so, in close cooperation with the medical team, as the minor is at risk of appreciable harm if treatment or feeding, or both, are not enforced.

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Recent Advances

Clinical pharmacology and therapeutics

Alasdair Breckenridge

Therapeutic practice rarely changes greatly as a result of a single investigation or trial. Traditionally, experiments carried out in the laboratory lead to small scale studies in humans, some of which may be translated into larger controlled clinical trials, which, if successful, may begin to influence patient management. The time scale of this process varies greatly. At one end of the spectrum a new biotechnology product may be developed with great rapidity, tested in a small cohort of patients, and be used by specialists within seven to eight years of its initial design. On the other hand valuable information on drugs of proved therapeutic value may languish in the literature for some 10 to 15 years before being widely accepted into clinical practice (for example, thrombolytic drugs after myocardial infarction). Dissemination of the results of research is as important as the original research itself, and implementation may represent an even bigger hurdle.

It is not an easy task to describe the advances in clinical pharmacology and therapeutics over the past year. I will start with the general issue of cost effective prescribing, which has moved up the political agenda in Britain after the publication of two influential reports. I will then cover four specialist therapeutic areas (AIDS, post myocardial infarction management, neurodegenerative disease, and diabetes), where treatment has become clearer because of positive or negative trial results. Finally, I will discuss the clinical exploitation of experimental findings on nitric oxide, which will have important roles in many diseases.

Cost effective prescribing

The issue of therapeutic cost effectiveness is not new, but several events have occurred recently to give the topic special prominence. Firstly, the latest reforms in the NHS have left all health care professionals questioning how burgeoning drug costs, which now account for £3.3bn out of a total NHS budget of £30bn, can be contained without prejudicing patients' welfare. Secondly, the Audit Commission, which is responsible for the external audit of the NHS in England and Wales, has turned its attention to prescribing in general practice¹ and identified several areas where savings could be made. The commission calculated that some £425m of the total general practice prescribing budget of £2.6bn in England and Wales was being wasted in overprescribing, in using drugs of limited clinical value, or in using expensive drugs where cheaper ones are equally effective (including generic equivalents). Though the commission recognised that many new expensive drugs had important

roles, it said that their introduction had to be managed carefully. Expensive prescribing is not always bad, but neither is it necessarily good. Expensive drugs used to prevent disease—inhaled steroids in asthma being a good example—might initially produce a rise in cost but could lead to reduction in hospital admission and thus overall savings (fig 1).

FIG 1—Patterns of prescribing for asthma in a sample of 3409 British practices. Source: Audit Commission

Thirdly, the health committee of the House of Commons issued its second report on priority setting in the NHS in 1994 and examined the NHS drug budget.² It made some interesting recommendations on both the pricing of drugs and their availability. The profits of the pharmaceutical industry from the NHS are currently negotiated in great secrecy between the Department of Health and the industry. The committee recommended that this process should be more open, saying that the impermeable secrecy which surrounds the working of the scheme militates against public confidence. The committee also recommended that a national prescribing list should be created so that at an appropriate time after licensing a drug would be reassessed for cost effectiveness and its suitability for funding by the NHS. In effect, this would extend the current selected list to all therapeutic areas. The government has now published its response, and though it has promised to consider many of the committee's recommendations, it has pleaded for time to implement them.³ The pharmaceutical industry's response is awaited with considerable interest. I believe that the topic of cost effective prescribing will remain the most important in therapeutics for several years to come.

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AIDS

An effective vaccine for the prevention and treatment of AIDS remains illusory despite some promising experiments in which two vaccine candidates have been shown to induce antibodies against not only the viral strain used in immunisation but also other strains. When this topic was debated at the United States sixth annual conference on advances in AIDS vaccine development, the overall feeling was that such vaccines were unlikely to work in a clinical setting, and large scale efficacy trials with them have been delayed.

On the drug front there is both good and bad news. First the bad news. The final clinical report of Concorde, the Anglo-French trial comparing the effect of giving zidovudine immediately to asymptomatic HIV seropositive patients with that of delaying it until the manifestations of the disease become apparent (or CD4 counts become persistently low), showed no significant differences in clinical outcome between the two approaches.⁴ There was, however, an indication of an early but transient clinical benefit in favour of immediate treatment and persistently higher CD4 counts in the immediate treatment group. These results are important for several reasons. Firstly, they show the fallibility of using surrogate markers alone to judge therapeutic efficacy in AIDS rather than real clinical end points, and this has implications for drug licensing. Secondly, the limited benefit of zidovudine in asymptomatic HIV positive patients must be assessed alongside its toxicity, its effect on quality of life, and its cost.

The European Australian Collaborative Group published two studies in asymptomatic HIV positive patients who were randomised to zidovudine or placebo. In the first study, in patients with CD4 counts greater than $400 \times 10^6/l$ the probability of disease progression over two years was halved by zidovudine.⁵ The second study in asymptomatic subjects with a lower CD4 count than those in the first trial ($200-400 \times 10^6/l$) showed that zidovudine significantly reduced the probability of developing symptomatic HIV disease and AIDS over the first 12 months but that this benefit was not maintained at two years.⁶ The combined results of all these trials have left confusion in the minds of both doctors and patients. It seems that reverse transcriptase inhibitors work for only a limited period, and it is a matter of individual choice at which stage this benefit should be exercised. Many British clinicians now favour delaying the start of zidovudine treatment until patients develop symptomatic HIV disease or their CD4 count falls appreciably. The debate has a long way to go.

The good news is that zidovudine given antepartum and intrapartum to pregnant women with mildly symptomatic HIV disease and to the newborn for six weeks reduced the percentage of children infected at 18 months to 8.3% compared with 25.5% in a placebo treated group (fig 2).⁷ The study could not define the long term effects of zidovudine in infected children and in the 80% of children born to infected mothers but who would not develop the disease themselves (only a fifth of infants born to HIV positive mothers acquire the infection).

The therapeutic cupboard in HIV disease still looks bare. A series of protease inhibitors which prevent the assembly and release of viral particles from infected cells shows encouraging preliminary effects on surrogate markers in patients, but whether this will be of clinical benefit is not yet known.

Myocardial infarction

Primary and secondary care doctors are confronted with a burgeoning and ever more confusing choice in dealing with patients with myocardial infarction at

every stage of its evolution. Early treatment with aspirin, thrombolytic drugs, magnesium, or nitrates can all be justified by published reports, while proponents of β blockers and angiotensin converting enzyme inhibitors can equally find support from clinical trials. The treatment of heart disease has recently been reviewed.^{8,9} What follows is a personal appraisal of one aspect of cardiovascular therapeutics, written for the non-cardiologist.

NEW MAJOR TRIALS

Four large clinical trials addressing various aspects of the management of acute myocardial infarction have been published in the past year.¹⁰⁻¹³ These studies are important because large scale clinical trials are now accepted to be the best way of assessing a treatment's efficacy and safety.

Thrombolytic drugs have at last been accepted as effective in the early management of myocardial infarction, and the question of which drug to use was addressed in the trial of global utilisation of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO).¹⁰ Recombinant tissue plasminogen activator given with heparin gave a lower mortality than streptokinase with heparin over two years' follow up (6.3% v 7.2%) and better early (90 minute) vessel patency. The study estimated that about 10 lives per 1000 patients treated would be saved by using recombinant tissue plasminogen activator rather than streptokinase. But here the issue of cost effectiveness raises its head. Recombinant tissue plasminogen activator is 5-10 times more expensive than streptokinase and there is concern that its widespread use will lead to fewer patients being given thrombolytic treatment. In most British hospitals recombinant tissue plasminogen activator is largely kept for patients who have previously received streptokinase and who cannot be given the drug for a second time.

Studies have shown that the angiotensin converting enzyme inhibitors enalapril and captopril can significantly cut down death rates from heart failure after myocardial infarction in patients with low cardiac output but that the drugs should be started only when the patient is haemodynamically stable.¹⁴⁻¹⁶ Starting treatment with enalapril within the first 24 hours after myocardial infarction seemed to increase mortality.¹⁷ In 1994 three new trials elaborated on these findings. Lisinopril and ramipril were shown to have similar benefits to enalapril and captopril.^{11,13} This might suggest a group effect for all angiotensin converting enzyme inhibitors, but of course the effective dose will vary among drugs. That the benefits of angiotensin converting enzyme inhibitors after myocardial infarction are greatest in high risk patients was again shown in the fourth international study of infarct survival.¹²

FIG 2—Kaplan-Meier plots of probability of HIV transmission to infants according to treatment group.⁷ Reproduced with permission; © Massachusetts Medical Society 1994

The role of angiotensin converting enzyme inhibitors in all patients after myocardial infarction, including those with normal myocardial function, is not yet clear and they cannot currently be recommended. There is great interest, however, in whether differences in distribution of the angiotensin converting enzyme genotype may give an insight into the pathogenesis and treatment of ischaemic heart disease.¹⁸

OPTIMAL MANAGEMENT

The optimal current management for patients with myocardial infarction seems to be as follows. Firstly, aspirin should be given as soon as the diagnosis is suspected, and there is evidence that this treatment is still greatly underused.¹⁹ Secondly, streptokinase should be given in hospital as soon as possible after the event (no great benefit accrues by starting in primary care). Thirdly, after two to three days patients in heart failure, with a low cardiac output, or with an extensive anterior infarct should be given an angiotensin converting enzyme inhibitor. The duration of use is still uncertain, and the dose must be individually adjusted because hypotension is the commonest adverse effect. β Blockers should still be reserved for patients not in heart failure—that is, those not likely to be given angiotensin converting enzyme inhibitors—and this treatment should be maintained for at least two years.

Neurodegenerative disease

One of the greatest current therapeutic needs is for a drug (or drugs) that arrests or reverses neuronal damage. More effort is probably being put into investigating approaches to containing brain damage after acute insult (such as stroke) and longer term neuronal degeneration (such as Alzheimer's disease) than into any other therapeutic area.

The presence of the apolipoprotein e4 allele has been linked to a high risk of late onset Alzheimer's disease and other neurodegenerative disorders and subjects with two copies of the allele have been shown to be eight times more likely to be affected by late onset Alzheimer's disease than those without the allele (Strittmatter W, 3rd international Springfield symposium on advances in Alzheimer's therapy, Springfield, Illinois, 1994).

The anticholinesterase tacrine became the first drug to be approved in the United States for treatment of Alzheimer's disease, but controversy remains concerning its therapeutic value. Enthusiasts point to a small delay in functional deterioration, which undoubtedly occurs in some patients, but it is difficult to predict which patients will benefit. Many patients taking tacrine suffer hepatotoxicity. The drug is not licensed for use in the United Kingdom.

Drugs as diverse as the non-steroidal anti-inflammatory indomethacin,²⁰ the monoamine oxidase inhibitor selegiline,²¹ and the peptidergic nootropic drug cerebrolysin²² have been investigated in short term studies in Alzheimer's disease, but the rationale for their use is not clear. An intriguing observation relates to the effects of nicotine in Alzheimer's disease. Central cholinergic systems are known to be important in human cognitive function (and this underlies the use of the anticholinesterase tacrine), and novel analogues of nicotine are being investigated.²³ Whether credence can be given to the alleged lower incidence of Alzheimer's disease in cigarette smokers remains an epidemiological and health care conundrum.

A better understanding of neurobiological receptor action and intercell signalling seems a prerequisite for the rational development of an effective cognition enhancing drug. Clinical need for an effective drug is

high, the level of research investment great, but therapeutic results remain disappointing.

Diabetes

Over the past year there have been three important advances in our understanding of the diabetic process. Firstly, the results of the diabetes control and complication trial have shown a direct relation between blood glucose concentrations and the risk of developing diabetic complications.²⁴ Secondly, the benefit of the angiotensin converting enzyme inhibitor captopril in delaying the progression of renal disease in patients with insulin dependent diabetes was shown to be maintained over two years in a large clinical trial²⁵ and this response may be genetically determined.²⁶ The cost benefit implications of this observation are thought to be considerable if the number of dialyses and renal transplantations can be reduced.

Thirdly, troglitazone, a new drug which is claimed both to sensitise and to increase the number of insulin receptors, has been shown to normalise blood sugar concentration in about half of non-insulin dependent diabetic patients.²⁷ The drug has short and long term benefits and seems to be a genuine advance in an area where there have been few drugs discovered over the past decade.

At a more mundane but equally important level, some advances in insulin delivery systems have been reported. The prospect of repeated daily injections of insulin remains a daunting problem for many diabetic patients, especially the young, and at last studies on intranasal and aerosol formulations of insulin seem to hold out promise of alternative and acceptable routes of insulin administration.²⁸

Nitric oxide: a tip for the future

Few science watchers will not be aware of the biological importance of nitric oxide. The speed of the unfolding of this story is breathtaking.²⁹ As recently as 1987 it was conclusively proved that nitric oxide was produced in living systems; since then the ramifications of the observation have had major implications in the control of at least three systems—cardiovascular, immunological, and nervous.

For many years it was thought that antianginal nitrate drugs acted by dilating peripheral vessels, allowing cardiac unloading. As it turns out, the basis of their action is almost certainly nitric oxide, released by breakdown of the drug (fig 3).³⁰ In 1987 Palmer and colleagues showed that nitric oxide was released from endothelial cells lining blood vessels, and it has since become evident that nitric oxide has a central role in determining vascular muscle contractility and relaxation³¹ together with other vasoactive compounds such as endothelin. Secondly, nitric oxide has been shown to play an aggressive part in the immunological system; it is released in relatively large quantities by macrophages and leads to suppression of lymphocyte func-

FIG 3—Simplified scheme depicting the mechanism of action of organic nitrates (RONO₂). Organic nitrate enters the vascular smooth muscle cell where it is biotransformed resulting in the release of inorganic nitrite (NO₂⁻) or nitric oxide (NO). Nitric oxide then activates guanylate cyclase.³⁰ Reproduced with permission

Recent advances in clinical pharmacology and therapeutics

AIDS

● Zidovudine has been shown to have benefit for only a limited period. The rate of mother to infant transmission of HIV is reduced by giving zidovudine to women intrapartum and to neonates

Myocardial infarction

● Thrombolysis with recombinant tissue plasminogen activator may be more effective than with streptokinase in reducing mortality over two years but is less cost effective.

● The angiotensin converting enzyme inhibitors lisinopril and ramipril have been added to the list of drugs shown to reduce death rates from heart failure after infarction in patients with low cardiac output

Neurodegenerative disease

● Apolipoprotein e4 allele has been associated with late onset Alzheimer's disease. Tacrine may produce a little benefit in a few patients but they risk hepatotoxicity

Diabetes

● A large trial has confirmed that captopril delays progression of renal failure in insulin dependent diabetes.

● Troglitazone has been shown to normalise blood sugar concentrations in non-insulin dependent diabetes

Nitric oxide

● Trials are being done using nitrate patches to delay onset of labour. The role of nitric oxide in memory, the autoimmune system, and many other systems is being investigated

tion.³² Scientists are now starting to investigate the longer term role of nitric oxide in the genesis of autoimmune disease. Patients with overwhelming infections such as septic shock have been shown to release large quantities of nitric oxide, resulting in massive vascular dilatation and life threatening hypotension.

The third—and in many ways the most exciting—role of nitric oxide is in the central nervous system. Nitric oxide is an important neurotransmitter at both central and peripheral level, working with other better understood control mechanisms. In particular, nitric oxide seems to have an important role in laying down memory pathways.³³ It may also protect nerve cells. On the other hand, excess nitric oxide seems to play a part in the acute damage of stroke and the longer term brain damage in senile dementia, Alzheimer's disease, and parkinsonism.

The therapeutic spin offs resulting from our better understanding of this simple molecule promise to change many aspects of therapeutics. Nitrates are already used to treat angina, and a nitrate releasing skin patch to delay the onset of labour is being investigated.³⁴ These are only the proverbial tip of the iceberg, and clinical trials on drugs that will either

deliver more nitric oxide to the appropriate sites in the body or inhibit nitric oxide formation where it is in excess already show considerable promise. If nitric oxide can do all this, what about the biological role of other small molecules such as ethene (C₂H₄) and carbon monoxide (CO).³⁵ In pharmacology, large is not necessarily beautiful and we will all be reading much more about nitric oxide in years ahead.

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