Editors' view

Moving about

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To cardiologists PK may mean pericardial knock; to ophthalmologists penetrating keratoplasty; to dermatologists the Prausnitz-Küstner reaction; to psychologists psychokinesis; to biochemists pyruvate kinase; and to pharmacologists protein kinase. But to clinical pharmacologists it means pharmacokinetics.

The term 'pharmacokinetics' seems to have been first used in print by Friedrich Hartmut Dost in a German text written in 1953 [1]. The *Oxford English Dictionary* gives the first English citation of the word as dating from 1960 [2], but on this occasion the editors of that authoritative and august work have nodded and have missed a slightly earlier example from 1959 [3].

Of course, the use of kinetic techniques to study drugs dates much further back than the 1950s, at least to the work of Widmark and Tandberg, who in 1928 published the first account of a one-compartment open model [4], and Teorell, who, among other things, extended the idea to two compartments in 1937 [5]. Other early examples of the use of pharmacokinetic techniques included a discussion of concentration versus time curves by Gehlen in 1933 [5] and a description of the kinetics of alcohol by Beccari in 1937 [6], with its implication of zero-order kinetics. And Harry Gold's studies of digitalis, including urinary concentration measurement to delineate its pharmacokinetics [7], long before sensitive bioassays and immunoassays allowed measurement in the plasma, constituted pioneering work that laid the foundations of modern clinical pharmacology.

It was not long before other textbooks on the subject started to appear. Rescigno and Segre's classic account, 'La Cinetica dei Farmaci e dei Traccianti Radioattivi' appeared in Italian in 1961 and in English in 1966 [8] and was followed by texts such as Notari's 'Biopharmaceutics and Pharmacokinetics' (1971), Gibaldi and Perrier's 'Pharmacokinetics' (1975), and of course John Wagner's 'Fundamentals of Clinical Pharmacoki-

netics' (1975), which was optimistically labelled 'First edition'. As someone once pointed out, it seems perverse to accord first editions the awe that book collectors do, when second and subsequent editions are so much rarer; no second edition of Wagner's text ever appeared. Since the 1970s several more books have been published, and there is now no shortage of instructive texts, at all levels from introductory to complex, and in several languages.

Although many of the tools that we now consider standard in pharmacokinetics were developed in the 1960s and 1970s, many of them in papers published in the *Journal of Pharmaceutical Sciences*, the uses of this essential pharmacological tool continue to expand. This is well illustrated by several papers in this issue of the *Journal*, the titles of eight of which contain the words 'pharmacokinetic' or 'pharmacokinetics' and four others of which deal with pharmacokinetic matters, even though the word is not mentioned in their titles. The range of topics covered is impressive:

- the different kinetics of bound and unbound drug [9], a distinction that is not made sufficiently often;
- metabolite kinetics [9];
- how a dosing strategy can be devised for patients with renal insufficiency [10];
- how renal transplantation affects pharmacokinetics [9];
- how hepatic cirrhosis affects pharmacokinetics [11];
- how pharmacogenetic polymorphisms affect pharmacokinetics [12–15];
- pharmacokinetics in children [16];
- population pharmacokinetics [17];
- the pharmacokinetics of drug interactions [12, 13, 18, 19];
- compartmental modelling [10, 18];
- pharmacokinetic/pharmacodynamic modelling [20].

The last two entries in this list remind us that the much abused compartmental model is alive and kicking, in the first case including a rare example of a four-compartment model with a non-linear function connecting two of the compartments. Although models that do not involve compartments are sufficient for deriving simple pharmacokinetic parameters, compartmental models do have their uses. And non-linearities are not perhaps allowed for sufficiently often in models of this kind.

The last item in the list is a category of which we would like to see more. There are those who feel that merely to describe the pharmacokinetics of a compound, in whatever detail and with whatever nuances, neglects the business end of drug therapy, namely pharmacological actions and therapeutic outcomes. But no drug can be developed without careful delineation of its pharmacokinetics, and if great care is taken over the design, performance, and analysis of a detailed pharmacokinetic study, that in itself should merit publication. Nevertheless, whenever possible it is of course desirable to link kinetics to dynamics.

Anyone who tunes in to the musings of the PharmPK discussion group, moderated by David Bourne, will be aware of the enormous diversity of the subject and the controversies it can still engender; the group's Home Page alone (<http://www.boomer.org/pkin/>) is highly instructive.

So think of this issue as a multicompartmental model. The largest compartment contains a pool of papers on pharmacokinetics, with representative examples of current work. Now dive into the pool. Of course, there are sharks in the water, but they won't attack you unprovoked. You won't, for instance, have to know about how to tackle simultaneous linear differential equations in order to take the dip.

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