Current controversies in therapeutics

A conference entitled ‘Current Controversies in Therapeutics’ was held at the Royal College of Physicians in January 1992. Its aim was to consider advances in areas where new drugs or new knowledge of pathophysiology require reassessment of existing therapies.

In her opening speech the President of the College, Professor Dame Margaret Turner Warwick, highlighted the importance of consensus statements on therapeutics, in setting standards for audit, and in improving the quality of care within the NHS. But she also pointed out that such ‘consensus’ is, at times, based on relatively poor knowledge, and that consensus statements may set therapeutics in stone and inhibit further development. There are also possible medicolegal aspects, as failure to implement such consensus may be seen as negligence. It is vital to be aware of the controversies and weaknesses surrounding such statements, and to steer a middle course between total lack of consensus and rigid agreement.

Cardiovascular disease

Heart failure—to stimulate, unload or betablock?

Dr H. J. Dargie (Western Infirmary, Glasgow) discussed the management of congestive heart failure, up to now largely dependent on diuretics to treat fluid retention. Recent trials have shown that, when given in addition to diuretics, enalapril, which inhibits angiotensin converting enzyme (ACE) and hence causes vasodilation, improves exercise capacity and decreases mortality from heart failure, in both severe and milder cases. This seems to result from a reduction in the rate of progression to more severe grades of heart failure. In these trials the adverse effects of the ACE inhibitors, until now a major disincentive to their use, were not a major problem and ACE inhibitors could be more widely used with confidence to treat heart failure in general practice. The use of inotropic agents in heart failure remains controversial: digoxin in atrial fibrillation is generally accepted (albeit on poor evidence), but its use in heart failure with sinus rhythm is still questioned, although meta-analysis of several trials suggests it is of benefit. Xamoterol, a beta adrenoceptor ‘modulator’, improved symptoms in mild cases of heart failure without fluid retention, but in practice it was associated with an increase in mortality, in part due to its use in patients with severe heart failure, for whom it was never intended.

Dr G. Jackson (Guy’s Hospital, London) considered the treatments which are of proven value in myocardial infarction, such as thrombolysis and aspirin, as well as other less-often-used therapies such as intravenous atenolol (currently used in only 15% of infarctions, although betablockers are more widely used in secondary prevention), and intravenous nitrates (particularly if there is congestive heart failure). Calcium antagonists, in contrast, may be harmful if given acutely, although verapamil may be useful as secondary prevention in selected patients. While the prophylactic use of anti-arrhythmic drugs was put in doubt by the CAST trial, amiodarone does decrease mortality in patients with post-infarct ventricular arrhythmias.

Early angioplasty after infarction may have a role in reperfusion if thrombolysis is contraindicated, but its routine use is associated with an unacceptably high mortality. ACE inhibitors given very early after infarct often cause hypotension, but delaying their administration until the third day may bring benefits by reducing dilation of the left ventricle.

Two points were raised in discussion: first, the possible benefits of intravenous magnesium after infarct, which Dr Jackson considers unproven and not to be used in preference to therapy of proven value; and second, that it is not yet clear whether combining two or more interventions would decrease mortality more than any one intervention.

The potential of ACE inhibitors

Professor P. S. Sever (St Mary’s Hospital Medical School, London) examined the use of ACE inhibitors as first-choice therapy in hypertension. Although there are theoretical advantages, trials of ACE inhibitors have looked only at surrogate end-points and not mortality, nor are there as yet adequate data on long-term safety. Meta-analysis of earlier trials of antihypertensives such as thiazides and betablockers have shown the expected degree of benefit from the treatment of hypertension on cerebrovascular accidents but less than expected on ischaemic heart disease. This traditional view is challenged by recent trials of the use of thiazides and betablockers in elderly hypertensive patients, which have shown a reduction in all cardiac events and mortality.

The recommendations of national and international hypertension societies are that the first-line drug should be (in the absence of contraindications) thiazides, or alternatively betablockers, particularly in patients with concomitant ischaemic heart disease. ACE inhibitors are appropriate where these drugs cannot be used and where they are not themselves contraindicated, as in peripheral vascular disease because of the risk of renovascular hypertension, or in fertile
female (teratogenesis) or black patients (less effective), and may be of particular value in diabetics where they may decrease microalbuminuria (as do calcium antagonists).

**Asthma**

**Beta agonists—saints or sinners?**

**Professor Anne E. Tattersfield** (City Hospital, Nottingham) examined the evidence that the regular use of inhaled beta agonists in asthma might be harmful. Studies from New Zealand suggested that fenoterol, a potent beta2 agonist given in high doses, was associated with a higher risk of dying from asthma than other beta agonists, but could not exclude that fenoterol may have been given selectively to patients with more severe asthma. In another study patients with intermittent rather than regular beta agonists had less morbidity despite effective bronchial dilation. This suggests that factors such as an increase in bronchial reactivity, or failure to seek other therapy, or cardiac arrhythmias, might be involved, or perhaps that beta agonists worsen asthma by overcoming a protective reflex. If fenoterol does indeed increase mortality in long-term use, it is unclear whether this might be a class effect common to other beta agonists, including the new long-acting beta2 agonists such as salmeterol. Professor Tattersfield counselled caution in advising major changes in prescribing, since despite 2,000 deaths from asthma per year in the UK, there are still 400,000 patients with asthma who do not die. Until we know more, major alterations in therapy are not justified.

**Steroids as first-line therapy?**

**Professor P. J. Barnes** (National Heart and Lung Institute, London) supported the view that inhaled steroids should be the first-line therapy in asthma, now that we understand asthma to be an inflammatory disease. A comparison of inhaled steroid with a beta2 agonist used as first-line therapy over two years showed a marked benefit for the steroid, with improved peak flow at all times of the day and fewer symptoms. However, it is not yet proven that inhaled steroids decrease mortality or even the long-term decline in pulmonary function seen in asthmatic patients. The adverse effects of steroids are worrying, in particular the increase in bone turnover. Steroids should be used in the lowest effective dose and with appropriate delivery systems, so that such problems are minimised. Other immunosuppressants, such as methotrexate, may also be increasingly used in the future.

**Consensus on asthma therapy?**

**Professor T. J. Clarke** (National Heart and Lung Institute, London) described the national guidelines on the management of asthma published in 1990 and the need to implement them in the community. He contrasted national differences in the management of asthma, comparing the UK with Japan where steroids are hardly ever used, North America where theophylline is still very popular, and parts of Europe where desensitisation is still widely used. (Unfortunately, he did not comment on national differences in outcome; eg the declared death rate from asthma in the US is considerably lower than in the UK. Does this represent a true difference in outcome or fashions in diagnosis?) The importance of self-management and training of patients in use of the inhaler devices, in the objective measurement of lung function, in recognising the symptoms in deteriorating asthma, and taking responsibility for their own treatment was emphasised.

**Neurological and psychiatric disease**

**Drug withdrawal in epilepsy—when and how?**

**Dr D. W. Chadwick** (Walton Hospital, Liverpool) discussed whether it is possible to stop antiepileptic therapy. In a trial, over 1,000 epileptic patients, free of fits for a mean of 3.2 years and mostly on single drug therapy, were randomised to either maintenance antiepileptic medication or drug withdrawal. Fifteen patients died during follow-up (only two during seizures, both on maintenance therapy). Patients on maintenance therapy had fits at a rate of 10% per year, in large part due to drug noncompliance. Patients whose therapy was stopped had a 35% recurrence rate for fits in the first year, but only 10% per year thereafter. Predictors of successful withdrawal were a long seizure-free period before the trial, shorter duration of therapy, and therapy with only one drug, all reflecting the severity of the epilepsy. The use of EEGs added nothing to these clinical indicators. An unselected group of epileptic patients were asked whether they wished to stop therapy: 81% wished to continue drugs (particularly because they feared losing their driving licence) and only 10% did not (almost all fertile women), with 9% undecided. It is clear, therefore, that while patients can be advised and informed of the risks and benefits, they must make their own decision.

**Ischaemic stroke—is drug treatment feasible?**

**Dr P. A. G. Sandercock** (Western General Hospital, Edinburgh) discussed future possibilities of drug treatment for cerebrovascular accidents. Cerebrovascular accidents differ in aetiology, about 15% being due to haemorrhage and the rest to infarct. Even within ischaemic strokes, a distinction can be made between lacunar strokes involving small vessels in which the prognosis is good, and more serious main-vessel thrombosis such as middle cerebral artery. Trials of thrombolytics, calcium antagonists, haemodilution, or steroids have not yet shown any benefit. There is a need for large simple clinical trials, similar to those
undertaken in myocardial infarction, of these and other therapies to determine efficacy and risk of adverse effects, and to identify subgroups which might be helped by specific therapies. A large international stroke trial is due to start in late 1992, which will involve a study of aspirin with or without heparin. There followed some heated discussion over whether it was ethical to give patients aspirin or subcutaneous heparin in such a trial without first excluding haemorrhage stroke by CT scanning.

Can we help the ageing brain?

Professor L. L. Iverson (MSD Neuroscience Research Centre, Harlow) considered whether drugs might help the ageing brain. Dementia, especially of the Alzheimer type, is common and there is no effective therapy. The cholinergic pathways are particularly affected in dementia, hence trials have been performed using either acetylcholine agonists (disappointing) or cholinesterase inhibitors, such as tacrine or physostigmine (slight but definite benefit, but limited by drug toxicity). A better understanding of the pathophysiology of Alzheimer’s disease is required to identify other targets for therapeutic intervention, such as the neurotoxic beta-amyloid found in the plaques of Alzheimer’s disease.

Benefits and risks of new antidepressants

Dr S. A. Montgomery (St Mary’s Hospital, London), while discussing the potential benefits of the new antidepressants, the 5-HT re-uptake inhibitors, emphasised the safety in overdose of the new agents compared with the risks of overdose of most of the tricyclic antidepressants. He dismissed the suggestion that one of the new drugs, fluoxetine, might be associated with an increase in suicides. This was first suggested in 1990, but since then has been extensively examined in prospective studies as well as by meta-analysis of previous trials, with the conclusion that fluoxetine neither provokes nor prevents suicide attempts. However, although the new drugs are recommended on the grounds of their safety in overdose, they are no better than older drugs in efficacy, and Dr Montgomery made a plea for more effective antidepressants.

Infectious disease

When to treat HIV disease

Professor I. V. D. Weller (Middlesex Hospital, London) spoke about antiretroviral therapy in HIV infection. While the use of zidovudine is widely accepted when AIDS-related complex or other illness occurs, its use in asymptomatic infection, even in patients with low CD4 lymphocyte counts, is more controversial. In the only study so far published, over 3,000 patients were randomised to either placebo or zidovudine at two dose levels. The end-point was the development of AIDS or AIDS-related complex. The trial was stopped early after a mean follow-up of only one year, because disease progression seemed to be halved (from 8% to 4% per year). No difference between the two dose levels of zidovudine was seen (and the correct dose remains controversial), nor was there any improvement in mortality. If this applied to Dr Weller’s own HIV patients (400 of whom might qualify for zidovudine on the trial criteria), and half were given zidovudine and half no therapy, after one year eight of the treated patients would have progressed compared with 15 not treated. Many of these ‘progressions’ would have been minor, and it is uncertain whether overall survival would be improved. On the other hand, 192 treated patients would remain well apart from zidovudine side-effects, compared with 185 untreated. Whether the benefits of zidovudine outweigh its toxicity is a matter for decision between the doctor and the patient.

‘Hospital only’ antibiotics

Professor R. G. Finch (City Hospital, Nottingham) asked whether it was worthwhile to restrict the use of certain antibiotics to hospital only. He concluded that it was not, as resistance is likely to occur despite such restriction, and that what was needed was more rational prescribing of existing antibiotics, including a common antibiotic policy between hospital and general practitioners. Trends of resistance among microorganisms needed to be carefully followed, but the development of fund-holding general practices and trust hospitals may make such work of less importance to purchasers in the short term and may reduce laboratory utilisation.

Preventing malaria

Dr P. A. Winstanley (KEMRI-Kilifi Research Unit, Kenya) said that the overall rate of imported cases of malaria in the UK is stable but that the more serious Plasmodium falciparum malaria is becoming more common. He stressed the importance of preventing mosquito bites, primarily by using impregnated mosquito nets and appropriate clothes after dark, with prophylactic antimalarial drugs as a secondary measure. Appropriate prophylaxis depends on the degree of risk of malaria in the area visited and the pattern of resistance to chloroquine (when chloroquine with proguanil, or mefloquine alone are recommended). Drug therapy as a population measure in Africa is excessively expensive, and should be targeted at high-risk groups such as pregnant women, patients with sickle-cell disease, and possibly all children. Much more important is the impregnation of bed nets, and home spraying to reduce the mosquito population. The economic importance of malaria in much of Africa was stressed. Future possibilities may include
development of a vaccine, although the cost might be prohibitive in the third world, and new drugs such as artemether, a semisynthetic derivative of a Chinese herbal medicine.

Metabolic disease

When and how to treat hyperlipidaemia

Dr G. R. Thompson (Hammersmith Hospital, London) said that population screening for hyperlipidaemia would not be cost-effective, given the large number of people with high cholesterol levels. Priority should be given first to patients with known coronary heart disease, second to those with multiple risk factors for coronary heart disease or genetic hyperlipidaemia, third to all men, and fourth to all post-menopausal women. The first choice is dietary treatment but if this fails the level of cholesterol determining drug treatment would vary, from a total cholesterol of 5.2 mmol/l in the highest priority group up to 7.8 in the lowest priority groups. He declared that lipid-lowering therapy was beneficial in preventing, and possibly even reversing, coronary heart disease, citing trials in which a decrease in LDL caused regression in atheroma in coronary disease or especially in iliofemoral bypass grafts. He dismissed the failure of the primary prevention trials to show any decrease in overall mortality because of a relative increase in mortality due to noncardiovascular causes, on the grounds that the trials had insufficient power to consider mortality as an end-point, and that there was no reason to suppose that cholesterol-lowering agents might promote violent deaths. The potential for controversy and argument here was great, but the audience did not rise to the occasion.

Risks and benefits of HRT

Professor J. O. Drife (University of Leeds) discussed the controversies over hormone replacement therapy (HRT) in three areas—bone, breast, and cardiovascular system. Osteoporosis is common in older women, in part due to lack of oestrogen but also to other factors such as smoking and lack of exercise. Oestrogen given soon after the menopause undoubtedly prevents bone loss and reduces the possibility of fractures, although there is little if any replacement of bone already lost. But it is still unclear whether, when HRT is stopped, rapid bone loss resumes, as occurs after the menopause, or whether the protection against fractures is maintained and, if so, for how long. Meta-analysis of recent trials shows a tendency towards breast carcinoma in patients on prolonged HRT, and particularly in those on higher-dose HRT. In this respect, oestrogens opposed by progestogens (for endometrial protection) might be worse than oestrogen alone. Early menopause increases the risk of the most common cause of death in women, myocardial infarction. Again HRT is protective (by about 50%) as long as it is taken, but the benefit seems not to persist once the HRT is stopped. This conclusion is based on early trials in which unopposed oestrogens were used in relatively selected patients; here too the benefits might be limited if progestogens are included; or the results may be less clear when a wider population is included in the trial—a common problem in extrapolating trial data to clinical practice.

There is no consensus on how long HRT should continue, although most gynaecologists recommend approximately eight years, but longer periods would be reasonable if the patient desired.

Clinical toxicology

Any help from preclinical drug testing?

Professor D. S. Davies (Royal Postgraduate Medical School, London) wondered whether preclinical drug testing can predict drug toxicity in man. Although effective at identifying safe doses for man and assessing the reversibility of toxicity, preclinical testing is only moderately effective at identifying therapeutic ranges, and is often quite poor at identifying the organ likely to be affected by toxic effects—perhaps because animal testing depends on histopathological examination of the organ, whereas human testing usually involves more sensitive investigations such as liver function tests. More sophisticated pharmacokinetic studies in animals are needed to match the drug’s likely use in man, and to consider how pharmacokinetic measurements such as peak plasma levels or ‘area under the curve’ relate to drug toxicity. Carcinogenicity and reproductive toxicity studies were developed for industrial chemicals, and may not be suitable for therapeutic drugs.

Predicting adverse drug reactions

Professor B. K. Park (University of Liverpool) raised the question whether it was possible to foresee suppos edly unpredictable adverse drug reactions by a better understanding of the drug’s metabolism, and by identifying individual patients who might be inherently at risk. An example of the former is the study of the antimalarial amodiaquine; when used as prophylaxis it may cause agranulocytosis or hepatotoxicity due to an unstable immunogenic metabolite which could have been predicted from knowledge of the chemistry of the molecule. An example of the second approach is the detection of patients with a deficiency of the enzyme epoxide hydrolase who are at risk of adverse reactions to certain anticonvulsants, in particular carbamazepine. Such patients may be identified by genotyping for the deficient enzyme, but this is not, as yet, a clinical practicality.
Better reporting

Dr Susan M. Wood (Medicines Control Agency, London) described the importance of spontaneous reporting of adverse drug reactions by 'yellow card' which may give the first warning of previously unknown reactions, characterising them and perhaps identifying risk factors. But this depends on the doctor recognising that an adverse effect has occurred, difficult if it resembles background disease. There is considerable underreporting even of serious reactions, as low as 6% of all adverse reactions in some studies. Reporting rates are determined only in part by the toxicity of the drug, but also by the marketing of the drug and by publicity given to any reactions.

To improve reporting rates, yellow cards must be readily available, and high-risk groups such as anaesthetists and hospitals are targeted. Publicity, especially about a drug withdrawal, stimulates reporting, but a sustained effort to keep the reporting of adverse effects in the forefront of doctors' minds is essential. In the future, it is possible that reports may be initiated by pharmacists or even by patients.

Are hospital formularies any use?

Professor J. C. Petrie (University of Aberdeen) explained the development of the Grampian formulary for drug prescribing, developed and used by both hospitals and general practitioners. The aims of the formulary are to contain costs without impairing quality of care, to help in choice of drug, as an educational and audit tool, and to promote communication between hospitals and general practitioners. Formularies inevitably impose some restriction on freedom to prescribe, and they may fail where they are produced without consensus or where no attempt is made to enforce them (in hospital at least). They are unpopular with the pharmaceutical industry, who claim that formularies may result in less funding for research. Future priorities will be closer communication between general practitioner and consultant on prescribing, and the development of pharmacoconomics to help direct the choice of drug.

Who pays?

Professor M. D. Rawlins (University of Newcastle upon Tyne) directed attention to a topic mentioned in passing by almost every other speaker, that of the rising national drug bill and attempts by government to control it. This could be by price control (by negotiation between government and the pharmaceutical industry, and to a limited extent at consumer level by prescription charges), by restricting availability (for instance, the limited list), and by controlling overall expenditure—an approach particularly favoured in the UK. Hospitals have a cash-limited budget within which to fund their drug spending, assisted by therapeutics committees, formularies, generic substitution, and by contracting with drug companies. In general practice, the budget is not cash-limited, and general practitioners now operate within the Indicative Prescribing Scheme whereby a hypothetical amount is set for their drug spending for the year, although any clinically justified overspending is acceptable. This seems to be fairly successful at containing spending by increasing awareness of costs and promoting review of prescribing practice.

Hospitals offload much of their spending on drugs onto the non-cash-limited community budget whenever possible. General practitioners object to this because of problems of responsibility, competence and medicolegal liability, and, most important, poor communication from hospitals, as well as because of the cost to their practices. Agreements between hospitals and general practitioners must be reached on shared-care protocols—another echo from earlier in the conference.

The future

Cytokines—more promise than progress

Professor J. H. L. Playfair (University College & Middlesex School of Medicine, London) discussed cytokines, such as tumour necrosis factor, the various interleukins, and haemopoietic colony stimulating factors, which showed great promise in theory but which, with the exception of a few limited areas, have yet to make any major impact in therapy. Their high cost will also limit their use.

Comment

This conference provided many useful overviews of the state of the art in a variety of areas. However, there were only occasional fragments of new information which would have been unfamiliar to the regular journal reader. On the whole, controversy flared only occasionally, and the meeting might have been better for some deliberately provocative presentations rather than reviews (however good) of the published data. Not all speakers gave specific consideration to the controversies surrounding their area of expertise. Certain themes were recurrent: the development of consensus, which, in the absence of very large trials in an area, seems to depend on the statistical technique of meta-analysis—a technique which itself causes controversy among some statisticians, and is not well understood by clinicians to whom it may give a false impression of certainty rather than probability. A second theme was the effects on clinical practice of the present reforms in the NHS, whereby clinicians may be expected to be clinical budget managers—a development to which the profession is often hostile but which we ignore at our peril. It leads to an increasing concern for value for money in therapeutics, and a growing importance
of health economics and pharmacoconomics, as we no longer just ask what is best for the individual patient, but also how to maximise the available resources to produce the greatest health gain for the greatest number of patients.

Heart and sudden death

A conference on ‘The Heart and Sudden Death’ was held at the Royal College of Physicians on 28 November, 1991.

The aim of the conference was to discuss whether it is possible to identify the clinical, electrophysiological, and pathological features that would indicate whether an individual might be at risk of sudden death from cardiac arrest. Recent developments in cardiopulmonary resuscitation, anti-arrhythmia treatment, and myocardial salvage have made this a practical and worthwhile aim.

Dr R. E. Ideke (Duke University Medical Center, Durham, North Carolina) described the electrophysiological basis of ventricular fibrillation. Animal studies involving the mapping of ventricular activity have given valuable insight into the electrophysiological events that occur during fibrillation. It is possible to identify multiple wavelets of electrical activity which produce a mixture of propagation, fragmentation, fractionation, and block. The rate of activation in ventricular fibrillation is much faster than in ventricular tachycardia and is characterised by spiralling waves of activity in a figure-of-eight pattern. By analysing the frequency of activity, it is possible to assess the duration of ventricular fibrillation. Although results from animal work cannot necessarily be extrapolated to the human heart, it is tempting to speculate that this may have clinical relevance, allowing us to decide when further resuscitative measures are unlikely to be fruitful.

Professor M. J. Davies (St George’s Hospital Medical School, London) gave an account of the pathophysiology of sudden death. It was based on an experience of more than 300 patients under the age of 69 who had died in Wandsworth within one hour of the onset of symptoms. Sixty-five per cent of these patients were shown by post-mortem angiography to have occlusive coronary disease but most of them had no previous history of heart trouble. Most deaths occurred at home between the hours of 8 am and 10 am. This confirms data from other world-wide studies and suggests perhaps that one should think twice before getting up in the morning!

Angiographic findings characteristically show irregular, high-grade stenoses, plaque rupture, and super-added thrombus. Platelet emboli are apparent downstream where there is evidence of myocardial damage. In most cardiac deaths there is evidence of an acute ischaemic insult, while in the remainder there is either left ventricular hypertrophy or evidence of previous scarring. Thus the final common pathway of ventricular fibrillation may be arrived at as a result of either acute ischaemia or a pre-existing ventricular abnormality.

In 2–3% of patients the cause of death remains unknown despite thorough autopsy and toxicology. In these cases it is likely that a fatal arrhythmia has occurred, and some of these patients do have a past history of intermittent palpitation or ectopic activity.

Professor P. J. Schwartz (University of Milan) looked at the autonomic determinants of sudden death. Autonomic status may influence ventricular excitability. High sympathetic tone tends to reduce ventricular stability; moderate vagal tone is protective, but excessive vagal drive can provoke ventricular fibrillation. The provocation of ventricular arrhythmias during episodes of myocardial ischaemia may also be modified by autonomic tone.

Baroreceptor sensitivity has become a focus of recent attention, particularly as baroreceptor depression has been shown to increase the risk of sudden death independent of left ventricular ejection fraction.

Heart-rate variability relates to baroreflex sensitivity, and there is increasing evidence that increased vagal activity may protect against ventricular fibrillation. The mechanism is unclear but may relate to the reduction in myocardial oxygen consumptions secondary to a reduction in heart rate.

Professor R. W. F. Campbell (Freeman Hospital, Newcastle upon Tyne) considered the prognosis of patients with out-of-hospital ventricular fibrillation or sustained ventricular tachycardia. The main predictors of survival following out-of-hospital cardiac arrest appear to be either the presence of ventricular fibrillation or whether or not the event was witnessed. However, even if ventricular fibrillation occurs while the patient is in hospital, there remains a small proportion of patients who cannot be resuscitated.

Assessment of patients at risk should include delineation of the coronary anatomy, together with an assessment of left ventricular function and the heart’s electrical stability. Even in the absence of myocardial infarction, major coronary disease imposes a high risk of ventricular arrhythmia, and this is aggravated if the left ventricular ejection fraction is reduced.

Dr W. J. McKenna (St George’s Hospital Medical School, London) identified some groups of patients who were at particularly high risk of sudden death.