Diabetic foot.

Definition.
A group of syndromes in which neuropathy, ischaemia and infection lead to tissue breakdown resulting in morbidity and possible amputation (WHO 1995).

Epidemiology.
10% of the population over 65 has diabetes and this number is increasing. 15% of patients with diabetes will develop a foot ulcer. Foot complications are the commonest reason for hospitalisation of diabetic patients. 14 – 25% of those with a foot ulcer will eventually require an amputation. Diabetes accounts for 60% of all amputations. Over 10 years, 5.4% of Type I diabetics and 7.3% of Type II diabetics will require an amputation (Moss SE 1996).

Pathology.
Non-occlusive anatomic and physiologic abnormalities are found in the microcirculation of diabetic patients which together with neuropathy and an impaired immune system leads to high rates of lower limb infections. There is also an increased risk of macro vascular atherosclerotic disease with a greater propensity for occlusive arterial disease of the distal popliteal and tibial arteries with relative sparing of the arteries in the foot. Calcification of the arterial media is common. There is thickening of the capillary basement membrane which impairs leukocyte migration and may cause tissue hypoxia. The charge on the basement membrane is altered which leads to albumin leakage from capillaries. Endothelium dependant vasodilatation is impaired in diabetics. This may be a result of over production of oxygen free radicals. Administration of Vitamin C, an oxygen free radical scavenger, restores and improves endothelium dependant vasodilatation in diabetics.
Platelet abnormalities are seen in diabetics with increased thromboxane release and increased aggregation. There are also elevated fibrinogen levels.
Transcutaneous pO_2 of diabetics presenting with foot ulcers is usually higher than non diabetics with foot ulcers. Thus there may be no rational for the use of hyperbaric oxygen.
Polyneuropathy involves the autonomic and somatic systems. Autonomic neuropathy results in shunting of blood through arteriovenous connections in the microcirculation, leading to ineffective tissue perfusion. Autonomic neuropathy also leads to drying of the skin. Normally when sensory fibres are stimulated, substance P is released from nerve endings, which triggers mast cells to release histamine. This process is attenuated in diabetics and may contribute to the reduced inflammatory response to foot infection. Motor neuropathy leads to dysfunction of the small muscles of the foot. The metatarsals become flexed and toes drawn up – claw toe. There is also an increased cavus deformity of the arch of the foot. These create pressure points below the metatarsal heads and tips of the toes. Sensory neuropathy diminishes awareness of pressure points by reduced pain sensation. Sensorimotor neuropathy initially involves the distal lower extremity and progresses centrally. The neuropathy is usually symmetrical.
Neuropathic ulcers, the most common type in diabetic feet, result from tissue damaging mechanical loads applied to an insensate foot.
Micro vascular disease results from loss of autoregulatory function with impaired hyperaemic response to heat and inflammation.

Wound healing and its impairment in the diabetic foot.
There are four phases to wound healing:
1. Coagulation – needed for haemostasis and wound protection. Platelets become activated and degranulate releasing growth factors.
2. Inflammation – neutrophils and macrophages, whose function is impaired in diabetics, aid in wound debridement.
3. Migration/proliferation – excessive deposition of some matrix proteins e.g. collagens and fibronectin, has been reported in diabetics.

4. Remodelling

Microcirculatory abnormalities in diabetics include decreased capillary size, thickening of the basement membrane and arteriolar hyalinosis. The thickened basement membrane leads to altered diffusion and leukocyte migration. Impaired endothelial function may be due to reduced nitric oxide synthetase.

Diabetic ulcers appear to be stuck in the proliferative phase. Wound debridement may restart to wound healing process.

Clinical findings.
Infection – The clinical definition of infection is the presence of purulent secretions or at least two of erythema, warmth, tenderness, pain or induration. The inflammatory response is blunted in diabetics with diminished erythema, induration and oedema.
With infected ulcers tissue specimens should be obtained for culture. The infection is often polymicrobial. Commonest organisms – staph, enterococcus, streptococci, pseudomonas, proteus, E. coli.
Osteomyelitis – Osteomyelitis is present if bone is visible or palpable on probing. Metal wound probe has a 90% positive predictive value. Other investigations - X ray, bone scan, MRI. Surgical excision of infected bone is always required to achieve healing. An ESR above 70mm/h also suggests bone infection.
Ischaemia – absent pulses
Neuropathy – vibration and proprioception are the first to go. Vibration is tested with a 128 Hertz tuning fork on the dorsum of the great toe. There are also absent ankle reflexes and sensory loss as assessed by 10 gram monofilament.

The initial assessment must try to differentiate between neuropathic and ischaemic foot lesions. MRI may help differentiate between neuropathic osteoarthropathy (Charcot foot) and osteomyelitis.

Neuropathic ulcer	**Ischaemic ulcer**
Painless	Painful
Normal pulses	Absent pulses
Regular margins, punched out appearance	Irregular margins
Plantar surface of foot	Toes
Presence of calluses	Callus absent
Loss of sensation, vibration and reflexes	Variable sensory findings
Increase blood flow due to AV shunts	Decreased blood flow
Dilated veins	Collapsed veins
Dry warm foot	Cold foot
Bony deformity	No bony deformity
Red appearance	Pale cyanotic

Charcot foot (osteoarthropathy).
This is an exaggerated inflammatory response to any cause of inflammation e.g. soft tissue injury, osteomyelitis, fracture, surgery. It results in increased osteoclastic activity. It may be suppressed by tumour necrosis factor (TNF) antagonist e.g. Infliximab. Can also try bisphosphonates or calcitonin.

Treatment.
The largest study on antibiotic treatment of diabetic ulcers showed similar efficacy for ertapenem and piperacillin/tazobactam. Sever infections require 2 to 3 weeks of treatment, except when the infected bone has been excised when one week should suffice.
Gentamicin impregnated collagen (Collatemp G) may be useful.

Dermacyn – a superoxide solution for wound cleansing, applied directly to wound.
Continuous antibiotic infusions are better than intermittent infusions.
Linezolid or Dartomycin for MRSA.
Silver or iodine based dressings may be helpful.
Ultrasound debridement is claimed as being good for debriding diabetic foot ulcers. It seems to work by causing cavitation. Claims of induced angiogenesis, decreased oedema, triggering of mast cell degranulation, 99% effective at killing bacterial spores and that it may help break down bacterial biofilm have been made. Some claim that it requires a GA but others say it can be done after EMLA application.

Non surgical treatments.
Vitamin C – improves endothelial vasodilatation.
Aspirin – improves platelet function.
Nutritional supplements can provide zinc and Vit C to aid wound healing (Cubitan). Arginine has also been shown to be useful with pressure ulcers (Desneves Clinical Nutrition 2007). Arginine is a substrate for protein synthesis, collagen deposition, cell proliferation, T lymphocyte function and is a precursor of nitric oxide. Resource® Arginaid® (Novartis) contains 2100kJ (500kcal), 21g protein, 500mg Vit C, 30mg zinc and 9g arginine.

Maggot therapy seems to be effective for debridement and acceleration of healing. Mayan Indians wrapped wounds with a dressing made from sun exposed beef that would pulsate, apparently with maggots. Ambrose Pare, chief surgeon to Charles IX and Henri III of France used maggots in war wounds. It might reduce antibiotic use and the risk of amputation. Necrotic, suppurative, draining, gangrenous wounds are best suited to larval therapy. The most commonly used maggots belong to the family Calliphoridae, specifically Lucilia sericate (greenbottle blowfly) and Phormia regina (blackbottle blowfly). These only feed on necrotic tissue. The family Sarcophagidae (flesh flies) and the species Cochliomyia hominovorax (screw worm) should be avoided as these devour living tissue. The mechanism of action includes secretion of proteolytic enzymes which liquefy the necrotic tissue, ingestion of the tissue by the larvae, physical presence of the larvae increasing exudate from the host which washes out the bacteria, bacteria being ingested and killed by the larvae and the crawling action of larvae stimulating granulation tissue. Maggots are good for MRSA infections.

Patients should be councilled never to walk in the same shoes that caused the foot ulcer. Pressure relief on ulcers is important. Total contact casts can lead to rapid ulcer healing. These should be changed weekly.

Achilles tendon lengthening can also reduce ulcer recurrence rates.

The main purpose of surgery is to remove infected and necrotic tissue back to a healthy base that will support granulation tissue and allow healing by secondary intention. All infected bone should be excised.
Many diabetics will require revascularisation to allow adequate healing. Bypass to a patent dorsalis pedis artery gives best results in terms of wound healing. Restoration of pulsatile flow to the foot is the aim of revascularisation. Angioplasty is a further option.

Systemic review of antimicrobial agents for chronic wound (O'Meara BJS 2001).
Systemic agents – Amoxycillin plus clavulanic acid (Augmentin) did not improve wound healing. Clindamycin and cephalexin did not improve wound healing.

Hyperbaric oxygen therapy (HBOT) for chronic wounds.

HBOT has antimicrobial effects and increases oxygenation of hypoxic wounds. This may enhance the neutrophil killing ability, stimulate angiogenesis and enhances fibroblast activity. So there may be improved ulcer healing rates in diabetics but amputations rates are unchanged.

Cochrane review October 2003 - Diabetic foot ulcer - Pooled data from 3 trials (118 patients) showed a reduction in the risk of major amputation when adjunctive HBOT was used, compared to the alternative therapy (RR 0.31, 95% CI 0.13 to 0.71, NNT = 4, 95% CI 3 to 11). There was no significant difference in minor amputation rate (pooled data of two trials with 48 patients). Healing rates were reported in one trial (Abidia 2003) which showed a improvement in the chance of healing 1 year after therapy (RR for failure to heal with sham 2.3, 95%CI 1.1 to 4.7, P = 0.03), although no effect was determined immediately post HBOT, nor at 6 months. The authors concluded that in patients with diabetic foot ulcers, HBOT significantly reduced the risk of major amputation and may improve the chance of healing at 1 year. The application of HBOT to these patients may be justified where HBOT facilities are available, however, economic evaluations should be undertaken. In view of the modest number of patients, methodological shortcomings and poor reporting, this result should be interpreted cautiously however, and an appropriately powered trial of high methodological rigour is justified to verify this finding and further define those patients who can be expected to derive most benefit from HBOT.

Apligraft.

A bioengineered skin substitute composed of living fibroblasts and keratinocytes derived from neonatal foreskin combined with type 1 bovine collagen. Apligraft resembles human skin histologically, makes proteins and growth factors and if wounded, can heal. It may speed up wound healing but evidence of benefit is limited.

Painful diabetic peripheral neuropathy.

Gabapentin is good. Duloxetine (60mg or 120mg per day) is also useful – NNT = 6 (Sultan BMC Neurology 2008).