HISTORY OF PHARMACOKINETICS

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1. THE TERM AND ITS MEANING

The term *pharmacokinetics* was first introduced by F. H. Dost in 1953 in his text, *Der Blütspiegel-Kinetic der Konzentrationsabläufe in der Frieslaufflüssigkeit* (Dost, 1953). However, some of the subject matter was published before the word was coined. It is also of interest that the first English language review of the subject matter, published in 1961, was entitled the *Kinetics of Drug Absorption, Distribution, Metabolism and Excretion* and did not include the word *pharmacokinetics* (Nelson, 1961).

Pharmacokinetics has been defined in a number of ways. Literally, the word means the application of kinetics to *pharmakon*, the Greek word for drugs and poisons. *Kinetics* is that branch of knowledge which involves the change of one or more variables as a function of time. The purpose of pharmacokinetics is to study the time course of drug and metabolite concentrations or amounts in biological fluids, tissues and excreta, and also of pharmacological response, and to construct suitable models to interpret such data. In pharmacokinetics, the data are analyzed using a mathematical representation of a part or the whole of an organism. Broadly then, the purposes of pharmacokinetics are to reduce data to a number of meaningful parameter values, and to use the reduced data to predict either the results of future experiments or the results of a host of studies which would be too costly and time-consuming to complete (Wagner, 1968 and 1975). A similar definition has been given by other authors (Gibaldi and Levy, 1976) as follows: 'Pharmacokinetics is concerned with the study and characterization of the time course of drug absorption, distribution, metabolism and excretion, and with the relationship of these processes to the intensity and time course of therapeutic and adverse effects of drugs. It involves the application of mathematical and biochemical techniques in a physiologic and pharmacologic context.'

In this historical review emphasis is placed on pharmacokinetic theory and not on applications of that theory.

2. ORIGINS OF THE SUBJECT MATTER

The origins of the subject matter of pharmacokinetics are both multinational and multidisciplinary.

Buchanan in England in 1847, while describing ether anesthesia, clearly understood that the brain content of anesthetics determined the depth of narcosis and depended upon the arterial concentration, which in turn was related to the strength of the inhaled mixture. Moreover, he pointed out that for short ether inhalations, the speed of recovery was related to redistribution of ether in the body. He calculated the amounts of ether inhaled, exhaled and retained during induction with this short acting anesthetic (Buchanan, 1947; Butler, 1964).

From Germany, in 1913, Michaelis and Menten published what is now known as the Michaelis–Menten equation for describing enzyme kinetics. In pharmacokinetics, this same equation is used to describe the elimination kinetics of ethanol, salicylate, phenytoin and several other drugs (Michaelis and Menten, 1913).

Swedish investigators, Widmark and Tandberg, in 1924 published equations appro-
priate to what are now called: (a) the one-compartment open model with bolus intra-
venous injection and multiple doses administered at uniform time intervals, and (b) the
one-compartment open model with constant rate intravenous infusion (Widmark and
Tandberg, 1924).

In the United States, Haggard, in the same year (1924), published his classical articles
on the uptake, distribution and elimination of diethyl ether. He considered the distribu-
tion of ether on theoretical grounds and also showed that the drug in brain approached
equilibrium more rapidly than drug in the body as a whole and that this was the result of
the high proportional blood flow to brain (Haggard, 1924a–1924e; Butler, 1964). These
articles have always been considered a part of the basic physiology literature, but it is
obvious that they deal with the subject matter of pharmacokinetics as well. Other contri-
butions of physiologists in the United States in the early years included those of Moller
et al., of Jolliffee and Smith who introduced the concept of renal clearance and of
Hamilton et al. who reported on studies of the intravascular transport an indicator such
as a dye (Moller et al., 1929; Jolliffee and Smith, 1931; Hamilton et al., 1931). It was
Hamilton et al. who introduced the following equations:

$$V = \bar{t}Q \tag{1}$$

$$\bar{t} = \frac{\displaystyle\int_0^\infty tC\,dt}{\displaystyle\int_0^\infty C\,dt}. \tag{2}$$

In Eqns (1) and (2), V is the volume of the system, $\bar{t}$ is the mean transit time, Q is the
blood flow, and C is the indicator concentration in plasma at time t. The numerator of
the right-hand side of Eqn (2) is the area under the first moment of the concentration–
time curve, while the denominator is the area under the concentration–time curve. Equa-
tion 2 has reappeared in pharmacokinetic articles published in 1978 and 1979 (Yamaoka
et al., 1978, Benet and Galeazzi, 1979).

In 1932, Widmark theorized that, following ingestion of ethyl alcohol and its equilibra-
tion in body fluids, it disappears from the blood at a constant rate (zero-order elimin-
ation) (Widmark, 1932). Much later, Lundquist and Wolthers and Wagner et al. showed
that with moderate doses of alcohol, its elimination from human blood obeyed
Michaelis–Menten kinetics and not zero-order kinetics (Lundquist and Wolthers, 1953;
Wagner et al., 1976a). The reasons for the misinterpretation of Michaelis–Menten kin-
etics as zero-order kinetics were discussed by Wagner (Wagner, 1973a).

During the period 1939 to 1950, Dominquez in the United States made significant
contributions with articles on the pharmacokinetics of creatinine, mannitol, xylose and
galactose (Dominguez, 1934; Dominguez and Pomerene, 1934; Dominguez et al., 1935;
Dominguez and Pomerene, 1944, 1945a,b; Dominguez et al., 1947a and 1947b; Dom-
inguez, 1950). He introduced the concept of the volume of distribution and defined it as
the hypothetical volume of body fluid dissolving the substance at the same concentration
as that in plasma (Dominguez, 1934). Dominguez was also the first to derive and apply
Eqn (3) to estimate the rate of absorption of a substance as a function of time. In Eqn (3),
dA/dt is the rate

$$\frac{dA}{dt} = V\frac{dC}{dt} + VkC \tag{3}$$

of absorption at time t, V is the volume of distribution, C is the plasma drug concen-
tration at time t and k is the first-order elimination rate constant.

In 1937, Teorell, a Swedish physiologist and biophysicist, published two remarkable
articles which many now attribute as being the foundations of modern pharmacokinetics
(Teorell, 1937a,b). The model of Teorell was one of the first physiologically-based

pharmacokinetic models. It comprised a five-compartment scheme representing the circulatory system, a drug depot, fluid volume, kidney elimination and tissue inactivation. Actual physiological volumes were used for the various regions of the model. For many years he was unaware that he had made significant contributions to what later came to be known as pharmacokinetics. However, at the *Conference on Pharmacology and Pharmacokinetics, Problems and Perspectives* held at the Fogerty International Center at the National Institutes of Health in Bethesda, Maryland, U.S.A. 1972, which he attended, Teorell's contributions were recognized.

Bioavailability theory and testing has become an important topic in pharmacokinetics. Bioavailability is a term used to indicate the measurement of both the relative amount of an administered drug that reaches the general circulation intact and the rate at which this occurs. In the early years, bioavailability was called physiological availability. The concept was introduced by Oser and his associates in 1945, and their experimental work involved measurement of the bioavailability of vitamins administered in tablet form relative to their bioavailability administered in solution form (Oser *et al.*, 1945, Melnick *et al.*, 1945).

The literature on the theory and application of isotopic (radioactive) tracers contributed much to compartmental modeling and this helped in the advance of pharmacokinetic theory. Here there were many contributors and I shall cite only some of the important articles (Solomon, 1949; Lax and Wrenshall, 1953; Reiner, 1953; Solomon, 1953; Hart, 1955; Robertson, 1957; Russell, 1958; Cornfield *et al.*, 1960; Shore, 1961).

Lapp in France, in the period 1948–56, reported on a number of kinetic studies, principally involving excretion kinetics. Compounds he studied included salicylate, stovarsol, uric acid, arsenic, sulfur, chlorine, sodium, rubiazol C, quinine, a soluble bismuth compound, sulfisoxazole and N'-acetylsulfisoxazole. He pointed out the application of kinetic data in therapeutics (Lapp, 1948, Lapp, 1949; Lapp, 1950a, Lapp, 1950b; Lapp and Speiser, 1950; Lapp and Lapp, 1952; Lapp, 1952; Lapp and Nicolay, 1954; Lapp and Scius, 1954; Lapp, 1956a; Lapp, 1956b).

In 1948, Boxer and Jelinek in the United States considered the kinetics of the rise and fall of streptomycin blood concentrations with repeated dosage. They derived the equations applicable to the maximum and minimum concentrations for the one-compartment open model with bolus intravenous injection when multiple doses are given at equal time intervals, but actually applied them to the case when streptomycin was administered intramuscularly (Boxer and Jelinek, 1948). During the next year, 1949, there were two other contributions from the United States. Goldstein published the first comprehensive review of the interaction between drugs and plasma proteins (Goldstein, 1949) and Gaudino published equations defining a two-compartment open model and applied them to inulin kinetics (Gaudino, 1949).

The Dutch School made initial contributions in 1950 when DeJong and Wijans and Van Gemert and Duyff discussed the mathematical relationships between the dosage regimen and the pharmacological response. These appear to be the first articles concerned with optimization of dosage regimens of drugs (DeJong and Wijans, 1950; Van Gemert and Duyff, 1950).

In 1951, Bray and his colleagues at the University of Birmingham in England, published the first of an extensive series of articles concerning the kinetics of formation of benzoic acid from benzamide, toluene, benzyl alcohol and benzaldehyde, and its conjugation with glycine and glucuronic acid (Bray *et al.*, 1951).

In Germany, in 1953, Dost published the first edition of his book (Dost, 1953), discussed in the beginning of this chapter. *Der Blütspiegel* was an outstanding book for its time and fully covered the so-called one-compartment open model with its various forms of input. A revised edition of his book entitled *Grundlagen der Pharmacokinetik* was published in 1968.

The year 1953, when *Der Blütspiegel* was published, marks an appropriate termination of the section on the *Origins of the Subject Matter* of pharmacokinetics. The next reasonably well-defined historical period appears to be from 1954 to 1961. During this period a

few, but not many, of the articles actually concerned with subject matter in the area of pharmacokinetics used the term *pharmacokinetics*. The year 1961 was chosen to end this second historical period, since, during that year, the English language reviews of Nelson (Nelson, 1961) and Wagner (Wagner, 1961) were published and considerable acceleration in interest in pharmacokinetics occurred from that time onwards.

3. THE PERIOD 1954–1961

In 1954 Butler *et al.* published an important article concerning elimination, accumulation, tolerance and dosage schedules of phenobarbital. This drug has a long elimination half-life, varying from about 2–6 days in man, and they showed that when administered once a day, accumulation was still occurring on the twelfth day. They also showed that plasma drug concentration, during a day at steady state, rises to a peak and falls to a trough, even when the half-life of a drug is long. Many investigators appear not to recognize that the term *steady-state concentrations* does not mean constant or the same concentrations when drug is administered orally. When equal doses are administered at uniform time intervals the steady-state is characterized by the concentration, time profile reproducing itself between any two doses. If two or more doses are given each day at non-uniform time intervals (such as 0, 6 and 12 hr), then the steady-state would be characterized by the concentration, time profile reproducing itself each day.

Studies of the kinetics of elimination of glucose from blood during and after a continuous intravenous infusion (Jokipii and Turpeinen, 1954), and of the rate of absorption of water from the stomach and small bowel of human beings (Scholar and Code, 1954), are considered part of the classic literature of physiology but are also important in pharmacokinetics. A parallel exists with an article concerning the volumes of distribution and clearance values of intravenously injected creatinine in the dog (Sapirstein *et al.*, 1955). This study with creatinine is the first article where an intercompartmental clearance was mentioned and defined mathematically. Similarly, drug clearance (plasma clearance) was apparently first defined as the ratio of the intravenous dose to the area under the plasma concentration–time curve from zero to infinite time by Hoenig and Schück (Hoenig and Schück, 1956). Berman, who has made many important contributions to compartment model-building, made an early contribution with Schoenfeld (Berman and Schoenfeld, 1956). The importance of the apparent elimination half-life of a drug in terminating its action was emphasized by Swintosky and co-workers and by Butler (Swintosky *et al.*, 1957; Butler, 1958).

During this period Brodie, then at the Laboratory of Chemical Pharmacology, National Heart, Lung and Blood Institute, National Institutes of Health, published some of his classic pharmacology articles, which are important in pharmacokinetics. These were his articles on the gastric secretion of drugs (Shore *et al.*, 1957) and on the kinetics of penetration of drugs and other foreign compounds into brain and cerebrospinal fluid (Mayer *et al.*, 1957; Brodie *et al.*, 1960). Riegelman, at the School of Pharmacy, University of California, San Francisco, who has made many contributions to pharmacokinetics, initiated his publications in the area with an article on the kinetics of rectal drug absorption (Riegelman and Cromwell, 1958). One of the earliest articles showing a correlation between response and serum drug concentration reported a study of serum phenytoin concentrations as a function of dosage, the time required to reach steady-state concentrations and a correlation between phenytoin serum concentrations and the degree of electroencephalographic abnormality in patients with epilepsy (Schiller and Buchthal, 1958). Although not a part of the pharmacokinetic literature, the publication by Williams of an extensive compilation on metabolism of drugs and other organic compounds, was an important milestone and the information that the book contained was useful in pharmacokinetic studies (Williams, 1959).

Nelson, initially at the School of Pharmacy, University of California, San Francisco and later at the School of Pharmacy, State University of New York at Buffalo, made a number of important contributions to pharmacokinetics and biopharmaceutics. Prob-

ably the most important of these was his demonstration of dissolution rate-controlled absorption of drugs (Nelson, 1959; Nelson and Schaldemose, 1959).

The concept that total body water could be divided into plasma, interstitial-lymph, dense connective tissue and cartilage, inaccessible bone water, transcellular and intracellular components later aided physiologically-based pharmacokinetic model-building (Edelman and Liebman, 1959). An elegant article on the pharmacokinetics of halothane anesthesia stimulated many studies on the uptake of halothane and other anesthetic agents (Duncan and Raventós, 1959). Duncan and Raventós reported that halothane in arterial blood reached steady state after about 1 hr of anesthesia, although the brain, liver and fat continued to take up the anesthetic for many hours. During the elimination of halothane, its arterial blood concentration decreased logarithmically with a half-life of 14 min. The venous blood concentration of halothane decreased rapidly at first, then followed its rate of decrease in the fatty tissues, with a half-life of 45 min. Other important contributions during this period were: (a) publication of a fundamental integral equation (Stephenson, 1960); (b) introduction of a curve-fitting method based on polyexponential equations (Perl, 1960); and (c) introduction of the use of the analog computer for fitting and simulating pharmacokinetic data and in model building (Garrett et al., 1960; Wiegand and Taylor, 1960; Taylor and Wiegand, 1960).

During this period and later, both Nelson and Krüger-Thiemer attempted to consolidate pharmacokinetics into a single scientific discipline. Krüger-Thiemer, who worked for many years at the Forchungsinstitutes Borstel, Germany, was particularly interested in the theory and application of pharmacokinetics to dosage regimens of sulfonamides and antibiotics. He made a marked impression with his first English language paper concerning this subject (Krüger-Thiemer, 1960a), subsequently publishing many other articles in both German and English (Krüger-Thiemer, 1960b; Krüger-Thiemer, 1961; Krüger-Thiemer and Schlender, 1963; Krüger-Thiemer et al., 1966).

During the late 1950's Brodie and associates elaborated the pH-partition hypothesis and discussed its application in the mechanism of absorption of drugs from the gastrointestinal tract (Schanker, 1960). Other contributions during this period were (a) the work of Jenne et al. on the interpretation of isoniazid and p-aminosalicylic acid concentration–time curves (Jenne et al., 1960); (b) investigations of Wagner et al. with sustained release prednisolone formulations and their testing in the dog, in man and in vitro (Wagner et al., 1960); (c) the development by Jacquez et al. of physiologically-based pharmacokinetic models (Jacquez et al., 1960); (d) studies by Onchi and Asao on the absorption, distribution and elimination of diethyl ether in man (Onchi and Asao, 1961); (e) early work on the intestinal absorption of salicyclic acid by Japanese investigators (Nogami and Matsuzawa, 1961); and (f) the first of many articles by Levy on salicylates (Levy et al., 1961).

4. THE FIRST GROWTH PERIOD, 1961–1972

Subsequent text will indicate the scope of pharmacokinetics as well as pointing out minor and major landmarks in development of the theory of pharmacokinetics, along with some applications. As with any similar review there will be inadvertent omissions and possibly misplaced emphasis, but the author sincerely tried to be fair to everyone who has contributed to pharmacokinetic theory.

Biopharmaceutics may be defined as the study of the influence of formulation on the therapeutic activity of a drug product. It encompasses all possible effects of the dosage forms on biological response, and all possible physiologic factors which may affect the drug contained in the dosage form and the dosage form of the drug itself (Wagner, 1971). In 1961 the author published a review article entitled: Biopharmaceutics: Absorption Aspects which caught the eye of many pharmaceutical and other scientists (Wagner, 1961). This review, along with that of Nelson (Nelson, 1961), resulted in a marked rise in interest in pharmacokinetics. During this period, a number of books in the area of pharmacokinetics appeared. These are listed in Table 1.

In 1962, Pharmakokinetik und Arzneimitteldosierung, the first symposium with a title

TABLE 1. *Books Dealing with Pharmacokinetic Principles Published between 1961–1972*

The Mathematical Approach to Physiological Problems (Riggs, 1963)
Uptake and Distribution of Anesthetic Agents (Papper and Kitz, 1963)
Pharmacogenetics (Kalow, 1965)
Drug and Tracer Kinetics (Rescigno and Segré, 1966)
Grundlagen der Pharmacokinetik (Dost, 1968)
Multicompartment Models for Biological Systems (Atkins, 1969)
Biopharmaceutics and Relevant Pharmacokinetics (Wagner, 1971a)
Biopharmaceutics and Pharmacokinetics: An Introduction (Notari, 1971)
Guidelines for Biopharmaceutical Studies in Man (Dittert *et al.*, 1972)
Schering Workshop on Pharmacokinetics (Raspé, 1970)
Tracer Methods for *In Vivo* Kinetics: Theory and Applications (Shipley and Clark, 1972)

incorporating the term pharmacokinetics, was held in Borstel, Germany. The proceedings of this symposium were subsequently published in volume 12 of *Antibiotica and Chemotherapia*. The book and the symposium were potent forces in disseminating pharmacokinetic knowledge.

Publishing in the endocrinology area in 1963, Tait wrote a clear exposition of the meaning of clearance (metabolic clearance rate) and its relationship to hepatic blood flow, as well as the effect of postural changes on effective hepatic blood flow (Tait, 1963). It was not until ten years later that Rowland *et al.* made significantly greater use of the clearance concept (Rowland *et al.*, 1973).

A method of estimating the amount of drug absorbed per milliliter of the volume of distribution *versus* time from either blood (serum or plasma) concentration–time data or urinary excretion data, based upon the one-compartment open model, later came to be known as the Wagner–Nelson method (Wagner and Nelson, 1963). An analogous method, based on the two-compartment open model, was later called the Loo–Riegelman method (Loo and Riegelman, 1968).

The representation of certain mammillary N-pool systems by two-pool models was the subject of an interesting article published in 1964 (Shaney *et al.*, 1964). The problem of vanishing exponential terms in polyexponential equations was again treated considerably later (Wagner, 1976a; Ronfeld and Benet, 1977). These theoretical articles suggested that, if a panel of subjects were administered the same dose of drug by the same route of administration and the resulting blood (serum or plasma) concentration–time data were fitted by polyexponential equations with the statistically optimum number of terms per data set, different subjects would require different numbers of terms. Experimental verification of this prediction came with the data of Kalow and co-workers (Endrenyi *et al.*, 1976). They administered an intravenous dose of 125 mg of sodium amobarbital to seven pairs of identical twins and to seven pairs of fraternal twins. Blood samples were taken at uniform intervals and plasma was analyzed for amobarbital by a GLC method. Concentration–time data were fitted via a nonlinear estimation program and a digital computer to polyexponential equations where the optimum number of terms was decided by a statistical F-test. Results are shown in Table 2. These results may be attributed to the relative magnitudes of the coefficients and exponents characterizing the curves of the

TABLE 2. *Results of Computer Fitting Amobarbital Plasma Concentration–Time Data* (Endryi *et al.*, 1976)

Optimum number of exponential terms	Number of subjects	Percentage of subjects
1	5*	18
2	16	57
3	7	25
Total	28	100

*One of these 5 subjects gave only one exponential term on each of three different occasions.

various subjects. The authors stated: 'Variability in the number of detectable exponential terms (emphasis being given to the word 'detectable') does not necessarily imply that, in different subjects, the disposition of amobarbital is characterized by differing numbers of compartments.' The author of this chapter now thinks it is much preferred to speak or write about monoexponential, biexponential and triexponential equations rather than one, two or three compartment open models.

Several reviews were published during this period. One covered the stimulatory effect of chronic drug administration on drug-metabolizing enzymes in liver microsomes (Burns et al., 1963)—which has implications in pharmacokinetics. Another dealt with the pharmacokinetics of halothane and ether (Butler, 1964). The third was titled *Pharmacokinetics* and was the first time this topic was covered in *Annual Reviews of Pharmacology* (Wagner, 1968b). In this period, an interest in pharmacokinetic drug interactions began with the report of the effect of phenobarbital on lowering plasma concentrations of both bishydroxycoumarin and phenytoin (Cucinell et al., 1965).

Beckett and Rowland related diurnal urine pH variations with pH-dependent renal clearance of a drug. This article led to a large body of research which had implications in therapy, in drug product evaluation using urinary excretion data, in basic research, and in tests for 'doping' in sport (Beckett and Rowland, 1965).

The articles of Levy (Levy and Nelson, 1965; Levy, 1966; Levy et al., 1969; Nagashima et al., 1969) considered the kinetics of pharmacologic response and brought into focus relationships between intensity and duration of a pharmacologic response and the plasma drug concentration.

The simultaneous fitting of blood norepinephrine–time data and blood pressure–time data by Segré was also an advance in this important area of pharmacokinetics (Segré 1968). A logarithmic–logistic equation was also suggested to relate intensity of response to blood concentrations (Wagner, 1968a).

In 1965 Wagner et al. published a simple equation to estimate time-average steady state (blood, serum, or plasma) concentrations, C_{av}, from the availability factor, F, the dose, D, given every τ hr, the volume of distribution, V, and the apparent elimination rate constant, k, as shown in Eqn (4). At the time of its publication this equation was referenced to the one-compartment open model. Gibaldi and Weintraub later showed that in multicompartment systems Eqn (4) could be written as Eqn (5) where λ_z is the terminal exponential coefficient and the product $V\lambda_z$ is the clearance (Gibaldi and Weintraub, 1971). Still later Perrier

$$C_{av} = \frac{FD}{Vk\tau} \qquad (4)$$

$$C_{av} = \frac{FD}{V\lambda_z\tau} \qquad (5)$$

and Gibaldi showed that one must multiply both sides of Eqn (5) by the volume of distribution steady state, V_{ss}, to obtain the amount of drug in the body for a multicompartmental system (Perrier and Gibaldi, 1973).

It was during this period that pharmacokinetic articles which had a considerable impact on therapeutics began to appear and clinical pharmacokinetics was really 'born'. Noteworthy were the articles of Dettli on drug accumulation and dosage in patients with impaired renal function (Dettli et al., 1967; Dettli, 1970); of Jelliffe on digoxin dosage (Jeliffe, 1968); of Orme and Cutler who correlated kanamycin clearance with creatinine and inulin clearances (Orme and Cutler, 1969; Cutler and Orme, 1969); of Nagashima et al. on the anticoagulant action of warfarin (Nagashima et al., 1969); and that of Levy on the non-linear elimination kinetics of salicylate (Levy et al., 1972).

It was also during this period that Garrett further illustrated the usefulness of the analog computer (Garrett and Lambert, 1966) and Berman published details of his nonlinear estimation program, called SAAM, to be used in model-building with large digital computers (Berman and Weiss, 1966).

The mathematics of the rate of drug accumulation in the one-compartment open linear system was apparently first considered in 1968 (Wagner and Northam, 1968; Van Rossum, 1968). A year later, exact solutions were given for the number of doses required to reach various percentages of the steady state value for the one and two-compartment open model with first-order absorption (Wagner and Northam, 1968; Wagner, 1969).

Physiologically-based models were introduced to describe the handling of drugs by the artificial kidney (Dedrick and Bischoff, 1968), as well as the pharmacokinetics of thiopental (Bischoff and Dedrick, 1968) and methotrexate Bischoff et al., 1971).

The years 1967–1969 also provided many theoretical articles which later became part of classical pharmacokinetics. These articles included: (a) a new method of estimating drug bioavailability (Wagner, 1967); (b) shortcomings in pharmacokinetic analysis by conceiving the body to exhibit properties of a single compartment (Riegelman et al., 1968a); (c) the relationship between drug concentration and amount of drug in the body (Gibaldi et al., 1969); (d) the influence of route of administration on the area under the plasma concentration–time curve (Harris and Riegelman, 1969; Gibaldi and Feldman, 1969); (e) the effect of mode of administration on drug distribution in a two-compartment open system (Gibaldi, 1969); (f) volume terms in pharmacokinetics (Ronfeld and Benet, 1969) and (g) an analysis pointing out that the displacement of drugs from plasma proteins would have only a trivial effect on the plasma concentration of unbound drug, when the binding was less than 90% (Gillette, 1968). Also, in 1969, Metzler introduced the nonlinear digital computer program called NONLIN, which subsequently became very widely used (Metzler, 1969).

It is simplistic to interpret apparently multiexponential concentration–time curves on the basis of linear compartment models. Plasma protein binding and/or tissue binding of drugs are often nonlinear processes. During 1971, several authors discussed the implications of such nonlinear binding and some developed useful models (Gillette, 1971; Coffey et al., 1971; DiSanto, 1971; Wagner, 1971). During the same year, Smolen published a series of articles on assessment of drug absorption using pharmacological data (Smolen and Schoenwald, 1971; Smolen, 1971).

Suzuki et al. (Suzuki et al., 1970a,b) and Ho and Higuchi (Ho and Higuchi, 1971) discussed multicompartment diffusional models for the absorption of neutral, acidic, basic and and amphoteric drugs and applied the theory to the buccal absorption of n-alkanoic acids. These were the first in a long series of articles employing these models. At the end of this period, namely 1972, Benet published the first general treatment of linear mammillary models (Benet, 1972). This was followed later by general treatments by other authors (Vaughan and Trainer, 1975; Pedersen, 1978).

5. THE SECOND GROWTH PERIOD, 1973–1979

5.1. LITERATURE

During this period pharmacokinetic literature grew at a very rapid rate. By the end of 1972 there were several journals which published pharmacokinetic articles. Examples of these are: Journal of Pharmaceutical Sciences; European Journal of Clinical Pharmacology (from Vol. 3, No. 1, December 1970 to date; formerly Pharmacologia Clinica); International Journal of Clinical Pharmacology and Biopharmacy (formerly International Journal of Clinical Pharmacology, Therapy and Toxicology); Clinical Pharmacology and Therapeutics; and Journal of Clinical Pharmacology.

During 1973–1979 these journals continued to publish their share of pharmacokinetic articles, and, in some cases, the number increased each year. For example, in Clinical Pharmacology and Therapeutics, the numbers of articles published, which dealt with aspects of pharmacokinetics, were 43 in 1973, 63 in 1974, 88 in 1975 and over 100 in 1976.

However, many of those publishing articles in the pharmacokinetic area desired their own forum, hence speciality journals were established. The three most important of these

are: *Journal of Pharmacokinetics and Biopharmaceutics*, Vol. 1, No. 1, published in February, 1973; *Clinical Pharmacokinetics*, Vol. 1, No. 1, published in January, 1976; and *Biopharmaceutics and Drug Disposition*, Vol. 1, No. 1, published in July–September, 1979. Some other journals established during the same years, namely *European Journal of Drug Metabolism and Pharmacokinetics*, *International Journal of Pharmaceutics* and *Therapeutic Drug Monitoring*, also published many articles in pharmacokinetics.

Clinical Pharmacokinetics contains, in addition to mainly review articles and some original articles, a list of *Current References in Clinical Pharmacokinetics*. This section contained 465, 503 and 448 references for the years 1976, 1977 and 1978, respectively. During this period many books were published (Table 3).

5.2 MODELS

Models for elimination by the intact liver. As far back as 1963, Tait, in a review on the use of isotopically labelled steroids, stated: 'the metabolic clearance rate can be considered to be the blood flow through a hypothetic organ which completely and exclusively extracts the steroid' (Tait, 1963). He also gave examples where hepatic clearances of hormones were decreased both by change from the recumbent to the upright body position and by disease states, such as cirrhosis and congestive heart failure.

Two types of well-defined quantitative models have been developed which attempt to describe the elimination of substrates from the intact liver. One of these models has been called the *well-stirred* model (Pang and Rowland, 1977a,b,c) or the *venous equilibration* model (Bass, 1979). It was primarily developed by Rowland (Rowland *et al.*, 1973) but many others have made significant contributions (Gibaldi and Feldman, 1969; Gibaldi *et al.*, 1971; Perrier and Gibaldi, 1972; Perrier *et al.*, 1973a; Evans *et al.*, 1973; Shand *et al.*, 1973, 1975 and 1976; Branch *et al.*, 1973; Branch and Shand, 1976; Wilkinson, 1975; Wilkinson and Shand, 1975; Wilkinson and Schenker, 1976, Pang and Rowland, 1977a,b,c; McLean *et al.*, 1978; Kornhauser *et al.*, 1978). The other model has been called the *parallel tube* model (Pang and Rowland, 1977a) as well as the *sinusoidal perfusion* model (Bass, 1979). In quantitative terms this model has been stated most clearly by Bass *et al.* (Bass *et al.*, 1976; 1977; 1978; Bracken and Bass, 1979), but several others have been involved in its evolution (Goresky and Bach, 1970; Winkler *et al.*, 1973; Goresky *et al.*, 1973; Winkler *et al.*, 1974; Keiding *et al.*, 1976; Keiding, 1976; Keiding and Chiarantini,

TABLE 3. *Books Dealing with Pharmacokinetic Principles Published between 1973–1979*

Drug Dosage Form Design and Bioavailability (Swarbrick, 1973)
Pharmacokinetik (Gladtke and von Huttingberg, 1973)
Clinical Pharmacokinetics, A Symposium (Levy, 1974a)
Basics of Bioavailability and Description of Upjohn Single Dose Study Design (Chodos and DiSanto, 1974)
Anesthetic Uptake and Action (Eger, 1974)
Manual de Iniciacion a la Biofarmacia (Farmacocinetica Aplicado) (Plá Delfina and Pozo Ojeda, 1974)
Pharmacology and Pharmacokinetics (Teorell *et al.*, 1974)
Fundamentals of Clinical Pharmacokinetics (Wagner, 1975a)
Drug Disposition and Pharmacokinetics with a Consideration of Pharmacological and Clinical Relationships (Curry, 1974)
Biopharmaceutics and Pharmacokinetics. An Introduction, Second Edition (Notari, 1975)
Pharmacokinetics (Gibaldi and Perrier, 1975)
The Effect of Disease States on Drug Pharmacokinetics (Benet, 1976)
Pharmacokinetics of Psychoactive Drugs: Blood Levels and Clinical Response (Gottschalk and Merlis, 1976)
Biopharmaceutics and Clinical Pharmacokinetics (Gibaldi, 1977)
Industrial Bioavailability and Pharmacokinetics Guidelines, Regulations, and Controls (Martin and Doluisio, 1977)
Drug Disposition and Pharmacokinetics, Second Edition (Curry, 1977)
Clinical Pharmacokinetics: Proceedings of an International Symposium at Salzgitter-Ringelheim (Ritschel, 1977)
Pharmacokinetics (Schöfeld, 1978)
Pharmacokinetics, An Introduction (Gladtke, 1979)
Textbook of Biopharmaceutics and Clinical Pharmacokinetics (Niazi, 1979)
Drug Disposition in Humans. The Basis of Clinical Pharmacology (Creasey, 1979)

1978; Bass and Robinson, 1979). This last model has both a primitive undistributed form as well as a distributed form (Bass, 1979). The *well-stirred* model describes the liver as a well-stirred compartment with the drug in the hepatic venous blood being in equilibrium with that in the liver. The *parallel tube* model regards the liver as a series of parallel tubes with enzymes distributed evenly around the tubes and the concentration of drug declines along the length of each tube. One article of Bass gets to the crux of the difference between the two theories (Bass, 1979). There are experimental data supporting both models, and some experimental data that are not adequately explained by either theory (Pang and Gillette, 1978). The analogy between the perfusion-limited isolated organ system and the two-compartment open model with elimination from the peripheral compartment provided a physiological basis for classical pharmacokinetic compartment models (Rowland *et al.*, 1973). The articles cited in this section also clarify that the determinants of hepatic clearance are liver blood flow, the activity of drug metabolizing enzymes and the binding of drug in blood to serum proteins and cellular elements.

From the experimental findings and theoretical considerations, a number of very useful equations were derived which relate such variables as total area under the blood concentration-time curve (AUC), the intravenous dose (D) or oral dose (D_{po}), clearance of drug (CL), availability (F), extraction ratio (E) and effective liver blood flow (Q). For a drug which is exclusively eliminated by liver metabolism and completely absorbed, a novel way to write one of these relationships is shown as Eqns (6) and (7) where CL_H is the hepatic clearance, CL_H/F is the intrinsic hepatic clearance, $F = 1 - E$ and $V_{max,i}$ and $K_{m,i}$ are the maximum velocities and Michaelis constants for the various

$$CL_H = \frac{1}{\dfrac{1}{Q} + \dfrac{1}{(CL_H/F)}} \tag{6}$$

$$\frac{CL_H}{F} = \sum_{i=1}^{n} \frac{V_{max,i}}{K_{m,i}} \tag{7}$$

biotransformation reactions occurring in the liver. One can see from Eqn (6) that when intrinsic hepatic clearance is small relative to blood flow then

$$\frac{1}{CL_H/F} \gg \frac{1}{Q}$$

and hepatic drug clearance is controlled by the metabolism reaction(s) and is essentially independent of liver blood flow. Conversely, when intrinsic hepatic clearance is large relative to blood flow, then hepatic drug clearance approaches hepatic blood flow. When intrinsic hepatic clearance is usually assigned a new symbol such as CL_{int} rather than writing it as CL_H/F or $CL_H/(1 - E)$; this can get one into trouble since one might not realize when the variable CL_H is separated or not.

General treatment of linear mammillary models. As indicated above, Benet published methods to obtain the integrated expressions for the amount of drug in the central (compartment no. 1) or in any peripheral compartment of an *n*-compartment mammillary model, where elimination could occur from any one or more compartments, but where input was always into the central compartment only (Benet, 1972b). Vaughan and Trainor later derived a general disposition equation for a linear mammillary model with *n*-compartments, and used it to define disposition equations for the central compartment when drug input takes place into the central or into a peripheral compartment. Equations describing the entire time-course of drug in a particular compartment after intravenous, intramuscular, oral and rectal drug administration were presented (Vaughan and Trainor, 1975). Pederson later published another general treatment for input into one or more compartments and elimination from one or more compartments. Two approaches were described: one based on a full Laplace transformation and one that avoids trans-

formation of the input function(s) and the use of convolution integrals. The latter approach is important when dealing with complex input functions not having a simple Laplace transform (Pederson, 1978).

Cancer chemotherapy models. Jusko proposed a pharmacodynamic model for the quantitative analysis of dose–time–cell survival curves produced by the administration of cell–cycle-specific chemotherapeutic agents (Jusko, 1973). Himmelstein and Bischoff developed predictive models to simulate cancer cell populations under treatment with cytotoxic drugs, with both direct-acting and cell–cycle-specific drugs. Models of cell growth kinetics were combined with simple pharmacokinetic models to complete the cell–drug interaction system (Himmelstein and Bischoff, 1973a). These models were applied to the treatment of L1210 leukemia in mice with ARA-C (1-β-D-arabinofuranosylcytosine) and the results of various treatment schedules were simulated; the simulated data agreed quite well with experimental data (Himmelstein and Bischoff, 1973b). Physiologically-based pharmacokinetic models for anticancer drugs were reviewed by Chen and Gross (Chen and Gross, 1979a).

Other physiologically-based pharmacokinetic models. The physiological pharmacokinetic approach to the modeling of drug distribution was reviewed (Himmelstein and Lutz, 1979). One advantage of such modeling is that it allows extrapolation outside the range of data, with some confidence, if the dominant mechanisms of transport are sufficiently well understood. Another advantage is that one may scale from a species of one size to that of a larger or smaller size. The compartments of such models correspond to anatomical spaces so that biochemical interactions, including drug effects or pharmacodynamics, may be incorporated in the model.

Two experimental methods are important with respect to these models. Rane *et al.* described a method to predict intrinsic clearance for an *in vivo* model from enzyme kinetic data obtained *in vitro*. They reported a remarkably good correlation between hepatic clearance predicted by the method and the clearance observed in isolated liver preparations. The method, in effect, utilizes Eqn (7) above (Rane *et al.*, 1977). Important parameters in the development of physiologically-based models are the tissue-to-plasma partition coefficients. The estimation of these parameters have been discussed in detail (Chen and Gross, 1979b).

Stochastic models. Several articles dealing with stochastic theory of one- and two-compartment systems (Purdue, 1974), as well as the solution for an *n*-compartment system with irreversible time-dependent transition probabilities (Cardenas and Matis, 1974), have appeared. In addition, a general time-independent stochastic model was described (Faddy, 1976). Vaughan and Hope discussed applications and advantages of a recirculatory stochastic pharmacokinetic model for representing drug distribution and elimination (Vaughan and Hope, 1979).

Linear plasma protein and tissue binding. Levy and Yacobi showed that the total plasma clearance of the highly plasma protein bound drug, warfarin, in rats was a linear function of the free (unbound) fraction of drug in plasma (Levy and Yacobi, 1974b; Yacobi and Levy, 1975 and 1977).

Gillette has published articles which illustrate the importance of linear plasma protein and tissue binding in drug disposition (Gillette, 1971 and 1973; Gillette and Pang, 1977) and the literature on such binding has been well reviewed (Wagner, 1973b; Jusko and Gretch, 1976). Simple pharmacokinetic models incorporating linear plasma protein binding, linear tissue binding and first-order elimination of free (unbound) drug were studied intensively (Wagner, 1976b; Gibaldi and McNamara, 1978).

Based on an equation of Gillette (Gillette, 1971), Wilkinson and Shand proposed that Eqn (8) would apply, where V is the apparent volume of distribution of a drug with respect to the total systemic venous drug concentration, V_B represents the blood volume, V_T represents the volume of

$$V = V_B + V_T\left(\frac{fu_b}{fu_T}\right) \tag{8}$$

other tissues of the body into which the drug distributes and fu_T and fu_b are the fractions of drug present in the unbound form in the tissue and blood, respectively (Wilkinson and Shand, 1975). Gibaldi and McNamara showed a derivation of an equation with the same form as Eqn (8), but the symbols were defined as follows: V_B is the plasma volume, V_T is the difference between the volumes of total body water and plasma, and fu_T is the fraction of drug unbound in tissue (i.e. the weighted average fraction of free drug in extraplasma space) and V is the steady-state volume of distribution (Gibaldi and McNamara, 1978). This is a considerably different interpretation of the equation. The latter equation was then used to derive some other relationships concerning the effect of plasma protein and tissue binding on the biologic half-life of drugs (Gibaldi et al., 1978). However, Øie and Tozer pointed out that the interpretation of Gibaldi and McNamara did not take into account that plasma proteins are also distributed throughout the extracellular fluids. They derived a much more complicated expression for the volume of distribution of a drug (Øie and Tozer, 1979).

Nonlinear pharmacokinetics and models. Evidence of nonlinearities in pharmacokinetic data goes back to the early 1930's, with the origination of the concept that ethyl alcohol is sometimes eliminated at a fixed rate, independent of its concentration in the body. The author's review article (Wagner, 1973b), contained references to over 160 articles which suggest evidence of nonlinearities in drug absorption, distribution, metabolism and excretion and the pharmacokinetics of drug action. A later review also presented extensive evidence of nonlinearities (Jusko and Gretch, 1976). Nonlinear elimination kinetics will be considered first, followed by nonlinear plasma protein and tissue binding.

By means of theoretical considerations and simulations it was shown that an apparent increase in the biological half-life of a drug with increasing dose could result from product inhibition if the dissociation constant for the drug metabolite–enzyme complex is appreciably lower than the Michaelis constant for the drug–enzyme complex, if drug metabolite concentrations remain relatively constant for some time as a result of slow elimination of the metabolite, and if the level of drug in the body does not appreciably exceed the apparent *in vivo* Michaelis constant (Perrier et al., 1973b). A theory which explains phenomena exhibited by pooled nonlinear pharmacokinetic systems and equations relating pooled Michaelis–Menten constants Vm_p, Km_p, to microscopic constants Vm_i, Km_i was presented (Sedman and Wagner, 1974). A model, based on physiologic considerations, was shown to describe the entire time course of blood alcohol concentrations after four different doses of alcohol administered orally (Wilkinson et al., 1977). If elimination obeys Michaelis–Menten kinetics, the rate of accumulation depends not only on the magnitudes of the maximal velocity and Michaelis constant but also on the rate of drug input to the body. Simulations of the time course of drug accumulation were carried out for phenytoin—a drug whose elimination obeys Michaelis–Menten kinetics (Wagner, 1978; Ludden et al., 1978; Lam and Chiou, 1979). These theoretical predictions were supported by the measurement of phenytoin serum concentrations (Allen et al., 1979).

Kunka and Mattocks showed that one of the nonlinear models of DiSanto (1971) and Wagner (1971b) adequately described the pharmacokinetics of acetazolamide in the rabbit (Kunka and Mattocks, 1979). The model employed involved two saturable tissue binding sites and first-order elimination of free (unbound) drug. Extraction of propranolol by the perfused rat liver was shown to be dose-dependent (Evans et al., 1973). This article, by Evans et al., is unique in that it is the only work with physiologically-based modeling in which the parameters were simultaneously and statistically best fitted to the data. The pharmacokinetic analysis provided new insight into the biology of the system which was not apparent from the raw data, or from any simple manipulation thereof. The clinical importance of the nonlinear plasma protein binding of disopyramide was emphasized. In the 12 patients studied, at any given total disopyramide plasma concentration, there was approximately a twofold range in the fraction of disopyramide unbound to plasma proteins. Hence mean plasma protein binding data or data on protein binding obtained from pooled plasma are of little value in a given patient, for

predicting unbound disopyramide concentrations from measurements of total disopyramide concentrations (Meffin *et al.*, 1979).

Simulation of plasma drug concentration–time profiles for a number of systems incorporating nonlinear plasma protein and/or tissue binding were reported. For the extensive conclusions the original articles should be consulted (McNamara *et al.*, 1979a,b). One of the conclusions of this work was that for nonlinear plasma protein and/or tissue binding models there will always be a pronounced 'α-' or 'distribution' phase after cessation of an infusion for any length of time, whereas in a linear pharmacokinetic system the 'α-' or 'distribution' phase tends to disappear the longer is the infusion time. However, in linear systems it is not only the infusion time but also the value of the ratio $C_2\lambda_1/C_1\lambda_2$ which determines the degree of disappearance of the α-phase (Kampman, 1979); here C_1 and λ_1 are the coefficient and the exponential coefficient respectively, of the first term and C_2 and λ_2 are the coefficient and exponential coefficient of the second term of the biexponential equation for a linear system after bolus intravenous administration.

How the area-dose and area-initial plasma concentration relationships may be used to study nonlinear processes was explored and a general theorem proven. Assuming Michaelis–Menten elimination kinetics and Langmuir type tissue binding, several area-dose and area-initial plasma concentration relationships were derived (Chau, 1976).

Miscellaneous. Pharmacokinetic models and the basic concepts involved in applying models to blood, urine, bile and tissue levels of drugs and metabolites were reviewed (Garrett, 1973). The principle of area analysis was used in the development of a metabolic and pharmacokinetic model for an extensively biotransformed drug, N_4-ethoxyacetyl-sulfamethoxazole in the monkey (Kaplan *et al.*, 1973). The first attempt to define quantitatively by radioautography the rate and extent of metabolism of a cephalosporin antibiotic in animals and man was made by Cabana *et al.* They also established, by renal and metabolic clearance measurements, the definite role of the kidney in drug metabolism. Their studies demonstrated that the renal clearance of desacetylcephapirin, an active metabolite of cephapirin, was not proportional to its plasma concentration and that the clearance far exceeded renal plasma flow (Cabana *et al.*, 1975). Niazi defined a volume of distribution as a function of time for a multicompartment model; it equals the usual value, based on area considerations, in the log-linear phase of plasma concentration–time data (Niazi, 1976). A linear recirculation model for drug disposition in which disposition is regarded as the result of repetitive passes of the drug around the circulation was described (Cutler, 1979). A new definition of a compartment in pharmacokinetic modeling was published (Cutler, 1978a).

5.3. MODEL-INDEPENDENT METHODS

The convolution integral of Stephenson (Stephenson, 1960) is useful in linear systems analysis (Cutler, 1978b). Numerical deconvolution methods were described and illustrated by several authors (Rescigno and Segré, 1966; Benet and Chiang, 1972a; Wagner, 1975b; Cutler, 1978c,d).

Dost's law of corresponding areas was stated as: 'the ratio of the area beneath the blood level–time curves, after oral administration to that following intravenous administration of the same dose, is a measure of the absorption of the drug administered' (Dost, 1968). When 'absorption' is equated with 'efficiency of absorption' both Nüesch (Nüesch, 1973) and Vaughan (Vaughan, 1977) offered proofs of Dost's law. However, a drug may be completely absorbed but only a fraction of the dose reach the circulation intact as a result of the 'first pass' effect. Hence, Wagner suggested that Dost's law of corresponding areas be replaced by Eqn (9), where F is the fraction of the dose, D_{p0}, which is absorbed $(0 \leq F \leq 1)$, F^* is the bioavailability

$$FF^* = \frac{\left[\int_0^\infty C\, dt\right]_{p0}}{\left[\int_0^\infty C\, dt\right]} \cdot \frac{D}{D_{p0}} \tag{9}$$

factor due to the first-pass effect $(0 \leq F^* \leq 1)$, D and D_{po} are the intravenous and oral doses, respectively, and the integrals are the total areas under the concentration–time curves following oral and intravenous administration, respectively. He also showed that for some models $F^* = 1$ and for others $F^* \neq 1$ (Wagner, 1976c). In the real world we also know that drugs with high hepatic clearances have a significant liver 'first-pass' effect and that other drugs are metabolized as they pass through the gut wall, which also would make F^* less than unity. Dost also extended his method to obtain an absorption profile of the drug via a graphical procedure, which was shown by Galeazzi and Benet to be the graphical equivalent of the Wagner–Nelson method (Galeazzi and Benet, 1976; Wagner and Nelson, 1963). Still later Dost (Dost, 1970a,b) extended his graphical procedure to multicompartment systems, but this was shown to be inappropriate (Galeazzi and Benet, 1976).

Some model-independent prediction methods for use in pharmacokinetics were discussed by Amidon et al. (Amidon et al., 1975). One of these was a method to estimate the asymptote of a curve when the values of the function are approaching the asymptote according to first-order kinetics (monoexponential function). Their method employed three concentration–time points and was extended to any number of points (Wagner and Ayres, 1977). These methods are most useful for estimating the area under a concentration–time curve from zero to infinite time or the cumulative amount of a drug excreted in the urine in infinite time after a single dose of drug. The method was later extended to biexponential processes (Newburger et al., 1979).

An important parameter in pharmacokinetics is the volume of distribution steady state, which has had an interesting history. If the kinetics are linear then the time course of the plasma drug concentration, C, following a single i.v. bolus dose will be given by Eqn (10). The volume of distribution steady state, V_{ss}, is then given by Eqn (11),

$$C = \sum_{i=1}^{n} C_i \, e^{-\lambda_i t} \tag{10}$$

where A_{eq} and C_{eq} are respectively the amount of drug in the body and the plasma drug concentration at equilibrium (i.e. the instant in time when the rate of change of drug in the one or more peripheral compartments of the n-compartment mammillary model is equal to zero), $k_{12}, k_{21}, \ldots k_{1n}, k_{n1}$ are the forward

$$V_{ss} = \frac{A_{eq}}{C_{eq}} = \left[1 + \frac{k_{12}}{k_{21}} + \cdots + \frac{k_{1n}}{k_{n1}} \right] V_1 = \frac{\bar{A}_{ss}}{\bar{C}_{ss}} = \frac{D \sum_{i=1}^{n} C_i/\lambda_i^2}{\left[\sum_{i=1}^{n} C_i/\lambda_i \right]^2} = \frac{D \int_0^\infty tC \, dt}{\left[\int_0^\infty C \, dt \right]^2} = \bar{t}CL \tag{11}$$

and reverse first-order rate constants between the peripheral compartments and the central compartment, V_1 is the volume of the central compartment, $\bar{A}_{ss}$ and $\bar{C}_{ss}$ are the average amount of drug and concentration, respectively, at steady state in the n-compartment mammillary model with elimination from the central compartment only, D is the dose after bolus intravenous injection, $\bar{t}$ is the mean residence time [see Eqn (2)] and CL is the mean drug clearance. Riggs first defined V_{ss} for the two-compartment open mammillary model with elimination from the central compartment only (i.e. $n = 2$), using the second and third equalities of Eqn (11) (Riggs, 1963). V_{ss} and other 'volumes of distribution' were discussed later (Riegelman et al., 1968b). A volume of distribution was defined by the equivalent of the fifth equality of Eqn (1) in a footnote of a table in a chapter by van Rossum (van Rossum, 1971). The derivation of the fifth equality of Eqn (11), based on the fourth equality was given by Wagner (Wagner, 1976d). Oppenheimer et al. (Oppenheimer et al., 1975) defined a noncompartmental volume of distribution with the sixth and seventh equalities of Eqn (11). Benet and Galeazzi clarified that this noncompartmental volume of distribution was equivalent to the V_{ss} which had been used for many years, and that the integrals in the sixth equality of Eqn (11) could be estimated

directly from C, t data without use of a model at all (Benet and Galeazzi, 1979). Hence a volume that was originally defined very restrictively has evolved into a model-independent term.

5.4. OPTIMAL INPUT CALCULATIONS

A safe method for rapidly achieving plasma concentration plateaus (i.e. steady-state concentrations) based on the two-compartment open model and involving two consecutive infusion rates was reported (Wagner, 1974). Later a general derivation was made and applied to steady-state concentrations of lignocaine (Vaughan and Tucker, 1976). In addition, a general method was described for computing drug regimens which are optimal in the sense of minimizing the sum of squared deviations of the predicted drug concentration in a compartment from a desired concentration in that compartment (Wheeler and Sheiner, 1976).

5.5. COMPUTERS AND STATISTICAL ANALYSIS

Several important statistical aspects of pharmacokinetic analysis were discussed (Boxenbaum et al., 1974). These included selection of appropriate equations, weighting of data, precision of parameter estimates, analysis of weighted residuals, and criteria useful in selection of the final model. Colburn et al. published a digital computer program which utilizes the nonlinear least squares regression program NONLIN (Metzler, 1969) to fit particular models to concentration–time data when the data are collected during repetitive dosing of the drug (Colburn et al., 1976). Sheiner et al. described a method of estimating population characteristics of pharmacokinetic parameters from routine clinical data (Sheiner et al., 1977). Several drug concentration values from each individual, along with dosage information and the results of other routinely assessed variables suffice for purposes of analysis. The generality and appropriateness of the analytic technique were demonstrated by analysis of a set of data derived from 141 patients who were receiving digoxin. The usefulness of statistical moments of concentration–time data was emphasized (Yamaoka et al., 1978). A digital computer study using simulated data with random error indicated no difference in the precision and accuracy of parameter estimation when several different equations were fitted to the data, each set of which related to the same model (Wong et al., 1979).

In 1974, AUTOAN, a decision-making pharmacokinetic program, was made available, and subsequently described (Wagner, 1975a). This program is really a large so-called DFUNC subroutine of the digital computer program NONLIN (Metzler, 1969).

5.6. BIOAVAILABILITY

Factors affecting the magnitude of the 'first pass' effect were discussed in detail (Riegelman and Rowland, 1973; Benet, 1978) and the effect of the route of administration and the distribution of the drug on drug action were reviewed (Benet, 1978). A method was proposed for estimating the bioavailability of a drug whose elimination from a one-compartment body model occurs by one or more apparent first-order processes in parallel with one capacity-limited or Michaelis–Menten pathway (Martis and Levy, 1973). Some new methods of estimating drug bioavailability under single dose and quasi- and nonsteady-state conditions were described in detail (Kwan and Till, 1973; Till et al., 1974, Kwan et al., 1975). The use of data derived from the monitoring of the time variation of the intensity of a pharmacological response or effect following dosing has been championed by Smolen; such data can be utilized in bioavailability assessment (Smolen and Wiegand, 1973; Smolen, 1976a,b). An excellent example of how to differentiate between liver and gastrointestinal 'first pass' metabolism was reported (Cotler et al., 1976). Albert et al. (Albert et al., 1979) showed that within-lot and between-lot uniformities in bioavailability of methylprednisolone from commercial tablets are very similar,

suggesting that the observed variability in serum methylprednisolone concentrations was not the result of manufacturing variables. Some important aspects of estimating bioavailability of digoxin were discussed and illustrated (Wagner and Ayres, 1977).

5.7. DRUG INTERACTIONS

Rowland and Matin pointed out that since many drug–drug pharmacokinetic interactions are dependent on the concentrations of the interacting species, the degree of interaction should be a graded phenomenon varying with the drug and/or metabolite concentration and thus drug administration and time. They discussed the interaction of phenobarbital with griseofulvin, sulfaphenazole with tolbutamide, and warfarin with phenylbutazone and stressed the importance of measuring not only intact drug administered but also metabolites in drug interaction studies (Rowland and Matin, 1973). Levy reviewed some pharmacokinetic approaches to the study of drug interactions (Levy, 1976). A steady-state blood concentration method for detecting and quantitating drug–drug interactions was illustrated by the ethanol–propranolol interaction in the cat (Wagner et al., 1976b). Gillette and Pang used a blood flow rate-limited (physiologically-based) type of model to indicate the possible effects of drug interactions on measurable variables (Gillette and Pang, 1977).

5.8. CLINICAL PHARMACOKINETICS

As indicated in a previous section of this chapter the number of published articles specifically in the clinical pharmacokinetics area had reached at least a rate of 400–500 articles per year by 1979. In writing this section no attempt has been made to review and/or evaluate this large body of literature or to choose what the author considers to be the most important articles, as was done in most of the other sections of this chapter. Rather, the few articles discussed below are merely examples of the literature.

One type of clinical pharmacokinetic article may be classified as educational, where the purpose is to acquaint those unfamiliar with pharmacokinetics with the terminology and examples. This type is exemplified by the articles of Gibaldi and Levy entitled *Pharmacokinetics in Clinical Practice*, which were published in the *Journal of the American Medical Association* (Gibaldi and Levy, 1976a,b), and by the article of Dettli, in which he discussed examples of pharmacokinetic analyses which influence the practice of therapeutics (Dettli, 1973).

Another type of article consists of a compilation and quick reference. An example here is the article of Pagliaro and Benet who critically compiled values of terminal half-lives, percent drug excreted unchanged in urine, and changes of half-life in patients with renal and hepatic dysfunction (Pagliaro and Benet, 1975).

A third type of article is one directed at describing pharmacokinetic monitoring of a drug during therapy. The specialty of clinical pharmacokinetics encompasses the rational employment of theoretical pharmacokinetics to evolve practical guidelines for drug therapy in patients, with subsequent assessment of the utility and appropriateness of such guidelines by monitoring serum concentrations. The article of Koup et al. describing a system for guiding and monitoring theophylline therapy serves as an example in this area (Koup et al., 1976).

A fourth type of article is the review, frequently bearing a title such as 'The Clinical Pharmacokinetics of Drug X'. The issues of the journal *Clinical Pharmacokinetics* have carried many such reviews and these now are too numerous to be listed.

The fifth type of article is the 'original literature' type where new experimental data are presented. An example here is the article by Klotz et al. who reported on the effect of age and liver disease on the disposition and elimination of diazepam in adult men (Klotz et al., 1974). The prolongation of the apparent elimination half-life of diazepam was shown to be caused by two different mechanisms: (1) in liver disease metabolic clearance is decreased; (2) in aging the volume of distribution of the drug is increased. The authors

also explored the role of altered disposition in the frequency of side effects resulting from administration of diazepam.

Pharmacokinetics should not be viewed in isolation, but rather as a tool to improve rational drug therapy. The rapid growth of pharmacokinetics during the past two decades has been made possible largely by vast improvements in analytical methodology. Listed below are ideas (see Acknowledgement) on the possible future use of pharmacokinetics in patient care. Some of these are being performed at the time of writing, but perhaps their use will become more widespread in the future.

Future use of pharmacokinetics for patient care include:

(1) Individualization of patient dose and dosage regimen.

(2) Use of pharmacokinetic parameters as variables to guide rational synthesis and testing of new chemotherapeutic agents.

(3) Development and use of non-invasive methods of assessing drug concentrations in patients.

(4) Characterization and prediction of the time course of the intensity of pharmacologic effects.

(5) Continuation and improvement in the use of pharmacokinetics in the assessment of the bioavailability of a drug, from different dosage forms and the same dosage form made by two or more manufacturers, or given by different routes.

(6) More emphasis on a comparison of intra- and inter-subject variabilities in pharmacokinetic parameters.

(7) Possible development of a 'sub-therapeutic cocktail' of various compounds, followed by routine analysis of biological samples taken from the patient, to obtain profiles of the compounds which would reflect the magnitudes of pharmacokinetic parameters which, in turn, would be useful in guiding therapy in the drugs.

(8) Aid in determining the mechanism of drug–drug interactions and their avoidance.

(9) Use of pharmacokinetic principles to guide in the use of some drugs in some patients.

(10) Development of pharmacokinetic laboratories and/or centers throughout the world to guide physicians in their use of drugs.

(11) Prediction of pharmacokinetics of drugs in man from results obtained in animals, using physiologically-based models and scale-up factors.

(12) Use of pharmacokinetics as a diagnostic tool, such as in acetylation testing.

(13) Improvement in the quality and specificity of drug use in patients.

(14) Identification of optimum methods to accelerate drug elimination from the body in cases of toxicity and/or overdosage.

(15) Identification of active metabolites of drugs and quantitation of their role in producing the overall response following drug administration.

(16) Development and use of sophisticated digital computer programs to obtain population estimates of pharmacokinetic parameters and their variabilities, which, in turn, would aid in drug therapy of other patients.

(17) Education of physicians and other health professionals concerning what pharmacokinetics can do in improving the rational use of drugs.

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