Clinical pharmacology and therapeutics into the future

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Clinical pharmacology sits at the interface between basic pharmacology and the effective drug treatment of human disease. Because of the dominance of pharmacotherapy in modern therapeutics, clinical pharmacology has become indispensable for the development of new treatments as well as for the proper understanding and practice of contemporary medicine.

Clinical pharmacologists have not only been strikingly successful in advancing therapeutic knowledge but, especially in the UK, they have also developed a broader leadership role in the provision of health services. Nevertheless, there remain areas of activity where the influence of the discipline has been less impressive, and where there are real opportunities for the future of the subject.

Research at the interface

By acting as a bridge between basic sciences and clinical practice, clinical pharmacologists can rightly claim substantial credit (Table 1). The breadth of research has meant that the range of techniques used is more extensive than in almost any other clinical discipline, and in their quest to resolve particular problems, clinical pharmacologists have been unafraid (and unashamed) to adopt methods ranging from chemistry and molecular biology at one extreme to epidemiology at the other.

Clinical pharmacological research has been especially prominent in the fields of cardiovascular, respiratory and geriatric medicine, and its exponents have made major contributions in developing novel (and highly effective) approaches to the management of patients with self-poisoning. Clinical pharmacologists have also contributed substantially to aspects of reproductive and psychiatric medicine; as well as to specific areas related to the treatment of infectious diseases (e.g. human immunodeficiency virus [HIV] infection), blood disorders (e.g. thromboembolism) and neurology (e.g. anticonvulsants). It is also encouraging to see the emergence of clinicians with primary expertise in disciplines such as cardiology, neurology and psychiatry acquiring

and utilizing the additional skills of clinical pharmacology in order to pursue their own clinical research agenda.

There are, however, areas that have (with a very few notable exceptions) been largely neglected by clinical pharmacologists. These include, most particularly, paediatrics and oncology. It is tempting to speculate that, had clinical pharmacologists given greater attention to the special therapeutic problems in these fields, some of the current problems (as discussed later) might have been avoided.

Leadership

Considering the relatively small size of the discipline, UK clinical pharmacologists have assumed a major leadership role in relation to the management and provision of health care generally, as well as in prompting safe and effective drug therapy.

At a local level, clinical pharmacologists have been, and continue to be, a dominant force in local drug and therapeutic committees. While their influence obviously varies, they unquestionably set the tenor and tone of local discussions on the content of local formularies and prescribing governance. At a regional level, clinical pharmacologists have acquired extraordinary influence as deans of medical schools (including those at Dundee, Glasgow, Liverpool, Sheffield and Southampton).

Nationally the influence of clinical pharmacologists has been remarkable. It includes four (out of six) chairmen of the Committee on Safety of Medicines; the chief executives of both the Medicines Control Agency and the Medical Devices Agency; recent chairmen of the Medicines Commission, the Education Committee of the General Medical Council and the Committee on Toxicity; as well as the current chairmen of the British National Formulary and the National Institute for Clinical Excellence's Appraisal Committee. Both the editors of the *Drug and Therapeutics Bulletin* have been clinical pharmacologists. And, moreover, different individuals have occupied all these various positions!

But ...

Although the science underpinning clinical pharmacology is unassailable, and the influence of its UK practitioners considerable, there is much more that could, and should, have been done.

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Table 1 Areas of substantial and successful clinical pharmacological research.

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- 1 Exploring the therapeutic potential of novel pharmacological mechanisms
 - 2 Exploring the therapeutic potential of new therapeutic products
 - 3 Extending the therapeutic uses of existing therapeutic products
 - 4 Identifying mechanisms of therapeutic efficacy
 - 5 Identifying unwanted effects of drugs
 - 6 Investigating mechanisms of drug toxicity in man
 - 7 Developing strategies for optimizing drug therapy
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Improving the skills of prescribers

Clinical research is pointless if, ultimately, it fails to bring benefit to patients. It is therefore immensely depressing to read, in almost any study examining the care given to patients, our modest impact. Two examples, from areas that clinical pharmacologists claim as their own, are salutary. Community studies in the UK reveal that less than 20% of elderly patients with hypertension are diagnosed, treated and adequately controlled [1]; less than 25% of patients with atrial fibrillation receive anticoagulants [2]. These conspicuous failures in delivering high-quality care are global and (at least in developing countries) are not obviously related to the resources available for health care.

These failures in translating the findings of research into clinical practice are the result, in part, of the poverty of our current undergraduate and postgraduate teaching programmes in clinical pharmacology and therapeutics. The standards set by the General Medical Council for teaching basic prescribing skills are woefully inadequate. The Council gives little guidance to medical educators as to the scope and content of what, in a modern world, can reasonably be expected of prescribers by patients and the public. Worse still, the influence of clinical pharmacologists to correct these deficiencies within their own institutions appears to be minimal. To compound the problem, the interest of specialists in other disciplines in teaching the elements of therapeutics within their own areas, is (at its mildest) generally limited.

Clinical pharmacologists must adopt two principles in order to reverse this unacceptable position. Firstly, the issue of this 'therapeutic deficit' should be raised at every level. This not only includes the General Medical Council, individual medical schools and the Royal Medical Colleges, but also the NHS (especially those responsible for clinical governance) and the general public. It seems incredible that new nurse prescribers will undergo more training (before they can prescribe from a limited list of drugs) than medical students (who, on qualifying, are permitted to prescribe anything in the *British National Formulary*). Secondly, clinical pharmacologists should develop (and share) innovative approaches to teaching the

elements of competent prescribing. They should ensure even closer links with their colleagues who teach basic pharmacology to undergraduate students, and they should insist on an adequate assessment of their students' competence as prescribers before qualification.

Research

The research agenda, for clinical pharmacologists, is already large but there are areas where input from the discipline is urgently needed.

Firstly, there are the two particularly neglected areas, oncology and paediatrics, where greater clinical pharmacological input is likely to bring substantial gains. The quality of the clinical development of anticancer drugs is substantially less than that of any other therapeutic class. Surrogate markers of uncertain validity, coupled with the too frequent absence of data from randomized controlled trials, often makes their evaluation and appraisal almost impossible. National drug regulatory authorities tend to regard the field as too difficult and, consequently, apply lower standards of evidence of efficacy and safety than in other areas.

Paediatricians also have serious problems in making modern pharmacotherapy available to children. It is claimed that around half the medicines prescribed for children are unlicensed for the particular purpose. Difficulties in undertaking clinical trials, lack of support by pharmaceutical manufacturers, and the intransigence of national drug regulatory authorities are often cited as the reasons for this continuing state of affairs. There are, indeed, real difficulties in making modern medicines available to children if the adult drug development paradigm is followed. Creative clinical pharmacologists, however, might be capable of devising novel strategies for developing children's medicines and allowing the benefits of modern pharmaceuticals to be more generally available.

Secondly, clinical pharmacological endeavour is needed to improve the evaluation of clinical efficacy and effectiveness. Better validation of surrogate markers of therapeutic efficacy, and improved approaches to identifying intermediate end-points, would allow improved evaluation of the long-term therapeutic benefits of products used in the management of chronic diseases. Furthermore, clinical pharmacologists could help in ensuring better quality-of-life instruments. Too many of those currently available fail to capture patients' perspectives on their particular disease and its treatment, and too many of the available instruments fail to correlate readily with measures of utility.

Thirdly, clinical pharmacologists could help in looking beyond the placebo-controlled randomized clinical trial. Although this is unquestionably the most robust approach for demonstrating the efficacy of a therapeutic agent, its

applicability to some areas of clinical practice is increasingly questionable. For most treatments, the critical question is not whether a new treatment shows absolute efficacy ('proof of principle'), but how it compares with existing therapeutic modalities. There is therefore an increasing need for new treatments to be compared with existing best practice.

Moreover, I am beginning to wonder whether randomized controlled trials will invariably remain acceptable to patients, their families and their friends. For example, in the case of new treatments designed to arrest the progression of chronic, neurological conditions such as Alzheimer's disease, Creutzfeldt-Jakob disease, or Huntington's disease, and where there is a plausible biological basis for their likely effectiveness, is it reasonable to expect some patients to accept randomization to placebo? There is, of course, the argument that the adverse effects of the treatment may be worse than disease itself, and recent experience following immunotherapy for Alzheimer's disease reminds us that this is not merely a theoretical possibility. Nevertheless, such devastating effects do not necessarily require randomized controlled trials for their recognition. Instead, I suggest that clinical pharmacologists should be seeking alternatives to conventional randomized trials on a case-by-case basis. These include developing the approach adopted in some studies with anti-HIV drugs [3]; and by revisiting techniques based on historical controlled trials. Other possibilities are also worth exploring and some of these, though in a different context, are discussed in a recent publication [4].

Finally, I believe that clinical pharmacologists should take a lead in ensuring that, where appropriate, the

results of research are translated into clinical practice. Clinical pharmacologists can no longer retreat into ivory towers, and expect their research findings to be implemented, without effort on their part. Implementation is not easy, and multifaceted approaches are likely to be needed. Successful implementation, however, could (and now should) be the final step of successful clinical research.

Conclusions

Clinical pharmacology has made substantial progress over the past 40 years and those who have been working in the discipline for much of the period can look back with some satisfaction on the progress that has been made. Nevertheless, there is much to be done. It is for this reason that I believe, for clinical pharmacology, the future is glorious.

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