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New Drugs for the 1990's, the Challenge for the Clinical Pharmacologist

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Clinical Pharmacology. Challenges for the 1990's.

Advances in molecular and cell biology have created many opportunities for developing novel and specific therapeutic agents. However, amidst all the excitement it is important not to forget some of our failures during the past decade for remedying those deficiencies also represents an important challenge.

One of the most common problems in the recent past has been getting the dose wrong! The development of both captopril and enalapril illustrate the problem, in the one case of dose related toxicity and the other of excessive pharmacological effect in vulnerable patients with heart/renal failure. The first challenge of the 1990's is to get the dose right for the diagnostic group!

The second challenge concerns individualisation of therapy. With a few exceptions (e.g. lithium, warfarin, phenytoin) there has been only modest progress in accurate individualisation of therapy. The reasons are complex including lack of accurate indices of pharmacological response or failure to demonstrate therapeutically useful concentration-effect relationships. Individual and population pharmacokinetic studies show a wide range of concentration for a given dose and, for some drugs

there is a similar wide range of concentration-effect relationship. But that is not the whole story. Pharmaceutical companies like to promote a single dose (preferably once a day) and lazy physicians are too willing to accept it. Thus, the second challenge is to get the dose right for the individual.

The third challenge which I shall discuss concerns drug delivery systems, bioavailability and duration of action. When so many new drugs are peptides or proteins (erythropoietin, GCSF, octreotide) it is disappointing to note how little progress has been made with non-parenteral delivery systems despite much ingenuity. For drugs that are well absorbed but which have a short half-life some real progress has been made in developing slow release formulations but, largely because of the small intestine transit time, they are not as good as a drug which has a long half-life at the outset (e.g. amlodipine compared with sustained release nifedipine). There is also a worrying tendency to equate long terminal half-lives, measured with sensitive assays, with a prolonged duration of therapeutic effect and this is not always true. Thus, the third challenge is to design drugs or delivery systems that have optimal kinetic properties.

The fourth challenge is to improve the sensitivity of clinical trials, in an era when placebo controlled

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outcome trials are becoming difficult for ethical reasons. Are soft end points such as regression of cardiac hypertrophy in hypertension and fall in C-reactive protein in infection acceptable alternatives to hard end points such as major complications or death? They are tempting but they might be misleading. Anti-hypertensive therapy often causes resolution of ECG changes of cardiac hy-

pertrophy but has little effect upon coronary morbidity or mortality. If softened points are unacceptable is there any alternative to the very large simple trials advocated by Peto. Are concentration controlled trials likely to be useful? Thus the fourth challenge I shall discuss concerns the size and duration of clinical trials prior to marketing.