CHAPTER **28**

# HEMOPHILIC ARTHROPATHY: Considerations In Management

*Thomas J. Chang, D.P.M.*
*Shenin Mohamed, B. Sc. (Pharm.)*

In severe hemophilia, osteoarthropathy of one or more joints is a normal and common sequelae to recurrent episodes of acute, spontaneous hemorrhages into the joints. Due to chronic intra-articular bleeding, degenerative changes such as hypertrophy and inflammation of the synovial tissues result, followed by the subsequent release of proteolytic enzymes from the synovium that serve to further destroy the surrounding articular cartilage. Joints in which there is repeated hemarthrosis will suffer from longer and more intense episodes of intra-articular bleeding, and may become chronically affected by synovitis (Figs. 1A, 1B). Therefore, early treatment for the prevention of chronic synovitis is very important.[1-8] Arthropathy is often polyarticular, with the lower limbs more often affected than the upper limbs. In order of frequency, the knee joint is most often affected, followed by the elbow, and then the ankle.[3-5,8-14]

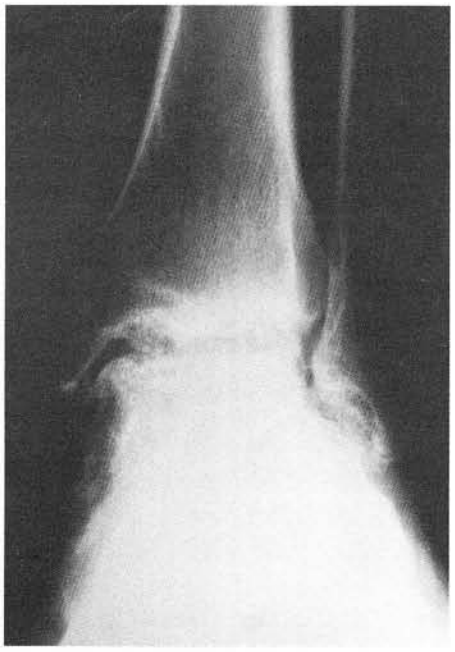

Figure 1A. Classic example of hemophilic intra-articular bleeding into the ankle joint with subsequent degeneration.

Before the era of replacement therapy with human clotting factor, there was no effective treatment that could be offered to these patients that could control spontaneous episodic hemorrhages. The only treatments available were non-invasive modalities such as immobilization and rest. However, with the advent of human factor VIII and IX replacement therapy, it has become possible to perform major surgical procedures on hemophiliacs such as total hip replacements, provided that hemostatic levels of clotting factor are secured during the perioperative period.[2,15,16] Ironically however, with the development of prophylactic factor replacement therapy, the need for surgical intervention to correct lower extremity pathology has dramatically decreased over the past ten years. Progress in the treatment for patients with hemophilia has significantly improved their quality of life, resulting in a population of hemophiliacs that are living longer and functioning without pain and factor deficiency associated complications.[17,18]

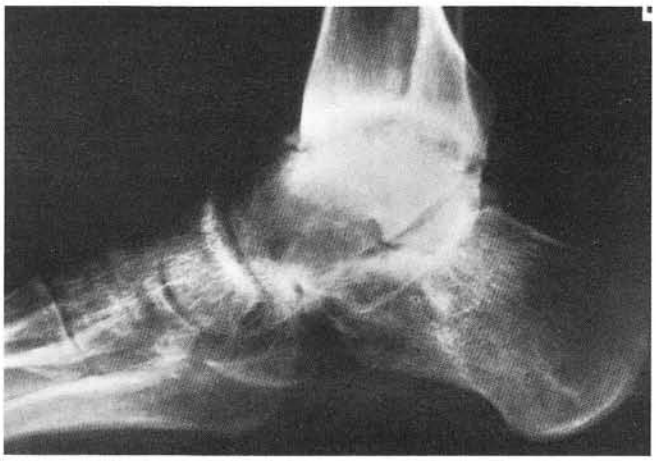

Figure 1B. Lateral view of ankle joint.

## NON-SURGICAL APPROACH TO TREATMENT

Patients with hemophilic arthopathy often experience early joint destruction, commonly followed by biomechanical malalignments such as joint contractures and limb angulations of the lower extremity. The most common deformities affecting the ankle and subtalar joint are fixed plantarflexion due to degenerative arthritis of the anterior ankle, varus hindfoot due to malalignment of the subtalar joint, and valgus rotation at the ankle due to differential overgrowth of the distal tibial epiphysis during adolescence or due to progressive degenerative disease during maturity. These disabilities often result in severe pain and physical limitations, motivating the patient to seek immediate relief.[18-23]

Conservative and prophylactic treatments should always be suggested and attempted prior to surgical intervention. Conservative treatment for ankle arthropathy involves the application of splints, wedge insoles and calipers. In addition, regular prophylactic transfusions of clotting factor may prevent recurrent intra-articular bleeds and the further development of hemarthrosis. Both of these factors will allow inflammation of synovial tissue to be resolved. For control of acute hemorrhages, factor replacement should be administered immediately. For recurrent, chronic episodes, factor replacement is given at frequent prophylactic intervals, at an adequate dosage to prevent breakthrough bleeding.[13-26]

Previously, it was thought that nonsteroidal anti-inflammatory agents to treat pain and inflammation associated with acute hemarthrosis, synovitis, and chronic arthritis in the hemophiliac, would result in an increased frequency of gastrointestinal bleeding as an adverse drug reaction. However, this has been found to be incorrect. Patients with chronic arthritis and synovitis may safely benefit from oral treatment with nonsteroidal anti-inflammatory agents. If analgesia is still inadequate, opioids should be added to the regimen.[17,27]

## CLOTTING FACTORS

Hemarthrosis imposes both functional as well as, economic limitations. Even if a transfusion of human clotting factor were given immediately, an acute hemarthrosis is extremely painful and limits the patient's ability to walk and participate in physically-demanding activities for at least one to ten days.[2-5,8-11] Surgery as well, can be very stressful for the patient, and runs the risk of exposing the patient to the development of antibodies against the high doses of clotting factor needed to be infused over a short perioperative period of time.[28,29]

There are two forms of hemophilia. Hemophilia A is when human clotting factor VIII is deficient, and Hemophilia B is when human clotting factor IX is deficient. Hemophilia A is further divided into three categories depending on their level of Factor VIII: Severe (<1%), Moderate (2%-5%), and Mild (>5%). Patients with severe hemophilia have been given human clotting factor VIII replacement therapy for prophylaxis in hemophilia A since 1958, and patients have been given factor IX replacement therapy for hemophilia B, since 1972. Regular prophylactic therapy, although expensive, should always be a therapeutic consideration in the management of all hemophiliac patients, as the efficacy of this treatment is such that, if started early enough, future needs for osseous or soft tissue surgical interventions become unnecessary. In fact, over the last twenty years, levels of prophylactic replacement therapy have been intensified, and generally started when the patients are one to two years of age. They are given at dosages high enough to prevent the level of factor concentrate from falling below one to two percent of normal, to reduce episodes of intra-articular bleeding.[2,11,17,26-28,30-34]

With the advent of clotting factor and the increasing availability of factor concentrates, there has therefore been a trend over the last 10 years of an increasing survival rate with an older average age of patients, reduced incidence of severe joint disability, and ultimately, a decreasing need for classic hemophilic surgery. However, it should be noted, that with the availability of coagulation factor replacement, it has made the option of reconstructive and corrective surgery for the relief of pain caused by severe arthropathy, a possibility. The regimen for the infusion of factor concentrates for surgery is based on specified protocols based on serum factor studies conducted before surgery, patient weight, and the presence of any inhibitor.[11,17,26-28,30,31]

To raise the level of serum clotting factor by 2%, one unit per kilogram of factor VIII must be infused. Thus, to raise the level of serum clotting

factor to 80% in a severe hemophiliac, 40 units per kilogram must be infused. For a 70 kilogram patient, this would mean 2800 units of factor. As the biological half-life of factor VIII is twelve hours, infusions must be administered every eight to twelve hours to ensure steady state levels of serum factor are maintained throughout the perioperative period. Concentrates may be administered by a bolus intravenous infusion or a continuous infusion.[17,27,35]

Approximately two hours before a major operation, the patient is usually given a transfusion to raise the serum level of the deficient clotting factor to levels of 80% and 150% of normal. Repeat doses may be given during the surgery if the procedure continues for longer than ninety minutes, or if the plasma factor concentration falls below thirty percent.[2-5,8] Transfusions are continued throughout the duration of the ten to fourteen day stay in the hospital, ensuring that factor levels are maintained between 30% to 40% of normal. They are then given at longer intervals after discharge, maintaining factor concentrations between 10% to 20% of normal. An adequate regimen serves to minimize the risk of spontaneous hemarthrosis in the immediate postoperative period.[36-38] For minor surgery, the serum levels are kept significantly lower and maintained for shorter time periods.[26,27,31,33,36,38]

## THE COST FACTOR

With respect to the economic burden, just a single transfusion to treat a minor episode of intra-articular bleeding is very costly. A single transfusion of factor VIII concentrate may cost between twelve hundred to fifteen hundred dollars. (In 1994, one unit of factor VIII concentrate at the University of North Carolina Hospitals was priced at approximately $1.01 for factor VIII produced by monoclonal antibody technique, or $1.23 for recombinant DNA factor VIII. The dosage of a transfusion for an uncomplicated acute hemarthrosis is 25 units per kg of body weight. Therefore a 50kg patient would require 1,250 units of factor; costing between $1,262.50 or $1,537.50, respectively, for a single transfusion).[8,36-39]

For major cases of hemarthrosis or surgery, several additional transfusions would be required. Despite the cost of multiple clotting factor infusions needed during the perioperative period, the number of transfusions required after a synovectomy or arthroplasty are significantly decreased by the end of the first postoperative year. Therefore, long term health care costs are reduced considerably through surgical intervention with the expected reduction in the number of intra-articular hemorrhages.[8,37,38]

## INHIBITORS

A major therapeutic complication in patients with severe hemophilia who receive multiple infusions of high doses of human clotting factor protein, develop IgG antibodies that specifically inhibit the activity of factor VIII or factor IX. After production of antibody, any subsequent infusions of factor concentrates will not result in increased levels of active clotting factor in the patient's serum. Instead, any additional exposure to human clotting factor proteins will stimulate further production of antibodies and increase the titer of inhibitor in the patient's serum. As a result, controlling episodes of spontaneous bleeding or providing perioperative hemostasis in patients in whom coagulation factor inhibitors have developed, becomes a major therapeutic challenge as ordinary replacement therapy becomes quickly inactivated in the patient's serum.[17,40-42]

When patients are not further exposed to factor VIII products for several weeks or months, the titer of serum antibody will decrease to very low levels spontaneously. But, just one single subsequent infusion of clotting factor will initiate an amnestic response in five to seven days. Thus, in these patients, surgery should only be considered in life-threatening emergencies. There is no single treatment modality available that provides safe and effective hemostasis in patients with high titers of these naturally formed circulating anticoagulants. These patients, therefore, present with an extremely difficult and even unsolvable dilemma.[17,32,40-46]

In clinical practice, patients with factor VIII inhibitor can be divided into two groups based on the level of inhibitor titer in the serum measured in Bethesda units. Twenty-five percent of patients are type 1, which are low responders with a low immunological response, and have between five and ten Bethesda units/ml of serum antibody titer. In such patients, hemostatic levels of factor VIII can simply be achieved by just increasing the dosage of

factor VIII concentrate to be infused. Seventy-five percent of patients, however, are type 2, which are the high responders with an anamnestic response, and have between ten to one hundred Bethesda units/ml of antibody titer. In these patients, alternative methods of securing hemostasis must be considered. For non-critical hemorrhages, these patients must rely on factor VIII inhibitor bypassing agents such as activated or nonactivated prothrombin complex concentrates. These agents are the most commonly used ones to treat episodes of spontaneous bleeding in patients with high titers of inhibitor. They are found to be effective only in approximately fifty percent of cases, and have limited clinical use. Efficacy of these agents is unpredictable, and the hemostatic dose is determined empirically as there are no lab tests available to monitor responses. They also run the risk of the development of thromboembolic complications, and as yet, their mechanism of action is unclear.[33,40,41,47-50]

One promising new agent that has been shown to be a safe and effective therapeutic alternative is recombinant activated factor VII, (rFVIIa). The rFVIIa activates the common coagulation pathway through the extrinsic blood clotting pathway at a point distal to the action of factor VIII. As a result, rFVIIa can initiate coagulation when complexed with the necessary exposed tissue factors at the injured site, regardless of whether there is a deficiency or inhibition of factor VIII present.[32,48,49,51-53]

However, the gold standard treatment and fully effective method at securing hemostasis in this situation would be to induce immunotolerance to infusions of human clotting factor VIII. Immunotolerance is defined as the permanent elimination of inhibitor from a patient's serum with the absence of an anamnestic response. This method is very time consuming and may take months to years to achieve. Despite the extremely high costs involved with no guarantees for its success, there may be no other alternative for controlling life-threatening hemorrhages in inhibitor-positive patients.[32,47,52,53]

## HIV FROM FACTOR REPLACEMENT

During the 1970s and early 1980s, the factor concentrates used were of only intermediate purity and were unfortunately associated with the transmission of Hepatitis B, Hepatitis C, and Human Immunodeficiency virus. Due to the fact that they are obligate recipients of commercial clotting factor, there was a steady increase in the prevalence of HIV-1 seroconversion among hemophiliacs between 1981 and 1987. Eighty percent of the HIV-seropositive hemophiliacs had already seroconverted by 1985, when the assay for HIV-1 antibody became available for clinical use. By 1995, seventy-five percent of patients with severe hemophilia A were HIV-1 seropositive, of which more than 1,800 developed clinical AIDS, and greater than 1,000 died due to AIDS-related complications. As of January 1988, the mortality of hemophiliac patients with AIDS was 58% of which 84% died within the first year after diagnosis.[54-56]

Within the last few years, with the advent of new purification and viral attenuation techniques, human clotting factor concentrates of very high purity have become introduced and the transmission of HIV-1 infection has virtually been eliminated. Due to the relatively recent availability of solvent detergent and pasteurization techniques to reduce the risk of virus transmission, the incidence of AIDS among hemophiliacs is directly related to the age of the patient and the severity of the factor deficiency. As such, there is a higher incidence of AIDS among hemophiliacs who are thirty-four years of age and older, versus younger adolescents and children.[54-56]

## INDICATIONS FOR SURGERY

Surgery should only be contemplated when the patient does not achieve any pain relief from alternative modalities and the patient's disability is severe. When episodes of bleeding become extremely frequent, prophylactic factor replacement regimes often become ineffective at controlling the recurrent hemarthrosis. Disability results, due to damage of the synovial tissue, inflammation, and loss of motion followed by degenerative arthritis.[3-7,19-23] As a result, despite replacement therapy, severe hemophiliacs often require surgical intervention of the affected joint at the young age of twenty or thirty years. The most common surgical approach is synovectomy, in an attempt to control repetitive intra-articular bleeds and joint pain, when the level of the arthropathy does not require reconstructive surgery. The second is conventional arthroplasties or arthrodesis, for correction or reconstruction of joint deformities.[2,28,30]

In the initial stages, when recurrent episodes of hemarthrosis lead to hypertrophic synovitis and boggy swelling around the affected joint, surgical synovectomy should be a serious consideration. The hypervascular synovial tissue, in the presence of deficiencies with coagulation will predispose the patient to relapsing episodes of hemarthrosis which will, in turn, exacerbate further synovitis.[2,8-10] The end result, is a painful arthritis. With synovectomy of the joint, hypertrophied, highly vascular synovium is excised and thus, the source of hemarthrosis is eliminated. Surgical synovectomy is one of the best treatments to date, in hemophilic arthropathy; a relatively uncomplicated procedure that is successful at significantly reducing the frequency of intra-articular bleeding and chronic joint pain. Unfortunately, joint mobility may not improve postoperatively and joint deterioration is not arrested, but continues to progress, although at a much slower pace.[2,13-16,24] Joint debridement is an effective method for restoring joint function with minimal risks and long-lasting benefits that appear to slow the evolution of radiographic pathology. When debridement fails to relieve pain, then replacement of the joint must be considered.[29]

Arthroplasty and arthrodesis are performed in end-stage joint disease and prove successful at completely abolishing hemarthrosis and symptoms of disabling arthropathy. However, in contrast to patients with rheumatoid arthritis, hemophiliacs undergoing arthroplasty will continue to have a lack of range of motion postoperatively due to the extensive involvement of periarticular soft tissue, residual weakness, and recurrent intramuscular bleeding.[1,2]

For optimum management and care for the surgical candidate, the facility should be adequately equipped with a special coagulation laboratory. There must be good cooperation between the hematologist, (proficient in the management of coagulation disorders), and the podiatric surgeon. The success of the surgery is also dependent upon the full cooperation and compliance of the patient and motivation to the rehabilitation program.[17,31,57] Most patient's activity level on follow-up is normal, and will achieve full unprotected weight bearing and ambulation without the assistance of crutches or orthosis after surgery.[3-5]

## SURGERY IN HIV POSITIVE HEMOPHILIACS

Hemophiliacs without AIDS do not have any increased risks for the development of post-operative wound infections, however, post-operative infections become a significant concern among those who are HIV-positive. Infections that are otherwise uncommon, such as septic arthritis and nosocomial infections during hospitalization become prevalent in the HIV infected population, especially among those with a CD4 count less than 200/mm$^3$. In managing hemophiliacs with AIDS, one should watch closely for early signs of infection and treat them aggressively. Longer therapies of prophylactic antibiotics should be a consideration when the CD4 count is less than 200/mm$^3$, if there is a break in the sterile infusion technique, or if the operative time is longer than two hours.[6,54-56,58,59]

The frequency of elective surgeries in hemophiliacs with HIV is significantly lower than in those patients who are not infected, due to several factors including: some surgeon's fears of exposure to the human immunodeficiency virus; fear that the patient will likely develop a postoperative infection; and uncertainty regarding the extent of the patient's life span to justify the procedure. But with the development of efficacious anti-viral medications, the prognosis of an HIV seropositive patient has become much more favorable and patients are able to live at least ten years from the time of HIV seroconversion to the progression of clinical AIDS.[54-56] As such, surgery should not be denied based on the previous reasoning.

Whether the hemophilic patient is HIV seropositive or not, surgical intervention should always be a serious consideration if it can offer the hemophiliac improvements in joint mobility, reduction in pain associated with hemarthropathy and allow for significant improvements in quality of life.

## CASE STUDY

A 31-year-old hemophilic male presented with a painful right ankle that was becoming intolerable with time, after a series of inversion injuries over the last 10 years. The pain was of a dull, aching nature, localized, non-radiating, and aggravated by weight-bearing activities and cold weather (Fig. 2A). The patient's condition would only mildly improve with RICE therapy. When unbearable, he would be forced to ambulate non-weight bearing on crutches (Figs. 2B, 2C). Over the last year, the pathology severely affected his independence and activity level, resulting in a significantly diminished quality of life.

Surprisingly the patient was not diagnosed with hemophilia A until the age of 17 years. The diagnosis was made after developing a hematoma in his hip after a groin injury during a sporting activity. Due to his late diagnosis, he had fortunately never been transfused with factor replacement until 1986. This in itself is the reason he has not contracted HIV as so many other hemophiliac blood recipients have prior to 1982.

A MRI reported the following findings: avascular necrosis of the right talus; ankle joint degeneration with periarticular osseous fragmentation; a cyst in the medial aspect of the talar dome; and fracture of the os trigonum with resultant hypertrophy of soft tissue posteriorly (Figs. 2D-2G). Prior to surgical intervention, a diagnostic intra-articular injection was recommended to further assess the contributions from the ankle. The cost of prophylactic factor replacement just for the injection was $3,000.00. After consultation with the hematologist, it was decided to bypass the injection and proceed with the surgery due to clinical and radiographic findings.

Surgery involved the following procedures: excision of the os trigonum fracture fragment; osteotomy of the medial malleolus to facilitate debridement and removal of the degenerative cartilage on the talar dome with drilling of the talar dome; cutting of a cortical window; curettage of medial talar dome cyst; and packing of the cyst with autogenous calcaneal bone graft (Figs. 2H, 2I). Factor VIII replacement therapy was monitored and continued postperatively. The cost of the replacement therapy for the complete peri-operative management totalled over $75,000.

At one-and-a-half years postoperative, the patient is doing extremely well with good function to his ankle (Figs. 2J, 2K). The number of intra-articular bleeds are decreasing and he is happy with his progress. Pain in the ankle is reported as ranging from minimal to none.

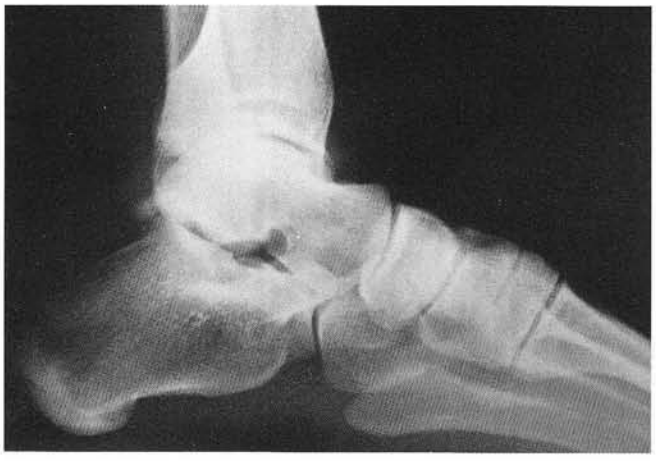

Figure 2A: Preoperative AP radiograph. Note the flattening of the talus and the cyst under the medial shoulder of the talar dome.

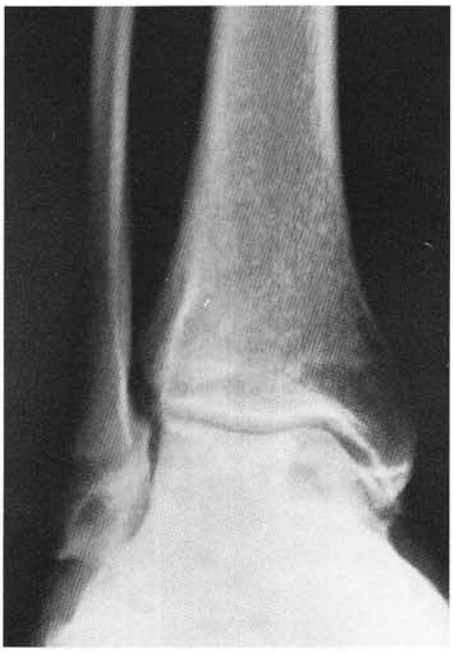

Figure 2B. Preoperative lateral radiograph.

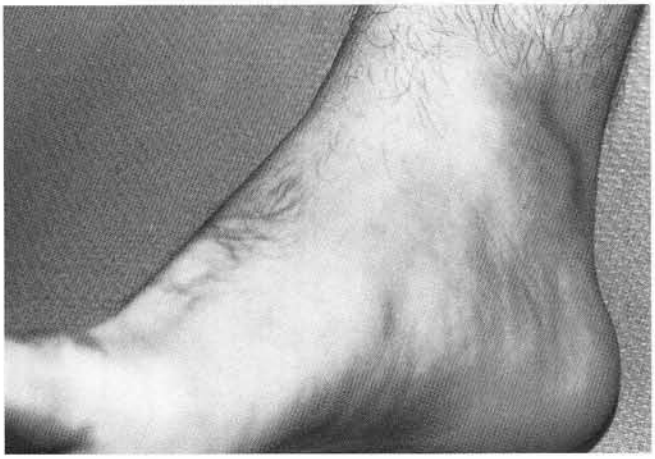

Figure 2C. Preoperative clinical photo. Note the fullness in the anterior and medial ankle region consistent with chronic inflammation in the joint.

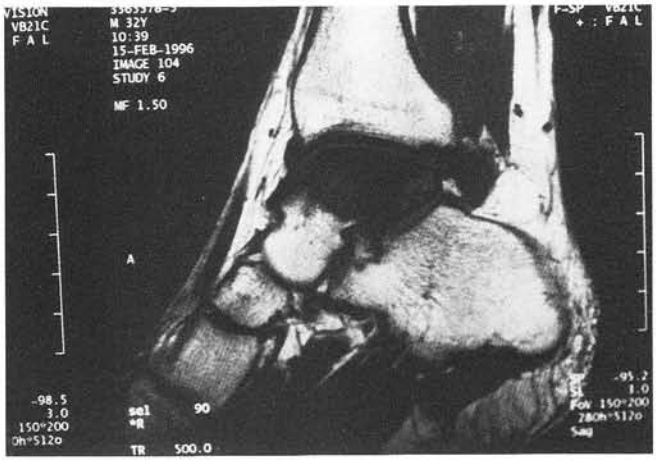


Figure 2D. Sagittal T-1 MRI image. Note the avascularity of the talar dome on the images.

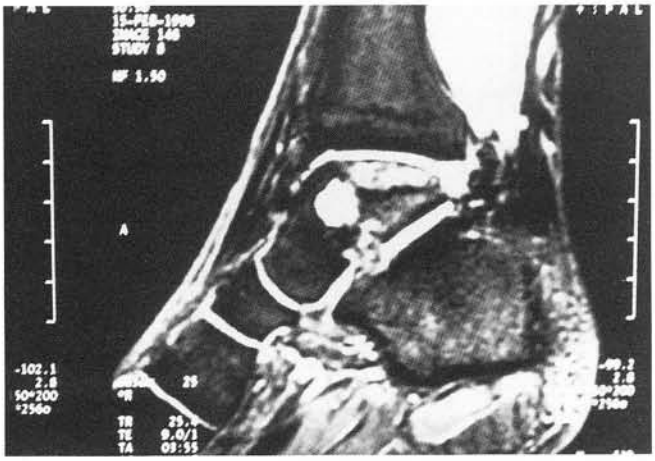


Figure 2E. Sagittal T-2 MRI image.

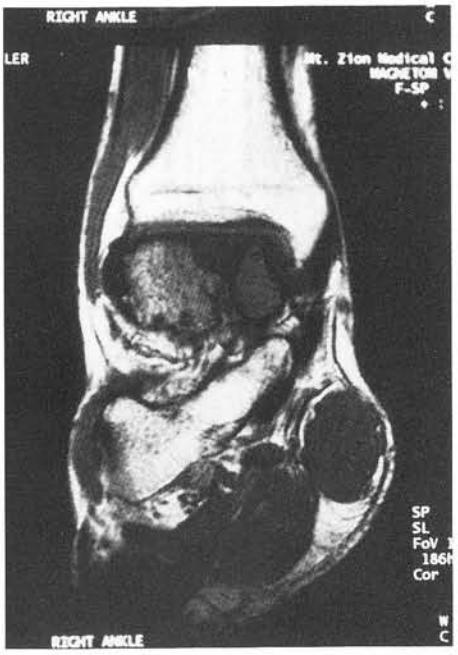


Figure 2F. Frontal T-1 MRI image.

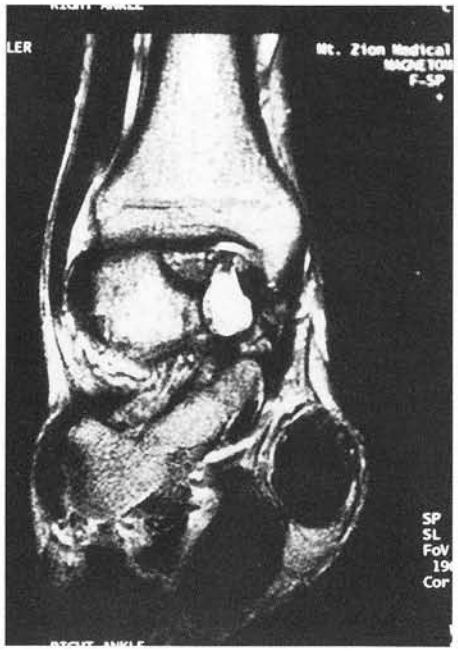


Figure 2G. Frontal T-2 MRI image.

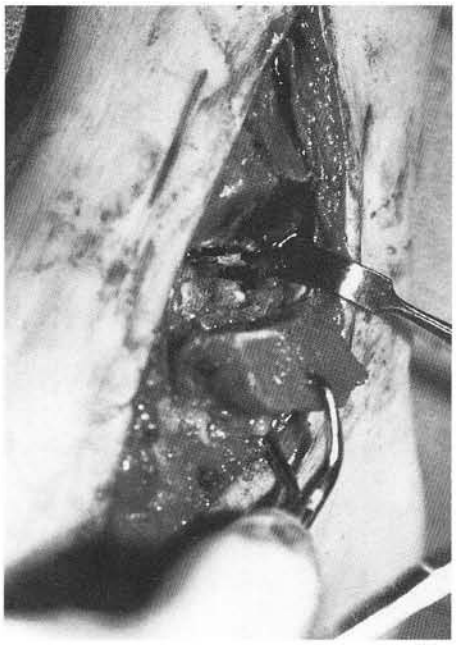

Figure 2H. Intra-operative photo showing exposure into the joint and medial face of the talar dome.

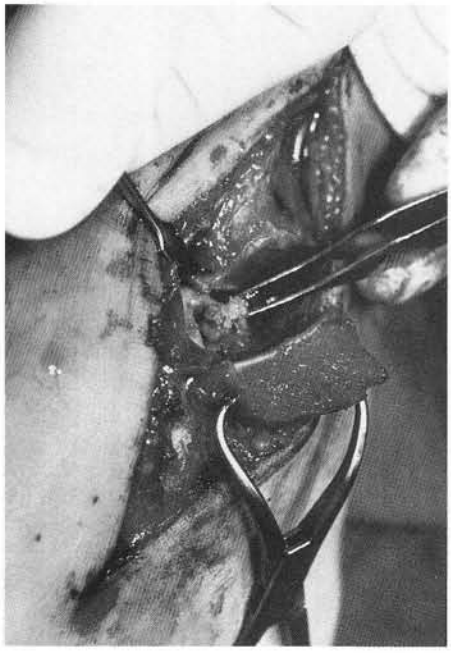

Figure 2I. Autogenous chips from the calcaneus are being placed through a cortical window in the medial wall.

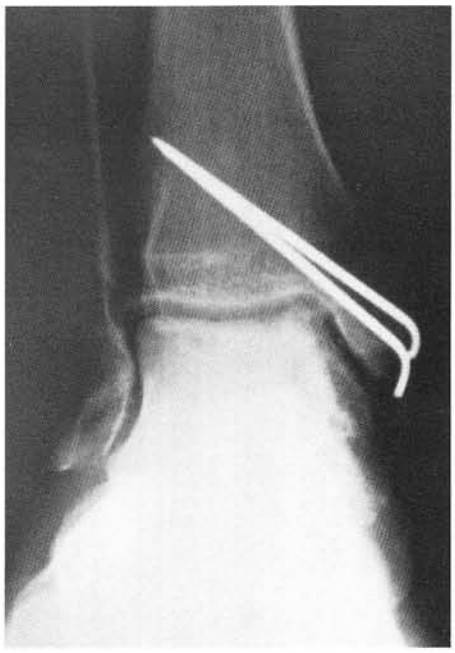

Figure 2J. One-and-a-half year postoperative AP radiograph. Note osseous healing of the medial cyst.

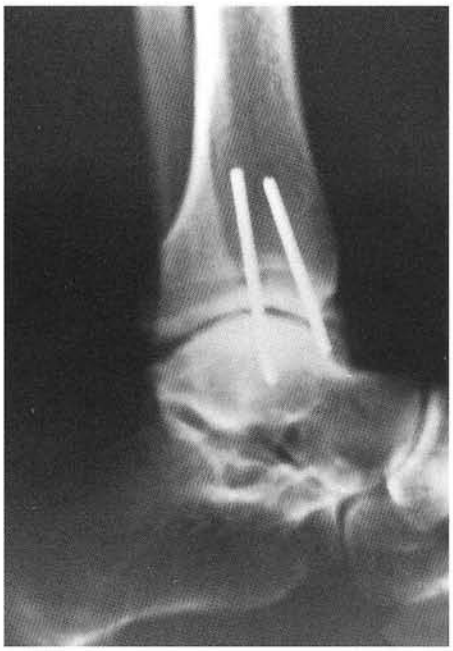

Figure 2K. One-and-a-half year postoperative lateral radiograph.

## SUMMARY

Proper conservative and surgical management options can only be recommended after a thorough understanding of the disease process. The advent of factor replacement therapy has dramatically changed the course of treatment and prognosis for this patient population. Although cost is still a significant factor, the long-term benefits without risk of disease transmission provides an optimistic outlook.

## REFERENCES

1. Teigland JC, Tjonnfjord Geir E, Evensen Stein A, Charania B: knee arthroplasty in hemophilia 5-12 year follow-up of 15 patients. *Acta Orthop Scand* 64(2):153-156, 1993.
2. Arnold WD, Hilgartner MW: Hemophilic arthropathy. Current concepts of pathogenesis and management. *J Bone Joint Surg* (Am) 59(3):287-305, 1977.
3. Horoszowski H, Heim M, Schulman S, et al: Multiple joint procedures in a single operative session on hemophilic patients. *Clin Orthop* 328:60-64, 1996.
4. Duthie RB, Dodd CAF: Chronic haemophilic arthropathy. In Duthie RB, Rizza CR, Giangrande PLF, Dodd CAF, eds. *The Management of Musculo-skeletal Problems in the Haemophiliacs.* 2nd ed. Oxford; Blackwell Publications:1994;159-189.
5. Horoszowski H, Heim M, Seligsohn U, Farine I: Use of the laser scalpel in orthopaedic surgery on haemophilic patients. In Seligsohn U, Rimon A, Horoszowski H, eds. *Haemophilia* Tunbridge Wells; Castle House Publishing Ltd:1981;189-194.
6. Ragni MV, Crossett, LS, Herndon JH: Postoperative infection following orthopaedic surgery in human immunodeficiency virus - infected hemophiliacs with CD4 counts < 200/mm3. *J Arthroplasty* 10(6):716-720, 1995.
7. Levine PH: Clinical manifestations and therapy of Hemophilias A and B. In Coleman RW, Hirsh J, Marder VJ, Salzman EW, eds. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice* Philadelphia, PA; JB Lippincott:1982;67.
8. Greene, WB: Synovectomy of the ankle for hemophilic arthropathy. *J Bone Joint Surg* 76-A(6):812-818, 1994.
9. Fabry, G.: Early biochemical and histological findings in experimental hemarthrosis in dogs. *Arch Orthop Traumat Surg* 100:67-173, 1982.
10. Mainardi, CL, Levine PH, Werb Z, Harris ED Jr: Proliferative synovitis in hemophilia: biochemical and morphologic observations. *Arthritis Rheumat* 21:137-144, 1978.
11. Canale ST, Dugdale M, Howard BC: Synovectomy of the knee in young patients with hemophilia. *Southern Med J* 81:1480-1486, 1988.
12. Casscells CD: Commentary: the argument for early arthroscopic synovectomy in patients with severe hemophilia. *Arthroscopy* 3:78-79, 1987.
13. Clark, MW: Knee synovectomy in hemophilia. *Orthopedics* 1:285-290, 1978.
14. DeGnore, LT, Wilson, FC: Surgical management of hemophilic arthropathy. In *Instr Course Lect* 38:383-388, 1989.
15. Wiedel, JD: Arthroscopic Synovectomy of the Knee in Hemophilia, 10 to 15 year followup. *Clini Orthop* 328: 46-53, 1996.
16. Bussi L, Silvello L, Baudo F, De Cataldo F: Results of synovectomy of the knee in haemophilia. *Haematolgica* (Pavia) 59:81, 1974.
17. Shopnick RI, Brettler DB: Hemostasis. *Clin Orthop* 328:34-38, 1996.
18. Lofqvist T, Sanzen L, Petersson C, Nilsson IM: Total hip replacement in patients with hemophilia. 13 hips in 11 patients followed for 1-16 years. *Acta Orthop Scand* 67(4):321-324, 1996.
19. Pearce MS, Smith MA, Savidge GF: Supramalleolar tibial osteotomy for haemophilic arthropathy of the ankle. *J Bone and Joint Surg* 76-B(6), 947-950, 1994.
20. Atkins RM, Henderson NJ, Duthie RB: Joint contractures in the hemophilias. *Clin Orthop* 219:97-106, 1987.
21. Houghton GR, Dickson RA: Lower limb arthrodesis in Haemophilia. *J Bone Joint Surg* (Br) 60-B:387-9, 1978.
22. Luck JV Jr: Surgical management of advanced hemophilic arthropathy. *Prog Clin Biol Res* 324:241-56, 1990.
23. Smith MA, Urquhart DR, Savidge GF: The surgical management of varus deformity in haemophilic arthropathy of the knee. *J Bone Joint Surg* (Br) 63-B:261-5, 1981.
24. Dyszy-Laube B, Kaminski W, Gizycka I, et al: Synovectomy in the treatment of hemophilic arthropathy. *J Pediatr Surg* 9:123, 1974.
25. Gamba G, Grignani G, Ascari E: Synoviorthesis versus synovectomy in the treatment of recurrent haemophilic haemarthrosis: long-term evaluation. *Thromb Haemost* 45:127, 1981.
26. Van den Berg HM, Nieuwenhuis K, Mauser-bunschoten EP, Roosendaal G: Hemophilia prophylaxis in the Netherlands. *Semin Hematol* 31:13-15, 1994.
27. Steven MM, Small M, Pinkerton L, et al: Nonsteroidal anti-inflammatory drugs in haemophilic arthritis. A clinical and laboratory study. *Haemostasis* 15:204-209, 1985.
28. Lofqvist T, Nilsson IM, Petersson C: Orthopaedic Surgery in Hemophilia 20 years experience in Sweden. *Clinical Orthopaedics and Related Research*. 332:232-241, 1996.
29. Merchan R, Magallon M, Galindo E: Joint debridement for haemophilic arthropathy of the knee. *International Orthopaedics* 18:135-138, 1994.
30. Ahlberg A: Treatment and prophylaxis of arthropathy in severe hemophilia. *Clin Orthop* 53:135-146, 1967.
31. Brettler DB, Levine PH: Factor concentrates for treatment of hemophilia: which one to choose? *Blood* 73:2067-2073, 1989.
32. Scharf R, Kucharski W, Nowak T: Surgery in Hemophilia A patients with factor VIII inhibitor: 10-Year experience. *World Journal of Surgery* 20:1171-1181, 1996.

33. O Marcaigh AS, Schmalz BJ, Shaughnessy WJ, Gilchrist GS: Successful hemostasis during a major orthopedic operation by using recombinant activated factor VII in a patient with severe hemophilia A and a potent inhibitor, *Mayo Clin Proc*, 69:641-644, 1994.
34. Teigland JC, Tjonnfjord GE, Evensen SA, Charania B: Synovectomy for haemophilic arthropathy: 6-21 years of follow-up in 16 patients. *Journal of Internal Medicine* 235:239-243, 1994.
35. Nilsson IM, Berntorp E, Ljung R, Lofqvist T, Petersson H: Prophylactic treatment of severe hemophilia A and B can prevent joint disability. *Semin Hematol* 31:5-9, 1994.
36. Aronstam A, Browne RS, Wassef M, Hamad Z: clinical features of early haemarthoses in severely affected adolescent haemophiliacs. *Clin and Lab Haematol* 6:9-15, 1984.
37. Greene WB, McMillan CW: Nonsurgical management of hemohilic arthropathy. *Instr Course Lect* 38:367-381, 1989.
38. Wilson FC, Mahew DE, McMillan CW: Surgical management of musculoskeletal problems in hemophilia. *Instr Course Lect* 32:233-241, 1983.
39. McMillan, CW, Greene WB, Blatt PM, White GC II, Roberts HR: The management of musculoskeletal problems in hemophilia. Part I. Principles of medical managment of hemophilia. *Instr Course Lect* 32:210-216, 1983.
40. Brown DC: Adverse events reported in association with the use of monoclonal antibody purified factor VIII: C-Monoclate. *Semin Hematol* 27: 16-17, 1990.
41. Nilsson IM, Berntorp E, Freiburghaus C: Treatment of patients with factor VIII and IX inhibitors. *Thromb Haemost* 70:56-59, 1993.
42. Nilsson IM, Berntorp E, Zettervall O: Induction of immune tolerance in patients with hemophilia and antibodies to factor VIII by combined treatment with intravenous IgG, cyclophosphamide, and factor VIII. *N Engl J Med* 318:947-950, 1988.
43. Rudowski WJ, Scharf R, Ziemski JM: Is major surgery in hemophiliac patients safe? *World J Surg* 11:378, 1987.
44. Brettler DB: Inhibitors of factor VIII and IX. *Haemophilia* 1(1):35, 1995.
45. Kasper CK: Treatment of factor VIII inhibitors. *Prog Hemost Thromb* 9:57, 1989.
46. Nilsson, JM: *Factor VIII/IX Antibodies in Hemophilia*. Malmo, Sweden; Pharmacia Plasma Products:1994;58-65.
47. Giatti L, Mannucci PM: Use of porcine factor VIII in the management of seventeen patients with factor VIII antibodies. *Thromb Haemostas* 51:379, 1984.
48. Kasper CK: Complications of hemophilia A treatment: factor VIII inhibitors. *Ann NY Acad Sci* 614:97-105, 1991.
49. Brettler DB, Forsberg AD, Levine PH, Aledort LM, Hilgartner MW, Kasper CK, et al.: The use of porcine factor VIII (Hyate:C) in the treatment of patients with inhibitor antibodies to factor VIII. *Arch Intern Med* 149:1381-1385, 1989.
50. Lusher JM, Shapiro SS, Palascak JE, Rao AV, Levine PH, Blatt PM. Efficacy of prothrombin-complex concentrates in hemophiliacs with antibodies to factor VIII: a multicenter therapeutic trial. *N Engl J Med* 303:421-425, 1980.
51. Hedner U: Factor VIIa in the treatment of haemophilia *Blood Coagul Fibrinolysis* 1:307-317, 1990.
52. Mariani G, Scheibel E, Nagao T, et al.: Immunotolerance as treatment of alloantibodies to factor VIII in hemophilia. *Emin Hematol Suppl* 31(4):62, 1994.
53. Nilsson J.M.: Immune tolerance. *Semin Hematol* 31(4):44, 1994.
54. Unger AS, Kessler CM, Lewis RJ: Total Knee Arthroplasty in Human Immunodeficiency Virus-infected Hemophiliacs. *J Arthrop* 10(4): 448-452, 1995.
55. Goedert JJ, Kessler CM, Aledort LM et al: A prospective study of human immunodeficiency virus type I infection and the development of AIDS in subjects with hemophilia. *N Engl J Med* 321:1141, 1989.
56. Greene WB, DeGore LT, White GC: Orthopaedic procedures and prognosis in hemophilia patients who are seropositive for human immunodeficiency virus. *J Bone Joint Surg* 72:2, 1990.
57. Goldsmith JC, Gordon EM: Treatment of hemophilia B: Serendipitous use of continuous infusion coagulation factor IX. *Throm Res* 70:265-267, 1993.
58. Ragni MV, Hanley EN: Septic arthritis in hemophiliacs: a new complication associated with HIV infection and bacterial sepsis. *Ann Intern Med* 110:169, 1989.
59. Weber DJ, Becherer PR, Rutala WA et al: Nosocomial infection rate as a function of human immunodeficiency virus type I status in hemophiliacs. *Am J Med* 91(3B):206S, 1991.

## ADDITIONAL REFERENCES

Hedner, U, Feldstedt M, Glazer S: Recombinant fVIIa in hemophilia treatment. In Lusher JM, Kessler CM, eds. *Hemophilia and von Willebrand's Disease in the 1990s* New York; Elsevier Science:1991;283-293.

Lethagen S, Egervall K, Berntorp E, Bengtsson B: The administration of desmopressin by nasal spray: A dose-determination study in patients with mild hemophilia A or von Willebrand's disease. *Haemophilia* 1:97-102, 1993.

Mannucci PM: Desmopressin (DDAVP) for treatment of disorders of hemostasis. *Prog Hemost Thromb* 8:19-45, 1986.

Mannucci PM, Bettaga D, Cattaneo M: The development of tachyphylaxis in patients with haemophilia and von Willebrand's disease after repeated doses of desmopressin (DDAVP). *Br J Haematol* 82:87-93, 1992.

Petrini P, Lindvall N, Egberg N, Blomback M: Prophylaxis with factor concentrates in preventing hemophilic arthropathy. Am. J. Pediat. *Hematol Oncol* 13:280-287, 1991.

Seremetis, SV: The clinical use of factor VIIa in the treatment of factor VIII inhibitor patients, *Semin Haemtol* 31(4):53, 1994.

Soreff J: Joint debridement in the treatment of advanced hemophilic arthropathy. *Clin Orthop* 191:179, 1984.