The disposition of a drug after administration to man or an experimental animal may be studied in several different ways. "Classical" kinetic theory is based on the development of simple compartmental models, in which volumes of distribution, intercompartmental clearance rates and systemic drug clearance (or elimination) are calculated from analysis of concentration–time data by the fitting of an appropriate mathematical model. The latter is usually a polyexponential equation, although some authors have attempted to fit other more complicated models (e.g. power and gamma functions) to improve the fit of the observed concentration–time changes.

The limitations of this approach include the need for large numbers of blood samples (with inadequate or inappropriate sampling regimens in the early period after drug administration resulting in poor characterization of the distribution phase, and hence compounded errors with calculation of the various intercompartmental rate constants); the need to assume instant equilibrium of drug within the circulation; and occasional uncertainty over a correct choice of mammillary model. A good example of the last problem has been the controversy over the best model to describe the elimination of atracurium [1]; while the proposed extrahepatic elimination of drugs such as morphine and propofol [2, 3] also questions the appropriateness of some of the simple kinetic models to describe their disposition.

A second approach to drug concentration–time modelling is that of statistical moment analysis. For further consideration of this method of data handling, the reader is referred to papers by Yamaoka, Nakagawa and Uno [4] and Nakashima and Benet [5].

In contrast with these two mathematical approaches, physiological modelling can be adopted—based on organ blood flows, membrane permeability, blood–tissue binding differences (measured as the partition coefficient), organ volumes (or masses) and the metabolic clearance rate. There are two types of physiological model: the flow-limited model and the membrane-limited one (fig. 1) [6]. In general terms, clearance of a drug in a flow-limited model can be described by the following equation:

$$V_e \frac{dC_z}{dt} = \dot{Q}_e (C_A - C_z / R_z)$$

where $\dot{Q}_e$, $C_z$, $R_z$ and $V_e$ = respectively, the blood flow, drug concentration, tissue: blood partition
coefficient and anatomical volume (or mass) of the tissue; $C_A =$ inflow drug concentration.

However, for most drugs given i.v. there is also partitioning of drug in the blood—between that bound to plasma proteins and the pharmacologically active free fraction. Under these circumstances, the general model needs to be modified to incorporate both free and bound drug concentrations, as only the former can cross the cell membrane and undergo metabolism. For this "membrane-limited model", we need to add in the equation, therefore, the free drug concentrations in both the extracellular and intracellular phases ($C_e$ and $C_i$), and the membrane permeability coefficient ($k$). Thus:

$$\frac{dC_e}{dt} = \frac{V_e}{Q} \left( C_A - C_e \right) - k \left( C_e - C_i \right)$$

In simple models, organ systems are often grouped together, to produce a "pooled anatomically compartmented model". The whole topic of physiological modelling has been reviewed well by Gershowski and Jain [7].

Mapleson recognized the limitations of conventional kinetic modelling with their assumption of instant equilibrium in the blood when he described the uptake and distribution of the inhaled anaesthetic agents [8]. The time to uptake into the brain (and other tissues) must relate to the circulation time from the lungs to the brain. To overcome these problems, he proposed four separate and distinct model simulations to describe the observed concentrations of volatile anaesthetic agents in different tissue compartments. These he termed:

O: the zero circulation time model (clearly inappropriate, for the reasons already given);

F: finite circulation time model;

M: finite circulation time model with longitudinal mixing;

P: separate pool model for arterial and venous blood (fig. 2).

For the two volatile agents that Mapleson used in these simulations (nitrous oxide, methoxyflurane), there was little to distinguish between models F and M, while observed concentrations in different body tissues were best fitted to model P.

In a study described in this issue of the Journal, Mapleson and his colleague Davis have turned their attention to physiological modelling of the i.v. drug pethidine (meperidine), based on averaged values for the characteristics of the main compartment masses and blood flows of "standard man" [9]. As may occur with mathematically based kinetic modelling when inappropriate weighting techniques, poor sampling regimens or incorrect "fitting" methods are used, so physiological modelling is liable to the introduction of errors if accurate estimates have not been made of the following: organ volume (or mass), organ blood flow and the different blood:tissue partition coefficients in the species under investigation.

How do the simulations of Davis and Mapleson compare with other data sets describing the distribution of pethidine? Some examples are illustrated in figures 3–6 of Davis' paper. Overall, there appears to be a good correlation between the mathematically determined average distribution–elimination plots and the calculated physiologically based model. However, the data sets available for comparison are based on small numbers of discrete populations; and there is therefore a need to validate the model by obtaining data from many more patients with different disease states (e.g. respiratory acidosis—see Davis' figure 7—cardiac failure, renal and liver diseases) or those receiving intercurrent drug therapies.

Fig. 2. The basic model and four derived models of the uptake and distribution of an inhaled agent (models O, F, M, P). The four derived models, of which only the arterial halves are shown, were constructed in terms of digital computer programs. $SV =$ Stroke volume; $Vi =$ expired tidal volume; $Ve =$ expired tidal volume. Compartments 1, 2 and 3 represent the visceral, lean and fat tissues, respectively. (Adapted from Mapleson [8] with permission of the author and publishers of the British Journal of Anaesthesia.)
Most other data examining the physiological disposition of i.v. anaesthetic agents have involved the barbiturates. Bischoff and Dedrick [10] developed four anatomical compartmental models (based on blood, viscera, lean and adipose tissues) to describe the disposition of thiopentone and methohexitone in humans and in dogs. The visceral compartment must be considered a composite or "pooled" compartment as it contains the brain, heart, liver and kidneys; therefore the prediction of the brain concentration per se is not precise. More comprehensive models for the i.v. barbiturates are those of Chen and Andrade [11], Gillis, de Angelis and Wynn [12] and Igarì and colleagues [13].

Another approach has been proposed recently by Henthorn, Avram and Krejcie [14]. While modelling the kinetics of thiopentone by conventional mathematical approaches, they incorporated the dye indocyanine green (ICG) into the injection bolus, so as to provide more information about the initial volume of distribution of the drug. ICG is highly protein bound and therefore remains firmly in the volume of distribution of the drug. ICG is highly protein bound and therefore remains firmly in the circulating blood volume. It represents, therefore, the "true" initial volume of distribution, which is small (about 3.2 litre). This probably represents the volumes of blood in the heart, lungs, great vessels and the highly perfused group of tissues. The remainder of the initial volume (about 3.8 litre; and determined from the distribution kinetics of the thiopentone) represents blood in "slower tissues". However, this technique is not without possible faults—such as the effects of first-pass partitioning of lipid-soluble drugs in the lung parenchyma [15-18].

One obvious advantage of the physiologically based model is that it may allow the anaesthetist to be able to predict the concentration of a drug at its site of action by the process of scaling of data from other species, and hence without the need for the complex kinetic-dynamic modelling favoured by the group from Stanford [19].

However, the modelling is only as good as the data on which it is based. The simulations of Davis and Mapleson can provide the clinical anaesthetist with new concepts about dosing requirements (for example, the regimen necessary for maintaining steady brain drug concentrations during i.v. anaesthesia) under different physiological conditions. It is to be hoped that more studies of this type will be conducted in man, and their results compared with the longer standing kinetic data sets.

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