of the molecule.[80]

GENE THERAPY

A number of trials of gene therapy in animals with genetically produced factor deficiencies have been performed, with some success. Most studies have addressed the use of adenoviral vectors to carry the corrected gene into the recipient. Host immunity to the adenoviral vector has thus far prevented permanent correction of the factor deficiency.[12,28,55]

CLINICAL PICTURE

Uncontrolled hemorrhage and repeated episodes of bleeding are the hallmarks of hemophilia. The severity of the disease varies from patient to patient, but it is constant in any one

patient. Clinical manifestations of hemophilia A and B are similar and dependent on the blood levels of factor VIII or IX. The level of hemostasis is normal when the blood level of either factor is at least 50 percent of normal. When the functional plasma level of the factor is 25 to 50 percent of normal, the hemophilia is *mild,* and excessive bleeding occurs only after major trauma or during surgery. When the plasma level of the factor is 5 to 25 percent of normal, the hemophilia is *moderate;* severe, uncontrolled bleeding occurs after minor injury or during an operative procedure. When the plasma level of the factor is 1 to 5 percent of normal, the hemophilia is moderately severe, with major hemorrhage occurring after minor injury or unrecognized mild trauma. When the plasma levels of factor VIII or IX are below 1 percent of normal the hemophilia is considered *very severe;* clinically there are repeated spontaneous hemorrhages into joints and bleeding into deep soft tissues.

Abnormal bleeding may occur in any area of the body. Joints are the most frequent sites of repeated hemorrhage. The sites next in frequency are muscles and soft tissues. In the severe hemophiliac the abnormal bleeding tendency may manifest in the neonatal period or early infancy. Ordinarily the ecchymosis and soft tissue bleeding are minor, resorb relatively readily, and are not detected by the parents. When the infant begins to crawl and starts bumping into objects, or with standing and falling, abnormal bleeding into joints and soft tissues is noted by the parents. At this stage the infant is usually seen by the pediatrician. It is crucial to have a high index of suspicion for hemophilia in order to prevent serious consequences or invasive treatment such as aspiration of the joints. About three-fourths of episodes of bleeding sustained by hemophiliacs are into either the joint, the deep soft tissues, or both.

HEMOPHILIC ARTHROPATHY

Site of Involvement. The weightbearing joints are most commonly sites of hemophilic arthropathy, with the frequency of involvement being, in decreasing order, the knee, elbow, shoulder, ankle, wrist, and hip. The vertebral column is rarely involved. Any joint, however, may be the site of pathologic change.

Pathophysiology. The pathophysiology was initially described by Konig a century ago.[58] There is first an initial stage of synovial reaction to the bleeding into the joint, followed by a later stage of cartilage degeneration and joint destruction. After injury, the synovial vessels rupture and the blood accumulates in the joint. Bleeding continues until the intra-articular hydrostatic pressure exceeds arterial and capillary pressure in the synovium. The resultant tamponade of the synovial vessels causes ischemia of the synovium and subchondral bone.

With repeated hemorrhage, hyperplasia and fibrosis of the synovium occur, and a vicious cycle of bleeding-synovitis-bleeding ensues.[100] Pannus formation by the proliferating synovial tissue erodes the hyaline cartilage peripherally, and compression of its opposing cartilaginous surfaces results in degeneration of articular cartilage centrally. Articular cartilage is also degraded by the action of proteolytic enzymes—lysosomal proteases, acid phosphatase, and cathepsin D.[100] Prostaglandin levels are also elevated in hemophilic arthropathy. There is an inflammatory process that invades and destroys cartilage. Loss of joint motion and contractual deformity due to the capsular synovial fibrosis follow. Local ischemia causes formation of subchondral bone cysts.

Repeated hemarthrosis causes marked dilation of the capsular and epiphyseal vessels. The resultant hyperemia and increased circulation to the part result in enlargement of the epiphysis and increased longitudinal length of the limb. Stimulation of growth may be asymmetric, resulting in valgus or varus deformity. Shortening of the limb may be produced by early closure of the physis. Osteoporosis and muscle atrophy are common.[99]

Clinical Findings. Clinical findings depend on the severity of hemorrhage and whether the hemarthrosis is acute, subacute, or chronic. In *acute hemarthrosis,* pain and swelling with distention of the joint capsule are the principal findings. A history of injury may not be elicited. With cessation of bleeding, the intensity of the pain decreases. The joint will assume the position of minimal discomfort, which is also the position of minimal intra-articular pressure. The hip joint, for example, is held in 30 to 65 degrees of flexion, 15 degrees of abduction, and 15 degrees of lateral rotation. Extension, wide abduction, and medial rotation of the hip are limited and painful, as they increase intra-articular hydrostatic pressure. The knee joint is held in flexion, with range of motion markedly restricted by protective spasm, pain, and the hemarthrosis. Local tenderness and increased heat are present. The overlying skin becomes tense and shiny. The intense pain of acute hemarthrosis subsides rapidly after the administration of factor VIII or IX.

Subacute hemarthrosis develops after several episodes of bleeding into the joint. Pain is minimal. The synovium is thickened and boggy. Joint motion is moderately restricted. Subacute hemarthrosis does not respond rapidly to administration of clotting factor. *Chronic hemarthrosis* develops after 6 months of involvement. Progressive destruction of the joint takes place, with the end stage being a fibrotic, stiff, totally destroyed joint.[4]

Differential Diagnosis. A difficult diagnostic challenge is the child with hemophilia and a superimposed joint infection. The diagnosis is often delayed because the symptoms are quite similar to those of hemarthrosis. In one series, most but not all children with infection had elevated white blood cell (WBC) counts. Associated risk factors included infected angioaccess catheters, pneumonia, and generalized sepsis. Affected joints should be treated with antibiotics and either repeated aspiration or arthrotomy.[35,98]

Radiographic Findings. Initially, radiographs of an affected joint disclose soft tissue swelling due to distention of the joint capsule. With repeated hemorrhage and resultant chronic synovitis there may be osteoporosis, enlargement of the epiphysis, subchondral cysts, narrowing of the articular cartilage space, and formation of peripheral osteophytes (Figs. 35–1 to 35–3). The final phase of hemophilic arthropathy is fibrous ankylosis (Fig. 35–4). On the basis of radiographic findings and the degree of cartilage destruction, Arnold and Hilgartner classified hemophilic arthropathy into five stages (Table 35–1).[4] In *stage I* there is only soft tissue swelling, but no skeletal abnormalities. *Stage II* is characterized by overgrowth and osteoporosis of the epiphy-

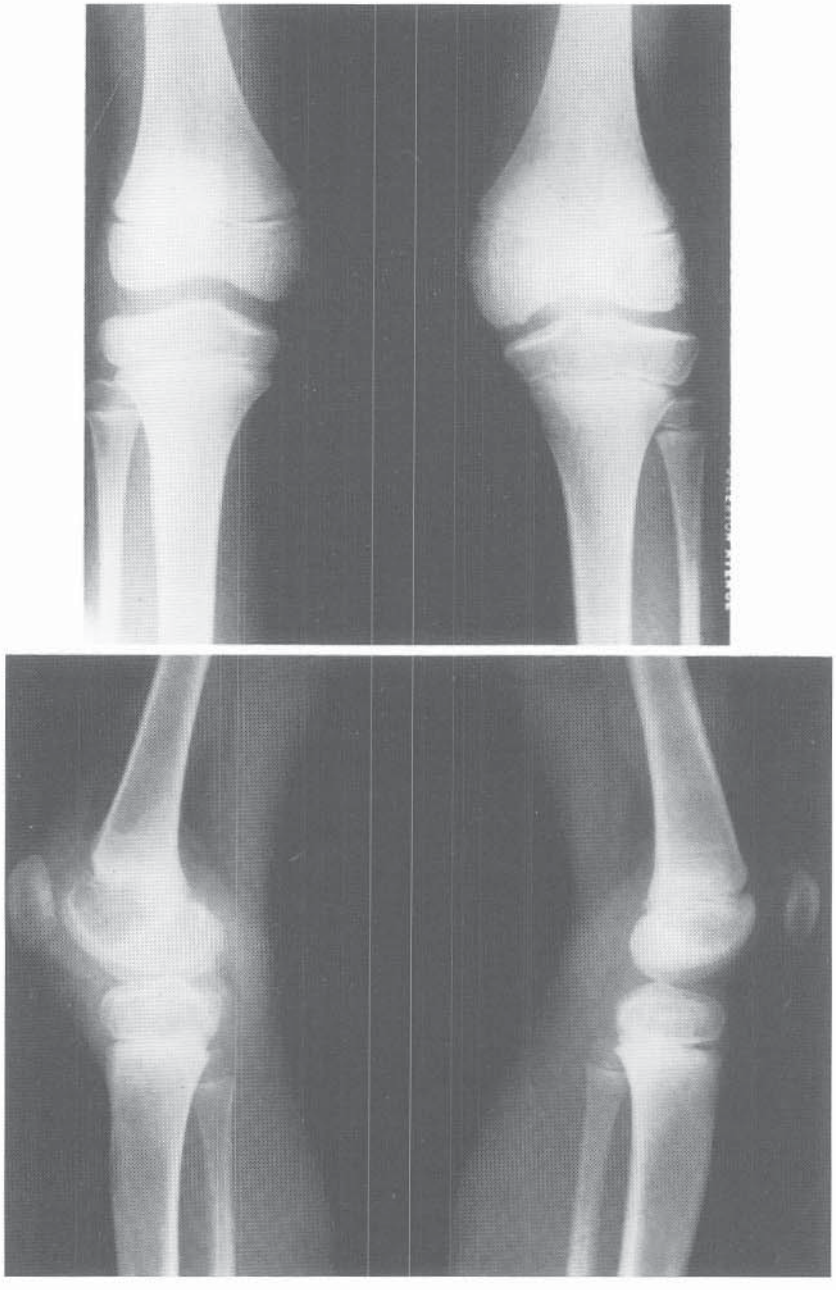

FIGURE 35–1 Hemophilic arthropathy of the left knee. Radiographs show the chronic synovitis and enlargement of the distal femoral epiphysis.

sis, but joint integrity is maintained—there are no bone cysts and no narrowing of the articular cartilage space. The radiographic stage II parallels the clinical stage of subacute hemophilic arthropathy.

In *stage III* there is minimal to moderate joint space narrowing with subchondral cysts, which occasionally communicate with the joint space. There is widening of the intracondylar notch of the knee and the trochlear notch of the ulna. In the knee there may be squaring of the patella. In stage III the articular cartilage is still preserved, indicating that with treatment, hemophilic arthropathy is still reversible.

In *stage IV* there is destruction of articular cartilage with severe narrowing of the joint space. The other osseous changes found in stage III—subchondral cysts, patellar squaring, and widening of the intercondylar or trochlear notch—are more pronounced. *Stage V* is characterized by total loss of joint space with fibrous ankylosis of the joint. There is marked incongruity of the articular structures, with severe, irregular hypertrophy of the epiphysis.

SOFT TISSUE BLEEDING

After a direct injury, a large hematoma may accumulate in the subcutaneous tissues. The blood usually is absorbed spontaneously; occasionally ulceration occurs, commonly on the forehead, the olecranon process, or the prepatellar area. This type of superficial hematoma usually remains fluid and fluctuant for a long time. Superficial soft tissue hemorrhage in the form of ecchymosis is common, especially in a subject with severe hemophilia; it is of not clinical significance.

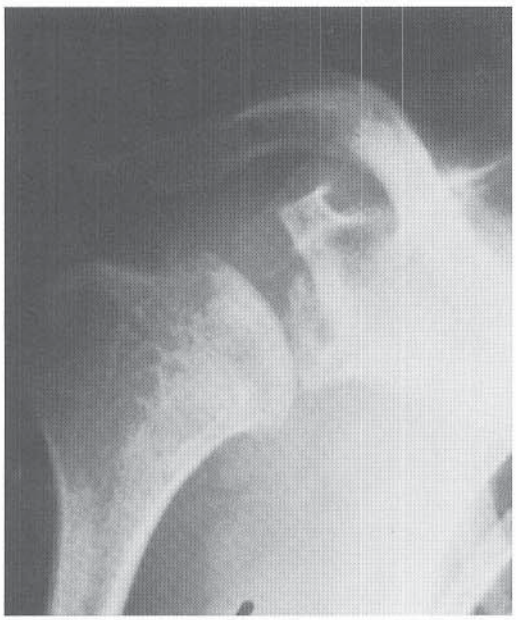

FIGURE 35–2 Hemophilic arthropathy of the shoulder.

Intramuscular and Intermuscular Hemorrhage. In the lower limb the most common site of bleeding is the quadriceps (44 percent), followed by the triceps surae (35 percent), anterior compartment (7 percent), adductors of the thigh (7 percent), hamstrings (6 percent), and sartorius (1 percent).[5] In the upper limb the most common site of bleeding is the deltoid (24 percent), followed by the wrist and finger flexors in the forearm (23.5 percent), the brachioradialis (19.5 percent), the biceps (14 percent), the wrist and finger extensors in the forearm (11 percent), and the triceps (8 percent).[95] The presenting complaint is pain on movement or at rest.

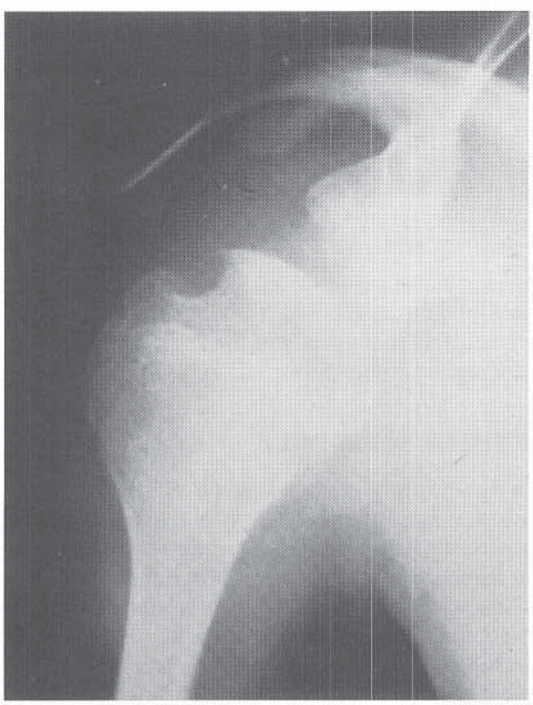

FIGURE 35–3 Hemophilic arthropathy of the shoulder.

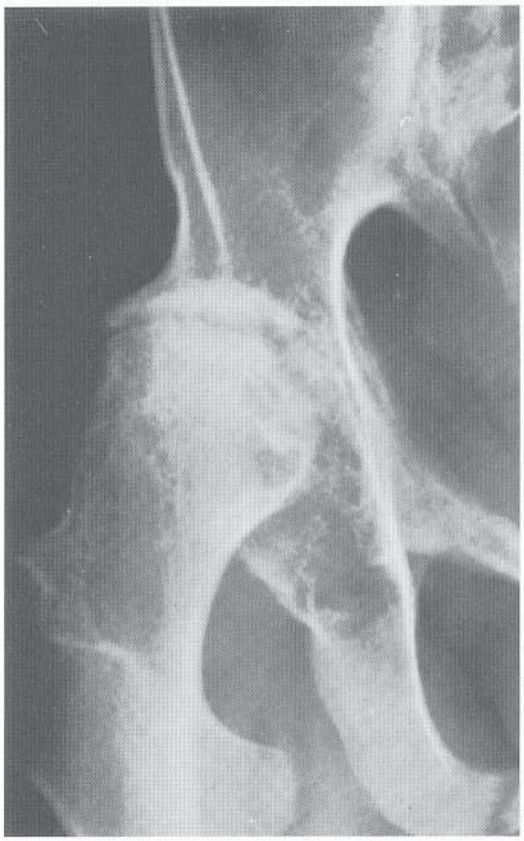

FIGURE 35–4 Fibrous ankylosis of the hip as a result of hemophilic arthropathy.

Hemorrhage in the quadriceps muscle may occasionally be painless and manifest only as "stiffness" or "weakness" of the knee. Physical findings consist of local tenderness and swelling with limitation of motion of the adjacent joints. Bleeding in the deltoid muscle will restrict shoulder motion,

TABLE 35–1 **Radiographic Staging of Hemophilic Arthropathy**

Stage I
Soft tissue swelling
No skeletal abnormality
Stage II
Overgrowth and osteoporosis of epiphysis
Stage III
Mild to moderate joint narrowing
Subchondral cysts
Patellar squaring
Widening of intercondylar notch of knee and trochlear notch of elbow
Stage IV
Severe narrowing of joint space with cartilage destruction
Other osseous changes very pronounced
Stage V
Total loss of joint space with fibrous ankylosis

From Arnold WD, Hilgartner MW: Hemophilic arthropathy: current concepts of pathogenesis and management. J Bone Joint Surg 1977;59-A:287.

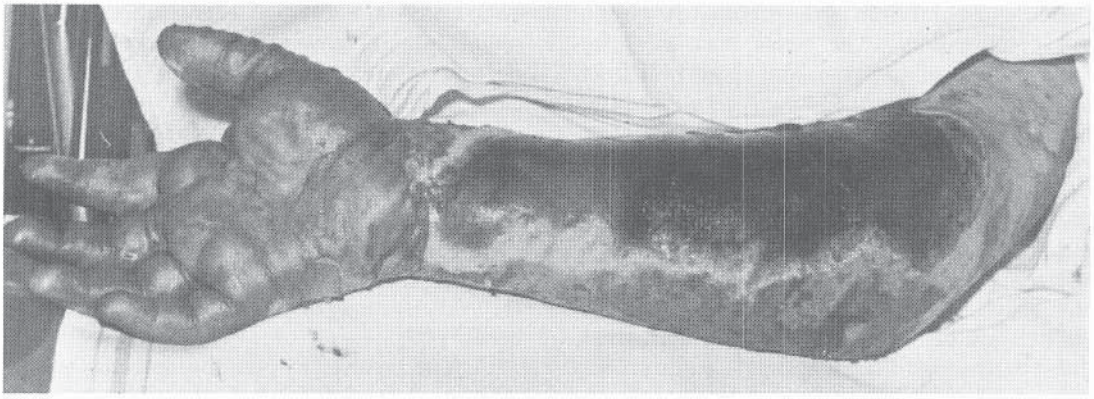

FIGURE 35–5 Volkmann's ischemic contracture of the forearm following fracture of both bones in a hemophilic boy.

especially abduction and, to some extent, rotation, flexion, and extension of the shoulder. Bleeding in the forearm flexors will restrict motion of the fingers, wrist, or elbow, either individually or in combination.

Hemorrhage into the iliopsoas muscle or retroperitoneum may mimic a variety of surgical or medical emergencies such as appendicitis or renal colic.

Ischemia and fibrosis of muscles with subsequent myostatic contracture result from bleeding within muscles or among muscles contained in a firm fascial compartment.[62,73,74,83] Hemorrhage within the calf muscles will produce fixed equinus deformity. Bleeding in the volar surface of the forearm may produce Volkmann's ischemic contracture with flexion deformity of the digits and wrists (Fig. 35–5).

The echo pattern varies with the duration and anatomic site of the hemorrhage. In the soft tissues a hematoma initially displays increased echogenicity as compared with surrounding soft tissues; within 3 to 4 days, relatively echo-free areas develop in the bleeding site. Ordinarily, in 10 days the established hematoma is relatively echo-free. A soft tissue hematoma may be of uniform texture, separating muscle planes, or it may interdigitate with muscle fibers, producing a mottled appearance with poorly defined margins. On follow-up ultrasound examination the intramuscular hematoma may have resolved spontaneously or may have progressively liquefied, with decreased internal echoes and the development of well-defined borders. A sudden increase in echogenicity indicates a fresh hemorrhage.

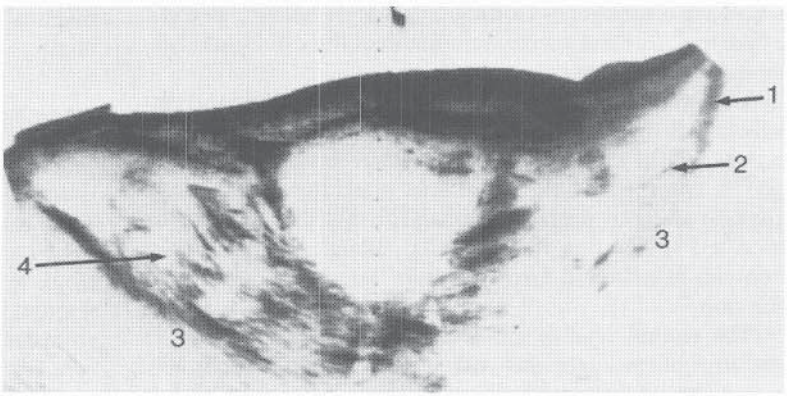

FIGURE 35–6 Ultrasonographic findings in soft tissue bleeding in the iliopsoas muscle on the right. *1*—Normal iliopsoas. *2*—Fascial plane. *3*—Iliac bone. *4*—Bleeding in the iliopsoas.

ULTRASOUND.* Diagnostic ultrasound is routinely performed in hemophiliac patients in whom hemorrhage into joints or soft tissues is suspected. It is noninvasive and can be performed at the bedside with minimal disturbance of the patient.

Hemorrhage into superficial joints such as the knee, elbow, ankle, or wrist is readily determined on physical examination. The diagnostic value of ultrasound is in the identification of bleeding into the hip, shoulder, and deep soft tissues, such as the iliopsoas or retroperitoneum (Fig. 35–6). Effusions into these deep anatomic sites are readily detected on ultrasound.

The echo pattern of bleeding into joints shows a mixture of echo-free fluid within the joint and a variable amount of echogenic material floating free. In its initial stage, hemarthrosis is sometimes uniformly echogenic, in contrast to the echo-free appearance of joint effusions from other causes such as toxic synovitis or septic arthritis.

NERVE PALSY

Neuropraxia in hemophilia is primarily due to compression of a nerve from the hematoma. The femoral nerve is most frequently involved, as it is in a closed, rigid compartment limited by the iliacus fascia. The psoas sheath is easily distensible. Brower and Wilde reported six cases of femoral nerve

*See references 9, 57, 60, 81, 89, 108, 124, 128, 129.

palsy,[11] and Goodfellow and associates described 20 cases of femoral nerve compression.[37] The nerve next most frequently affected is the median nerve. The ulnar, radial, sciatic, peroneal, and lateral femoral cutaneous nerves may also be involved.[20]

A history of injury, such as twisting of the limb or strenuous use, may be obtained in some cases. Pain is the presenting complaint and is soon followed by weakness of the affected muscle groups.

In femoral nerve palsy, the hip is held in moderate flexion and some lateral rotation. Extension and medial rotation of the hip are limited and painful. On palpation a tender mass in the iliac fossa extending to the iliac crest and groin may be present. There will be anesthesia or hypoesthesia in the areas of the cutaneous distribution of the femoral nerve. Quadriceps paralysis in varying degrees is often present. Ultrasound and CT will demonstrate the iliacus hematoma. With adequate factor replacement the natural course is one of gradual and steady recovery, usually within 12 months.*

HEMOPHILIC PSEUDOTUMOR

The term hemophilic pseudotumor refers to a progressive cystic swelling involving the musculoskeletal system. It is caused by uncontrolled hemorrhage within a confined space. The hematoma increases in size and causes pressure necrosis and erosion of surrounding tissues. The subjacent bone is frequently involved.[4]

The entity was first described by Starker in 1918, and in the subsequent 70 years fewer than 100 cases have been reported.[113] It occurs only in severely affected hemophiliacs who have a functional clotting factor level below 1 percent of normal. In these severe hemophiliacs the estimated incidence is 1 to 2 percent.

Valderrama and Matthews have described three ways in which such hemophilic cysts may develop. The *simple cyst* occurs within the fascial envelope of a muscle or muscles and is confined by the tendinous attachments. No bone changes are seen on radiographs. The cyst usually remains localized under the muscle fascia, though it may extend between muscle and fascia to point internally or through the skin.

The second type of cyst occurs in a muscle with wide and firm fibrous periosteal attachments and may eventually cause cortical thinning because of compressive interference with the periosteal and outer cortical blood supply.

In the third type, the pseudotumor originates as a subperiosteal hemorrhage and progressively strips the periosteum from the cortex until it is limited by the aponeurotic or tendinous attachments. The overlying muscle is raised or destroyed.[119] Most hemophilic pseudotumors are caused by subperiosteal hemorrhage. Occasionally one may arise from intraosseous hemorrhage.[51] In the past, intramedullary bleeding was thought to be a cause of hemophilic pseudotumor.[1,45,51] It was proposed that uncontrolled intraosseous hemorrhage increased the intramarrow pressure and caused necrosis of the marrow and inner cortex of the bone. With progressive bleeding and increasing pressure the cortex would perforate, causing elevation of the periosteum and bone necrosis. Pathologic examination of large hemophilic pseudotumors, however, has failed to demonstrate bone necrosis or resorption of the inner part of the cortex. Trueta cites MacMahon and Blackburn's case of cystic expansion of the metacarpal bone as a pseudotumor that probably had an intramedullary origin.[72,121]

The most common location of pseudotumors is in the thigh (50 percent of cases). Next in frequency are the abdomen, pelvis, and tibia (Fig. 35–7A).[45] Pseudotumor may also occur in the hand (Fig. 35–7B).[6] Pseudotumor involving the calcaneus may cause marked erosion of the calcaneal tuberosity.[16,59]

A bone involved by pseudotumor may sustain pathologic fracture. Before adequate factor replacement was available, pseudotumors caused death in the majority of patients; involved limbs were amputated. Valderrama and Matthews observed that the location of these tumors is related to the powerful muscle groups of the quadriceps femoris, triceps surae, gluteus maximus, and iliopsoas muscles, which have firm attachments between their fibers and the periosteum but not to any great extent with the bone itself. These muscles also have profuse vascular connections with the underlying periosteum and bone. Hemorrhage from these injured vessels will easily detach and elevate the periosteum.[122]

Hemophilic pseudotumor is essentially an expanding hematoma. CT will demonstrate that the lesion is of fluid consistency and will depict its true extent, bone destruction, and extraosseous abnormality.[91] MRI is also of great value in delineating the nature and extent of the pseudotumor. It is imperative that a hemophilic tumor not be mistaken for a malignant or expanding benign bone tumor. It should not be aspirated, nor should a biopsy specimen be taken for diagnosis, particularly without appropriate preoperative correction of functional factor deficiency.

FRACTURES

Fractures in hemophilia do occur; they may result from trauma or may occur pathologically after a trivial injury. They are most common in the lower limb, especially in patients with stiff knees, who sustain supracondylar fracture of the femur. Hematomas may be large, especially following femoral fractures. Uncontrolled bleeding into a closed fascial compartment may lead to Volkmann's ischemic contracture (see Fig. 35–5).

DISLOCATIONS

Intra-articular bleeding in the hip will stretch the joint capsule and cause subluxation and eventual dislocation of the hip. Floman and Niska reported a 6-year-old boy with hemophilia A who developed a spontaneous posterior dislocation of the hip due to repeated intra-articular bleeding. The prognosis for such dislocation is poor. In this patient, despite immediate reduction, the hip became ankylosed.[30] Other cases of hip dislocation in hemophilia have been reported by Teitelbaum,[119] Driessen,[23] and Boardman and English.[8]

Bleeding in the hip joint is a rare but serious problem in hemophilia. Increased intra-articular pressure, in addition to stretching the joint capsule, will cause avascular necrosis (AVN) of the femoral head with eventual joint space narrowing, subchondral irregularity and cyst formation, col-

*See references 1, 3, 6, 10, 21, 26, 31, 41, 45, 48, 72, 103, 106, 114, 120.

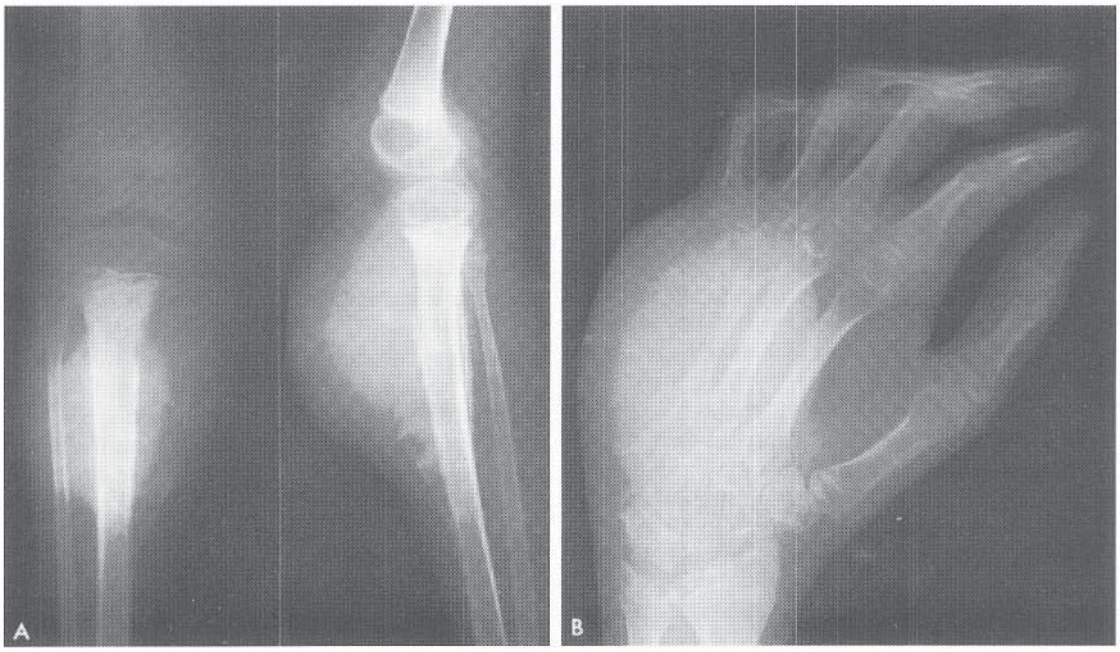

FIGURE 35–7 Hemophilic pseudotumor. **A,** Of the tibia. **B,** Of the hand.

lapse of the femoral head, osteoarthrosis and arthrokatadysis.[107,119]

MYOSITIS OSSIFICANS

Ectopic ossification in hemophilia, first described by Hutcheson, develops as a result of inter- or intramuscular bleeding.[49] Heterotopic bone formation around the hip joint restricts motion of the hip.[64] In the past it was thought to be a rare complication in hemophilia, but in a radiographic survey by Vas and associates it was found in 15 percent of patients; in most of their cases the disability was minimal.[123]

TREATMENT

The care of the hemophilic with musculoskeletal disorders requires a multidisciplinary approach by a team consisting of a hematologist, orthopaedic surgeon, physical therapist, nurse clinician, medical psychologist, social worker, and geneticist. There should be immediate access to a laboratory capable of preforming accurate factor VIII or IX assays and detecting factor antibodies. Factor material should be readily available for replacement therapy. The creation of multidisciplinary hemophilia clinics in children's hospitals has simplified the care of hemophiliac children. In this section the management of bleeding into the locomotor system is discussed.

MEDICAL MANAGEMENT

The objective of medical management is control of bleeding by hemostasis, achieved by IV administration of the appropriate coagulation factors. There are two major approaches. The first is treatment on demand, that is, at the onset of any bleeding episodes. The second approach is prophylactic replacement in patients with recurrent hemarthroses.

Treatment on Demand. The most common approach to the treatment of recurrent hemarthrosis is treatment on demand. It is suggested that factor levels of 30 to 50 IU/dL are optimal in controlling an acute hemorrhage. To achieve these levels in a patient with severe hemophilia (plasma levels less than 1 percent of normal), 15 to 25 IU/kg of factor VIII and 20 to 50 IU/kg/dL of factor IX are required. Repeated treatments may be required daily for 2 to 3 days to control the hemarthrosis. Aspirin products and nonsteroidal anti-inflammatory medications must be avoided.[97]

Prophylactic Treatment. Several studies have shown that ongoing prophylactic treatment reduces the incidence of hemarthrosis.[40] One study found that starting treatment at age 3 resulted in a better outcome than starting at age 5, but patients with prior repeated hemarthrosis had continued arthropathy despite prophylactic factor replacement.[32] Another study noted reduced bleeding frequency in 41 of 47 patients but an increase in the cost of clotting factors compared to treatment on demand.[82]

The dosage required to replace a factor deficiency depends on the patient's weight and plasma volume. The hematologist makes the calculation and is in charge of administering the factor. The orthopaedic surgeon, however, should be aware that 20 to 30 minutes after administration of the antihemophilic factor the plasma level will rise. The biologic half-life of factor VIII is 6 to 12 hours, whereas that of factor IX is 8 to 18 hours. In the management of bleeding into joint, muscles, and soft tissue, the dose of factor VIII or IX is calculated to raise the plasma level to 30 percent of normal. In severe hemarthrosis it may be desirable to raise the plasma level to 40 percent of normal.

Inhibitors of factors VIII and IX develop as a result of the immunologic response of the human body.[126] A low titer

of inhibitors may be circumvented by high-dosage factor VIII infusion. Other methods to overcome this life-threatening problem are the administration of prednisone and cyclophosphamide or the use of concentrations of prothrombin-activated material or of plasmapheresis.

Early Bleeding into Muscles and Soft Tissues. Early treatment of bleeding into muscles and soft tissues by self-administration of factor VIII or IX by the hemophiliacs or their parents at home has become effective. The dose of factor is calculated to raise the level to 30 to 40 percent of normal. The part is splinted in a comfortable neutral position in foam pillows or soft appliances. If the hemorrhage is in the lower limb, weightbearing is restricted by crutches or eliminated by confinement to bed or a wheelchair. As soon as the acute symptoms of pain and muscle spasm have subsided, the affected limb is gradually mobilized under cover of factor replacement. With early treatment (within 2 to 3 hours), the hemorrhage in the muscles will usually resolve within 3 to 5 days. Hemorrhages in the quadriceps femoris and biceps brachii take the longest time to resolve.[5,34]

Hemarthrosis. Acute bleeding into joints is an emergency requiring immediate attention. With proper education, instructions as to dosage schedules, and parents, many patients can be treated at home by themselves or by a family member. Immediate treatment of bleeding into joints results in less arthropathy and minimizes the extent of joint destruction. Home therapy permits factor replacement as soon as a bleeding episode take place. This type of patient self-help, however, has the disadvantages of inadequate follow-up, the possibility of transmission of hepatitis to a family member, and an increased risk of infection because of lack of appropriate sterile technique in handling of materials.[66,67] The parents should be instructed that if the bleeding is severe with marked distention of the joint, the child should be brought to the hospital within 4 hours of the onset of hemorrhage. It cannot be overemphasized that delay in instituting adequate treatment is the primary cause of crippling joint deformity in patient with hemophilia. A minimal or moderate intra-articular hemorrhage may not be so painful at the onset, and the child will continue to use and bear weight on the affected limb, causing continuous or intermittent progressive bleeding into the joint. Within a few days the joint will become markedly swollen, very painful, and inflamed by reaction to the blood and will develop fixed flexion contracture. Initially, in the event of associated bleeding into the periarticular tissues and muscles, pain and muscle spasm will be marked from the onset; the patient will be apprehensive of moving the limb and will be forced to rest and to seek medical attention.

The affected joint is temporarily immobilized in a molded, well-padded splint in a position of rest and minimum hydrostatic pressure. This position varies with each joint. For example, for the knee it is 35 to 45 degrees of flexion, and for the elbow it is 50 to 60 degrees of flexion. There are commercially available semiflexible splints (such as the Jordan splint) that provide partial immobilization and moderate compression.

Compression is effectively achieved with a rubber sponge placed over the site of hemorrhage and an elastic bandage. A second bandage may be applied intermittently over the first one to increase tension. The distal circulation should be carefully watched. Under no circumstances should a circular plaster cast be used; the swelling underneath will obstruct the blood flow and cause gangrene or compartment syndrome. The limb should be elevated to reduce hydrostatic venous pressure. Cold compresses in the form of ice bags are applied to the affected joint. The clotting defect is corrected by IV administration of antihemophilic factor.

Analgesics. Narcotic analgesics are used with care because in such a chronic disease, addiction can easily become a problem. Also, the course of the bleeding is best assessed by the patient, and under heavy analgesic he or she will be unable to give proper warning of continued bleeding. A diminution in the severity of the pain is the first indication of cessation of hemorrhage. The circumference of the joint is measured at intervals to determine whether there is progressive distention of the joint capsule. Also, analgesic drugs that contain aspirin, guaiacolate, and antihistamines inhibit platelet aggregation and prolong the bleeding time. Do not give such medication and produce a secondary bleeding disorder! If the pain is intolerable and does not respond to factor replacement and splinting, the pain medications to be given are propoxyphene (Darvon), acetaminophen (Tylenol), codeine, or methadone.

Aspiration. The need for joint aspiration has been debated. Some authors recommend aspiration only for an extremely tense hemarthrosis and avoid aspiration in ordinary cases, citing the risk of introducing infection, the discomfort to the patient, and the possibility that aspiration will incite more bleeding.[97] Other authors believe that removal of blood is critical to avoiding chronic synovitis. They feel that a large hemarthrosis is much more inviting to infecting organisms than the sterile aspiration of the joint.[39] Aspiration of the joint should be performed under strict aseptic conditions and under local anesthesia. Factors VIII and IX are administered IV and will reach an effective blood level 20 to 30 minutes later. This is the time to aspirate the joint, not after two or three infusions have already been given, because aspiration will be unsuccessful, owing to thickening and clotting of the blood. Aspiration is performed with an 18-gauge lumbar puncture needle with a stylet. One or at most two puncture wounds should be made with the needle. The joint is irrigated with normal saline solution until the return is clear. The compression dressing and posterior splint are reapplied. Administration of the factor is continued for 3 to 7 days following cessation of bleeding. At this time, physical therapy to mobilize the joint is initiated. Isometric muscle exercises are begun and are followed by gentle range assisted exercises, first with gravity eliminated and then against gravity. Between exercises the limb is protected in an appropriate splint. The range of motion of the affected joint is progressively increased. Weightbearing joints are protected with crutches with a three-point gait. Full weightbearing is not permitted for a minimum of 2 weeks, and longer if necessitated by limitation of joint motion and muscle weakness. It is imperative that transition to activity be gradual.

Subacute Hemophilic Arthropathy. Repeated episodes of bleeding into a joint in a relatively short time will result in synovial hypertrophy and persistent effusion. This is best managed nonoperatively by immobilization of the joint in

a well-padded splint and with factor replacement. Most subacute hemarthroses will resolve over a period of 3 to 4 weeks with this regimen of therapy. Aspiration is not indicated. Isometric exercises are performed to maintain muscle tone and strength. Initially, passive range-of-motion exercises are not allowed. Partial weightbearing with crutches is permitted. With resolution of the synovitis and effusion, the patient is gradually allowed to return to normal function.

If the subacute hemarthrosis fails to respond to 3 weeks of partial immobilization, physical therapy, and factor replacement, an intra-articular injection of corticosteroid may be given. Prolonged immobilization of the affected joint should be avoided, as it will result in marked muscle atrophy and restriction of joint motion. If the knee is involved, quadriceps atrophy will cause joint instability, leading to repeated trauma and bleeding.

Support of the lower limb in orthotic devices is indicated when the motor power of the quadriceps or triceps surae muscle is less than fair or when flexion deformity of the knee or equinus deformity of the ankle is present to such a degree that mechanical insufficiency of the lower limb predisposes the child to fall and sustain repeated injury. Rubbing and recurrent trauma to the opposite thigh or leg caused by the medial caliper is a real problem; it will cause soft tissue bleeding. Only a lateral upright is used. A well-padded plastic orthosis should be used whenever possible. When flexion deformity of the knee or equinus deformity of the ankle develops, appropriate splinting is utilized at night to keep the part out of the position of deformity. Ankle splinting may be done initially with ordinary posterior splints. Recurrent hemarthroses may be prevented by ankle support worn during activities. Air splints, free ankle polypropylene orthoses, and laceres have all been used. Shock-absorbent heel pads have also been shown to reduce the impact on the ankle, with fewer hemarthroses resulting.[42]

During the stage of subacute hemarthrosis, prophylactic factor replacement is administered in conjunction with an intensive physical therapy program. Graduated progressive resistive active and gentle passive range-of-motion exercises are performed immediately after infusion of the factor in the evening and the following morning. The patient is allowed to swim and perform ordinary physical activities of daily living. Contact sports should be avoided.

Chronic Hemophilic Arthropathy. Chronic hemophilic arthropathy can be prevented in most cases by effective and immediate treatment of acute hemarthrosis. The importance of prevention of chronic arthropathy with intra-articular fibrosis, cartilage destruction, and joint stiffness cannot be overemphasized.

In the management of chronic hemophilic arthropathy, four modalities of treatment are available: physical therapy, orthoses, traction and other corrective appliances, and surgery. The objective is to correct joint deformity and to restore function.

Nonsurgical Management. Nonoperative measures should always be employed prior to surgery. For flexion deformities of the knee and hip, a period of continuous traction is effective in relieving muscle spasm and increasing range of motion. Initially traction forces are in the line of deformity and are gradually altered to achieve correction. Split Russell traction is effective; the vertical force is exerted by a sling placed under the proximal tibia when the knee is involved; with the hip, the sling support is under the distal thigh. In cases of lateral rotation contracture of the hip, a medial rotation strap is added to the thigh. Houghton and Duthie recommend use of reverse dynamic slings to correct flexion deformity of the knee and elbow.[47]

Prophylactic protection with antihemophilic factor is usually not required for a child in traction. Once a neutral or nearly neutral position is obtained, well-padded plastic splints are used to maintain the part in the corrected position. Active exercises are begun to increase muscle power and range of motion of the joints. It is best to refrain from forceful passive stretching exercises.

If functional range of motion is not achieved after 2 or 3 weeks of traction, a wedging cast is applied. Posterior subluxation of the knee may be prevented by applying an extension-desubluxation hinge; it will lift the proximal tibia anteriorly as the knee is extended.[79,87,88,115] For safety, antihemophilic factor is administered when the cast is wedged. When full knee extension is achieved, the knee is immobilized for a period of 7 to 10 days, a plastic splint is utilized to maintain the correction, and physical therapy in the form of active exercises is begun. Gradually, partial weightbearing and three-point crutch gait are permitted. If bleeding occurs during this period of training, it is controlled by IV administration of antihemophilic factor. Crutch support is discontinued and full weightbearing is allowed when there is functional range of joint motion and at least fair strength of the quadriceps muscle.

Management of flexion contracture of the elbow follows the same principles as that of the knee. Equinus deformity of the ankle is treated by a dorsiflexion wedging cast. Forceful manipulation of a joint under general anesthesia is not recommended.

SURGICAL TREATMENT

If deformities caused by hemarthrosis cannot be corrected by conservative closed methods, one should not hesitate to perform open operations. If equinus deformity is very severe and rigid, tendo Achillis lengthening is indicated. Fractional lengthening of the hamstrings combined with posterior capsulotomy is performed for flexion contracture of the knee. On occasion, one may have to resort to osteotomy of the distal femur, tilting it anteriorly to correct flexion deformity of the knee.[101]

Open surgery has become relatively safe, provided the clotting mechanism is restored to near normal by the administration of antihemophilic factor, which should be continued for 3 weeks, with sutures removed on the 14th to 16th day postoperatively. Wounds and bone heal normally in hemophilic patients.

Hematologic Management. Before surgery is performed, the hematologist determines the factor level and performs tests to rule out the presence of factor inhibitors. During surgery and on the first postoperative day, the factor level should be raised to 100 percent by infusion of factor concentrate. During the first postoperative week, the factor level is maintained at 50 percent, and for the rest of the first postoperative month it is maintained at 30 to 40 percent by daily infusion of factor concentrate.

Synovectomy. The objective of synovectomy is to prevent progression of hemophilic arthropathy. The *rationale* for synovectomy in hemophilic arthropathy is based on the following considerations: mechanically, the vulnerability to trauma of the highly vascular synovial tissue is diminished by its excision, and biochemically, hemophilic synovial tissue has a high level of fibrinolytic activity that tends to prolong the bleeding episodes.[116,117] Also, the hypertrophic synovial tissue in hemophilia contains increased levels of acid phosphatase and cathepsin D, which are further elevated during bleeding episodes; these proteolytic enzymes destroy hyaline articular cartilage.[43,44,125] The chronic synovial inflammation is perpetuated by the elevated levels of prostaglandin E and polymorphonuclear leukocytes (due to chemotactic properties of the enzymes). Also, hemosiderin deposition in the synovium interferes with the production of collagenase, which may cause death of chondrocytes.

INDICATIONS. Synovectomy of peripheral joints, particularly of the knee, is indicated in patients with a history of severe recurrent hemarthrosis (two or three major bleeding episodes per month) and in those whose condition does not respond to aggressive medical management maintained for a period of at least 6 months. Medical management entails a prophylactic factor-replacement program that raises factor level to 30 to 40 percent of normal (factor replacement is administered every other day in hemophilia A and every third day in hemophilia B). Other indications are failure to respond to orthopaedic nonsurgical treatment consisting of physical therapy and protection with crutches and orthoses, and radiographic stage II or stage III hemophilic arthropathy (in stages IV and V, synovectomy is ineffective and contraindicated). In the elbow, repeated hemarthroses result in loss of forearm rotation and elbow extension. Limitation of rotation results mainly from hypertrophy of the radial head.[50] A reduction in the incidence of hemarthrosis has been reported after open synovectomy of the elbow with excision of the radial head to improve range of motion. Synoviorthesis with radioactive gold has also been reported to be effective in reducing hemarthroses.[102]

Arthroscopic synovectomy, open surgical synovectomy, and chemical synovectomy have all been recommended. Although open synovectomy has been used longer than the other methods, it is often complicated by loss of range of motion of the affected joint. Arthroscopic synovectomy is most useful when performed before severe degenerative changes have developed. Several reports have noted a significant reduction in hemarthroses without loss of motion after arthroscopic synovectomy. These procedures are difficult and often lengthy but avoid some of the motion problems of open approaches.[27,71,127]

OPERATIVE TECHNIQUE OF OPEN SYNOVECTOMY.[84] Synovectomy of the knee is performed under tourniquet ischemia. The surgical approach to the knee is through a long medial parapatellar incision that begins 5 cm above the superior border of the patella and extends to the medial border of the patella and then to the medial border of the proximal tibial tubercle. Throughout the operation, electrocautery is used to maintain strict hemostasis. The subcutaneous tissue, fascia, and capsule are divided and the knee joint is thoroughly inspected. The proliferative synovial tissue is excised first from the suprapatellar pouch, then from the medial and lateral recesses of the knee and intercondylar notch, including that around the cruciate ligaments, and finally from the menisci. The coronary ligaments must be preserved. The synovial tissue on the articular cartilage is removed gently with a moist sponge. Growth of the distal femoral physis must not be disturbed. Next, the joint is copiously irrigated with antibiotic solution, and Gelfoam mixed with a solution of injectable saline and thrombin is applied over the denuded tissues. The wound is packed with moist laparotomy pads, and after of several layers of Ace bandages have been applied for compression, the tourniquet is released. Five to 10 minutes later, the wound is inspected and thorough hemostasis is obtained. The previously applied Gelfoam is removed and the wound is closed in layers. Suction drainage is always inserted. A bulky compression dressing is applied, and the limb is immobilized in an above-knee plaster-of-Paris posterior splint. The suction drainage is removed in 2 or 3 days.

POSTOPERATIVE CARE. Isometric quadriceps and hamstring strengthening exercises are begun immediately. Active range-of-motion exercises should not be commenced early because they may result in massive hemarthrosis. Seven to 10 days postoperatively, gentle active assisted and passive range-of-motion exercises are started. Toe-touch weightbearing with crutch protection is allowed as tolerated. Active range-of-motion exercises are started about 2 weeks after surgery. Passive range-of-knee-motion excercises may also be performed with a continuous passive motion (CPM) machine 14 days following surgery, at first for several hours of the day during waking hours to ensure there is no bleeding into the joint, then for gradually increasing periods. During the third postoperative week the limb should be in the CPM machine all night and part of the day. Active exercises are performed intensively to develop quadriceps function. Gradually, full weightbearing is allowed.

PROBLEMS AND COMPLICATIONS. Postoperative loss of range of joint motion due to adhesions of the patellofemoral and tibiofemoral joints is a common and challenging problem following synovectomy for hemophilic arthropathy. In the series of 13 patients reported by Montane and associates, knee motion was reduced in 11 patients (85 percent); the average loss of range was 41 degrees. In the younger patients (less than 11 years) the postoperative loss of joint motion was greater, owing to lack of motivation and poor cooperation with the postoperative physical therapy program. One of the young patients subsequently required knee arthrodesis.[84] Manucci and associates reported marked decrease in joint motion, particularly flexion, in eight of 15 patients.[76] Kay and associates found decreased knee motion following surgery in nine patients, three of whom required postoperative manipulation under anesthesia; one of these patients sustained a supracondylar fracture of the femur during manipulation, but in the other two patients there was significant improvement of motion.[54] Arnold and Hilgartner recommended manipulation of the knee 2 to 3 weeks after synovectomy if joint motion was lost, and they stressed the importance of increasing factor levels to nearly 100 percent of normal.[4] The stage of arthropathy, adequacy of control of intra-articular bleeding at surgery and postoperatively, the degree of quadriceps and hamstring atrophy, and the patient's motivation and cooperation are important factors in determining the final range of motion. Intensive, prolonged physical

therapy and use of the CPM machine are vital following synovectomy.

Massive bleeding may occur in the joint during the immediate postoperative period following synovectomy or during the habilitation phase of treatment. This may require aspiration or surgical arthroscopic evacuation of the hematoma.

Despite these complications, the results reported in the literature indicate that chronic recurrent hemarthrosis and the pain in chronic hemophilic arthropathy can be effectively eliminated after open synovectomy, which also appears to slow the pace of progression of the disease.*

Synoviorthesis. A number of methods of synovial ablation using intra-articular radioactive substances have been reported. Children have been infrequently treated in this manner because of unresolved concerns of future oncogenesis. Rifampicin injected intra-articularly has been shown to reduce synovial proliferation and the incidence of hemarthrosis. It seems most effective in younger patients and in smaller joints.[14,15] Radioactive synoviorthesis has been shown to be effective in treating recurrent hemarthrosis in patients with factor inhibitors.[69] Colloidal ^{32}P chromic phosphate has also been used to treat hemarthroses. In one series all patients had a reduced incidence of hemarthrosis. Half of the patients retained range of motion and the other half gradually lost motion. Radiographic scores worsened despite a reduction in the rate of hemarthrosis.[98] A reduction in the incidence of hemarthrosis of the elbow has been reported with synoviorthesis with radioactive gold.[102] Chemical and radioisotope synovectomy have been tried in the treatment of chronic hemophilic arthropathy.[2,33,116] The results have been dubious; at present, surgical synovectomy is the procedure of choice.

Total Joint Replacement and Arthrodesis. Deciding between total joint replacement and arthrodesis is difficult, and the decision should be individualized. Disabling pain is the prime indication for surgery. In case of bilateral knee involvement, total joint replacement is indicated with stage IV or stage V arthropathy when persistent knee pain is definitely due to joint derangement; there should be at least 45 degrees of knee motion. Arnold and Hilgartner reported the results of five total knee joint replacements in hemophiliac patient; relief of pain was impressive, and functional range of motion was preserved without serious complications.[4] Other encouraging results have been reported by Lachiewicz and associates, London and associates, McCollough and associates, Marmor, and Small and associates.[61,70,75,77,78,109] Goldberg and associates reported the results of 13 total knee arthroplasties of the semicontainment type in ten patients with hemophilia A with a follow-up of 2 to $6\frac{1}{2}$ years. All patients had severe pain and used crutches with wheelchairs for ambulation preoperatively. The results were graded as excellent or good in four, fair in eight, and poor in one (who required arthrodesis). They recommended total knee arthroplasty, with arthrodesis as the only other alternative.[36]

Total hip replacement is indicated in stage IV or stage V hemophiliac arthropathy when pain is persistent with severe disability not relieved by conservative measures.[22,90] Total joint replacement has been shown to have no adverse effects on the course of HIV infection in patients with hemophilia.[92] Arthroplasty of the elbow has been reported.[110]

Arthrodesis of the ankle, subtalar, and midtarsal joints in the foot, shoulder, or knee may be indicated when these joints are destroyed. The surgical technique is the same as in normal patients with the exception that percutaneous pins should not be utilized in hemophiliac patients, as they will need factor replacement at moderate levels until the pins are removed.[46,90] Arthrodesis of the hip is considered when the patient has a destroyed hip with little involvement of the other joints. The indication is stronger when the child is unlikely to abide by activity restrictions and likely to overstress a total hip replacement.

Neuropraxia. *Neuropraxia* is treated by factor replacement therapy in doses to attain factor levels of 80 to 100 percent of normal for 48 hours after onset of hemorrhage; the dose is tapered to maintain a level of 40 percent for 1 to 2 weeks. The limb is splinted. Gentle physical therapy is performed 7 days after the bleeding episode. Occasionally decompression of the entrapped nerve may have to be performed.[63]

Fractures. Fractures usually heal in the normal time.[8,9,18,29,56] Factor replacement should be to the level of 40 to 60 percent of normal on the day of fracture and the following day; subsequently it should be 20 to 30 percent for 7 or more days, depending on the degree of associated soft tissue injury.[29] Whenever possible, fractures are treated by closed reduction and immobilization in a cast. Pins should not be used for skeletal traction, as the patient will need prolonged replacement therapy. External fixators should be avoided. Open reduction and internal fixation are carried out when closed methods are not appropriate.

Pseudotumors. Greene has recommended that pseudotumors be excised whenever they are accessible, and believes they will continue to expand if left alone.[38] Prior to surgical intervention, angiography, CT, and nuclear MRI should be performed to provide accurate anatomic detail of adjacent vessels.[120] The pseudotumor per se is avascular.[118] The surgical extirpation of a hemophilic pseudotumor requires careful preoperative planning and extensive dissection.[41,94,103]

Radiotherapy has been utilized to control the expanding hematoma of hemophilic pseudotumors; irradiation will cause new bone formation and sclerosis of the cystic cavity. Its use may be considered in surgically inaccessible sites. It is important to shield the physis so as not to cause growth disturbance.[82] Amputation of a limb may be indicated when the patient is seen quite late and in a case in which deformity is so severe that the limb is of no use.[7,19,104]

In conclusion, with early treatment and proper collaboration between the hematologist and orthopaedic surgeon, deformities and crippling in patients with hemophilia can be prevented and corrected.

*See references 13, 17, 25, 54, 70, 76, 78, 84, 85, 93, 111, 116, 117.

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Sickle Cell Disease

Sickle cell disease is a genetic condition that, in the homozygous state, causes the red blood cells (RBCs) to become distorted into a sickle shape under conditions of low oxygen tension. The affected cells are dysfunctional, which causes a variety of symptoms related to reduced oxygen delivery to tissues. The disorder primarily affects black individuals, although cases in Caucasians have occurred in some countries, including Greece, Turkey, Sicily, Italy, and India.

ETIOLOGY AND PATHOPHYSIOLOGY

Sickle cell disease is caused by an autosomal dominant gene that results in the production of an abnormal hemoglobin termed hemoglobin S. This hemoglobin differs from normal adult hemoglobin by the substitution of valine for glutamic acid in the sixth amino acid position in each of the two β-polypeptide chains.[13] In *sickle cell trait* the individual receives the abnormal hemoglobin S gene from one parent; sickle cell trait occurs in approximately 10 percent of black people in the United States. Sickle cell disease is the homozygous state and occurs in 2.5 percent of the American black population.

Sickle cell disease also includes conditions in which the abnormal hemoglobin S is combined with other abnormal hemoglobin entities such as C, D, or E.[2] These are referred to as mixed hemoglobinopathies. Hemoglobin S may also be associated with other types of hereditary diseases, such as thalassemia, spherocytosis, or ovalocytosis.

SICKLE CELL CRISIS

Skeletal Manifestations

BONE INFARCTION. Bone infarction occurs in sickle cell disease when vessels are occluded by the sickled RBCs. Infarction mainfests as sudden pain in an extremity with swelling over the affected bone. In addition, other signs of an inflammatory process are present, including local warmth, erythema, and decreased motion of adjacent joints. Fever is uncommon. The most commonly affected bones are the humerus, tibia, and femur. Although bone infarction is more common than osteomyelitis (50 times more common in one study), infection must be ruled out. The erythrocyte sedimentation rate (ESR) is often mildly elevated. Technetium scans may show increased or decreased uptake, and gallium scans often show increased activity.[10]

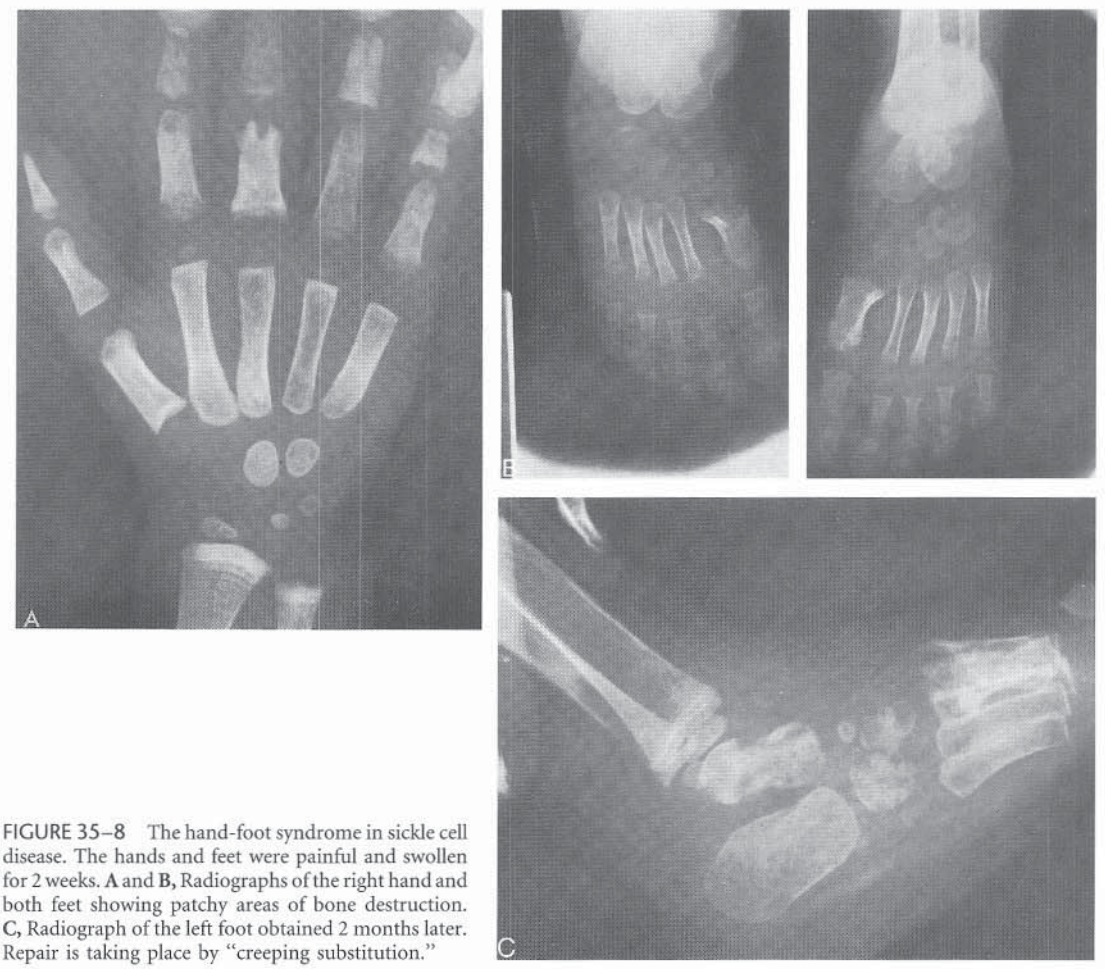

FIGURE 35–8 The hand-foot syndrome in sickle cell disease. The hands and feet were painful and swollen for 2 weeks. **A** and **B,** Radiographs of the right hand and both feet showing patchy areas of bone destruction. **C,** Radiograph of the left foot obtained 2 months later. Repair is taking place by "creeping substitution."

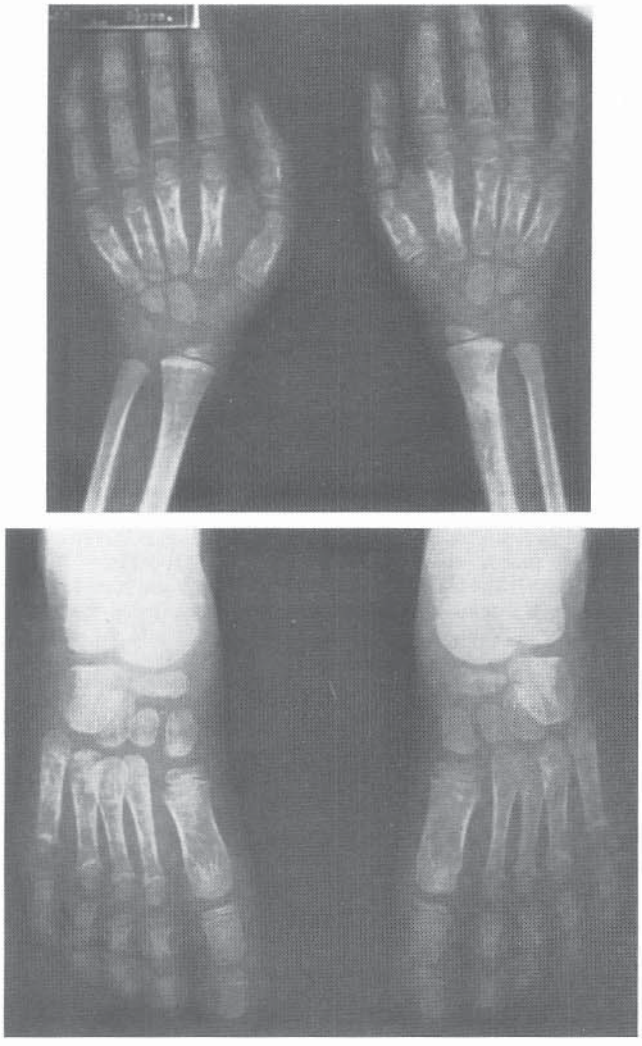

FIGURE 35–9 The hand-foot syndrome in sickle cell disease in an 8-month-old infant. Radiographs of the hands and feet reveal diffuse involvement of the short tubular bones, with patchy areas of destruction and some periosteal reaction.

The treatment of bone infarction is limited to analgesics and oral or IV hydration. Antibiotics are often given until the diagnosis of osteomyelitis is ruled out.[10]

OSTEOMYELITIS. Osteomyelitis is a frequent problem in children with sickle cell disease. In one study the annual incidence for a patient was estimated at 0.36 percent.[14] Both bone infarction and osteomyelitis are characterized by localized erythema, tenderness, and swelling. Both may also be accompanied by elevation in the ESR and a high leukocyte count. Both tests are useful in following response to treatment. Infection is confirmed by aspirating purulent material from the bone or by a positive blood culture.[3]

Radiographic studies may help the clinician differentiate between sepsis and infarction, but careful interpretation is essential. The radiographs in the early stages of either condition are normal or show only soft tissue swelling.[3] At about 2 weeks, both conditions will exhibit destruction of bone and periosteal reaction. Technetium and gallium scans may help make the differentiation, but both may be misleading as well.[10,11] Radionuclide scintigraphy is most useful in locating multiple sites of infection, especially in the pelvis and spine.

The treatment of osteomyelitis must take into account the altered immune status of the patient and the impaired blood flow to the bone. Prompt operative decompression of any abscesses is essential, and parenteral antibiotic therapy should be continued for 6 to 8 weeks.[3] The commonest organisms causing osteomyelitis in these patients are *Staphylococcus areus and Salmonella.* Younger patients are more likely to have *Salmonella* osteomyelitis.[3,15] Septic arthritis in this patient group may also be caused by *Salmonella.*[9]

THE HAND-FOOT SYNDROME. The hand-foot syndrome is characterized by swelling and tenderness of the hands and feet of children with sickle cell disease who are less than 6 years old (Figs. 35–8 and 35–9). It occurs in up to 58 percent of children with the disease and may be the presenting symptom. It appears after about 6 months of age, when hemoglobin F has been replaced by hemoglobin S.[7] It does not occur after the disappearance of the hematopoetic marrow from the hands and feet, at around age 6. The clinical findings of the hand-foot syndrome resemble those of osteomyelitis and include soft tissue swelling, limited motion, tenderness, and pain in the hands and feet of small children.[3,7] Although osteomyelitis is rare in the hands and feet of young children, the disorder must be considered in the differential diagnosis. In both conditions the WBC count and infectious indices are elevated. Higher elevations in the presence of significant fever suggest an infection. Blood cultures and aspiration of involved areas may provide the diagnosis. Antibiotic coverage should include coverage for *Salmonella* infection.[7]

VERTEBRAL INVOLVEMENT. Hyperplasia of the bone marrow in response to the hemolytic anemia of sickle cell disease causes radiographic changes in the vertebrae. The height of the vertebrae may be reduced and there may be bulging of intervertebral disks into the bodies (Fig. 35–10). Compression fractures may cause shortening of the trunk or the development of a kyphosis.

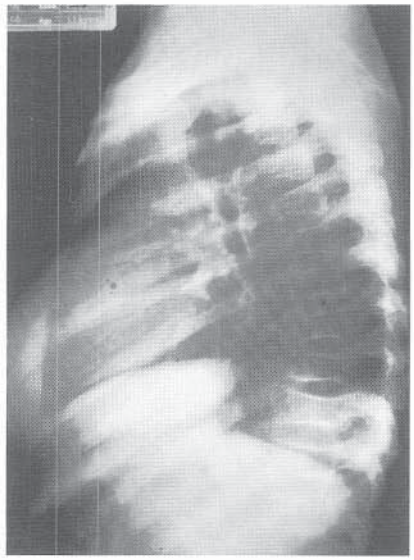

FIGURE 35–10 Sickle cell disease in an 11-year-old girl. Lateral radiograph of the spine shows reduction in the height of the vertebrae.

Vertebral collapse may be due to AVN of the vertebra.[16] Spinal osteomyelitis must always be considered in the differential diagnosis when spinal symptoms appear. In one center, 24 percent of patients evaluated for spinal disorders had osteomyelitis of the vertebrae.[16] Surgical decompression and anterior strut grafting is usually required to eradicate infection and preserve spinal alignment.

AVASCULAR NECROSIS. AVN of the femoral head eventually occurs in 19 to 31 percent of patients with sickle cell disease.[5] The humeral head may also undergo AVN, and this is usually better tolerated than AVN in the hip.[17] Total hip replacement is the eventual treatment for most patients with AVN. Unfortunately, the results are compromised by the disease, and complications are frequent.[5] In one series, five of eight arthroplasties required early revision. In addition, the investigators noted excessive blood loss, prolonged hospitalization, and medical or surgical complications in all patients, including those with sickle cell trait. They reported a failure rate of 50 percent by 5 years postoperatively.[8]

SURGICAL COMPLICATIONS. The use of a tourniquet in patients with sickle cell trait or sickle cell disease is considered undesirable by most authors because the hypoxia beyond the tourniquet will induce RBC sickling. One author reported using a tourniquet in 19 patients with sickle cell disease. The sickle cell patients had more complications than a control group, and these included bone pain, severe postoperative pain, jaundice, and tissue edema. All complications resolved within 2 weeks.[12]

Autologous blood can be used as well as blood salvaged from the surgical field, but both are difficult to store because of the potential for hemolysis and sickling.[4]

MISCELLANEOUS BONE CHANGES. A lower bone mineral density of between 6 and 21 percent is usually found in patients with sickle cell anemia.[1] Lucencies in the skull may produce a ground-glass appearance with loss of trabecular pattern. Changes in trabecular patterns of the long bones appear in younger children, corresponding to the location of active bone marrow.[6]

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Sickle Cell Disease

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