TO THE PATHOLOGY AND CLINICAL FEATURES OF HAEMOPHILIA

222
APPENDIX
222

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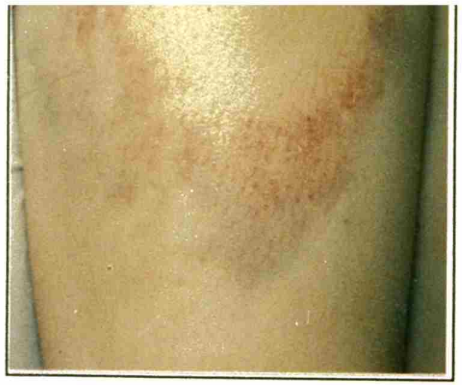
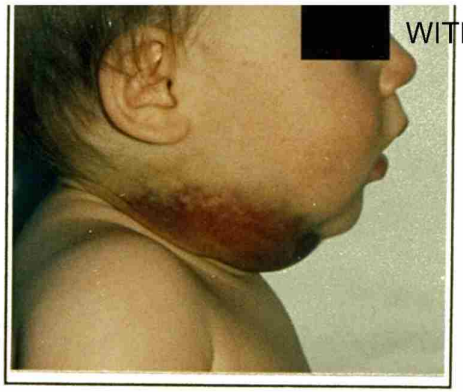
These pictures are arranged in two parts.
Part 1 illustrates the **natural history** of haemophilia without treatment or with inadequate treatment.
Part 2 illustrates how this pathology can be ameliorated or prevented by **treatment** with factor VIII or IX.

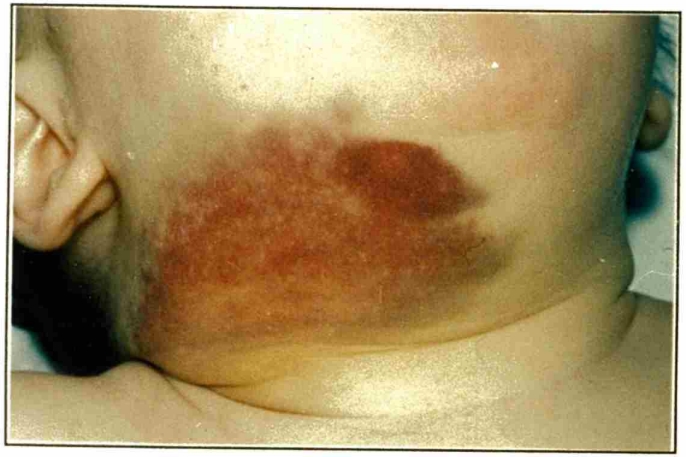
PART I



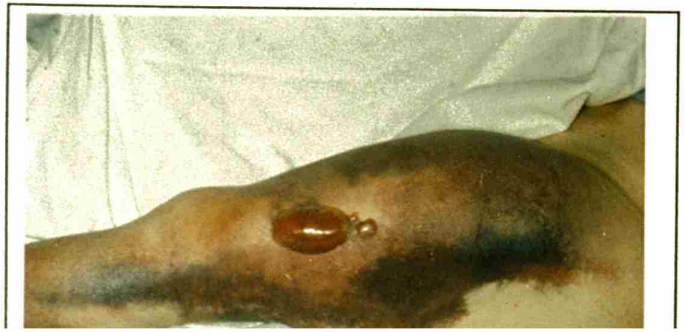
1. Haemophilic bruises are raised and spread through the tissues. Only the tension of the tissues prevents this spread.

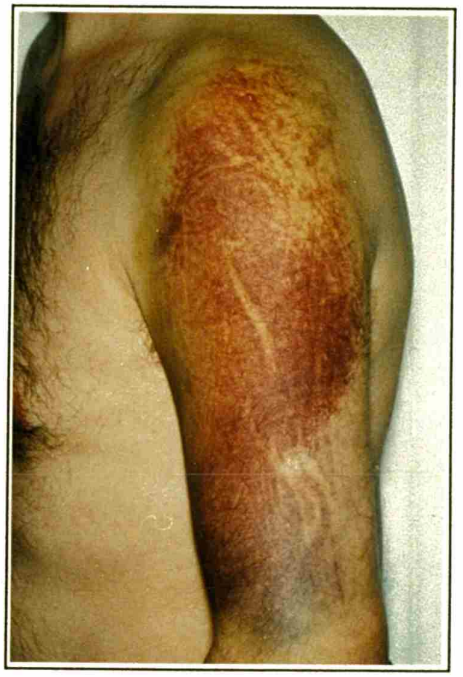


2. A boy of 9 months presenting with a typical haemophilic bruise.

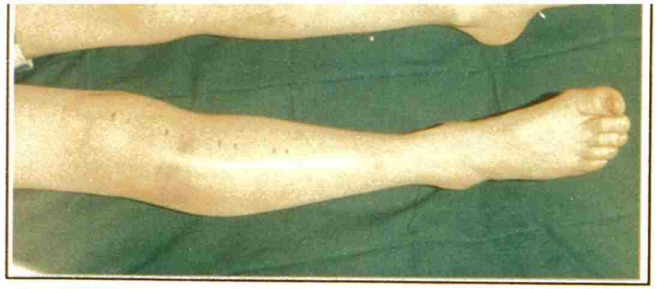


3. Here the lax tissues of the neck allow spread of the bleed which occurs in the absence of a clotting factor (in this case factor VIII).

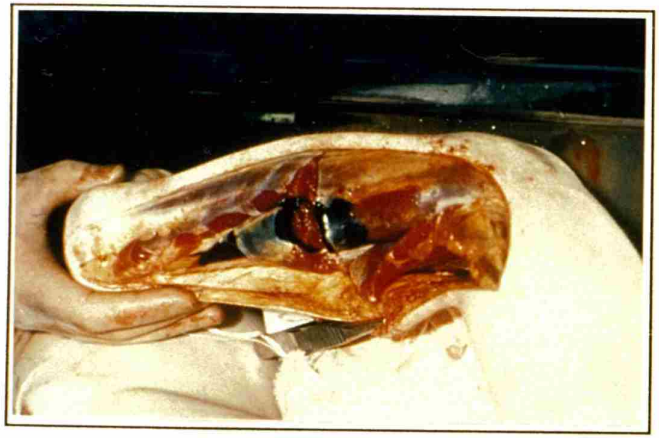




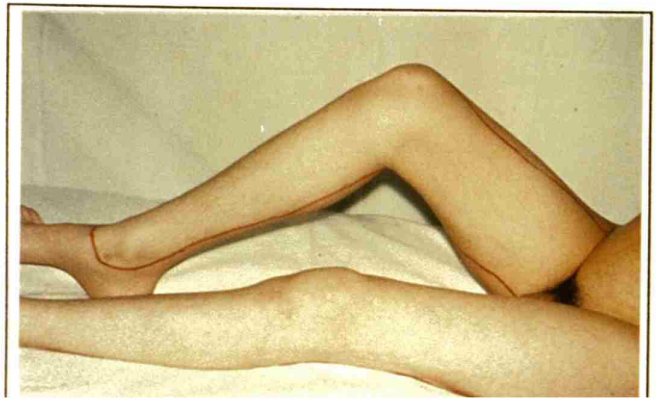
4. Extensive bruising following a simple knock to the upper arm of a man with haemophilia A (factor VIII deficiency).

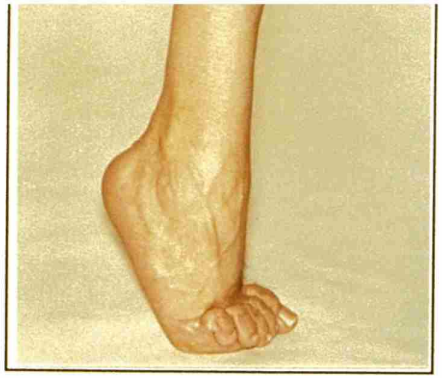


6. Deep bruising of the sort shown in pictures 4 and 5 involves muscle. Here deep bleeding has occurred in the calf muscles of a boy with haemophilia A.

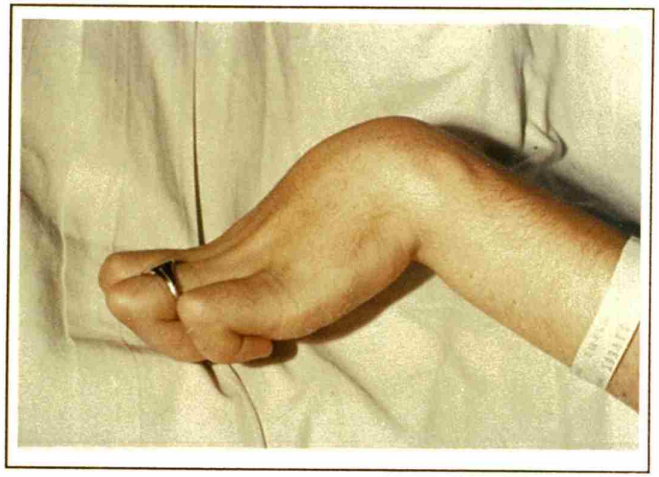


8. A post mortem picture of the forearm of a patient with haemophilia who was killed in a road traffic accident. Pre-mortem bleeding between muscle fibres and muscle sheath is clearly shown. Untreated this bleeding compresses muscle ...

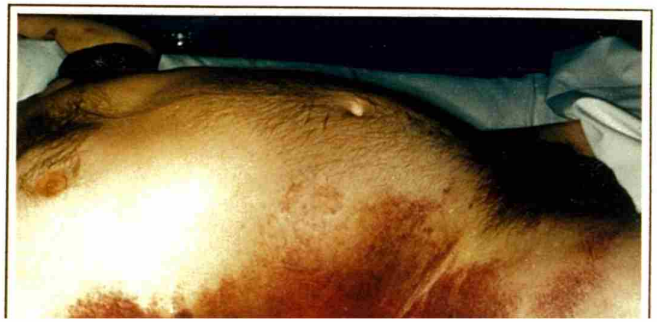


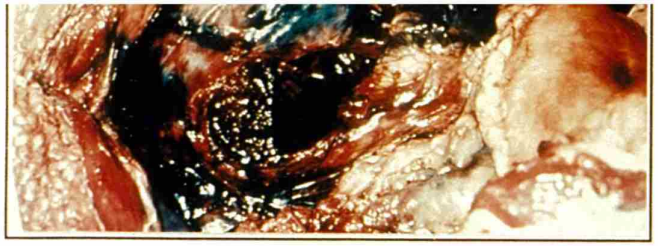


7. Bleeding of the sort shown in 6 can result in the death of muscle fibresand contractures.This patient could not put his foot to the ground and had to walk on the base of his toes.

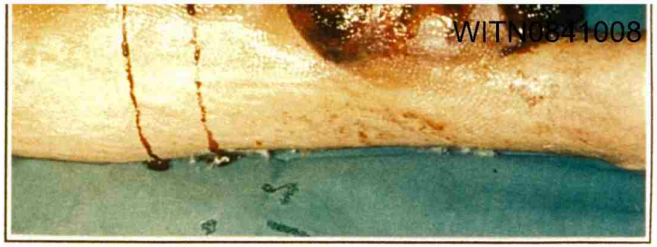


9. leading to contractures. This type of contracture of the hand is called Volkmann's ischaemic contracture.

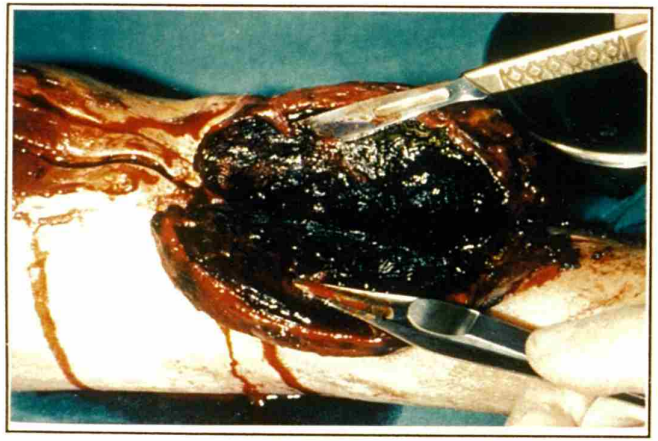




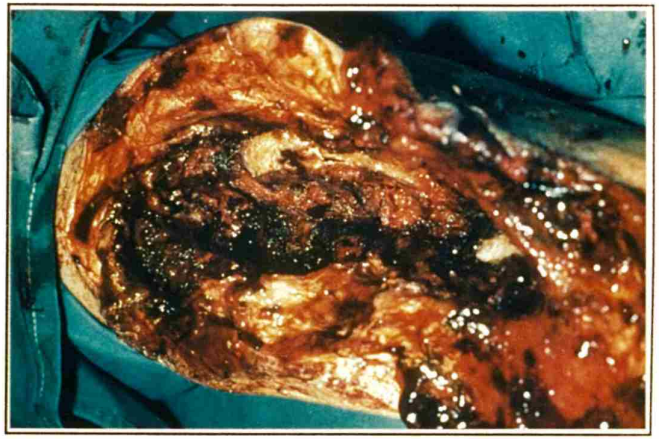
12. Haemophilic blood seeps through any tissue barrier as shown in this post-mortem picture from case 11. This patient's death was directly due to retro-peritoneal haemorrhage. He had an antibody to factor VIII which made conventional treatment ineffective.



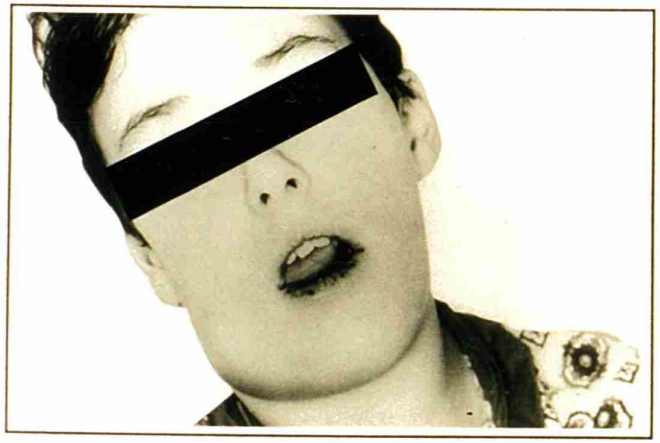
13. Chronic seepage of blood over time can result in massive pseudo-tumours. This picture shows the leg (from knee to ankle) of a patient with severe haemophilia A. The partially clotted blood has eroded the skin ...

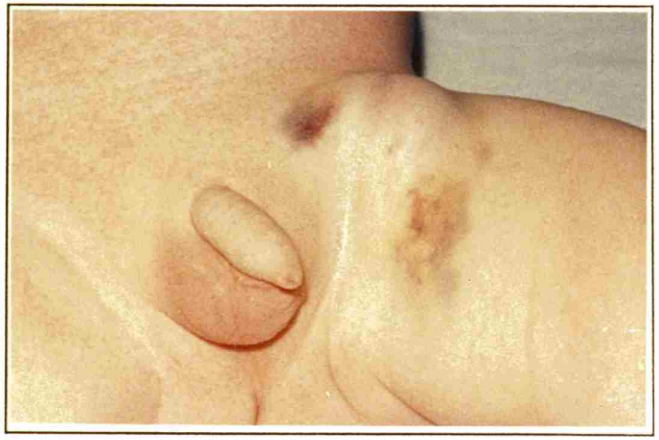


14. at operation huge clots are dissected out ...

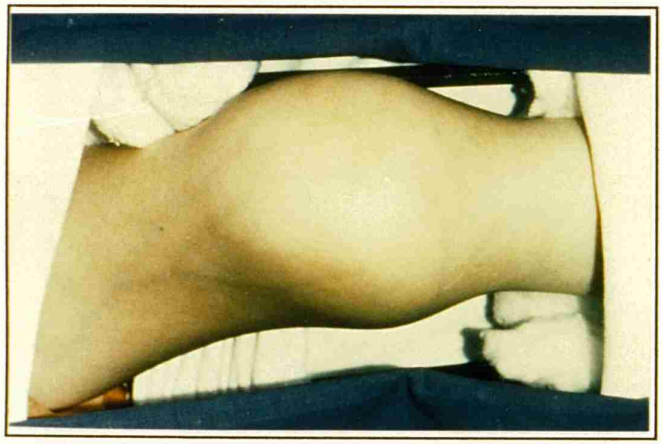


15. to reveal the infiltration of the underlying tissues, including bone.

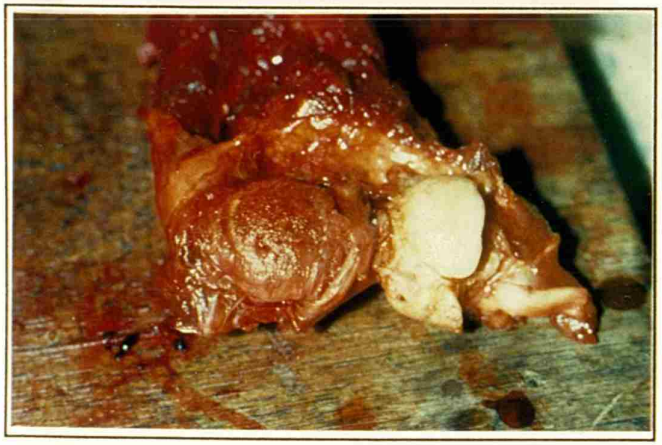


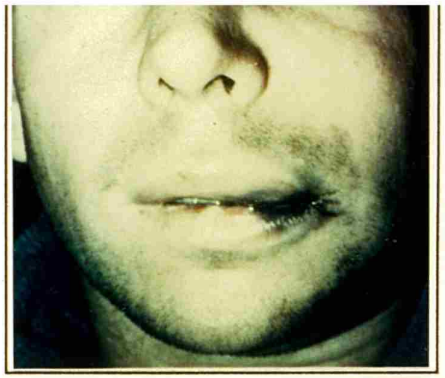


18. This two year old boy had an anti-epileptic drug given shortly before his death from brain haemorrhage and before treatment for his haemophilia. Within 20 minutes the intra-muscular bleed provoked by the injection had extended down two-thirds of his thigh.

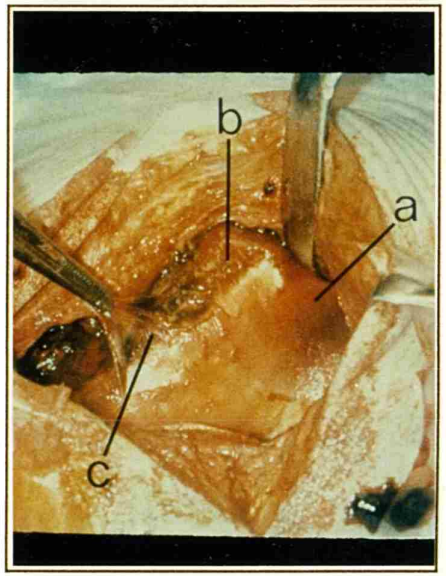


20. The majority of bleeds in severe haemophilia are into either muscles or joints. This is an acute joint bleed (haemarthrosis) in a young boy. Bleeds like this are usually spontaneous and exquisitely painful.

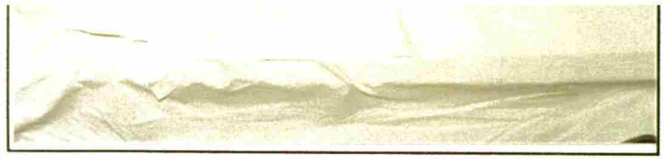




19. Dental block in untreated haemophiliacs can also be lethal. Here bleeding from the jaw of a patient with haemophilia B (factor IX deficiency) has involved the side of his head within 48 hours of the injection.

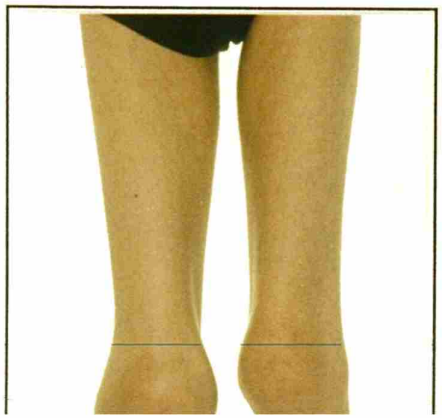


21. Lasting damage which eventually leads to chronic arthritis starts very early in the life of a haemophiliac. 21 shows a knee joint opened for evacuation of clot after a **first** haemarthrosis. (a) shows deep bruising below the cartilage. (b) shows an acute erosion of the surface of cartilage and (c) shows inflammatory tissue being lifted away. The changes herald break-up of the normal cartilage in the joint with repeated bleeds.

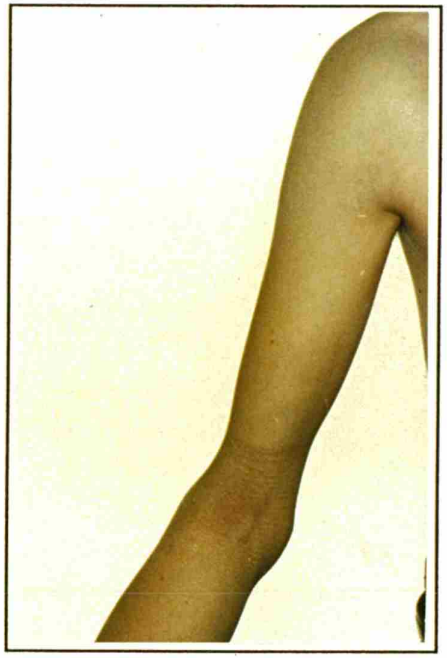


23. A series of acute joint bleeds (haemarthroses) can result in synovitis in which the joint membrane responds in an inflammatory way to repeated insults.

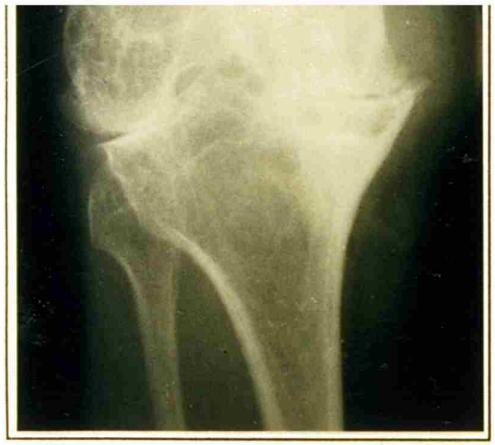
25. Shows a portion of this membrane suspended in saline. Each of the small fronds is rich with blood vessels which easily become trapped between the articular surfaces of joints, provoking further bleeding.



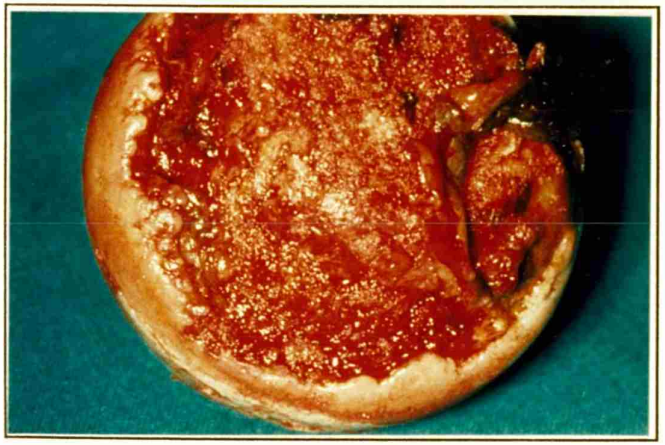
24. Following runs of bleeds the synovial membrane, which normally supplies the oil to lubricate a joint, hypertrophies and becomes laden with iron from red cell breakdown. The picture shows the brown synovial membrane in the joint of a severely affected haemophiliac.



26. When a joint has been subject to recurrent bleeds it falls into disuse and muscle wasting occurs, as in the upper arm musculature in this picture.

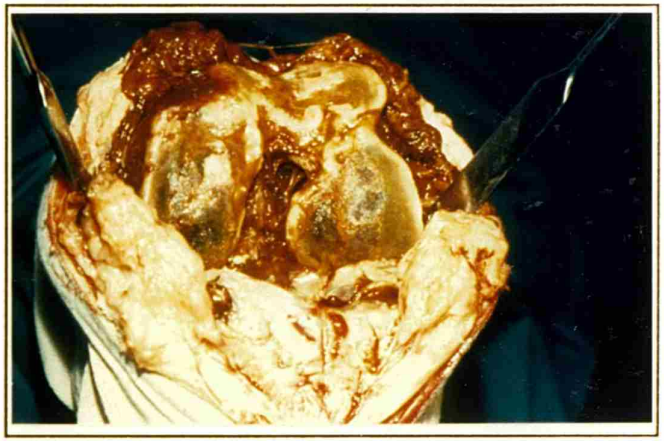


28. The X-ray appearances of chronic haemophilic arthropathy. The normal radiotranslucent 'gap' between the femur and the tibia has disappeared due to the erosion of cartilage from the ends of the bones. The bones rub against each other with resultant chronic pain. They are full of blood cysts and their softness produces incongruity of joint surfaces.

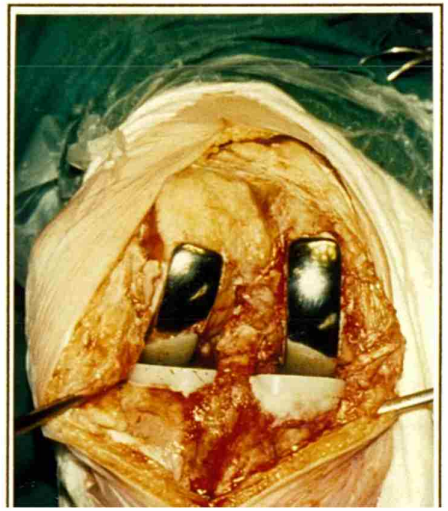


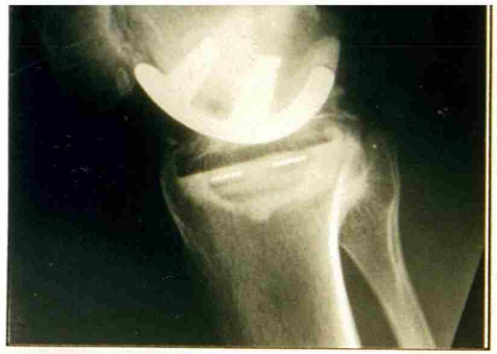
31. In this example of the end-stage of haemophilic arthropathy the head of femur, which is normally covered by whitish-pink translucent healthy cartilage, shows gross erosion which has revealed underlying bone.

29. The result of this pathology may be the sub-luxation of the tibia on the femur, shown here in a post-mortem picture.

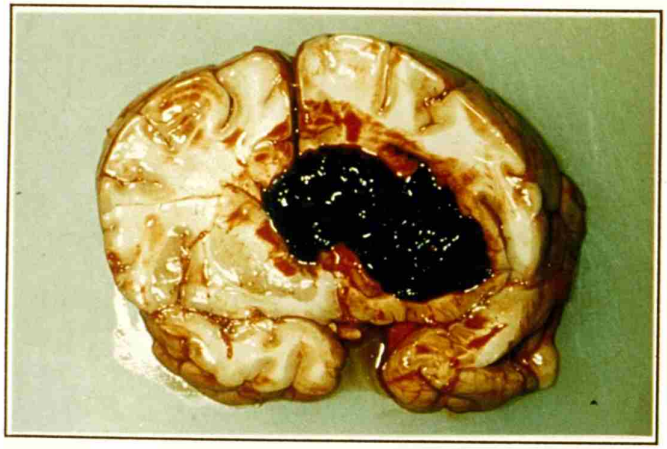


30. The lower end of the femur during surgery. The bone has been denuded of cartilage and the synovial membrane is laden with iron.

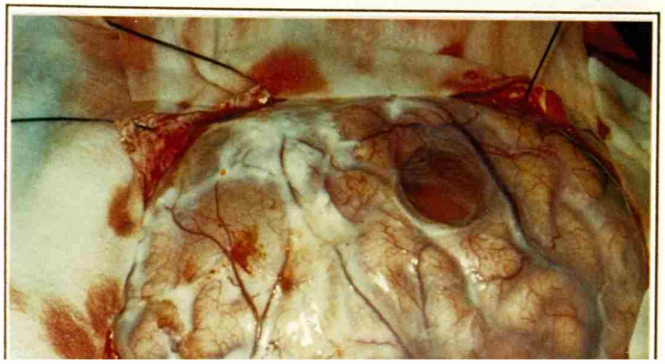


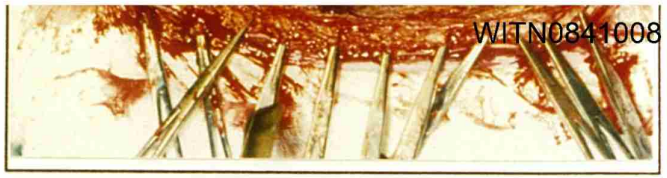


33. X-ray appearance, from the side, of one of these artificial joints. Surgery of this nature demands that sufficient factor VIII or IX is available to cover any complications.



36. Before AIDS the major cause of death in haemophilia was bleeding into the brain. This massive bleed killed the patient instantly.





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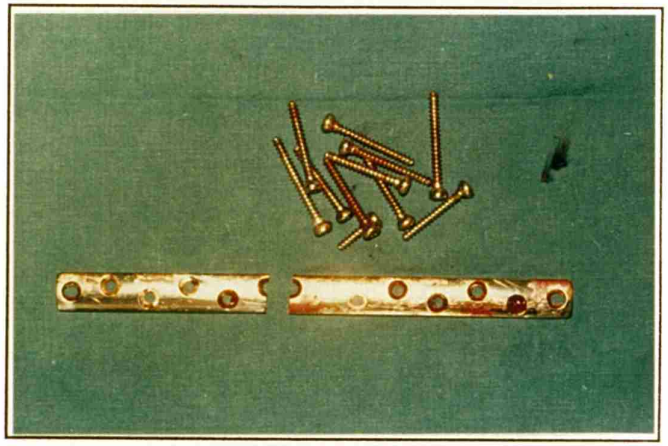
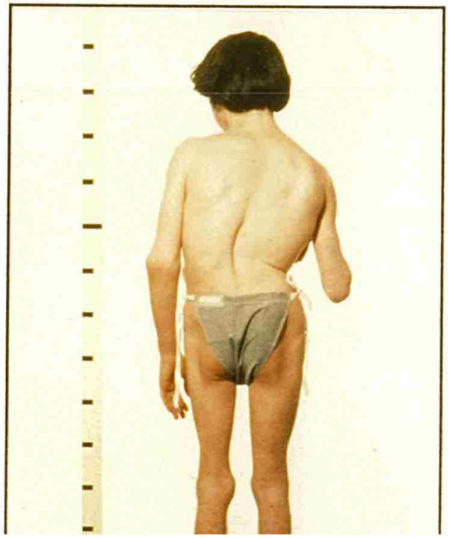
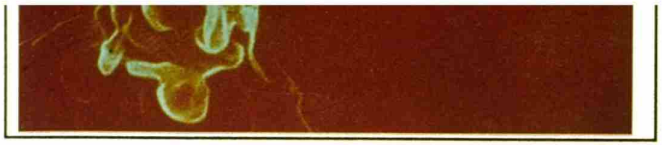


35 In 34 and 35 one such complication of major surgery is shown. This haemophiliac sustained a long bone fracture which required plating. With factor VIII cover he survived the first operation but then required surgery again when the plate itself broke.

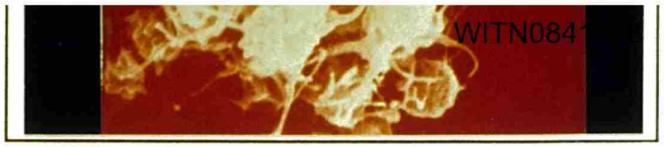


PART 2

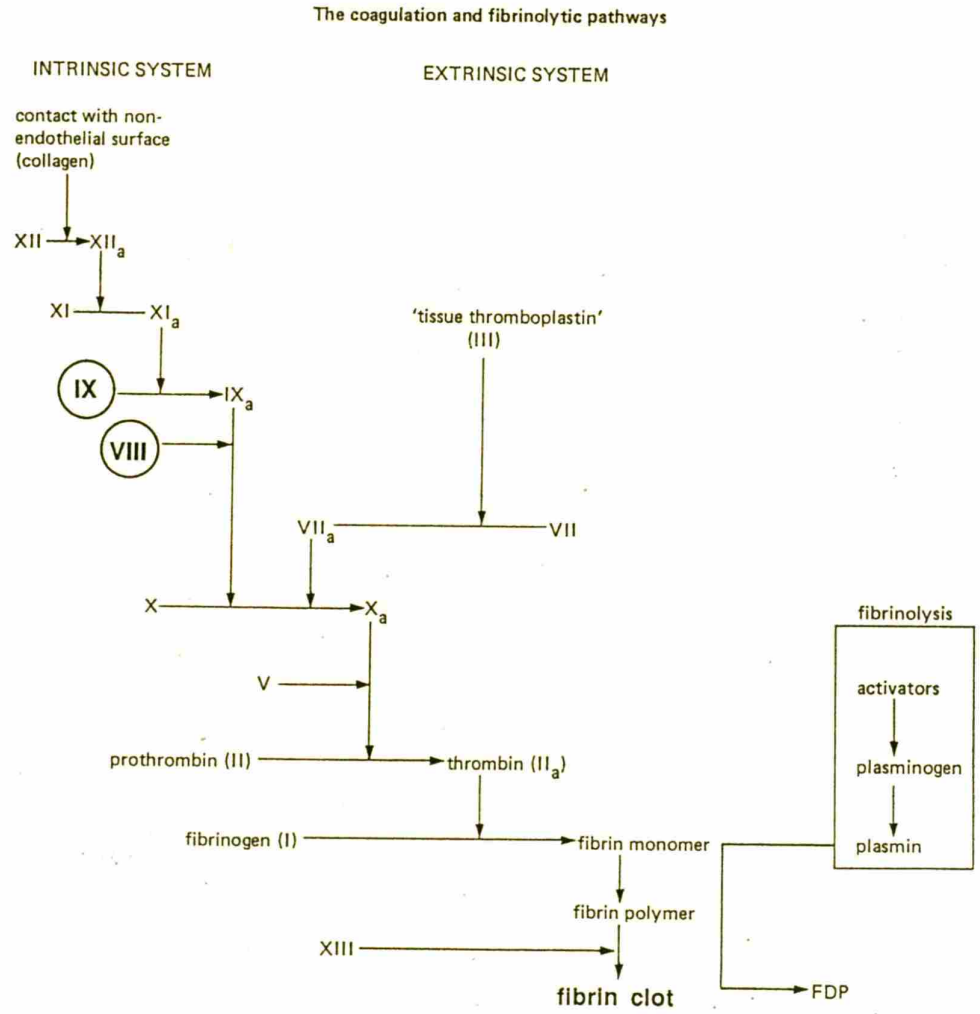
Some principles of treatment



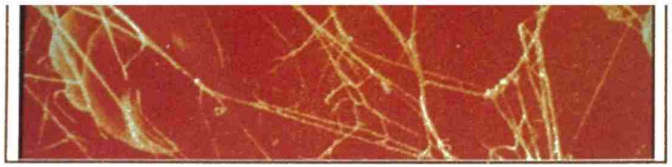
1. The normal mechanism of haemostasis (the cessation of bleeding after injury) initially involves the smallest of the cells in the circulating blood. Here two of these cells, the platelets, send out pseudopodia and stick together in response to injury of a blood vessel wall.



2. Shows the platelet plug formed as a result of this interaction between many platelets. This plug, which closes small gaps in vessel walls, is intact in haemophilia and prevents bleeds from scratches, grazes and pin-pricks.

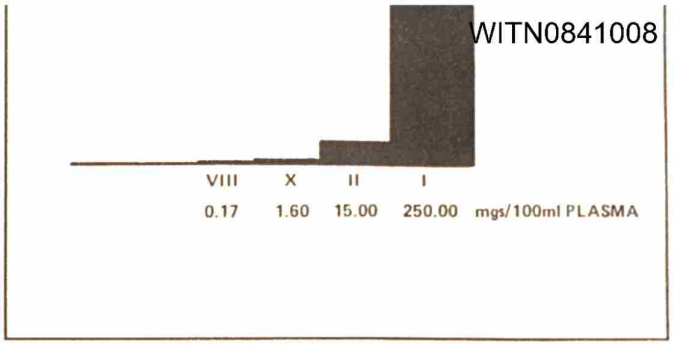


Factor IV (Ca++) and platelet phospholipid are vital at several stages

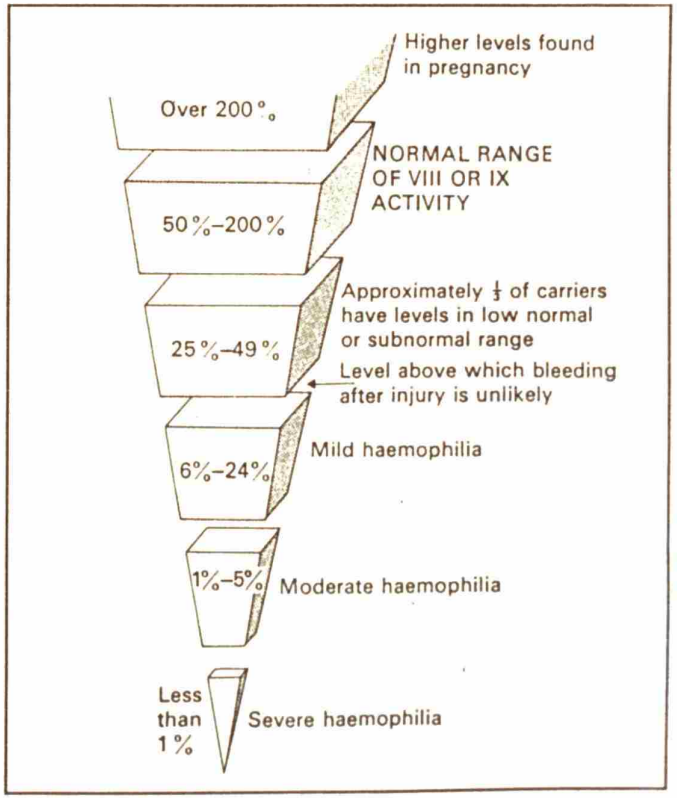


4. A network of fibrin, the end product of the clotting sequence which is sparked off by injury. In haemophilia this network fails to form quickly enough to stop bleeding.

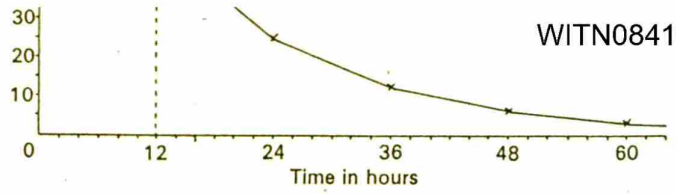
6 If one of the factors in the sequence is deficient or absent, the reaction cannot be driven to its end point, the production of fibrin, precisely where it is needed in the body, and bleeding will continue.



5. To make fibrin very small amounts of clotting factors early in the sequence activate larger amounts of factors later in the sequence. This leads to the conversion of fibrinogen to fibrin, which makes the blood clot. The process is an example of biological amplification, and is illustrated in the cartoon in 6.

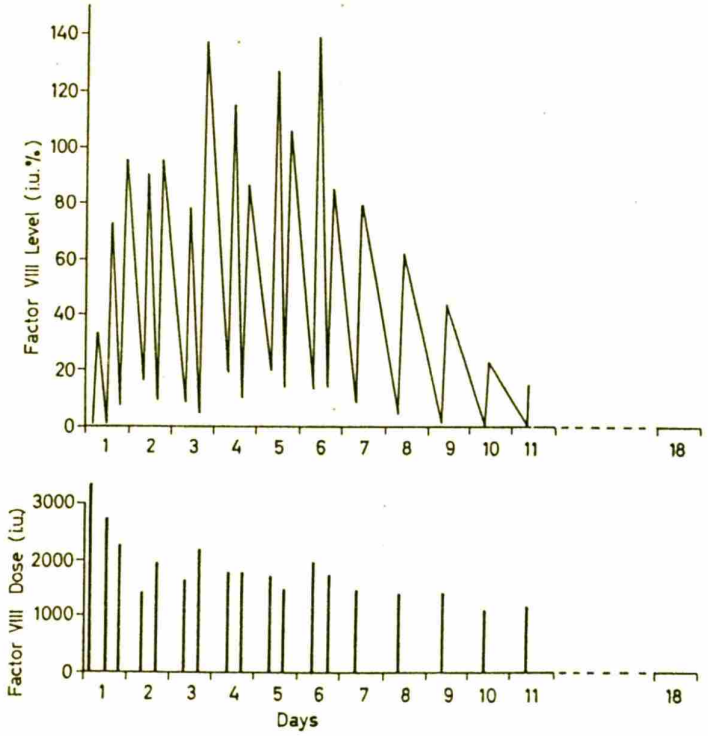


7 Haemophilia is a generic term encompassing all

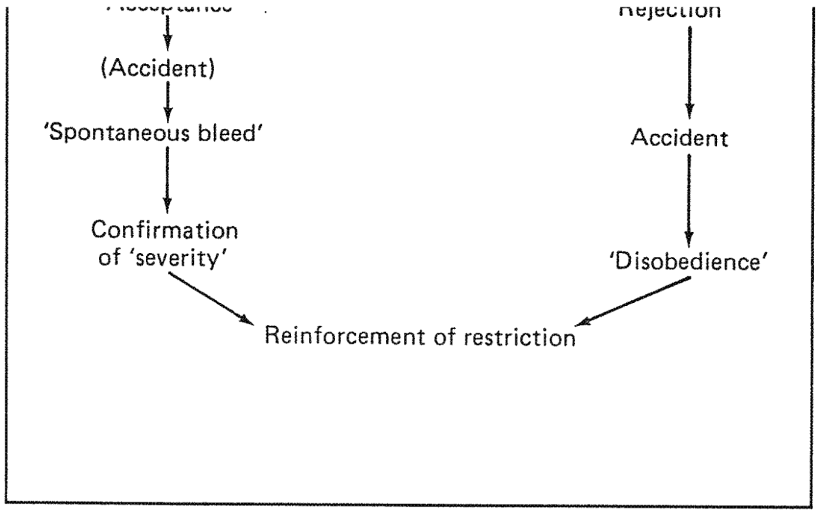


The decay of factor VIII activity at body temperature (decay is stopped if plasma is deep frozen)

9. Successful treatment depends on raising factor VIII or IX to haemostatic levels. 9 shows factor VIII response in a 14 year old severely affected haemophiliac with factor VIII antibodies. The patient underwent surgery with no post-operative bleeding.



10. 80% of bleeds in haemophilia A or B stop with only one conventional dose of factor VIII or IX. The graph shows that it requires increasingly higher dosage if the aim is to stop all bleeds straightaway. The response also depends on the extent of injury or



11. It used to be thought that less factor VIII or IX would be used if patients were sedentary and activities restricted. 11 shows that a child who is restricted can either pretend to accept that restriction and reinforce parental fears about severity of his haemophila with reinforcement of the restriction, or reject restriction with the same conclusion. We now know that exercise and normal everyday activities add strength and stability to joints and musculature, preventing bleeds.

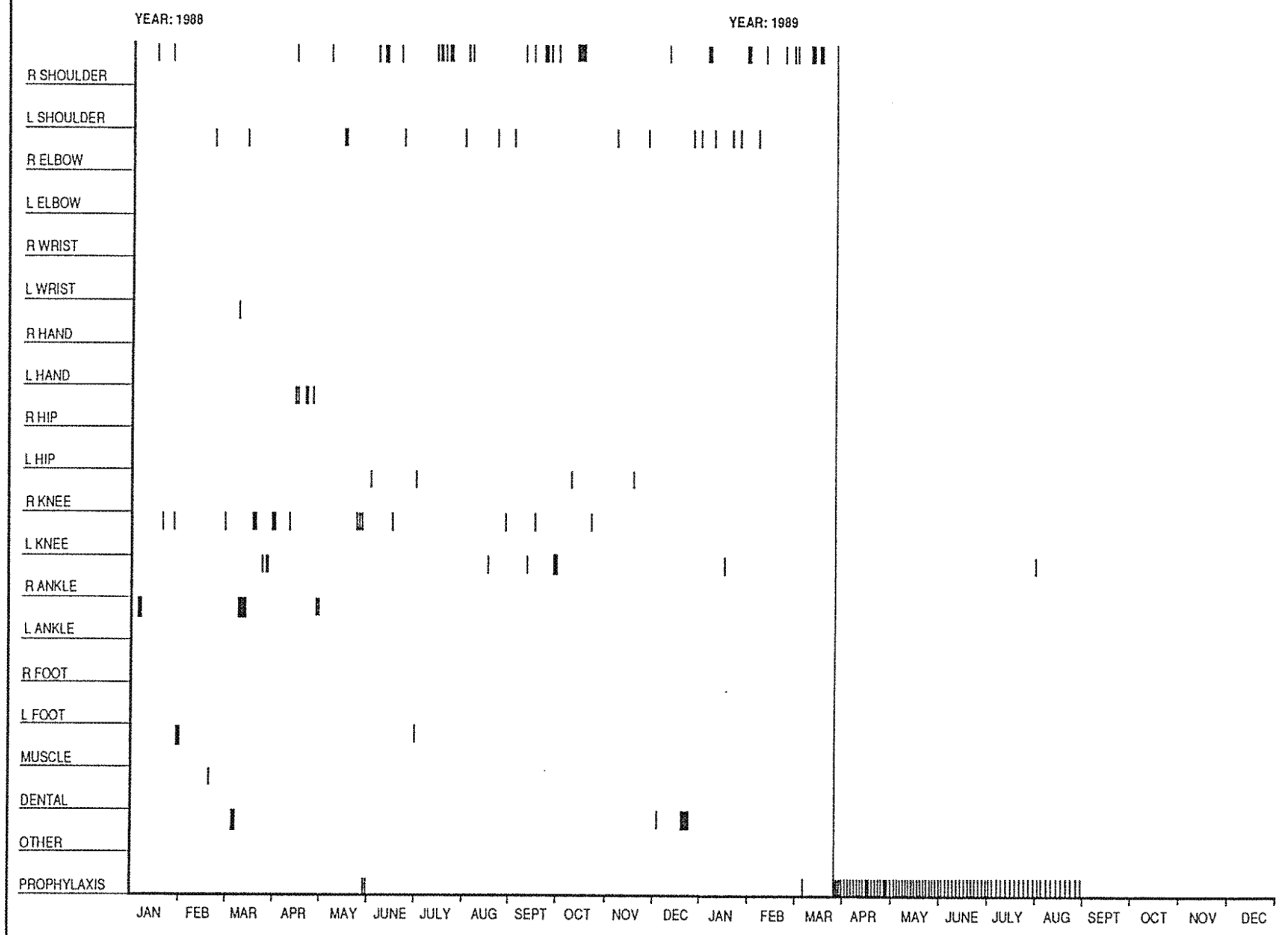
1. The earlier the better

Early treatment of a bleed prevents later damage. The more blood that is allowed to enter a joint or muscle the greater the subsequent damage to the tissues, and the longer the time taken for recovery. Early treatment usually allows an immediate return to school or work, and also diminishes the chance of arthritis and disability later in life.

2. If in doubt, treat

Trust your, or your child's, 'aura'. If you feel that a bleed might have started, treat it. Never wait until a joint is hot, swollen and painful. Do not worry that you may 'waste' the occasional treatment by injecting when a bleed is not present.

3. A shot in times saves VIII (*or* IX)


YEAR: 1988
YEAR: 1989
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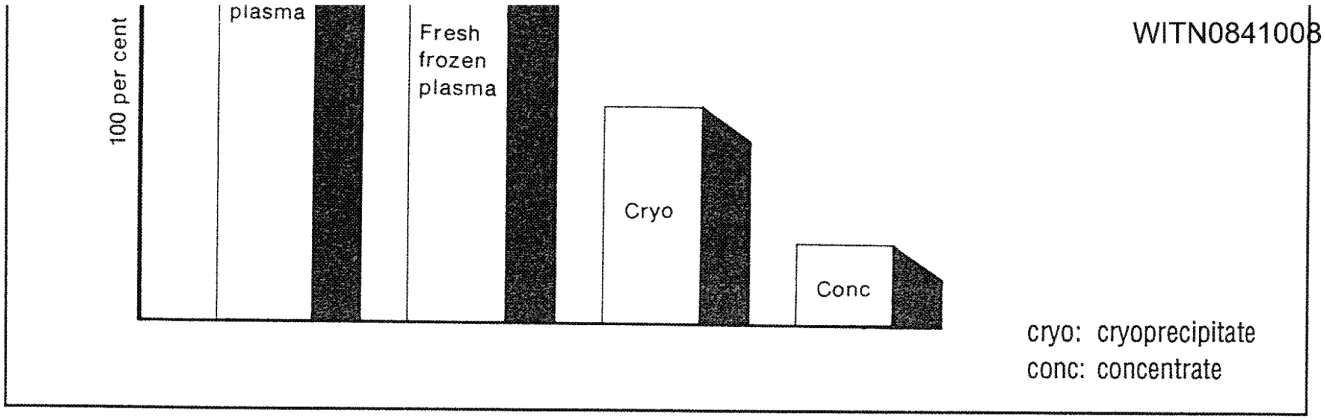
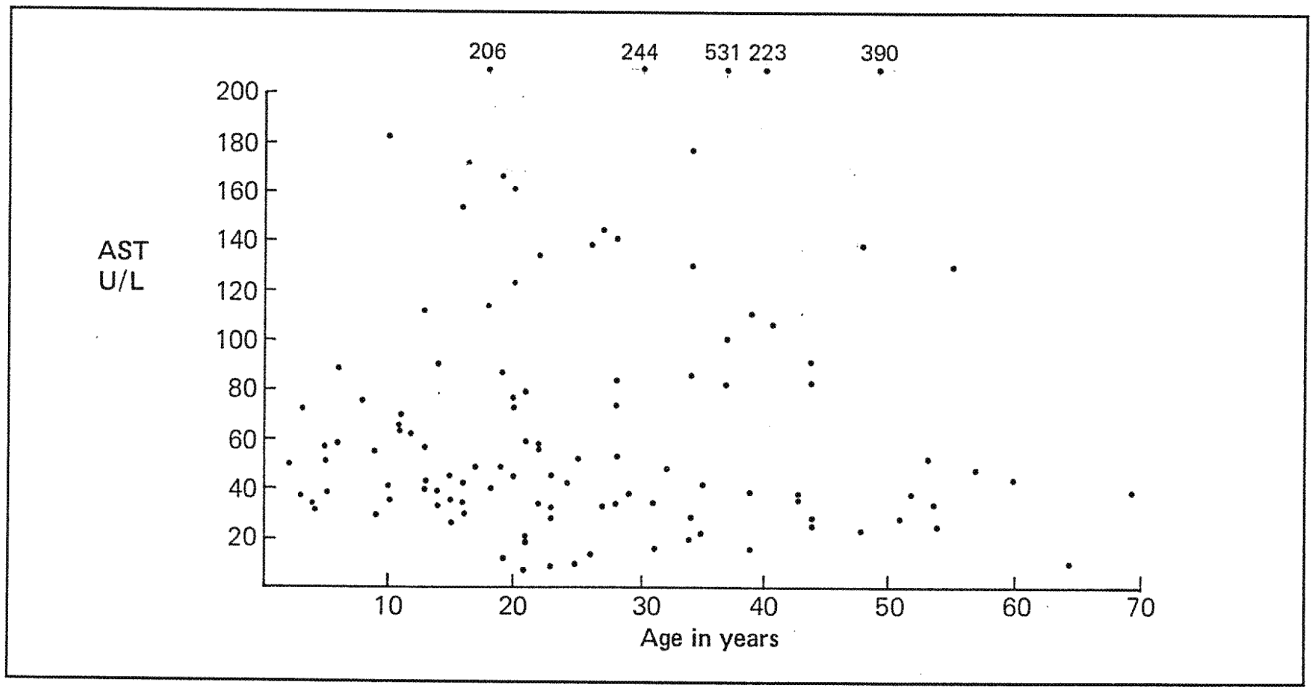


14. Factor VIII or IX concentrates are the materials of choice for home therapy, prophylaxis and surgical cover. Production of the concentrates requires more source human plasma or cryoprecipitate because the more sophisticated the product the less the yield of active clotting factor.



15. It was initially assumed that because of the multiple donations needed to make concentrate the incidence of hepatitis would be greater in haemophiliacs receiving concentrate than in those receiving single donor had only received cryoprecipitate, as well as in older patients who had received concentrate. The normal upper level of the particular liver function test shown (AST) is 37 U/l. Knowledge of the incidence and likely severity of such side