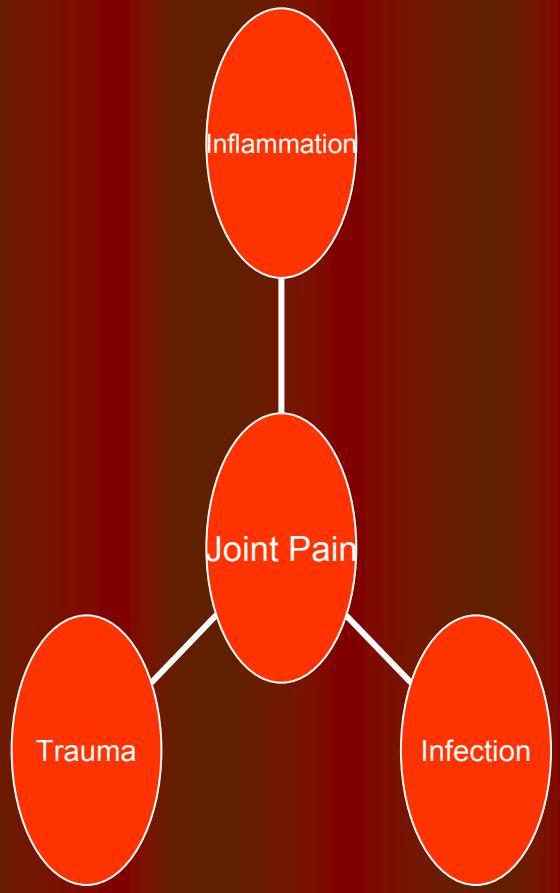
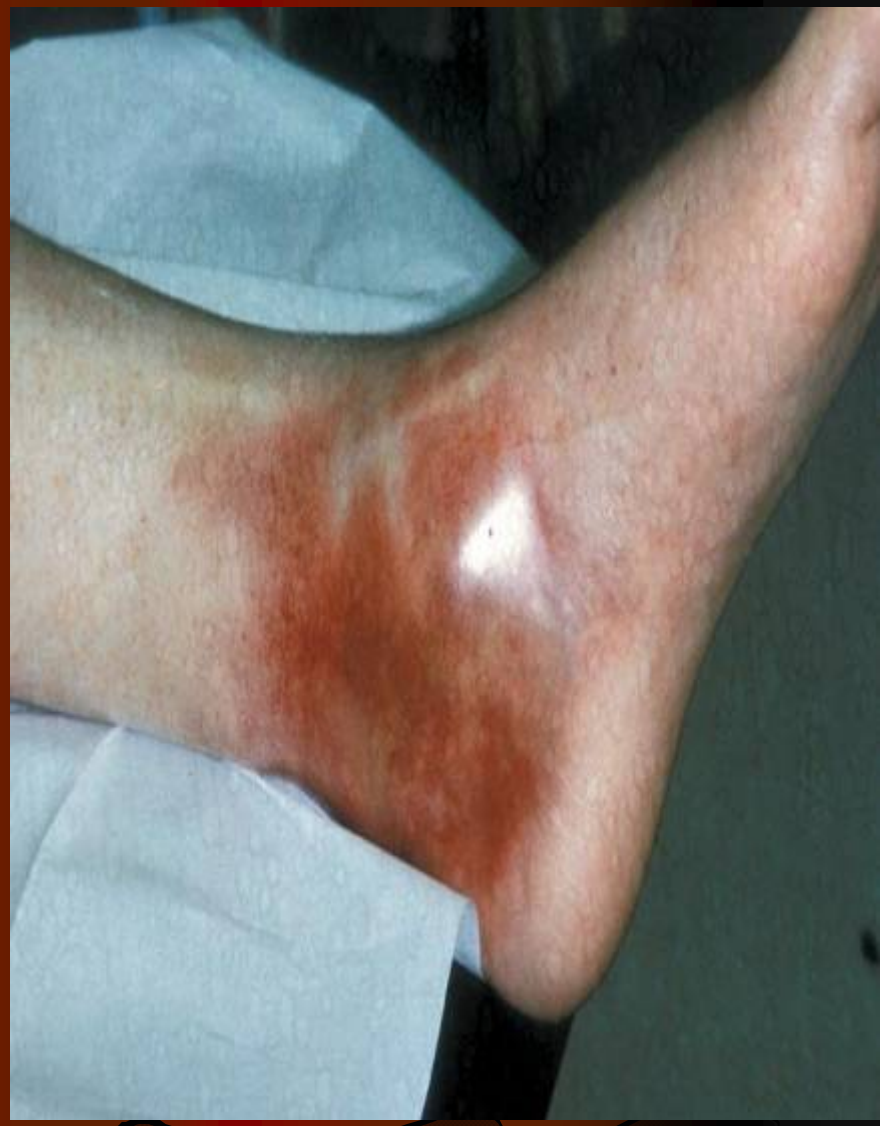
Haemophiliac arthropathy – inflammatory processes, radiological imaging and management

David A Kandiah,
Director,
Department of Rheumatology,
Royal Brisbane and Women's Hospital.

ACUTE MONOARTHRITIS:





Acute haemarthrosis

Evolution

- Management of haemophiliac arthropathy has changed in the past 50 years.
- We have gone from bed rest, joint immobilisation and FFP; to using prophylactic factor replacement and elective procedures medically and surgically.

CLINICAL FEATURES

- Bleeding into joints and soft tissues are characteristic in haemophilia. The severity of MSK manifestations correlates with the level of factor deficiencies.
- The resorption of intra-articular blood induces reactive synovitis with recurrent hyperplastic synovitis. The effect of chronic synovitis and impaired blood supply on the growth plate induces secondary cartilage destruction.
- Most common joints affected are knees and elbows. Other joints affected can be ankles, shoulders and hips. While ankles have the least induction of synovitis, bony ankylosis is common. This follows expansion of the epiphyses which become abnormal in shape and then fuse prematurely.

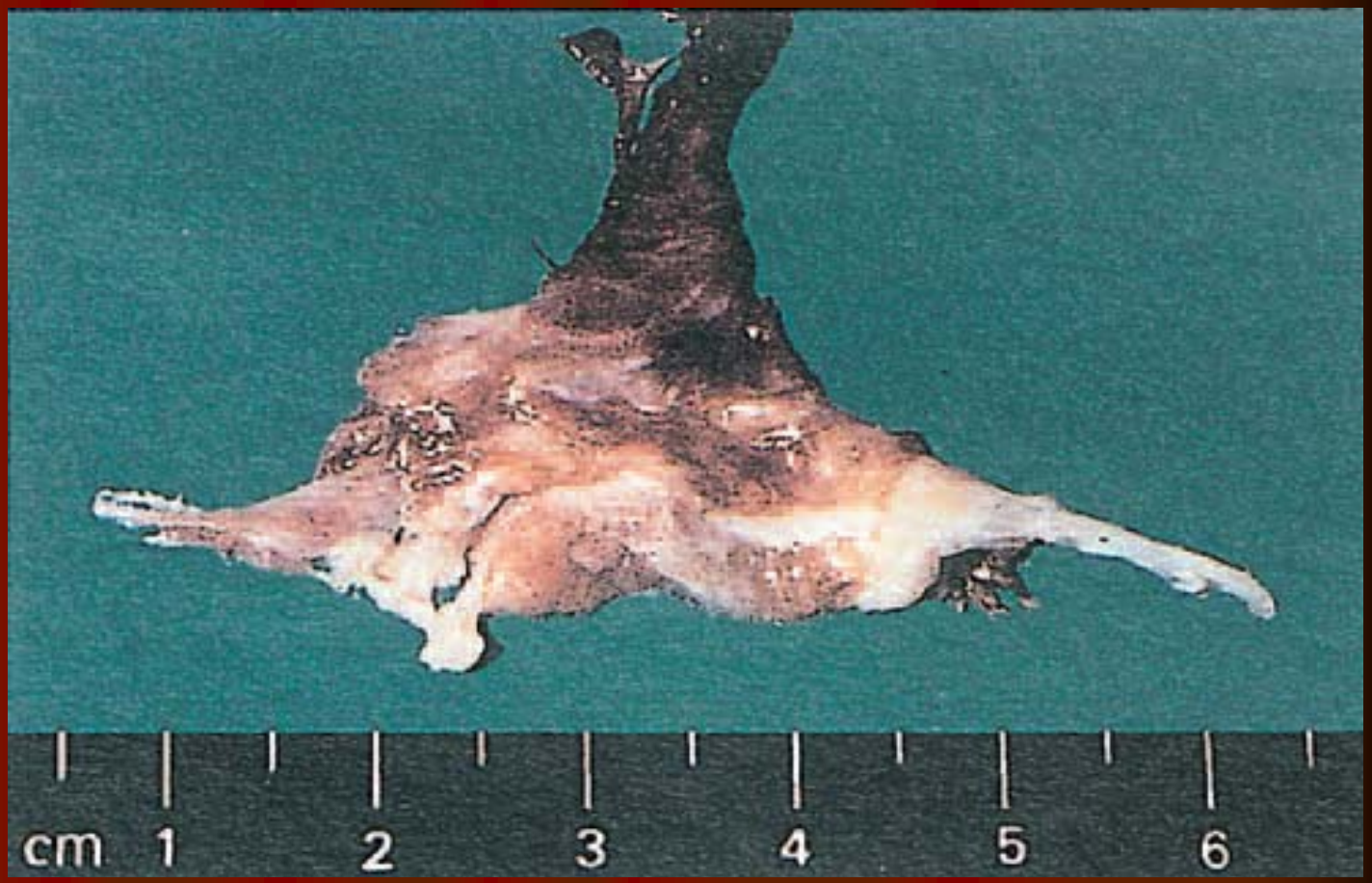
PATHOBIOLOGY 1

❖Following injury, the synovial vessels rupture, and blood accumulates in the joint. Bleeding continues until the intra-articular hydrostatic pressure exceeds that of the arterial and capillary pressure in the synovium. The resultant tamponade of the synovial vessels causes ischaemia of the synovium and subchondral bone.

❖With repeated haemorrhage, hyperplasia and fibrosis of the synovium will occur.

❖In-vitro human synovial cells exposed to ferric salts can produce dose-dependent c-myc expression *(Wen et al, Blood,2002;100:912-916)* which can stimulate synovial proliferation.

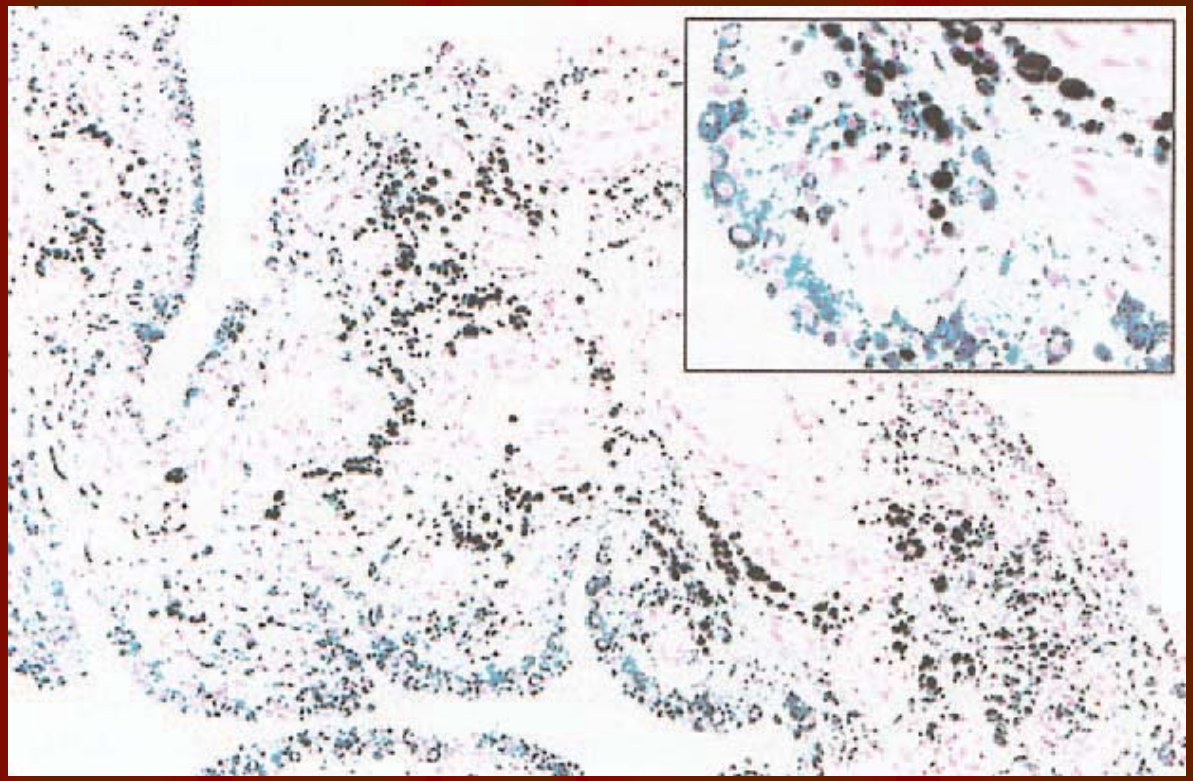
❖Inflammatory cytokines are also in increased concentrations e.g. TNF-α, Interleukins 6 and 1-β *(Rosentaal et al, JBJS, 1998;80-B:540-545).*



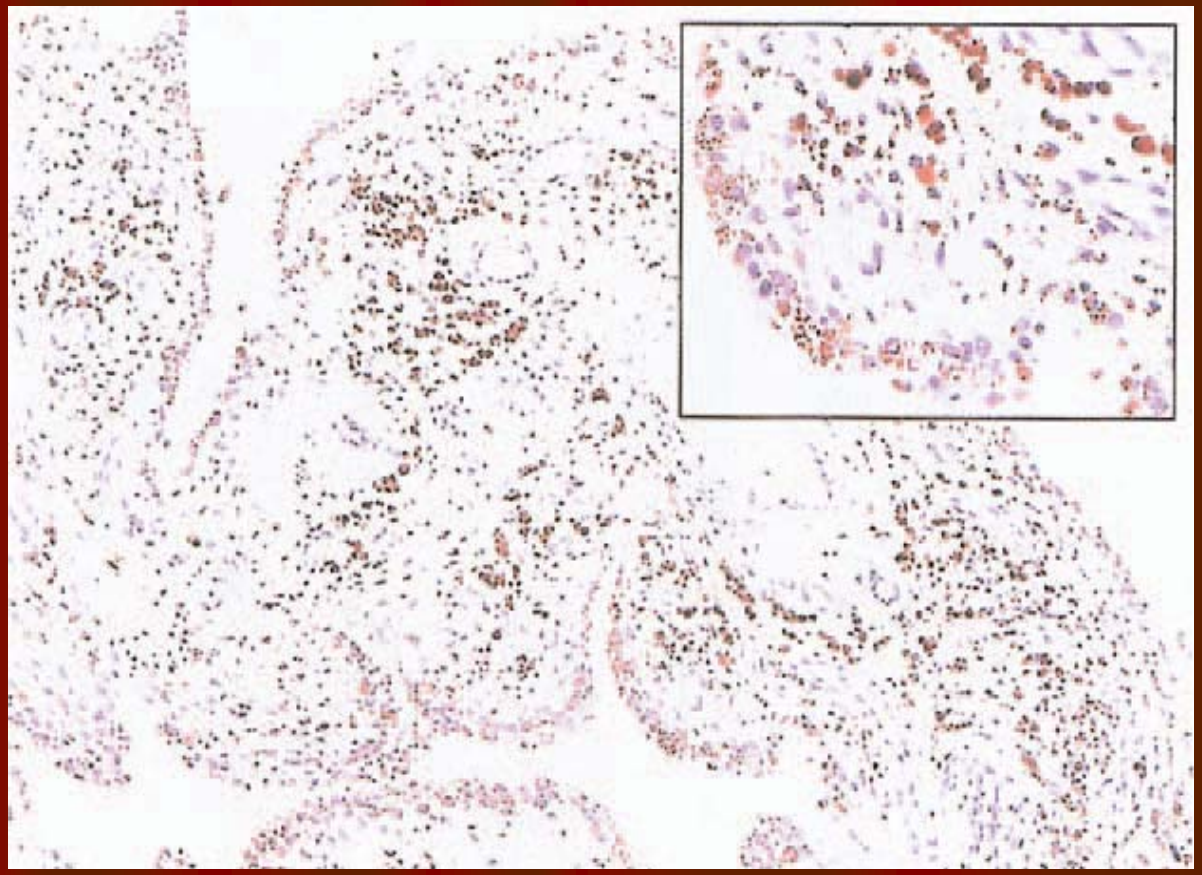
A synovial tissue biopsy from a patient with HA showing areas with brown haemosiderin deposits adjacent to tissue with a yellowish normal appearance. *From Roosendaal G et al, The Journal of Bone and Joint Surgery 1998;80-B:540-545.*

PATHOBIOLOGY 2

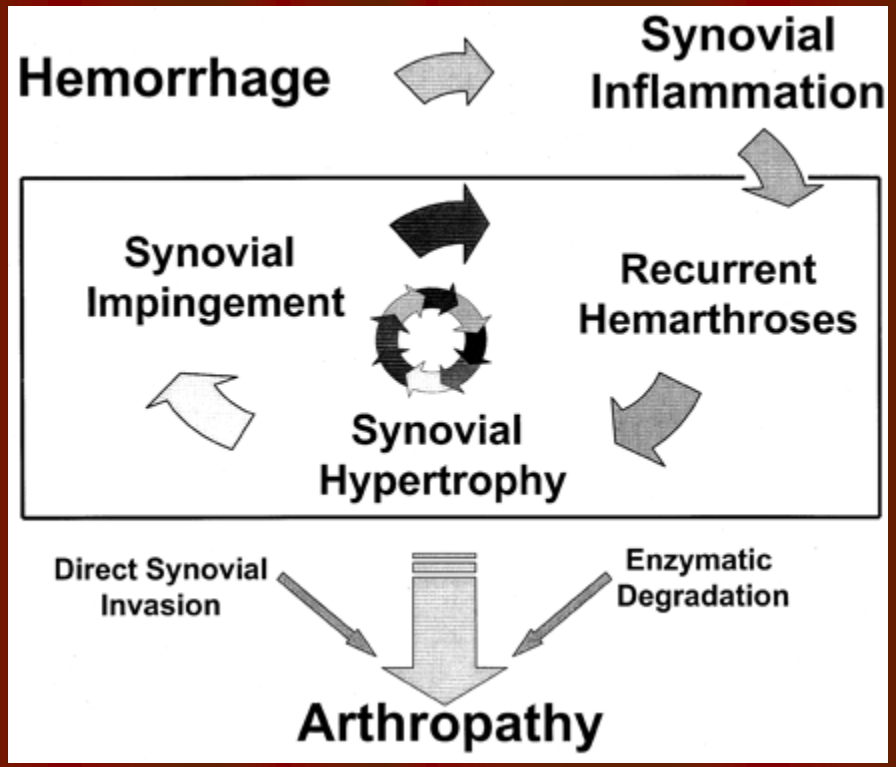
- Pannus formation by the proliferating synovial tissue will erode the hyaline cartilage peripherally, and compression of its opposing cartilaginous surfaces will result in degeneration of articular cartilage centrally. Macrophage infiltrate can be associated with pro-angiogenic factors e.g. matrix metalloproteinase-9 and VEGF.
- Inflammatory process invades and destroys cartilage. Loss of joint motion and contractural deformity occurs. Subchondral bone cysts are formed due to local bone ischaemia.
- Stimulation of growth may be asymmetrical, resulting in valgus or varus deformity. Shortening of a limb may be produced by early closure of the epiphysis.
- Osteoporosis and muscle atrophy are common.



Micrographs of synovial tissue. In haemosideritic synovium the lining cells show deposits as discrete granules, scattered throughout the cytoplasm. The deeper iron deposits are in dense intracellular and extracellular aggregates. *From Roosendaal G et al, The Journal of Bone and Joint Surgery 1998;80-B:540-545.*



Haemosideritic specimen showing diffuse lymphocyte infiltration and neovascularisation with no follicles of lymphocytes. *From Roosendaal G et al, The Journal of Bone and Joint Surgery 1998;80-B:540-545.*



From Luck et al. Journal of the American Academy of Orthopaedic Surgeons, 2004;12:234-245.

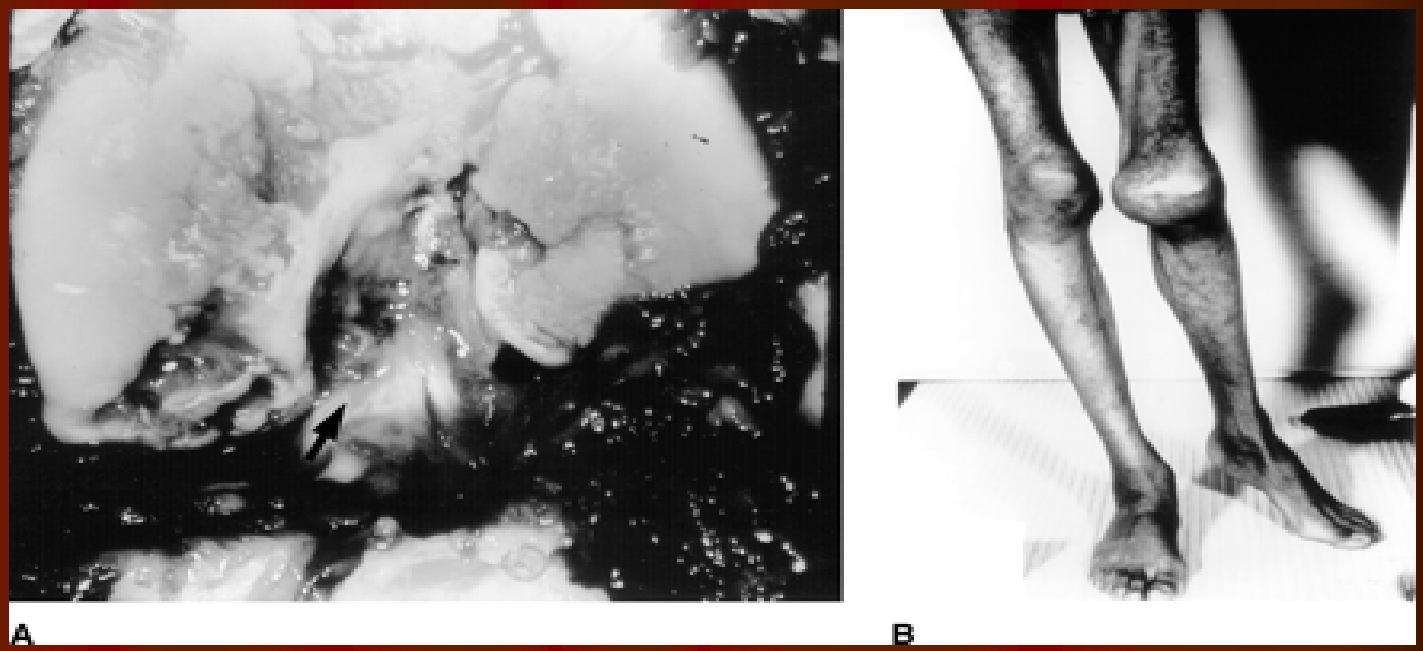
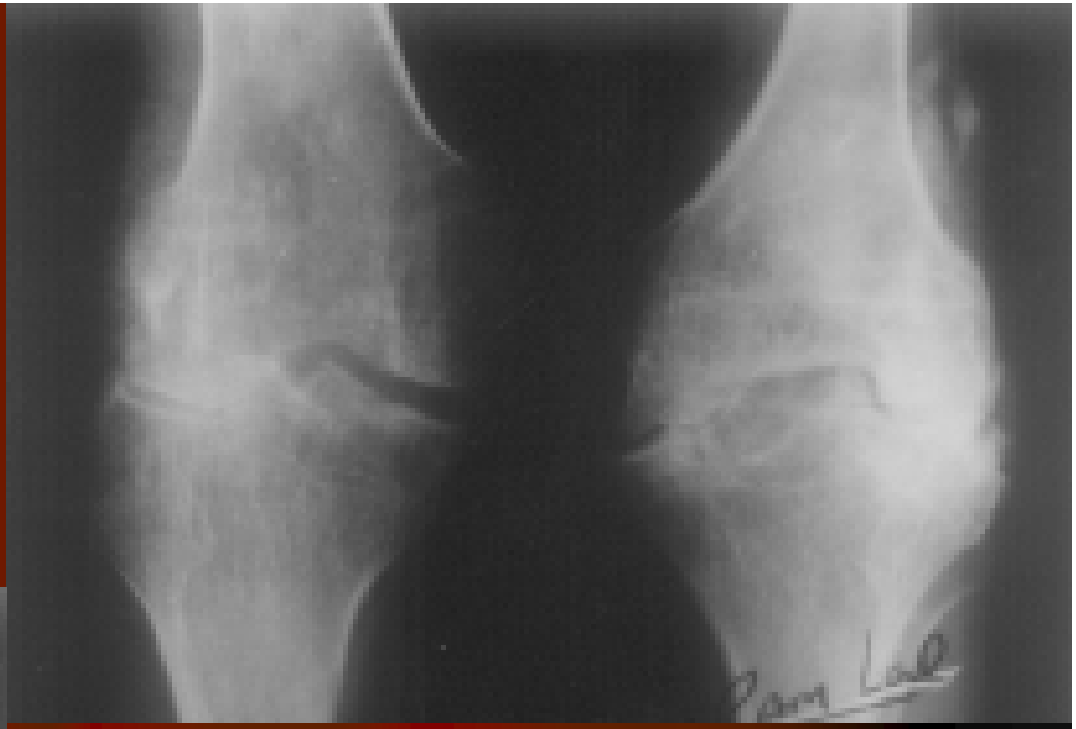
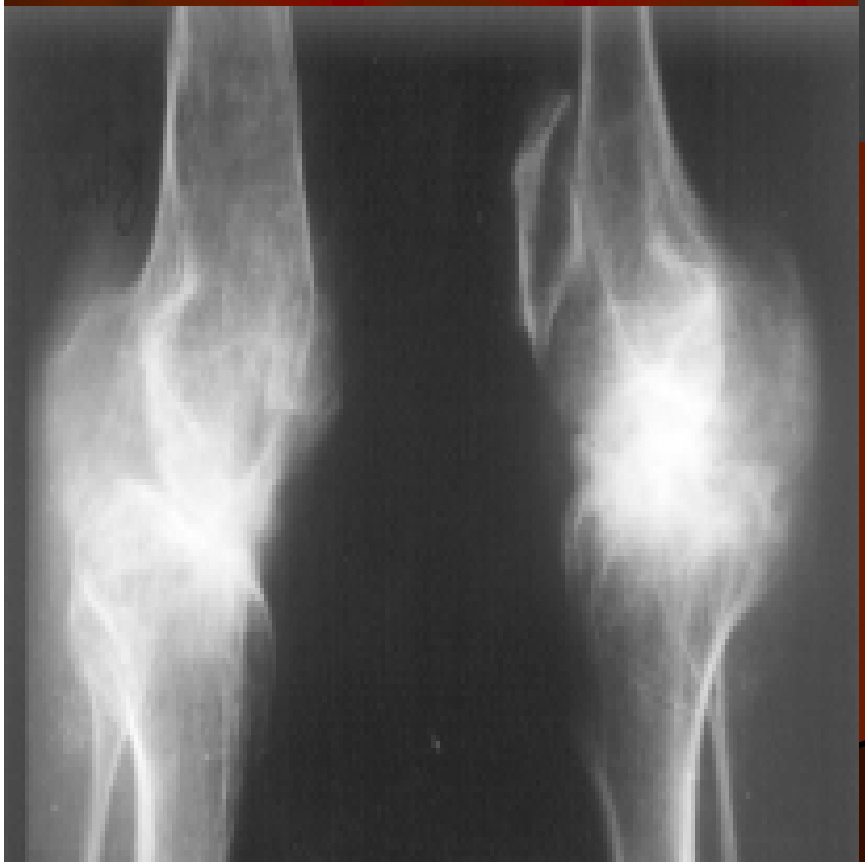


Figure A: The femoral articular surface at the time of open synovectomy in a 12-year-old boy with severe haemophilia, showing extensive full-thickness erosions of the trochlea and both femoral condyles. The anterior cruciate ligament (arrow) is intact. The synovium is hyperplastic and densely stained with hemosiderin. It is friable and easily trapped between the eroded joint surfaces, resulting in haemarthrosis. Despite the severe erosions, the radiograph was grade II with normal joint space. **B,** Fourteen-year-old haemophilic boy with advanced arthropathy. He has marked muscle atrophy and severe subluxation of the left knee. *(From Luck JV, Lin JC, Kasper CK, Logan LJ: Orthopaedic management of hemophilic arthropathy, in Chapman MW [ed]: Chapman's Orthopaedic Surgery, ed 3. Philadelphia, PA: Lippincott Williams & Wilkins, 2001, pp 3595–3616.)*

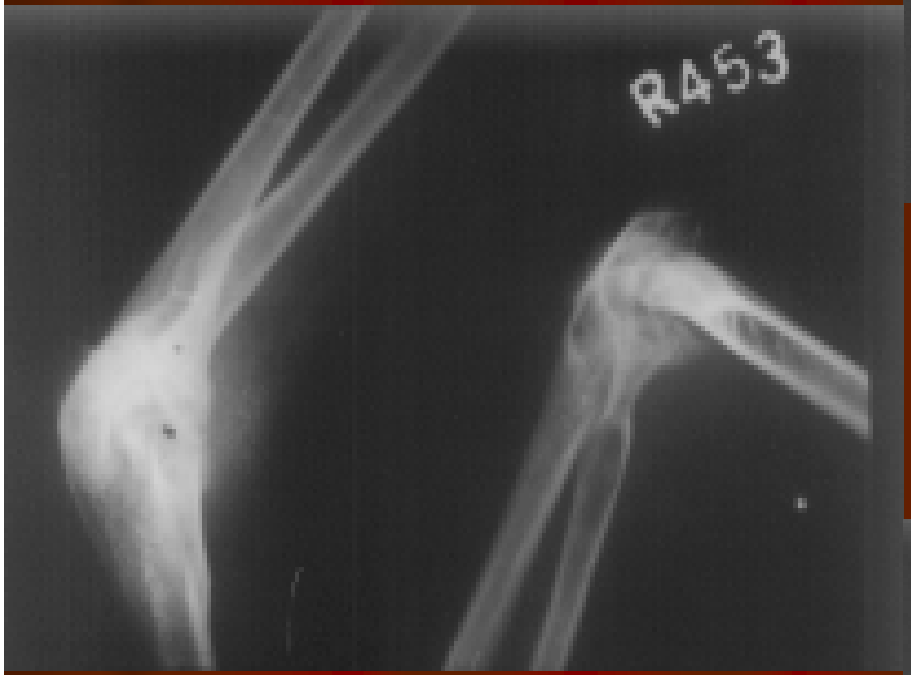
X-ray knee AP showing intercondylar notch widening with erosions of bony margins

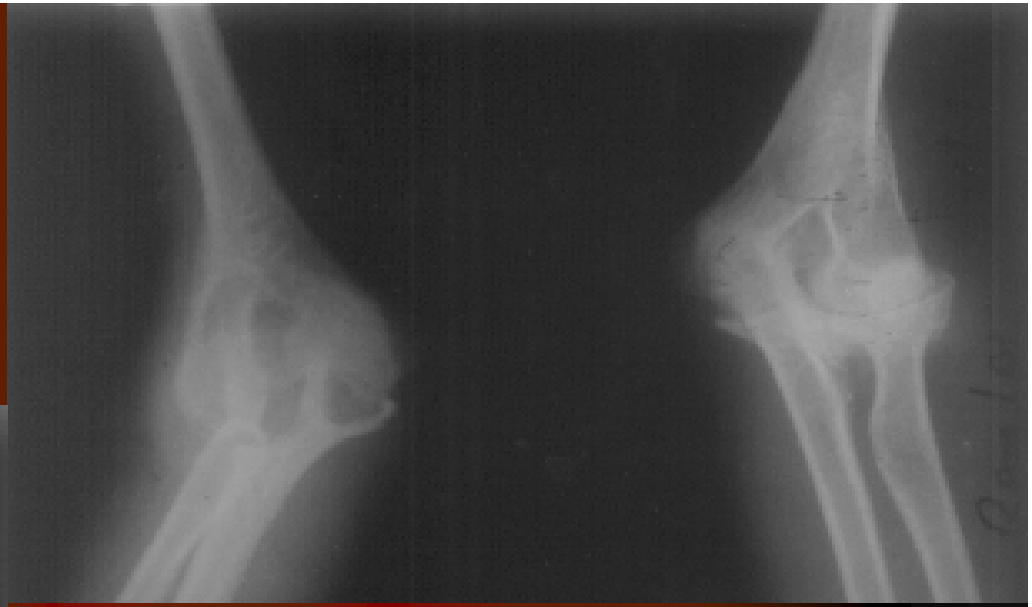




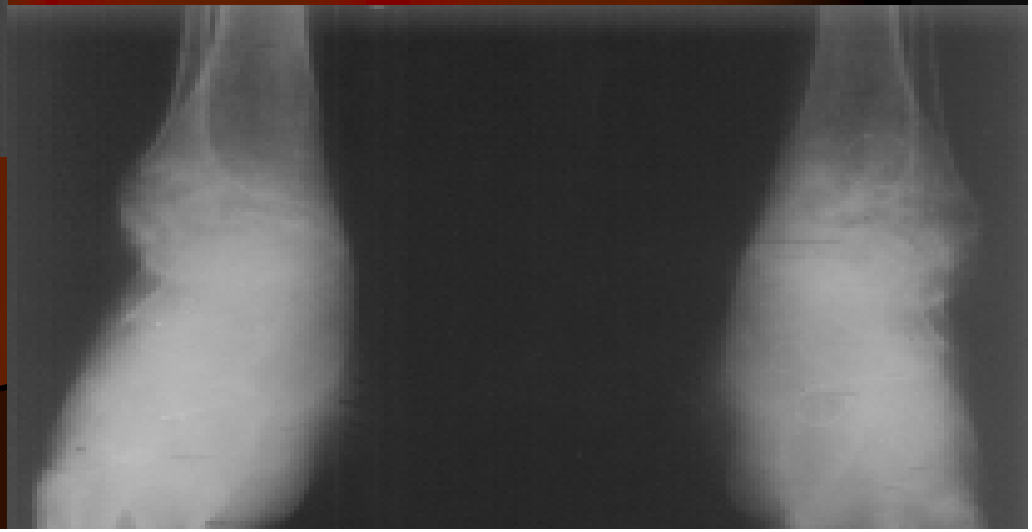
Lateral views of knee showing marked reduction in joint space and subchondral cysts

X-ray elbow showing enlarged and deformed radial head with juxta-articular cyst in the olecranon process.





Lateral views of elbow showing decreased and flattened joint space with radiodense effusions.



X-ray ankle joint AP showing soft tissue swelling with multiple central and marginal erosions and decreased joint space.

Radiology

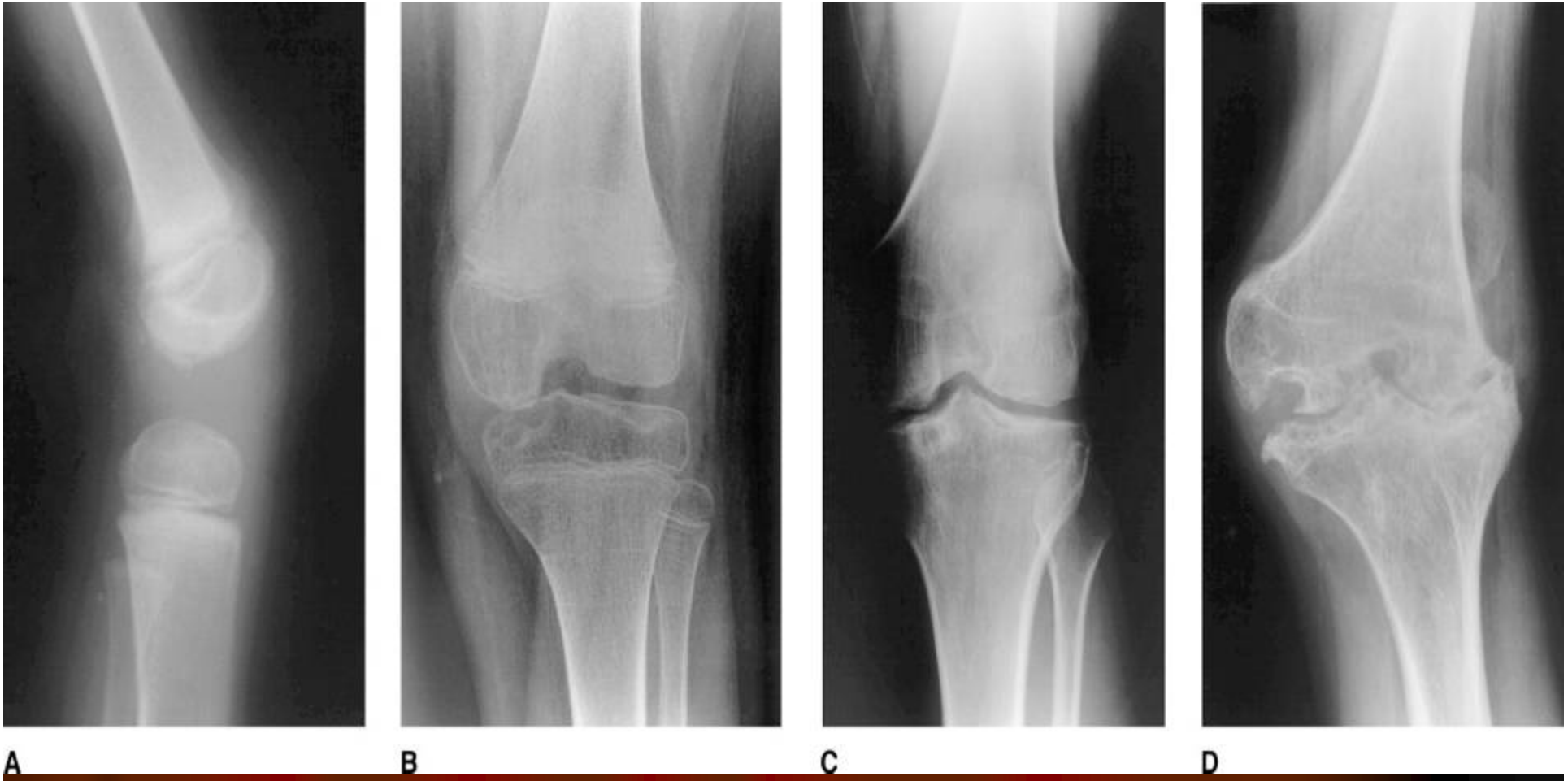
- Haemophilic arthropathy is classified into five stages (Arnold-Hilgartner system).

- **Stage I** - there is only soft-tissue swelling, but no skeletal abnormalities.
- **Stage II -** characterized by overgrowth and osteoporosis of the epiphysis, but joint integrity is maintained. There are no bone cysts and no narrowing of the articular cartilage space. The radiologic Stage II parallels the clinical stage of subacute haemophilic arthropathy.
- **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 intercondylar 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 haemophilic arthropathy is still reversible.

- **Stage IV** - there is destruction of articular cartilage with severe narrowing of the joint space. The other osseous changes found in Stage III-i.e., subchondral cysts, patellar squaring, and widening of intercondylar or trochlear notch are more pronounced.

- **Stage V** - 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.

- The modified Arnold-Hilgartner system has 4 stages eliminating stage II.



Modified Arnold-Hilgartner classification of haemophilic arthropathy. **A,** Grade I. Lateral radiograph of a 4-year-old boy with severe haemophilia who presented with early chronic synovitis. Note the popliteal soft-tissue fullness indicative of synovial thickening and osteopenia of the tibial epiphysis. **B,** Grade II. Anteroposterior radiograph of an 11-year-old boy with severe haemophilia, demonstrating normal cartilage interval, early joint surface erosions, widened epiphyses, and juxta-articular osteopenia. **C,** Grade III. Anteroposterior radiograph in an adult with moderate haemophilia. The medial compartment has surface irregularity, subchondral cysts, reactive sclerosis, and partially narrowed cartilage interval. **D,** Grade IV. Anteroposterior radiograph in a severe, adult hemophiliac with complete loss of cartilage interval, extensive surface erosions, a large synovial cyst, tibiofemoral subluxation, and lateral subluxation of the patella.

- Delaying prophylactic treatment can result in a definite deterioration in radiological scores for every year after the first joint bleed *(Fisher et al, Blood, 2002;99:2337-2341).*

- More than half the MRI findings were not present on plain radiographs *(Manco-Johnson et al, NEJM 2007;357:535-544).*

CASE STUDY 1

- Male patient born 15/6/2000.
- Lives Sunshine Coast.
- Recurrent bleeds into left knee.
- Has had high levels of Factor VIII inhibitor with undetectable levels of intrinsic factor VIII.
- Left leg shortening and pain.

Lab No	Time/Date	F8	F8I	F8RF	F8BU	F8DD	HPCOM		
41652-1433	c 13:26 17-Jun-09	<0.01 L	60.00	34.00	1.50	1/40	####		
41483-7749	c 09:10 28-Apr-09	<0.01 L	52.00	63.00	0.65	1/80	####		
39822-4278	c 09:30 08-Jan-09	<0.01 L	78.00	51.00	0.98	1/80	####		
37444-9127	c 13:05 07-Jul-08	<0.01 L	480.00	42.00	1.20	1/400	####		
35745-7700	c 10:15 16-Apr-08	<0.01 L	1024.00	33.00	1.60	640	####		
35834-0985	c 12:50 15-Feb-08	<0.01 L	2960.00	27.00	1.85	1600	####		
34391-6946	c 08:00 01-Nov-07	<0.01 L	3328.00	40.00	1.30	1/2560	####		

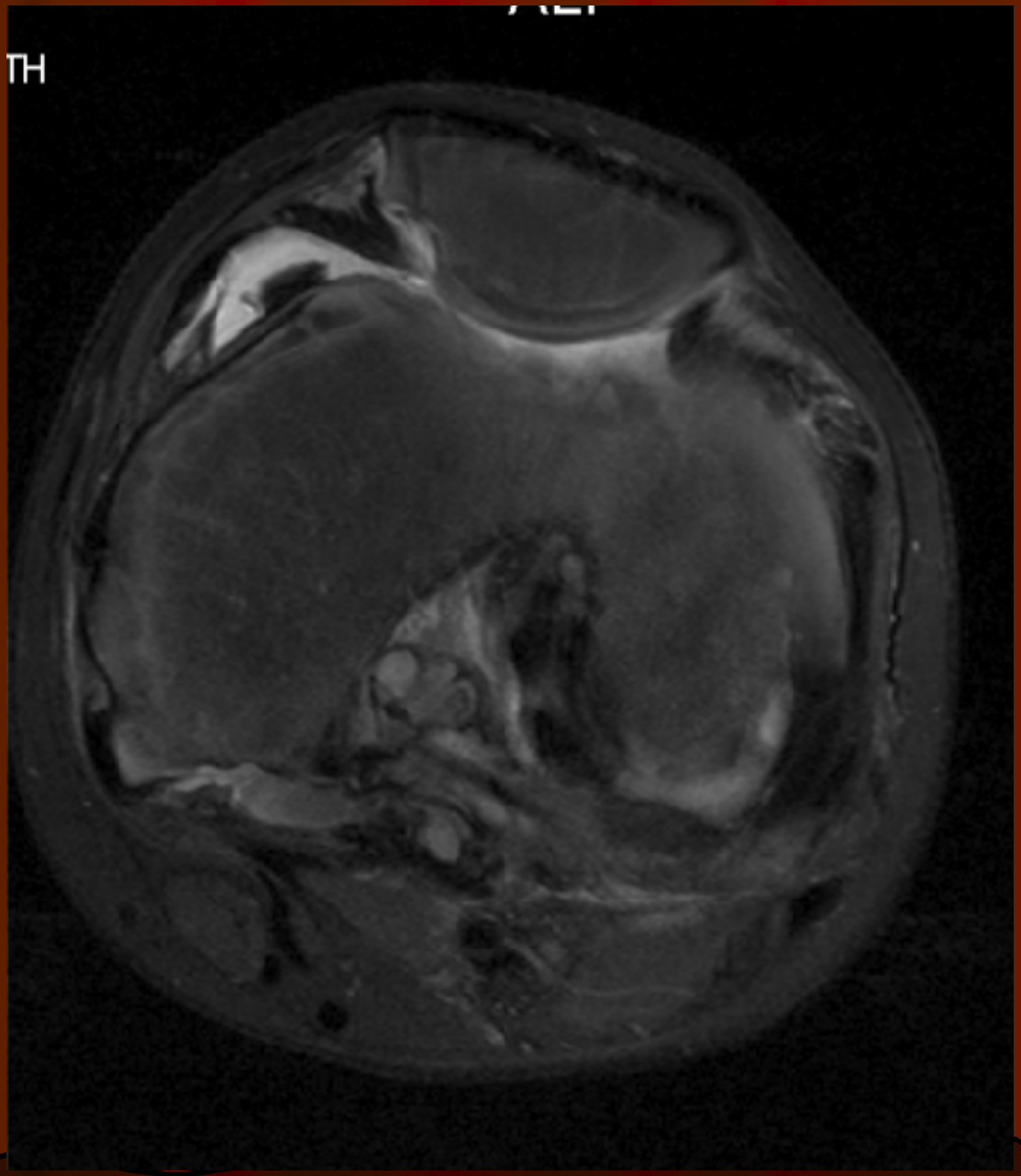
Haemophilia Comment

Factor 8 and Factor 8 Inhibitor assays performed on heparin neutralised sample.

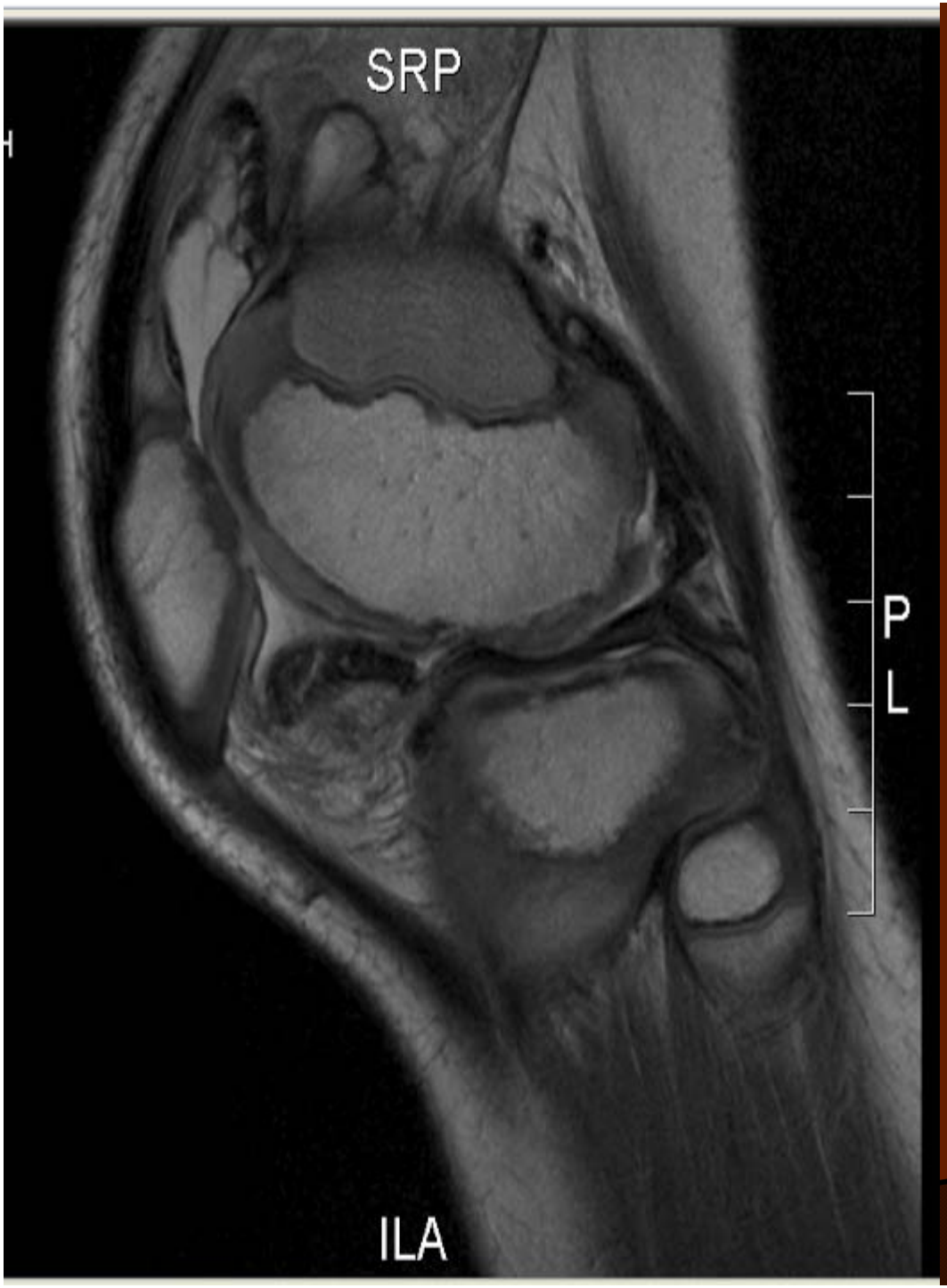
Clinical Notes

Haem A. Inhibitor undergoing taler

F5 Shift Left F6 Shift Right F7 Graphics F8 Cumulative Type SF7 Full Print



Diffuse synovial thickening with haemosiderin deposition. The synovium is up to 4 mm in thickness. There is loss of cartilage at the weightbearing surface of the medial and lateral femoral and tibial condyles. The cartilage loss involves the growth plate. Squaring of the epiphyses is noted. Cartilage loss also involves the patella facets.


SRP
P
L
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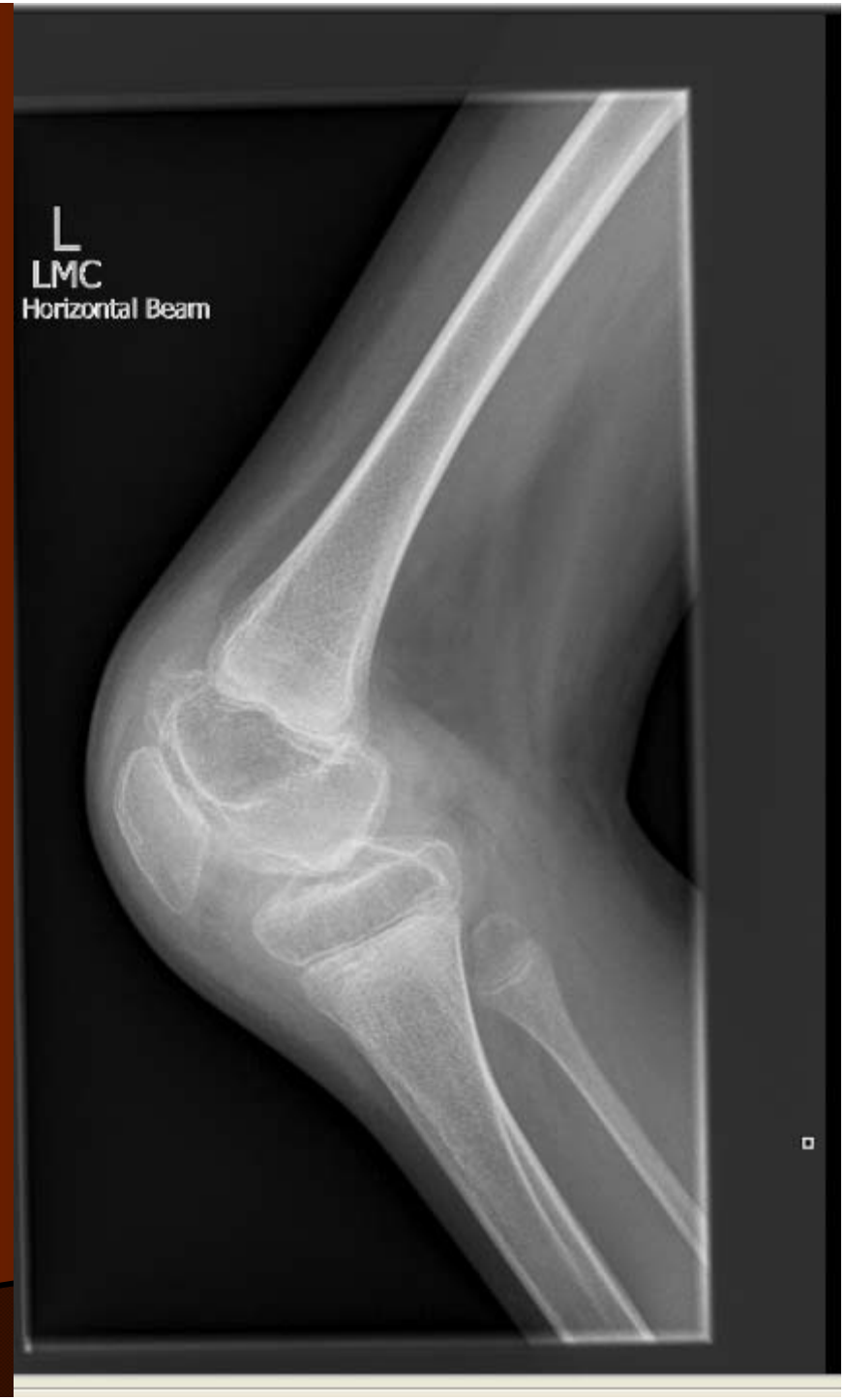

L
LMC
Horizontal Beam

Management

Standard of care:

- Factor VIII concentrate prophylaxis.
- Anti-inflammatories (care with use).
- Local and systemic steroids.
- Local ice applications with semi-rigid bandages and a soft heel.
- Physiotherapy – trying to preserve range of movement, protect joint from further injury and bleeds and maintenance of muscle strength.

Current options

- About 15% of factor VIII deficient patients and a smaller percentage of factor IX-deficient patients develop clotting factor inhibitors.
- These patients need to have non-surgical methods of treating their haemophiliac arthropathy.
- Haemarthrosis in the undamaged joint is treated with aspiration, restorative physical therapy, and possibly splinting.
- In the later stages, aspiration of the joint is for pain relief and improved range of movement.

Remember referred pain from bleeds elsewhere

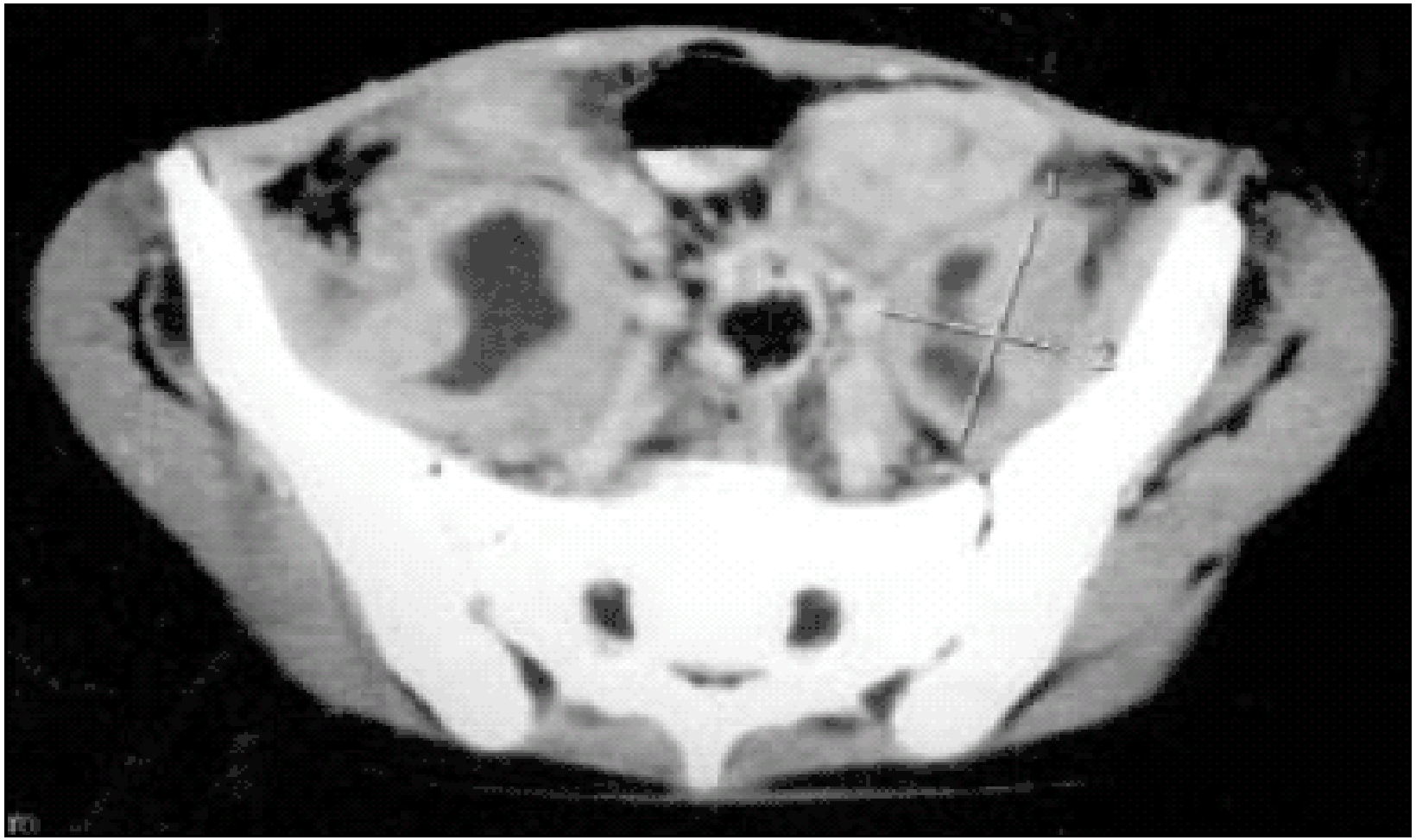
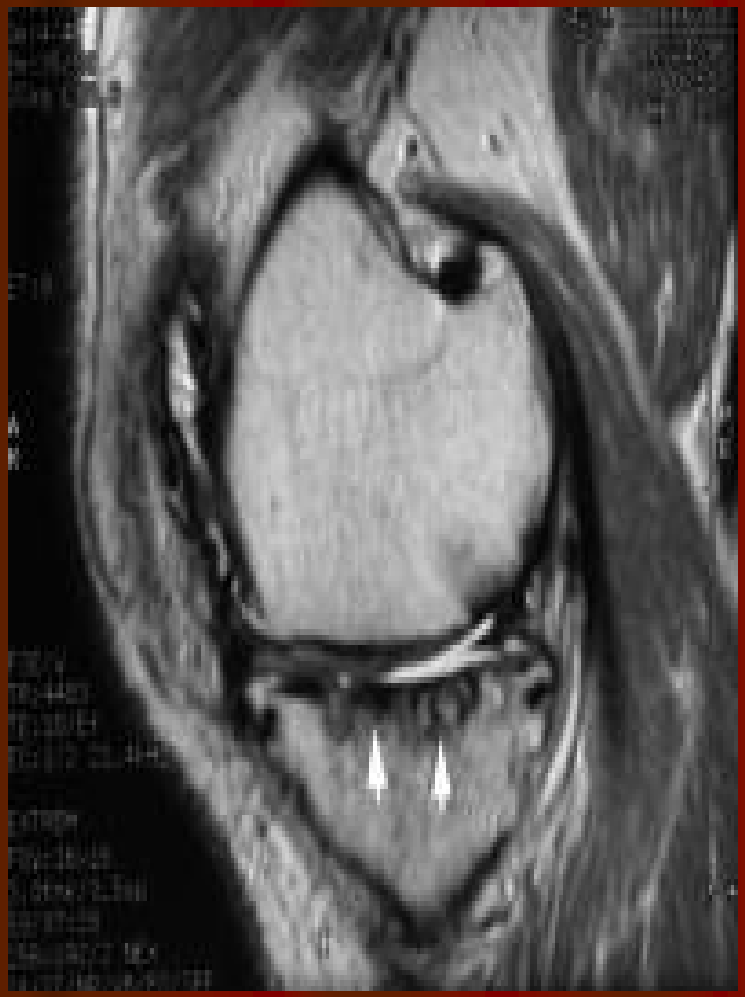


Fig. 1: Axial CT scan through the pelvis showing enlarged psoas muscles with central areas of fluid density.



Synovial masses can erode cartilage to produce subchondral cysts

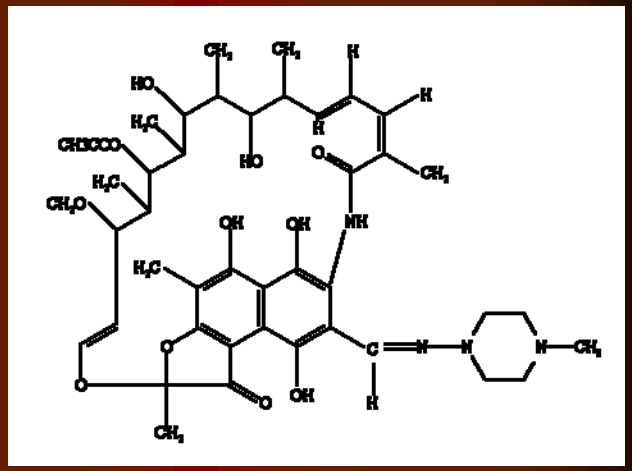
Options of treatment

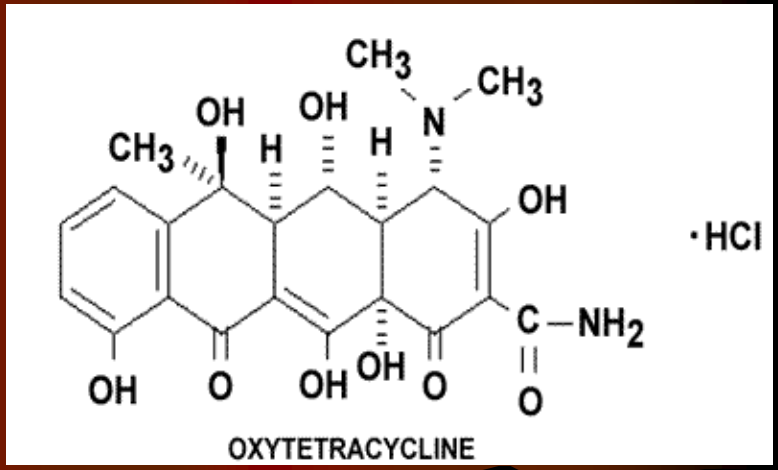
- Synovectomies:
- - chemical
- - arthroscopic

- Joint debridement
- Joint fusion
- Joint arthroplasty

Chemical synovectomy

- Osmic acid – potentially good but inferior results to Yttrium-90 (Ayral et al. Haemophilia,2001;Suppl 2:20-25)
- Other agents include Rifampicin, Oxytetracycline but up to 1-3 injections weekly (Gilbert and Radomisli. Clin Orthop Rel Res 1997;343:88-92).





OXYTETRACYCLINE

Radionuclide synovectomy (RS)

- The following have been used in haemophiliac arthropathy - Gold 198Au, Yttrium 90Y, Phosphorus 32P and Dysprosium (160D).
- The first published clinical report of radionuclide injection into joints, was in 1924. The introduction of colloids containing Yttrium-90 was in 1968.

PRINCIPLES OF RADIOSYNOVIORTHESIS

- A β-emitting radiocolloid is injected into a joint and the particles are phagocytosed by synovial lining cells.
- The β-energy released effectively triggers an active irradiation of the surrounding synovial tissue. A vasculitis results from the radiation effect which occludes the microvascular supply to the synovium. This decreases both fluid secretion and intra-articular pressure.
- The cytokine and enzyme levels within the joint decreases as there are fewer cells capable of releasing these agents. This reduces cell recruitment and proliferation. This can eventually result in a sclerosed and fibrotic synovial membrane.
- Concerns of leakage and chromosomal aberrations. No unexpected events have been noted over a 20 year follow-up of 1500 RA joints with Y-90.(Grove, 1995)

Radiosynovectomy agents

Radiopharmaceutical	Half-life (days)	Range in soft tissue (mm)
Au-198	2.7	1.2-3.6
Y-90	2.7	3.6-11.0
P-32	14	2.6-7.9
Dy-165	0.1	1.8-5.7

Siegel et al. J Am Acad Orthop Surg 2004;12:55-64

Radiosynovectomy in patients with Haemophilia

Study	No of treated joints	Radio-Pharmaceutical	Follow-up(years)	Joints with >75% decreased incidence of bleeding (%)
Merchan et al	38	Au-198	13-15	89
Dawson et al	34	Y-90	1	76
Rivard et al	92	P-32	1-15	78
Siegel et al	44	P-32	0.5-3	78
Fernandez-Palazzi et al	50	Au-198	10	69
Lofqvist et al	19	Au-198	1.5-15	58
Rodriguez-Merchan et al	67	Au-198	14	100
Siegel et al	125	P-32	2-10	82

Siegel et al. J Am Acad Orthop Surg 2004;12:55-64

Key management strategies

- In Grade 1 and 2 changes – stop the bleeding, reduce the volume of the synovium and re-establish ROM and muscle strength.
- In Grade 3 – consider synovectomy.
- In Grade 4 – treat pockets of synovitis.

Arthroscopic synovectomy

Second line of treatment because of:

- Surgical amounts of clotting factor replacement
- Extensive physiotherapy
- Hospitalisation
- Surgical expertise

- However does have access to majority of joint and allows remodelling of soft tissue lesions e.g. meniscal tears, chondral lesions.

Remember that not all MSK problems are related to Haemophilia

- 27 year old male with Haemophilia B.
- Previously known to be Hepatitis C positive(1990) but undetected Hep C RNA in 2001.
- 3 month history of inflammatory pain and swelling in legs.
- Inflammatory low back pain.
- Taking Nurofen-Plus with some relief of pain.
- Examination showed dactylitis and tenosynovitis of feet and legs.
- ESR 78

Diagnosis and Progress

- HLA-B27 associated tenosynovitis secondary to chlamydia urethritis.
- Difficult to control symptoms partially because of inability to use Indomethacin and partially due to distance travelled (from Tweed Heads).
- Started on Sulphasalazine.
- May need cortisone injection for plantar fascia under factor concentrate cover.

Thank you

Victoria and Albert with Alfred, Bertie, Alice, Vicky and Helena