day. The optimistic forecast varies from three to five years, but many transplanters doubt that success can be expected within the decade.

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Intraoperative use of thrombolytic agents

Should be available in every hospital treating acute limb ischaemia

Thrombolysis is an important advance in the treatment of acute limb ischaemia, and most district general hospitals now use the technique.[1] The changing pattern of acute leg ischaemia partially explains the method's popularity. Patients no longer present with simple emboli and normal underlying vessels; they are elderly and frequently affected by severe atherosclerosis. Acute ischaemia increasingly results from thrombosis in situ, a condition in which balloon catheter embolectomy merely adds further intimal damage and is rarely successful.[2] Urgent surgical bypass is the conventional treatment for acute thrombosis, but the operations are long and complex. In selected cases thrombolysis is an excellent alternative: peripheral thrombolysis is suitable for half the cases of acute leg ischaemia, and new bolus infusion techniques may extend the indications still further.[3]

Some patients, however, have an ischaemic neurosensory deficit that is too profound to permit time for peripheral thrombolysis, and some occlusions are still beyond the reach of percutaneous catheters. Some hospitals still do not provide a thrombolysis service, especially "out of hours."[4] In these cases surgical exploration with intention to perform embolectomy or distal surgical bypass is usually undertaken. When the thrombus is inaccessible or irremovable a short bolus infusion of a thrombolytic drug given intraoperatively has proved safe and effective at restoring patency.[5]

The technique entails instilling 100 000 units of streptokinase into the distal vessels over 30 minutes. The streptokinase is mixed in 60 ml isotonic saline and infused through a catheter with a syringe driver set at 99 ml/h with the arterial inflow clamped. Alternatively, the streptokinase may be mixed in 100 ml isotonic saline and given in five 20 ml boluses at five minute intervals. Unlike in peripheral thrombolysis, inserting the infusion catheter directly into the clot is unnecessary as the inflow is occluded and a high local concentration is automatically achieved. If intraoperative thrombolysis is used in addition to femoropopliteal bypass for thrombosis or popliteal aneurysm the proximal anastomosis can be completed while the infusion is running. The technique can be used during explorations of either the femoral or popliteal artery. When used after failed femoral embolectomy it has the advantage of avoiding the need for direct popliteal artery exploration.

Problems associated with streptokinase, such as allergy or haemorrhage, have not been reported after this procedure. There is little alteration in coagulation, and bleeding is unusual even if fasciotomy is subsequently necessary. Other thrombolytic agents such as urokinase and tissue plasminogen activator may be used.[6,7] Lysis may be faster with tissue plasminogen activator, though it is considerably more expensive. Tissue plasminogen activator is specifically indicated in patients previously exposed to streptokinase, an increasing number after its use in acute myocardial infarction. No specific postoperative anticoagulation regimen has been advised, but it is wise to use heparin, at least in low dose, until hospital discharge, followed by warfarin or antiplatelet treatment, depending on the clinical situation.

Intraoperative thrombolysis is an option whenever thrombus cannot be removed surgically. There are three settings where it has proved useful. The first is when substantial residual thrombus is present, which routine intraoperative arteriography shows happens after up to 30% of femoral embolectomies.[8] Even if arteriography is not available, clinical failure of embolectomy to restore the circulation is an indication that further treatment is required —accepting failure of an embolectomy without exploring other options is no longer permissible. When on table angiography shows residual thrombus, treatment with intraoperative streptokinase improves the run off in three quarters of patients.[9] Even if the thrombus is not lysed it may become less adherent, and repeat embolectomy may retrieve further clot. A second infusion of streptokinase is occasionally beneficial, or, failing this, it is sometimes possible to leave a catheter in situ for postoperative thrombolytic infusion, particularly if distal tibial vessels are involved.[10]

The second indication for intraoperative thrombolysis occurs when distal tibial vessels are thrombosed secondary to femoropopliteal thrombosis (including grafts) or acute occlusion of a popliteal aneurysm with distal embolisation. Instilling streptokinase to the run off can improve the chances of a successful femoropopliteal bypass unless distal obstruction is due to chronic atherosclerosis.[11] The combination of urgent surgical bypass with intraoperative thrombolysis may well become the treatment of choice for acute thrombosis of a popliteal aneurysm.[12] The third indication for intraoperative streptokinase is after distal embolisation during arterial reconstructive surgery or angioplasty—the "trash foot syndrome." Successful thrombolysis in this case is less certain and depends on whether the material that has embolised is atheroma or thrombus.[9]

Rigorous evaluation awaited

Rigorous evaluation of intraoperative streptokinase has yet to happen: surgeons who use the technique should develop methods of evaluating their results, such as measuring peripheral resistance or blood flow rates in addition to angiography. Newer techniques, such as isolated limb perfusion, in which a high dose of urokinase is infused into a limb with the circulation occluded by tourniquet, merit further investigation.[5,13] Although intraoperative thrombolysis cannot replace a planned approach with angiography and reconstruction in acute on chronic ischaemia, it has considerable

advantages in various vascular emergencies and can safely and effectively solve difficult clinical problems.

We wish to thank Raye Workman for her help in the preparation of this manuscript.

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The fish odour syndrome

The problems are psychosocial

The fish odour syndrome is characterised by an offensive body odour of rotting fish and abnormal excretion of trimethylamine in the breath, urine, sweat, saliva, and vaginal secretions. Since its recognition in 1970[1] some 35 cases have been reported, the largest series being that of Ayesh *et al* (p 655).[2,3] The smell is usually apparent in childhood, although it may be noticed first in infancy[4] or adulthood. It may be intermittent, and puberty, sweating, menstruation, and a high dietary intake of sea fish or foods rich in choline exacerbate the smell.

Three cases have been described in patients with serious physical disabilities,[1,2,5] but these were probably chance associations. All other patients with the condition have been healthy; their problems have been psychosocial.[6] Most have had low self esteem. Some were ostracised or ridiculed at school. Schoolwork suffered, and they became lonely and withdrawn. Those unable to detect their own odour had added anxiety.[3] Diagnosis was often delayed because doctors were unaware of the condition.

The underlying problem is a reduced ability to oxidise trimethylamine, an amine derived from the diet. The two major sources of this compound are choline and trimethylamine oxide, which is present in many salt water fish. Bacterial degradation of these precursors in the bowel releases trimethylamine, which is readily absorbed from the gut and, normally, oxidised almost completely by the liver to trimethylamine N-oxide. This compound is excreted by the kidneys and does not smell. The combined urinary excretion of trimethylamine N-oxide and trimethylamine of normal adults is around 40-50 mg a day, with more than 90% as the oxide.[3,7] In the fish odour syndrome the oxidation of trimethylamine is impaired.[3] Unoxidised trimethylamine is increased in urine, breath, sweat, and other secretions, causing the fishy smell.

Reports of trimethylaminuria include pairs of siblings,[3,4,8] suggesting that the defect is inherited. Smith *et al* have now investigated five affected families.[3] On a normal diet all the asymptomatic parents had normal urinary excretion of trimethylamine and trimethylamine N-oxide and no body odour. When stressed with an oral load of 600 mg trimethylamine, however, all showed reduced oxidising capacity. These results indicated carrier status for the defect and are strong evidence that it is an inherited autosomal recessive condition. From a study of 169 healthy volunteers a carrier frequency in Britain of at least 1% was proposed.[7]

The molecular defect is unknown. Trimethylamine is oxidised by liver microsomal mono-oxygenases containing flavin. These have broad specificity and also catalyse the oxidation of many pesticides, foreign compounds, and drugs.[9] The oxidation of trimethylamine has been studied in liver from only one affected patient. The oxidation system was defective, with a K_m for trimethylamine five times greater than normal.[10] Better understanding of the condition may come from genetic studies of flavin coding mono-oxygenases.[11-13] Further work is needed to define the relation between the various isoenzymes of these oxygenases and their relative importance in oxidising trimethylamine and to pinpoint the defect in trimethylaminuria.

The disorder is diagnosed by showing increased free trimethylamine in urine, with reduced trimethylamine N-oxide. Common problems causing body odour—poor hygiene, gingivitis, urinary infections, infected vaginal discharge, advanced liver and renal disease—and rare, inherited organic acid defects with a characteristic but non-fishy odour should be excluded. Samples should be collected into strong hydrochloric acid during an exacerbation, with the patient taking a normal diet but without fish for 48 hours. The analyses are technically difficult, and in Britain are available only through interested research groups. Nevertheless, establishing the diagnosis is essential. Patients and parents are helped by understanding what is wrong. A low choline diet (avoiding eggs, liver and other offal, peas, and soy beans) with the exclusion of sea fish reduces the excretion of trimethylamine and sometimes, but not invariably, reduces the odour. Measures to minimise sweating help. Short courses of antibiotics active on the gut flora (for example, metronidazole or neomycin[3]) or lactulose[8] may allow some dietary relaxation for important social occasions.

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