

Regional conference in Sheffield

Advances and controversies in treatment

A College regional conference was held at the Post-graduate Medical Education Centre, Northern General Hospital, Sheffield in September 1995. The conference was designed to update physicians on a wide range of medical topics, and to discuss controversies that were pertinent at the time. The presentations were given by local and national experts, and were well received by the large audience.

Endocrinology

The management of thyrotoxicosis

Professor A P Weetman (Northern General Hospital, Sheffield) gave a résumé of the current management of thyrotoxic patients. It depends above all on establishing the correct diagnosis, whether primary or secondary. Graves disease should be treated, in all patients under 50 years, with a six-month 'block and replace' regime of carbimazole, followed by thyroxine once euthyroid status is reached. During pregnancy antithyroid drugs alone should be used, propylthiouracil being the drug least likely to cause adverse fetal side-effects. When the mother has thyroid stimulating receptor antibodies, the infant may become thyrotoxic one week after birth when levels of transplacentally transferred antithyroid drugs have diminished. Patients treated with antithyroid drugs should be given a written warning of their possible side effects. If agranulocytosis occurs, treatment with these drugs must be permanently discontinued; transient granulocytopenia, however, resolves spontaneously. Radioactive iodine is used in thyrotoxicosis relapses during treatment with antithyroid drugs, unless the patient is pregnant or breast feeding. The risk of genetic abnormalities is minute (0.002%), thus conception is safe from six months after radioiodine treatment. Although a small but significant increase in the incidence of stomach cancer is noted, the overall cancer rate is not increased. Thyroidectomy provides a rapid cure and is the treatment of choice in large nodular goitres before planned pregnancy, and for resistant thyrotoxicosis in pregnancy and children.

Rapporteurs:

A M ROBINSON, MRCP, Senior Registrar to Sheffield Hospitals

C L ADAMSON, MB, ChB, Clinical Research Fellow, Northern General Hospital, Sheffield

Fluid balance

Professor P Baylis (Royal Victoria Infirmary, Newcastle upon Tyne) summarised the factors influencing fluid balance. The pituitary secretion of vasopressin is controlled by both osmoreceptor and baroreceptor input integrated in anterior hypothalamic cells, although baroreceptor input usually plays little part due to minimal fluctuations in blood pressure. Osmoreceptors in the anterior hypothalamus are sensitive to serum sodium and are of two types, leading to an increase or decrease in vasopressin secretion with hyper- or hypo-osmolality respectively. Vasopressin secretion produces a maximum antidiuresis at a concentration of 4 pmol/l; any further increase in plasma osmolality then causes thirst and thus regulates fluid intake, but there is no further increase in the degree of antidiuresis. Drinking stops before osmoreceptors can adjust to lowered plasma osmolality because the mechanism of swallowing appears directly to inhibit vasopressin secretion. Polyuria may be due to a greater fluid intake, a small vasopressin release or a decreased renal response to vasopressin. Diagnosis may be made either by water deprivation or by measuring plasma vasopressin following an osmotic stimulus. Chronic hypernatraemia may be caused by an isolated osmoreceptor defect where both thirst sensation and vasopressin response to hyperosmolality are suppressed yet baroreceptor stimuli continue to elicit vasopressin secretion, or may be a result of resetting the osmoreceptors to a higher setpoint yet with otherwise normal regulation. In the former case patients are at risk from the effects of hypo- or hypernatraemia, while in the latter there is no increased risk.

Growth hormone treatment in the adult

Dr R Ross (Northern General Hospital, Sheffield) reviewed the effects of growth hormone deficiency and growth hormone therapy. Growth hormone deficiency in adults increases the amount of subcutaneous fat and is associated with decreased fat metabolism, poor muscular development, and impaired psychological well being [1], and a higher risk of cardiovascular death. The most common cause of growth hormone deficiency is pituitary tumour or its treatment; it is diagnosed by measuring growth hormone, insulin like growth factor-1 (IGF-1) and IGF-BP3 secretion but these rates are influenced by age, gender and nutrition. Thus to confirm the diagnosis of growth hormone deficiency an insulin stress test should be performed, or in the presence of known pituitary disease a deficit of one other pituitary hormone should be confirmed. Treatment with growth hormone lowers body fat and raises fat-free mass, but total bone mass increases only in subjects with child-birth-onset growth hormone deficiency; it improves the quality of life in perhaps 50% of patients. It is very expensive (£5,000 a year) and only 50% of patients

continue with long-term treatment due to the side effects. These considerations must be borne in mind when deciding whom to treat, at what dose and for how long, and how to monitor treatment.

Another use for growth hormone may be for protein-malnourished people whose nutritional state is an important predictor of survival. These people are growth hormone resistant and have high levels of growth hormone and low levels of IGF-1, yet some patients do respond to growth hormone treatment with an increase in IGF-1, a cumulative positive nitrogen balance [2] and a better clinical outcome.

Clinical advances

Small bowel transplantation

Small bowel transplants are needed in children with congenital bowel anomalies or volvulus, and in adults with Crohn's disease or extensive bowel resection. Patients on long-term parenteral nutrition in the first year of life may develop cholestatic jaundice and will then require combined liver and small intestine transplantation. **Professor R F M Wood** (Northern General Hospital, Sheffield) described some of the challenges of small bowel transplantation. They arise because near perfect function must be obtained and complex immunological problems occur because the large amount of lymphoid tissue provides the potential for graft-versus-host-disease (GVHD), as well as rejection. Extensive migration of host T lymphocytes five days after transplantation leads to an early rejection reaction, and the migration of graft T lymphocytes to the host's Peyer's patches within 24 hours triggers GVHD. Cyclosporin A can prevent early rejection in the presence of continuing T lymphocyte migration, leading to stable chimerism. Before Cyclosporin A was available, mortality was mainly due to sepsis because of impairment of the intestinal barrier function, but now death after transplantation is caused by lymphoproliferative disease associated with cytomegalovirus infection and OKT3 usage. Of the seven small bowel transplant recipients in Britain, three are still alive. Further developments in immobilisation of both antigen recognition systems and cytokines must occur before small intestinal transplantation can become commonplace.

Interventional vascular radiology

Dr M Swarbrick (Royal Hallamshire Hospital, Sheffield) outlined some recent advances in interventional vascular radiology. *Arterial stents* used in occlusive disease become endothelialised *in situ*, thus reducing the risk of thrombus formation. They stabilise vessel walls and can be used for intimal flaps, dissection and small aneurysms, whereas angioplasty can weaken vessel walls and may induce distal thrombi. Stents cannot be used in small distal vessels because of

a high reocclusion rate but in proximal vessels they remain patent longer and have a lesser residual gradient than vessels treated by angioplasty. *Thrombolysis* can be used for critical limb ischaemia provided irreversible damage has not occurred. Lysis is successful in 40–78% of patients, however 51% have haemorrhagic complications which are mostly minor at the puncture site but severe in 5%. Death occurs in 1–2%, mostly due to cerebral haemorrhage. *Carotid angioplasty* is currently being studied at the Royal Hallamshire Hospital as part of the Cavitas Trial. Early results indicate that carotid angioplasty is relatively safe, can reduce stenosis to less than 50% and is clinically effective. *Endovascular management of aortic aneurysms* can be achieved by placing a covered stent within the body of an aneurysm. Although patients treated by the above procedures often have other health problems or limited life expectancy, the procedures are relatively non-invasive.

Adult respiratory distress syndrome

Dr T W Evans (Royal Brompton Hospital, London) discussed recent advances in the treatment of adult respiratory distress syndrome (ARDS). It is associated with a range of medical and surgical conditions, both pulmonary and extrapulmonary, and may vary from mild pulmonary oedema to dense inflammatory infiltrate, hypoxaemia and death. Pulmonary endothelial cells may be the target of inflammatory mediators, and subclinical endothelial damage also occurs in other organs. The aims of treatment are adequately to oxygenate the tissues and to provide multisystem support until recovery occurs. Continuous positive airways pressure (CPAP) is often adequate for respiratory support in mild cases although in more severe cases inverse ratio ventilation (IRV) or pressure controlled IRV causes less barotrauma. Extracorporeal membrane oxygenation (ECMO), intravascular oxygenation (IVOX), and the use of pulmonary surfactant to lower the pulmonary transfer coefficient, require further research before introduction into clinical use. Pulmonary hypertension is a significant cause of mortality in ARDS. In 50% of patients inhalation of nitric oxide has been found to lower local vascular resistance whereas intravenous vasodilators, including salbutamol, may adversely affect ventilation/perfusion. On withdrawal there may be a marked increase in vascular resistance and thus the side effects need to be further elucidated. Patients with ARDS secondary to trauma do well, but when it is associated with sepsis, mortality has remained high.

The Linacre Lecture

The role of matrix degradation in liver fibrosis

Professor M J P Arthur (University of Southampton) discussed the role of matrix degradation in liver fibrosis.

In cirrhosis, lipocytes proliferate. They are the predominant matrix-producing cells, forming collagen type I and III, with resulting fibrosis irrespective of the initial liver injury. Proliferation of lipocytes is mediated by platelet-derived growth factors produced by Kupffer cells, and by factors produced by hepatocytes undergoing apoptosis. The activated lipocytes produce monocyte chemotactic factor which is profibrogenic and increases mast cell response. As liver fibrosis progresses, interstitial collagenase activity diminishes so that there is less degradation of collagen I and III. Collagenase activation is also inhibited by the plasminogen activating system (PAS), components of which are expressed in lipocytes from injured but not from normal liver. Activated lipocytes also produce tissue inhibitors of metalloproteinase (TIMP) such as TIMP-1. TIMP is increased 4 to 5 fold in the sinusoidal lipocytes from fibrotic explants of human liver but there is no change in interstitial collagenase level. Thus liver fibrosis is a result of lipocyte activation and proliferation mediated by fibrogenic cytokines and other factors, with consequent alteration in matrix synthesis and degeneration. Current treatment of liver fibrosis includes removal of the stimulus, and anti-inflammatory drugs. Future therapeutic possibilities include inhibition of lipocyte activation, decreasing matrix synthesis, and enhancing matrix degradation; the last is Professor Arthur's preferred option.

Neurology

Movement disorders

Professor H Sagar (Royal Hallamshire Hospital, Sheffield) reviewed the recent changes in emphasis that have occurred in the treatment of Parkinson's disease. It is now thought that the cause is an environmental insult in patients with a genetic predisposition which leads to cell death in the substantia nigra. He dismissed the role of selegiline in the early treatment of the disease. He discussed the evidence that treatment with levodopa given as pulsatile treatment rather than as controlled release preparation is more likely to lead to motor complications. He suggested therefore that low-dose controlled release formulations should be used in the early part of treatment, followed by dopamine agonists as there is now some evidence that they might be neuroprotective. If fluctuations occur, the dose of levodopa should be increased until the patient is 'on'. To improve levodopa transport, selegiline and a high protein diet can be added. However, once complications have developed the mainstay of treatment is dopamine agonists. There is evidence that if one fails to produce desired effects, another should be tried; pergoline appears to be the most useful to date. The role of apomorphine was discussed, and although this drug still has to be given parenterally, it remains very useful for treating the on/off phenomenon; its therapeutic effect showed no fall-off

after a five year follow-up study; it can also be used if there is uncertainty about the diagnosis of Parkinson's disease. Future therapeutic possibilities include a role for surgery: pallidotomy may be useful for the treatment of akinesia and rigidity; thalamic stimulation may be as effective and is reversible.

Seizure disorders

Dr P Baxter (Sheffield Children's Hospital) discussed the problems of epilepsy from the patient's perspective. Patients with uncomplicated epilepsy have a poorer quality of life due to problems in gaining employment, restriction on driving and drug side effects. When the social progress of two children with similar IQs is followed, the one with epilepsy will fare the worse; this relates to prejudice at school, in particular lower expectations from teachers, who restrict patients' activities; also drugs such as vigabatrin and phenobarbitone may cause behavioural problems. Dr Baxter suggested that there should be no restrictions on childhood activity, drugs with adverse effects should be avoided and patients should be empowered to be more in control of their situation.

He also emphasised the need for specialist care, as it is important to make the correct diagnosis; to illustrate this point, he described Rolandic epilepsy which occurs in the morning in young teenagers but disappears by 16 years of age and does not require treatment, while Janz epilepsy is clinically similar but never remits and is made worse if treated with carbamazepine. Improvements in management may be expected from the newer drugs with fewer side effects and absence of drug interactions and the availability of controlled release preparations. Despite this improvement in the therapeutic options, he suggested that there was still a role for surgery in patients with intractable epilepsy.

Neuromuscular disorders

Dr R Petty (Royal Hallamshire Hospital, Sheffield) used *myasthenia gravis* as an illustration of autoimmune neuromuscular disorder, and showed how this model can be used to unravel other apparently autoimmune neurological disorders. Antibodies are pathogenic in the disease and reducing the antibody load should be the aim of treatment. Treatment would be aimed more specifically at antibody elimination, and animal models are being developed to produce antibody-generated antagonists against the autoantibody. In *Guillain-Barré syndrome* (GBS) patients with mainly axonal degeneration usually recover well while those with Miller-Fisher variant of GBS, an antibody against Gq16 is universally found in neuronal tissues. Its site of action is close to that of botulin toxin, which suggests that GBS has an autoimmune basis. This is further supported by a recent study in which treatment with

gangliosides inadvertently caused severe GBS in 7 out of 15 patients; these patients developed an IgG antibody to the ganglioside GM1 which has also been found in patients with previous campylobacter infection and axonal GBS.

The chronic inflammatory *demyelinating polyneuropathies* may also have an autoimmune basis, especially those 35% who have a monoclonal band in their blood; 60% of them have a severe sensory ataxia and an IgM band which binds to myelin associated glycoprotein (MAG), a component of myelin sheath. This ataxia responds poorly to steroids but can be treated with cyclophosphamide or chlorambucil.

Multifocal motor neuropathy with conduction block is a purely motor syndrome which mimics motor neuron disease but does not affect speech or swallowing and the EMG shows a patchy slowing of conduction. It is treatable with immunoglobulins, and probably has an autoimmune basis.

Cerebrovascular disorders

Dr G Venables (Royal Hallamshire Hospital, Sheffield) suggested that treatments aimed at primary prevention in high risk patients prevent only 5% of strokes. It is therefore important to develop therapy to reduce the immediate morbidity and mortality. At the onset of a stroke, a cascade of metabolic disturbances occurs which leads to cell death. It should be possible to interrupt this cascade at several steps and so reduce cell death. Lofarizine, an ion channel blocker, is presently being evaluated. So far, however, the only study to have shown an improved patient outcome was in patients treated in stroke units. Dr Venables felt it was beneficial to maintain the diastolic blood pressure below 110 mmHg, but due to impaired autoregulation of blood pressure following a stroke it might be more prudent to treat persistent mild hypertension later rather than during the acute event. Dr Venables said that there is no place for acute carotid endarterectomy, and aspirin does not improve outcome. The role of heparin is being evaluated at the present time in the International Stroke Trial. Studies on the use of thrombolysis in acute stroke have been stopped prematurely, but there may be a subgroup of patients who would benefit from this treatment. Haemodilution, calcium antagonists, steroids, praxilene, naloxone and glycerol have no place in the treatment of acute stroke.

Rheumatology

Early rheumatoid arthritis

Dr J Winfield (Nether Edge Hospital, Sheffield) described the present nation-wide study to determine the features of early rheumatoid arthritis of less than two years' duration which will be used to develop a rationale of when and whom to treat. Early results show the expected female predominance (2:1), with

an average age of 55. Nearly half the patients presented with an acute onset, but only a third initially had small joint involvement, while 17% (mainly elderly) presented with only large joint disease. Three years after the first patients were recruited, 47% have persistent disease, 14% have remitted, while the rest follow a relapsing/remitting course. There appear to be no predictive factors to date, the best indicator being the quality of life score. Most patients show an improvement in the first six months which is maintained for two years, but the disease then progresses. After the first year 95% of patients were on disease modifying treatment: sulphasalazine was the drug most often used, methotrexate was under-used at that stage of the study because its rise to prominence occurred later. Serious adverse drug events were few and all were reversible. However, overall mortality was higher than expected, mainly due to ischaemic heart disease. Although there were no deaths directly related to rheumatoid arthritis, nearly all the patients had lost at least four weeks' work due to the disease and a quarter had retired on medical grounds.

Why, when and how in the treatment of arthritis

Dr R Amos (Nether Edge Hospital, Sheffield) questioned previously published statements that rheumatoid arthritis is a mild disease. He suggested that such evidence had been based on population studies where few of the patients met all the necessary criteria for the diagnosis of rheumatoid arthritis. Most patients who do meet them will develop permanent joint damage and there will be an excess of deaths compared with the normal population. Patients with a normal acute phase response develop fewer erosions than those with a high response. Therefore the rationale for treatment must be to reduce the acute phase response. In this respect NSAIDs have no role, but can be used for symptomatic relief. The treatment of choice is the early use of disease modifying drugs that reduce the acute phase response as they are then better tolerated and more likely to affect outcome. Methotrexate is probably the most effective drug. If he himself had rheumatoid arthritis, Dr Amos would start sulphasalazine on day one, and add methotrexate after three months. There is no evidence to suggest that combining these drugs increases side effects and the drugs may work better together; finally, after five months he would add prednisolone at low dose. If the disease remits, the drugs should not be stopped as this would double the flare-up rate.

Nephrology

Drug induced renal disease

Dr A El Nahas (Northern General Hospital) reviewed the role of NSAIDs in renal disease by illustrating three cases, described as the good, the bad and the ugly.

These cases were based on the inhibiting effect of NSAIDs on prostaglandin activity; this prevents vasodilatation of the afferent arteriole and vasoconstriction of the capillary bed. The effects on the afferent arteriole can be beneficial in a young patient with chronic mesangiocapillary glomerulonephritis and heavy proteinuria. NSAIDs by their action on the arteriole can reduce proteinuria and slow the rate of decline of the glomerular filtration rate. However, NSAIDs given to a patient with chronic analgesic abuse and impaired renal function may precipitate acute or chronic renal failure because the kidney depends on the afferent vasodilatation to maintain glomerular filtration. If this is inhibited the glomeruli are under-perfused, and both prerenal failure and tubular necrosis can develop. Azapropazone appears to be the worst culprit. Improvement is likely in 90% of patients if the drug is withdrawn, but often four to six weeks of dialysis are required; full recovery occurs in only 50-70%. The third case illustrates the ugly side of the NSAIDs. The patient had congestive cardiac failure, intermittent claudication and was being treated with a diuretic and an ACE inhibitor. The patient was given a NSAID for arthritic pain and, due to unrecognised bilateral renal artery stenosis, developed acute renal failure secondary to afferent arteriolar hypotension. This is caused by the combined effect of the NSAID and ACE inhibitor. If the drugs are stopped, patients may improve, but often require dialysis for life. Such patients should avoid this combination of drugs if possible, but if that is not possible, renal function should be checked before and soon after starting the drug.

Update on lipid management

Professor L Ramsay (Royal Hallamshire Hospital, Sheffield) said that the Scandinavian Simvastatin Survival study [6] has convincingly shown that it is possible to identify patients who would benefit from having their total blood cholesterol level reduced by 25% from the starting point and so reduce their coronary heart disease risk. Because the benefit is apparent within two years, there should be no age barrier. Patients with other forms of macrovascular diseases are also at risk of coronary heart disease and should therefore also be aggressively treated if the total cholesterol is above 5.5 mmol/l. To assess the risk of coronary heart disease, a table could be devised relating to hypertension, left ventricular hypertrophy, smoking habits, presence of diabetes and age; it would then be possible to determine which patients should have their cholesterol measured, and at what level to treat it.

Clinical controversies

Are regular beta-agonists safe in asthma?

In this first of a series of debates concerning present controversies, the opponent was **Professor Anne**

Tattersfield (City Hospital, Nottingham). She opened by saying that there was no doubt that the right beta-agonist, given at the right time and in the right dose, could be life saving. However, the mortality peak in the 1960s coincided with the availability of isoprenaline over the counter, and since no other cause has been found it is presumed that this drug was responsible. The same case has been made for fenoterol which was associated with a mortality peak in New Zealand in the 1980s. This drug was also sold as a high dose formulation and again no other explanation has been found. There is some evidence that taking beta-agonists on a regular basis is less effective than taking them as required. When patients were changed from high dose beta-agonists to placebo and vice versa, more patients felt better on placebo than on treatment [3]. It has also been suggested that when beta-agonists are taken regularly their protective effect wears off and bronchial reactivity may increase. If the patient has poor lung function and little insight, this could prove to be a significant problem. In the case of long acting beta-agonists, Professor Tattersfield felt there was still some concern, although this was becoming less as experience grew. The early post-marketing surveillance of salmeterol has shown a non-significant three-fold increase in mortality. This needs to be followed-up as pharmacological studies with high doses of the drug have shown an increase in heart rate and a reduction in potassium levels. **Dr A Morice** (Royal Hallamshire Hospital) supported the idea that taking beta-agonists regularly is safe and that despite an increase in the sale of these drugs over the past few years, mortality from asthma has remained unchanged. He felt that if GPs educated their patients to use steroid inhalers more regularly and appropriately, then it was illogical but not dangerous to use regular beta-agonists. The problem in New Zealand could be due to the ethnic mix of patients living in a very rural setting who were less likely to seek help at the appropriate time. He quoted a study [4] which showed that regular salbutamol was better than taking it as required, and a meta-analysis of nebuliser studies suggested that this was a better form of treatment and was not associated with a higher mortality rate. However, in the subsequent debate Dr Morice said if a patient was *in extremis* and was given a nebuliser without oxygen, the patient's oxygen saturation could be further compromised and this would hasten his death.

Should everyone with angina or myocardial infarction have an exercise test?

Advocating the use of exercise tests **Dr K Channer** (Royal Hallamshire Hospital, Sheffield) said that the role of the physician in the management of ischaemic heart disease was to abolish symptoms and improve the patient's prognosis; the latter being the more challenging task. Surgery can benefit patients, but not all patients do well and it is therefore important to

identify who will benefit. The exercise treadmill test (ETT) does this by identifying patients with:

- greater than 3 mm ST depression which persists in the recovery phase
- exercise induced hypotension
- an early positive test
- symptomatic angina during the test.

Furthermore, if patients can complete the exercise protocol on the treadmill they have a better prognosis than those who only manage stage 1, especially if they have to stop because of chest pain. A group of patients can then be identified who require referral for angiography. On these criteria and with patients who have failed on medical treatment, it is possible to select a group of patients who will have a 90% intervention rate following angiography. Dr Channer then discussed the role of the ETT following myocardial infarction. He felt this was safe, prognostically useful and helped rehabilitation. **Dr G Oakely** (Northern General Hospital, Sheffield) opposed these views, pointing out that the question was whether *everyone* should have an exercise test. Many patients are physically incapable of performing an ETT adequately. A 60-year old man who smokes, has a positive family history and a non-specific ECG and is on quadruple therapy, should have an angiogram rather than await the results of an ETT. A negative ETT does not exclude ischaemic heart disease and correlates poorly with the pathology. In a recent study of patients after myocardial infarction [5] only 60% were able to undergo an ETT. Although the mortality was greater in patients with a positive test, the mortality in those who could not perform the test at all was four times higher again. Furthermore, most of the mortality occurred in the first 12 months which, in several hospitals, is the duration of waiting list time for angiography and surgery, and an ETT may delay this even more. However, the consensus was that an ETT appears to help the rehabilitation prospects of post-infarct patients, and should be part of their workup, if appropriate.

Endoscopy: too many, too few?

Dr S Riley (Northern General Hospital, Sheffield) reviewed the use of endoscopy over the previous years. The number of endoscopies has risen 8-fold since the 1970s, but the number of barium meals has dropped by only 40%. Endoscopy has several advantages because the patient's history is not very useful in making a diagnosis. The incidence of cancer is age-related and open access endoscopy for the over forties has increased the number of operable lesions. It was suggested that treating younger patients empirically would reduce the total number of endoscopies, but in response **Dr D Dawson** (Northern General Hospital, Sheffield) said that those patients that did have endoscopy, even if it was normal, were strongly reassured. Furthermore, early endoscopy leads to less sick leave and reduces drug treatment. Present figures show that there would not have to be a great increase in hospital resources to endoscope all patients referred by GPs, but this needs to be fully costed; and it may be possible, as already being tried in some centres, to employ nurse endoscopists.

References

- 1 Cuneo RC, Salomen F, McGauley GA, Sonksen PH. The growth hormone deficiency syndrome in adults. *Clin Endocrinol* 1992;**37**:387-97.
- 2 Miell JP, Taylor AM, Jones J, Buchanon CR, *et al.* Administration of recombinant insulin like growth factor-1 to patients following major gastrointestinal surgery. *Clin Endocrinol* 1992;**37**:542-51.
- 3 Sears MR. Prescribing of fenoterol and severity of asthma. *N Z Med J* 1990;**103**:21-2.
- 4 Chapman KR, Kesten S, Szala JP. Regular versus as needed inhaled salbutamol in asthma control. *Lancet* 1994;**344**:1379-82.
- 5 Gissi-3: the effects of lisinopril and transdermal glycerol trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;**343**:1115-22.
- 6 The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383-9.