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[Special Lecture]

Prediction of Drug Distribution in Body Based on Physiological Pharmacokinetics from Animal to Human and from Health to Disease

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Effectiveness and safety of a developing drug in a patient have to be predicted on the basis of accumulated animal experiments before a clinical study. A suitable dosage regimen for an individual patient has to be arranged on the basis of a prediction for effectiveness and toxicity to the case of disease. Many difficulties, however, exist in the prediction due to discrepancy in drug actions between human and animal, and also between disease and health. Especially, it is well known that a clinical study based on uncertain predictions of drug action frequently brings us ethical and economic problems on a development of new drug.

Recently, the discrepancy of drug action is widely recognized to come from the different level and the time course of active drug in the target tissue. We will be able to have a great progress to over come the present difficulty in the development of new drugs, if we can quantitatively predict the concentration profiles of drug in a human body, especially in diseases before the application of drug.

Scheme I— Factors for the Alteration of Drug Behavior in the Body.

1. Anatomic factors(organ weight, etc.)
2. Physiological factors(blood flow, etc.)
3. Biochemical factors(activities of drug metabolizing enzymes, and bindings of drug to plasma and tissue protein, etc.)

These three factors shown in Scheme I make difference on the drug concentration in a body. The anatomic factors involve body weight, tissue weight, circulative character of organ, and so on. The physiological factors mean mainly blood flows in various kinds of tissue and organ. The biochemical factors involve activities of drug metabolism, abilities of drug excretion, and bindings of drug to plasma and tissue.

Many researches have been studied on the correlation between these factors, for example, the body weight and the diagnostic variables, and the pharmacokinetics of drug. The correlation between standard drugs, for example, antipyrine, and thera-

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peutic drugs on kinetic properties have been used in order to predict the drug concentration in a patient.

These methods of prediction, however, lack generality and systematic consideration through variety of drugs, species of animal and conditions of disease, because the methods are not based on the actual and clear physiological mechanism. Notwithstanding the weak point, this method is practically worth enough for a certain drug.

The recent development of pharmacokinetics based on the physiological mechanism have made us realize usefulness to make a general system on the prediction of drug concentration profiles from animal to human, from health to disease, and also on drug interactions. From the view point of physiological pharmacokinetics, the plasma concentration of drug is a direct reflection of tissue distribution and activity of eliminating organ. A success of the prediction on plasma concentration, therefore, involves naturally that on tissue concentration, too.

Scheme II—Characteristics of Physiological Pharmacokinetics.

1. Compartment: actual(anatomic) tissues and organs.
2. Drug transfer between compartments: circulatory blood flow.
3. Drug disappearance: organ(intrinsic) clearance.
4. Drug distribution in tissue and organ: partition coefficient of drug between plasma and tissue(calculated from binding ratios of drug to plasma and tissue protein).

In the physiological pharmacokinetics(Scheme II), the time course of drug concentration in tissue is calculated from the mass balance equations applied everywhere in a body. The body consists of many kinds of tissue and organ, and moreover, the behavior of drug molecule in tissue is sometimes very complex. The equation of mass balance, therefore, becomes numerous and complex if we calculate strictly and precisely the mass balance. The integrated solution of many simultaneous differential equations of mass balance, however, is very difficult, even if we can use a well developed computer today.

The next two main assumptions are usually used in order to simplify the mass balance equation. At first, the equilibrium of drug concentration between tissue and capillary blood takes place instantaneously. This means that the transport of drug molecule across cell membrane is much quicker than the movement of drug with capillary blood flow. Secondly, the concentration of drug in the veinal outlet from tissue is equal to the mean concentration in whole capillary at the same time, and then the drug level in capillary is uniform from the inlet to the outlet in tissue.

This assumption looks peculiar because the drug in capillary must be reduced in concentration from the inlet to the outlet due to its distribution into cell and its elimination from organ. Notwithstanding the peculiarity, this assumption leads us to the simplest expression of mass balance equation and is called the well stirred model because of an analogue of organ to a liquid tank which is well stirred.

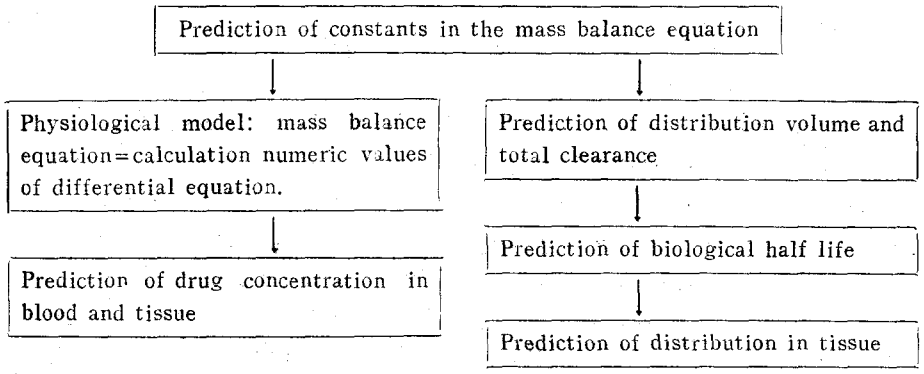
Scheme III—Equation of Mass Balance.

Tissue Volume(V_T)×Increasing Rate of Drug Concentration in Tissue(dC_T/dt)= Blood Flow through Tissue(Q_T)×Drug Concentration in Incoming Plasma(Cpi)/ Plasma Concentration Ratio of Drug to Total Blood Concentration(s)−$Q_T \times C_T$/ Partition Coefficient of Drug between Plasma and Tissue(K_{PT})/s −Fraction of Unbound Drug in Tissue (f_T)×Intrinsic Tissue Clearance (CL_T^{int})×C_T+Drug Administration Frequency and Metabolic Rate

Scheme III shows a definite equation of mass balance. The first line is the increasing rate of drug amount in tissue. It is expressed by the product of tissue volume and increasing rate of drug concentration. The second and the third lines are the influx of drug into tissue with blood flow. It is expressed by the product of whole blood concentration of drug and blood flow rate through tissue. In this equation, the whole blood concentration is expressed by the plasma concentration and the value of concentration ratio between whole blood and plasma. The fourth line is the outflux of drug from tissue with blood flow. It is expressed by the whole blood flow rate, the drug concentration in tissue, the partition coefficient between tissue and plasma, and the concentration ratio between whole blood and plasma. The fifth and the sixth lines show the rate of elimination. It is expressed by the free fraction of drug in tissue, the intrinsic clearance, and the concentration of drug in tissue.

This mass balance equation shows well a feature of the prediction method by means of the physiological pharmacokinetics. Any discrepancy of kinetic properties on various conditions is always described by the difference of the limited number of constants which appear in the equation of mass balance. This may be claimed to be over simplification. These constants like the intrinsic clearance and the partition coefficient between tissue and plasma, however, will be able to be calculated on the basis of the activities of drug metabolic enzyme and the drug binding properties to blood and tissue. I should say that the physiological pharmacokinetics always has the developing biological sciences for the background.

Scheme IV—Prediction of Drug Behavior in the Body by Physiological Pharmacokinetics.



Scheme IV shows the process of prediction by means of the physiological pharmacokinetics. In the process shown on the left side, at first the constants in the mass

balance equation are predicted from the mechanism of drug disposition in a body and from the correlation among species of animal and among conditions of disease. And then, the simultaneous differential equations are built using these predicted constants in the mass balance equations at the several main tissues and organs. Finally, the prediction of drug concentration in tissue and blood is made by the numerical integration of the differential equations using a computer. The animal scale-up technique which has shown beautiful success in a certain drug belongs to this method. In the animal scale-up, some constants of large animals are assumed to be the same as those measured by small animals.

The process shown in right side is an approximate prediction method tried newly by us. The concentration of drug in circulating blood can be estimated very roughly from the total clearance and the volume of distribution. We can also calculate the biological half life from these two values. The drug concentration in tissue can be easily predicted, if we know the partition coefficient between tissue and blood.

This method of prediction does not need the complex numerical computation with digital computer. It is also very easy to understand the effects of physiological constants and parameters on the distribution and degradation of drug in a body.

$$CL = \frac{Q \cdot fp \cdot CL_{int}}{Q + fp \cdot CL_{int} \cdot S}$$

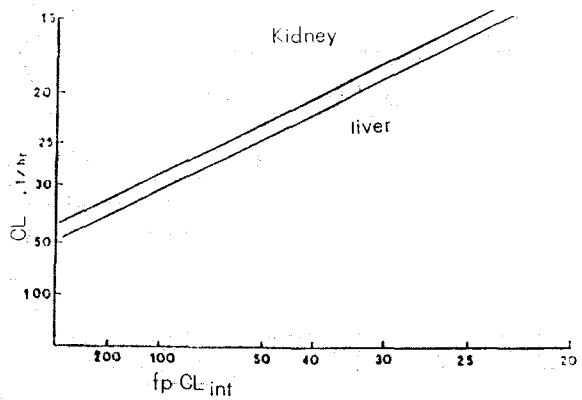


Figure 1—Organ clearance.

The total clearance is the sum of hepatic and renal clearances in most drugs which are mainly eliminated from liver and kidney. The product of organ clearance and arterial blood concentration flowing in the organ expresses the rate of drug elimination. The equation shown in Fig. 1 is derived from the mass balance equation. The organ clearance is calculated from the intrinsic clearance, the free fraction, the blood flow, and the ratio which represents the drug partition to blood cell. The maximum rate of drug elimination in organ is equal to the inflow rate of drug with blood flow into organ. When the product of free fraction and intrinsic clearance is much larger than the blood flow, for example, in the case of human liver, the product lager than two hundred, the organ clearance is almost equal to the blood flow.

When the product is small, less than twenty in human liver, the organ clearance becomes close to the product of free fraction and intrinsic clearance. The intrinsic clearance is reversely estimated from the total clearance and the metabolic or the excretion ratio of drug elimination. The intrinsic clearance is a limit of organ clearance when the blood flow rate is infinitely large and the free fraction is a hundred per cent. Then the intrinsic clearance represents the ability of drug elimination in the organ. In drug metabolic elimination, the intrinsic clearance is related to the total activity of metabolic enzyme in the organ.

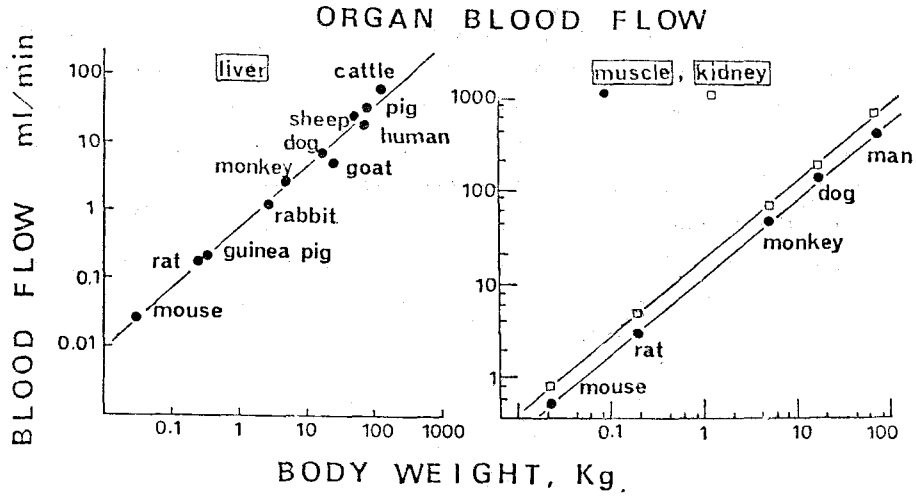


Figure 2—Body weight and blood flow.

Fig. 2 shows the relationship between blood flow and body weight in various animals. The left side is on the hepatic blood flow reported by Boxenbaum. The right side is on the renal blood flow reported by Bishoff. The blood flow in muscle is also shown in the figure. All data fit on a straight-line in a logarithmic graph. This relation means that the blood flow is proportional to the certain powers of body weight.

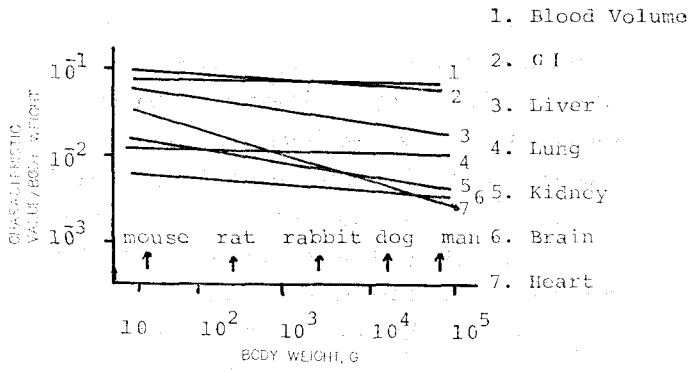


Figure 3—Body weight and organ weight.

The same relationship is known on weights of tissue and organ. Fig. 3 is made from the power number reported by Adolf. The power number on tissue weight is different in each tissue. The bigger animals have the smaller liver and kidney as compared with the body weight. The proportionality of blood flow and tissue weight to the body weight shows the possible prediction of these values from the other animals as the function of body weight only.

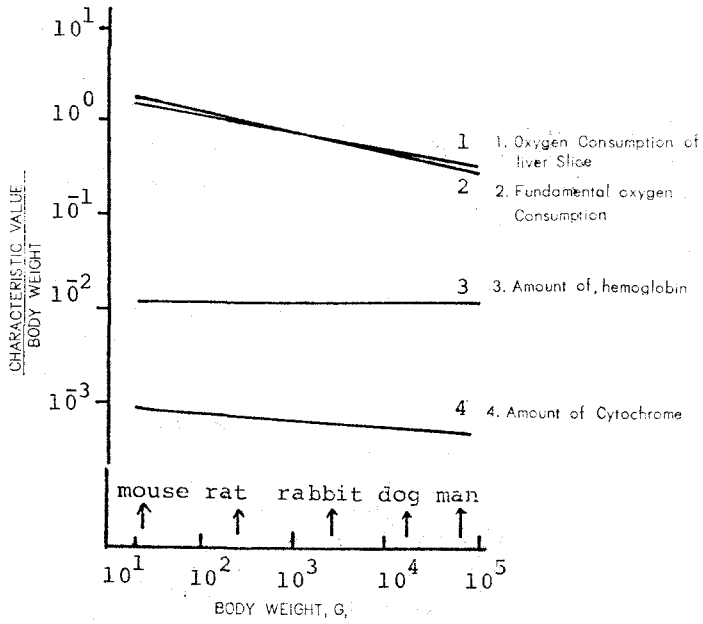


Figure 4—Body weight and physiological characteristic values.

Fig. 4 shows the same relationship on same physiological activities reported by Adolf like the tissue weight. As well known, the physiological activities per body weight are decreased with increasing the body weight among animals. The same relationship

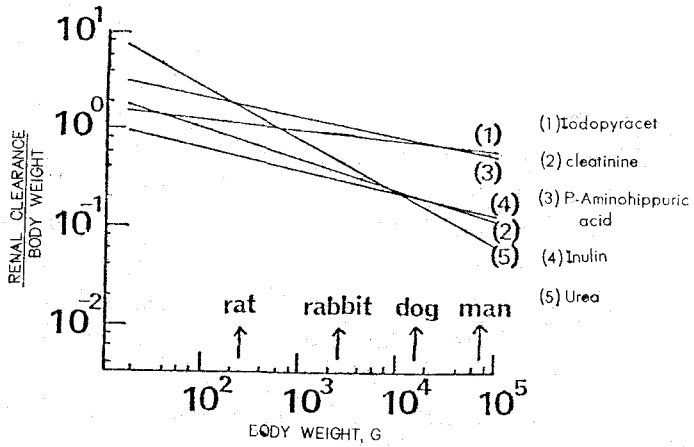


Figure 5—Body weight and renal clearance.

between the elimination clearance and the body weight can take place, since the drug elimination is also a reflection of physiological activities.

This graph shown in Fig. 5 is the relationship between renal clearances of some diagnostic drugs and body weights of various animals, which are made from the reports of Adolf. The renal clearance per body weight is decreased with increasing body weight. Since the mechanism of renal excretion of diagnostic and usual therapeutic drugs is related to each other, the same kind of relation to the body weight must exist in the renal clearances of therapeutic drugs.

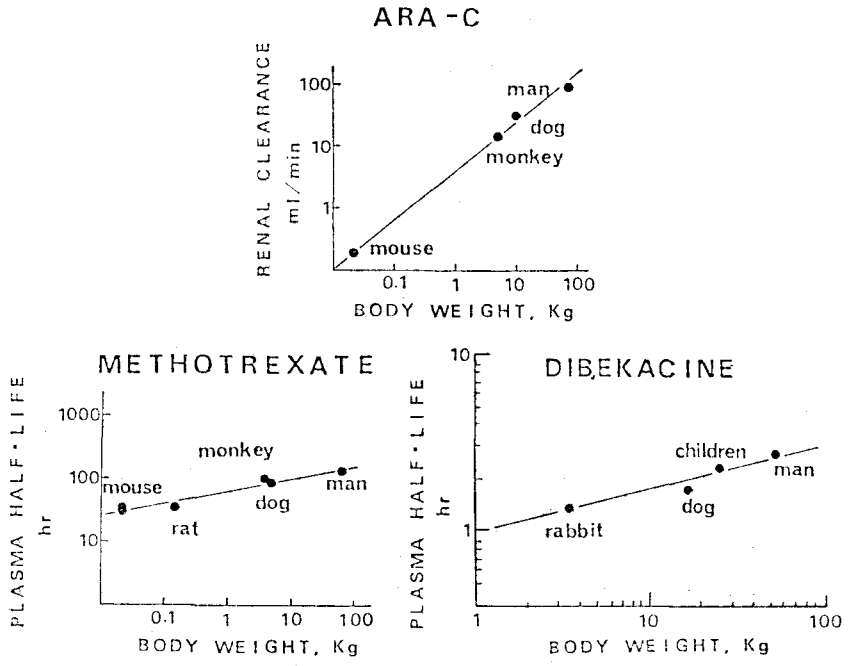


Figure 6—Body weight, renal clearance and plasma half life.

The graphs of Fig. 10 show the relationship between the renal clearance and the body weight on various animals reported by Dedrick who is one of the pioneers of physiological pharmacokinetics. In two drugs shown in lower part of this figure, the biological half life itself has directly a relation to the body weight. This can happen, if the distribution volume of drug is also proportional to the certain powers of the body weight as well as the renal clearance.

We calculated the renal clearances of several drugs which are mainly excreted into urine from various reports of pharmacokinetics. These clearances are plotted on a logarithmic graph as done by Dedrick. As seen in Fig. 7, the clearances of all animals show a good fit on a straight-line. This result tells us that the renal clearance of a drug in a human can be predicted from animal exeriments.

The renal clearances of therapeutic and diagnostic drugs are expressed as an exponential equations of body weight as shown in upper part of Table I. The values of

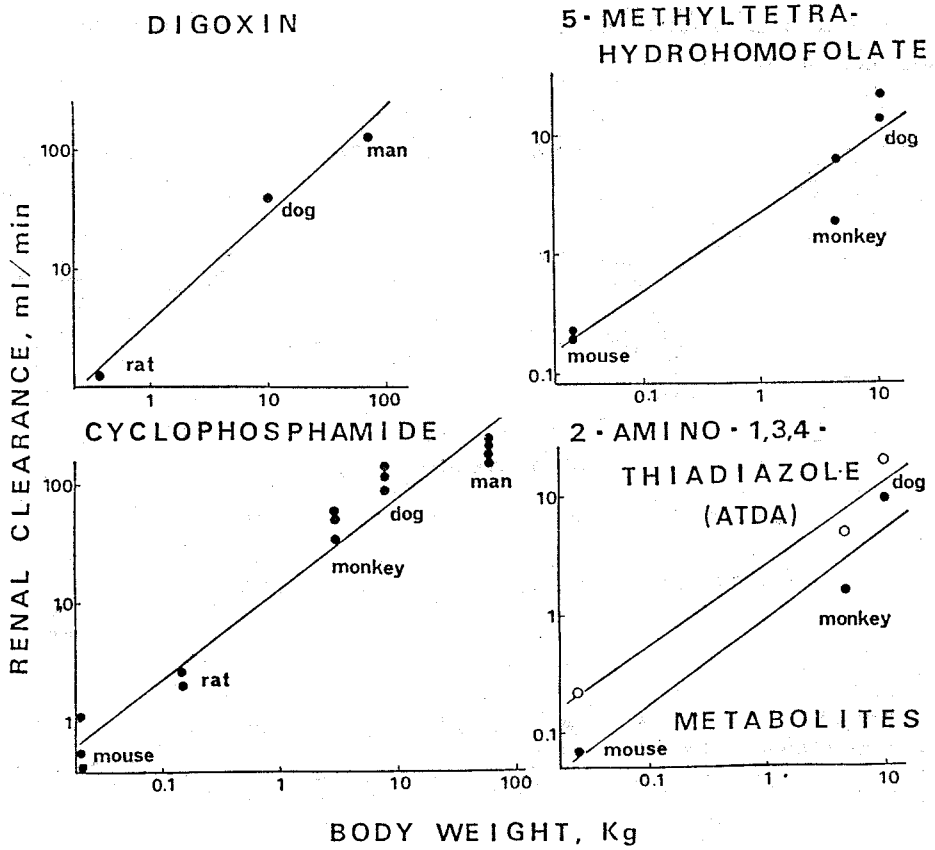


Figure 7—Body weight and renal clearance.

Table I—Renal Clearance vs. Body Weight

$CL_r(\text{ml/min}) = A \cdot W(\text{kg})^B$

- ☐ urea ····· $3.83 \cdot W^{0.72}$
- ☐ inulin ····· $5.92 \cdot W^{0.77}$
- ☐ creatinine ····· $8.22 \cdot W^{0.69}$
- ☐ iodopyracet ····· $16.70 \cdot W^{0.89}$
- ☐ p-amino hippurate ····· $22.61 \cdot W^{0.80}$
- ☐ digoxin ····· $3.56 \cdot W^{0.89}$
- ☐ 2-amino−1,3,4 thiaziazole (ATDA)····· $0.91 \cdot W^{0.73}$
- ☐ metabolite of ATDA····· $2.50 \cdot W^{0.68}$
- ☐ 5-methyltetrahydrohomofolate ····· $2.19 \cdot W^{0.65}$
- ☐ cyclophosphamide ····· $13.45 \cdot W_0^{0.76}$
- ☐ Ara-C ····· $3.81 \cdot W^{0.80}$

parameters A and B are listed here. The power numbers, B, are between 0.6 and 0.9 in all drugs. The B values on renal anatomic characters are 0.85 for the weight of kidney, 0.62 for the number of nephron, and 0.8 for the surface area of glomeruli. It

is very interesting that all B values of drug are always close to that on the anatomic characters. Any trial to construct B value on the basis of excretion mechanism, however, has not been reported, yet.

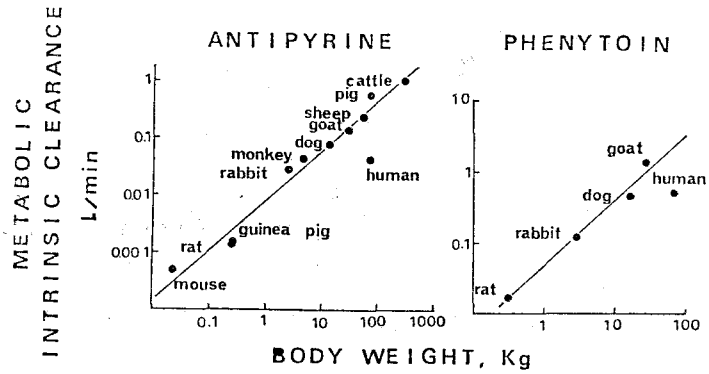


Figure 8—Body weight and metabolic intrinsic clearance.

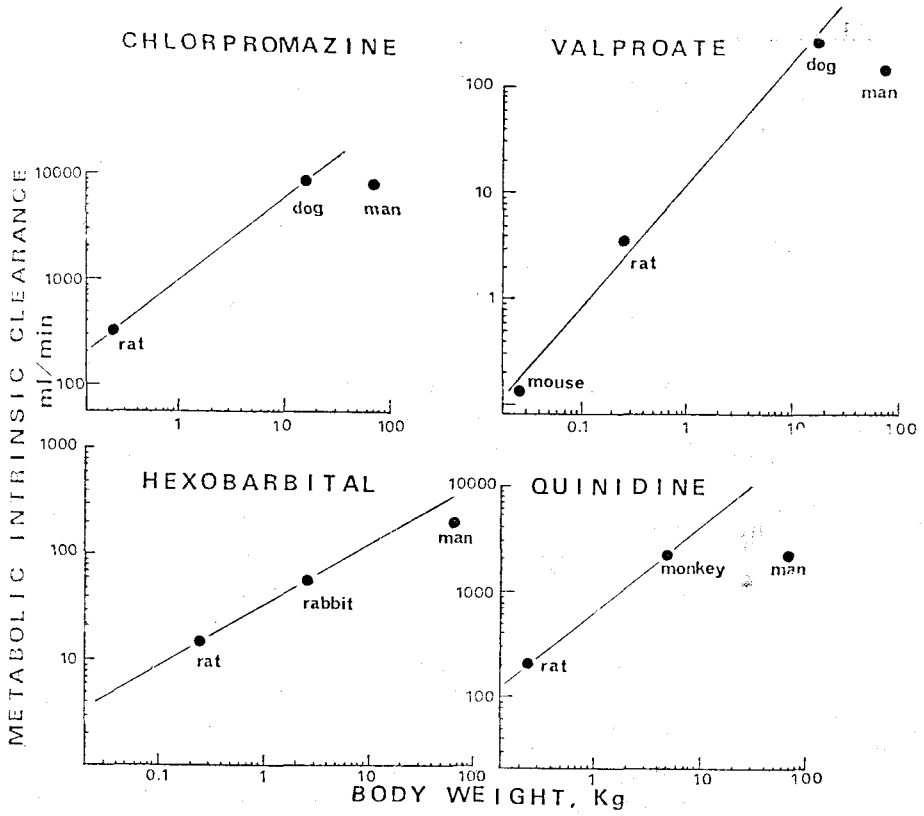


Figure 9—Body weight and metabolic intrinsic clearance.

Large discrepancy concerning the drug metabolism is often seen among the animal species, among the cases of disease, and even among individuals. The metabolic clearances are calculated from the area under curve of blood concentration and the meta-

bolic ratio of excreted drug in urine. This clearance is affected by not only activity of metabolic enzyme but also hepatic blood flow and free fraction of drug. The hepatic intrinsic clearances free from effects of blood flow and the free fraction are related to body weight like the Boxembaum. As shown in Fig. 9 his report shows us very interesting results in which only human is away from the regression line of the clearance to the body weight among animals. This uniqueness of human can not be found in the renal clearance.

We tried to make same graph as Boxembaum about four drugs of which informations about the pharmacokinetics and the binding to plasma protein are known enough for the calculation of the hepatic intrinsic clearance. As seen in Fig. 9 again only human is always separated to lower clearances from the regression line.

The quite same is seen in the other four drugs. This data are taken by us and a part of data is not reported, yet. As seen in Fig. 10 human has lower intrinsic clearance than those of amimals as compared with the body weight.

Fig. 11 shows a comparison on the metabolic intrinsic clearance between human and animal. All animals have larger clearance per body weight than that of human throughout the fifteen drugs investigated.

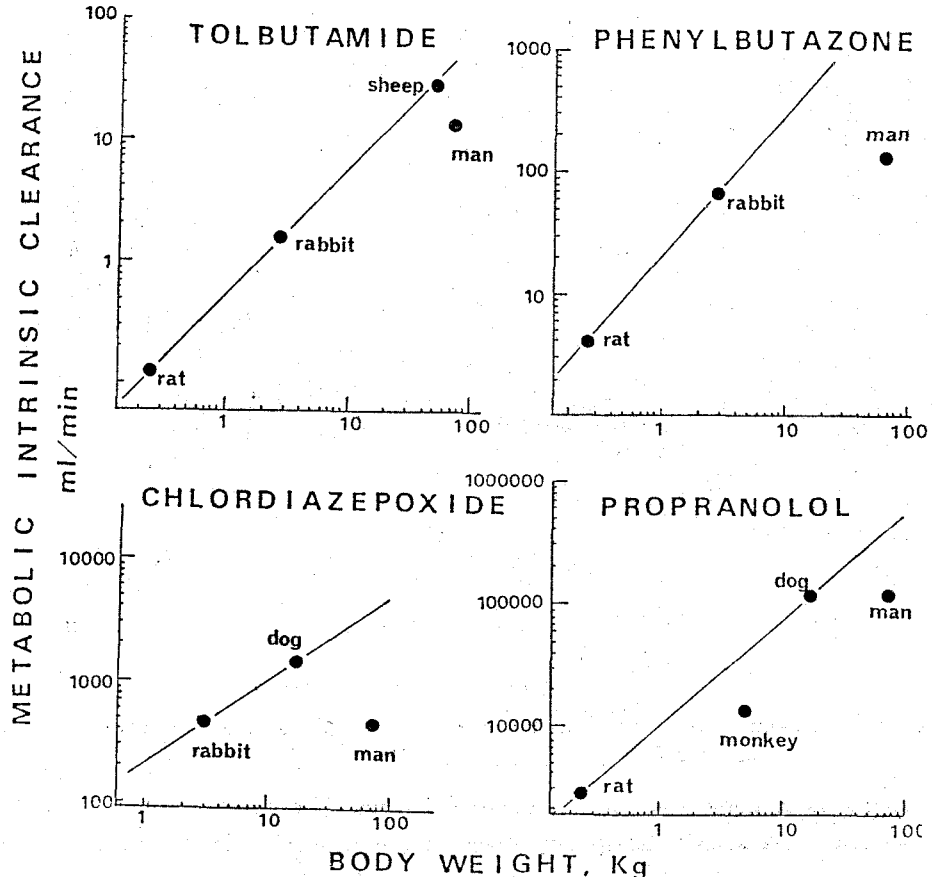


Figure 10—Body weight and metabolic intrinsic clearance.

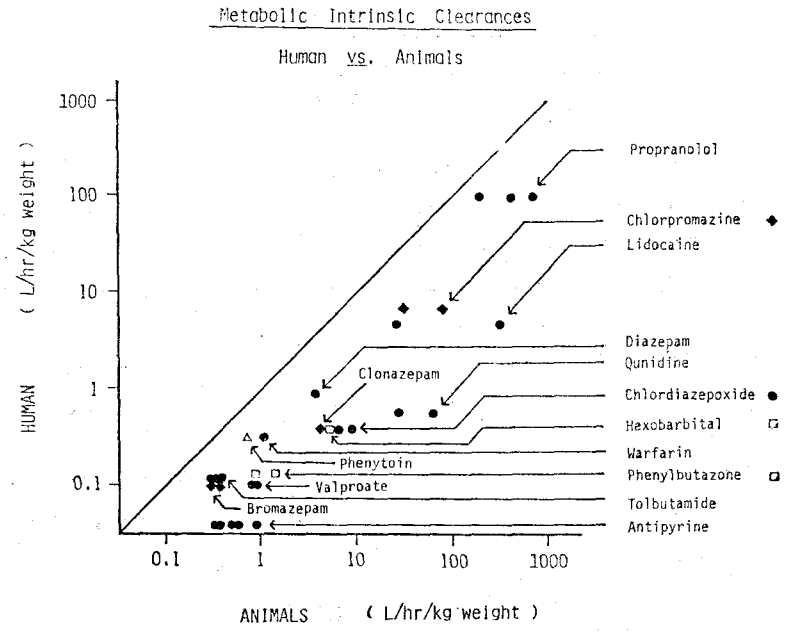


Figure 11—Metabolic intrinsic clearances in animals and human.

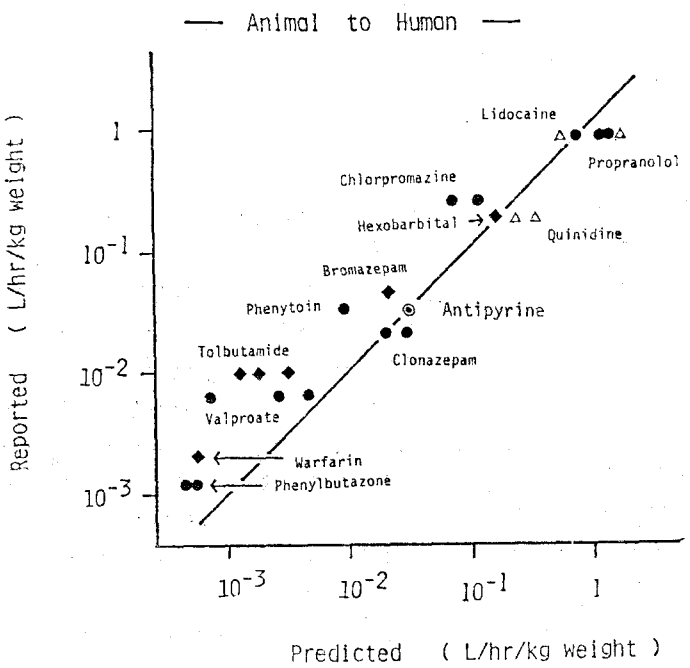


Figure 12—Human total body clearance predicted by antipyrine clearance ratios to those of animals.

The diagnosis of metabolic activity of an individual patient has been recently tried on the basis of clearance of antipyrine given to the patient. Antipyrine is not bound to plasma protein, negligibly excreted in urine, and has total clearance low enough to

be used for the metabolic intrinsic clearance without any correction. We tried to predict the total clearance of various drugs in human from animal data as the following procedure. The metabolic intrinsic clearance of a drug in an animal is multiplied by the clearance ratio of antipyrine to human in order to convert it into human value. From the hepatic blood flow and the free fraction reported on human and the converted intrinsic clearance, the total clearance is finally calculated. Fig. 12 shows the correlation between the total clearance predicted from this procedure and that reported by human experiment. A certain case gave us erroneous results. The average of predicted values from several animals, however, agrees closly with the reported value in all drugs. The intrinsic clearance and the free fraction are frequently varied with the blood concentration of drug. And also the large individual variation is also known in many drugs. The data plotted on this graph are gathered from the different reports. The dose given and assay method, therefore, are different each other. A progress of prediction will be expected by the standardization of these experiments.

Scheme V—Prediction of Distribution Volume(Vd)

VD: Value obtained by dividing total drug amount in the body at β-phase by plasma concentration at that time.

at β-phase, $dCt/dt = -Ct$

$$Vd_{\beta,t} = \frac{Vt \cdot Kp,t \cdot Qt}{Qt + Kp,t \cdot s \cdot (ft \cdot CL_t^{int} - Vt)} \quad \cdots\cdots(1)$$

at steady state, $dCt/dt = 0$

$$Vd_{ss,t} = \frac{Vt \cdot Kp,t \cdot Qt}{Qt + Kp,t : s \cdot ft \cdot CL_t^{int}} \quad \cdots\cdots(2)$$

Where $Vd_{ss,t}$ is the volume of distribution at steady state.

The volume of distribution is an important constant in order to indicate the blood-level of drug from the dose given in a body. Although several kinds of the volume of distribution are defined and used today, we consider so called Vd_β and Vd_{ss} in this time. The Vd_β is defined in the quasi steady state of drug concentration in blood and tissue. In this condition, the blood concentration is decreased with time along a straight-line on the semi-logarithmic graph. This phase on the time course of blood concentration is called beta phase. The Vd_{ss} is defined in the true steady state of drug concentration in blood and tissue. This condition can be reached through a constant infusion. The volume of distribution in whole body is always their total sum in all kinds of tissue. Muscle is the largest tissue in a body, and the large part of drug amount in a body is distributed in mnscle, even if the partition coefficient to muscle is rather small. Muscle, therefore, is dominant on the volume of distribution in most drugs. The Vd_β is calculated as seen in Scheme V. In this case, the rate of change in the drug concentration in tissue is substituted by the product of beta and drug concentration. The Vd_{ss} is calculated from the substitution of zero to the rate as seen in the lower line. The steady state distribution volume, Vd_{ss}, in tissue in which the

drug is not eliminated is equal to the product of partition coefficient and real volume of tissue.

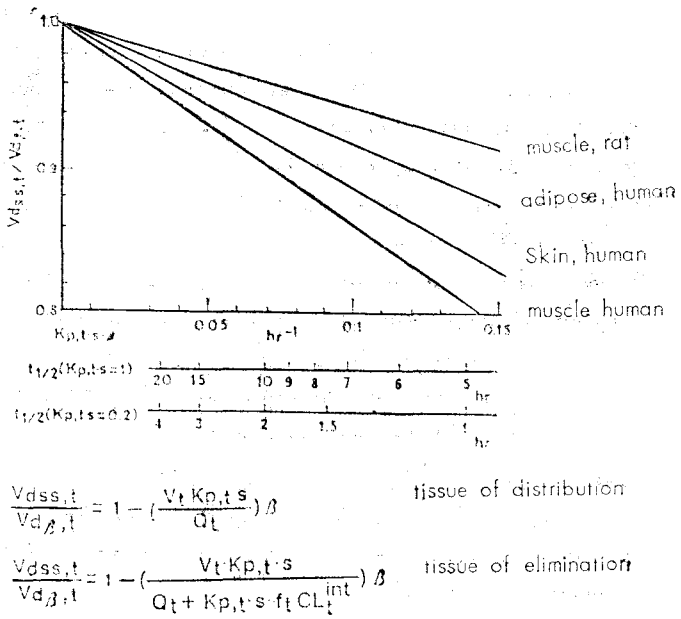


Figure 13—Results of model calculation for human and rat in muscle, skin and adipose.

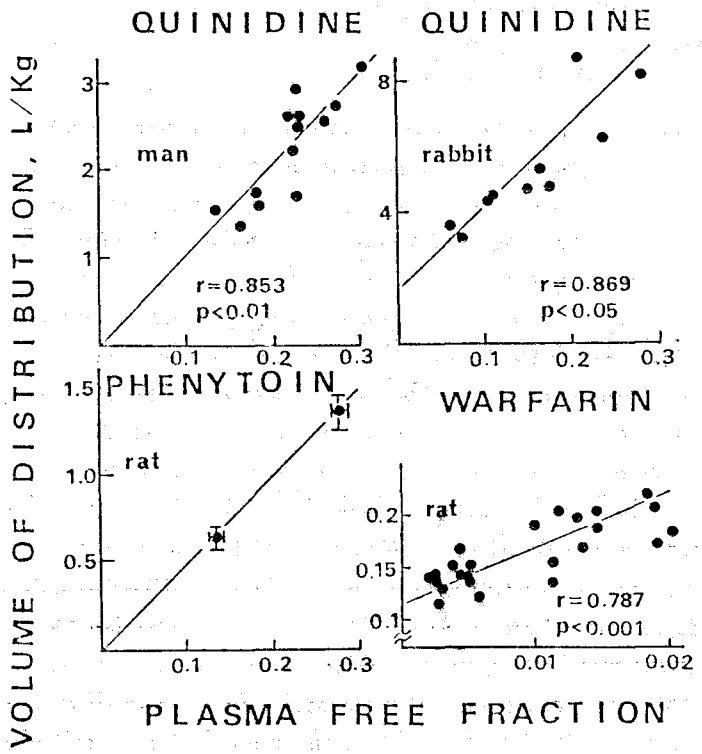


Figure 14—Plasma free fraction and distribution volume.

The volumes of distribution at the quasi steady state and the true steady state are not equal, unless beta is zero. The equation seen in Fig. 13 indicates that the ratio of both volumes of distribution decreases linearly with increasing of beta value. This graph is results of model calculation for human and rat in muscle, skin, and adipose that take usually large part of the volume of distribution. The volumes are not practically distinct each other, when the product of beta and partition coefficient is less than 0.15 because the ratio of volumes between the quasi and true steady states shows more than 0.8. This condition is satisfied by the half life longer than five hours, if the coefficient is as small as 0.2. In this case, drug can distribute in only outside of cell.

Only phenytoin among drugs shown in Fig. 14 has a good correlation between the free fraction in plasma and the volume of distribution per body weight among animals. The partition coefficient between plasma and tissue affects the volume of distribution. This partition is determined by the ratio on the free fractions between tissue and plasma. The correlation between the free fraction and the distribution volume, therefore, appears only in such drugs as the free fraction in tissue resembles each other among animals.

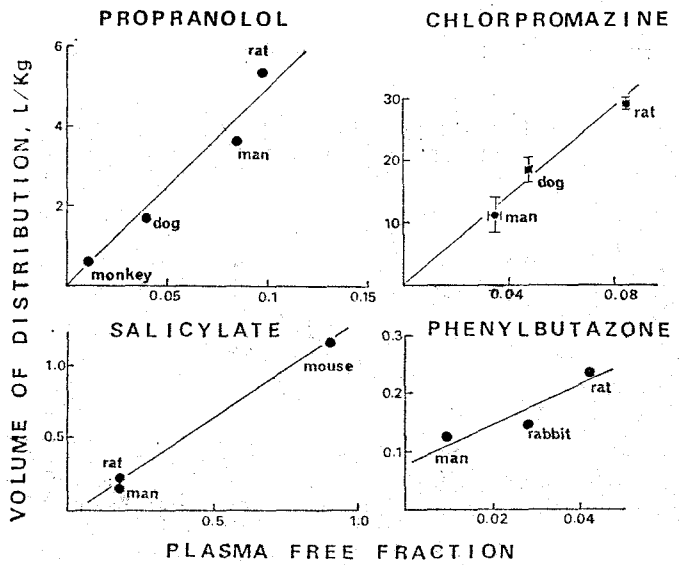


Figure 15—Plasma free fraction and distribution volume.

The variations of distribution volume were reported in the case of disease on kidney and liver. The graphs of Fig. 15 show that the distribution volume happens to correlate to the plasma free fraction in the case of these diseases. Propranolol was reported by Branch and furosemide by Rane.

We tried to calculate the same correlation from various reports of pharmacokinetics. As seen in Fig. 16 the volumes are found, but the degree of correlation is different with drugs.

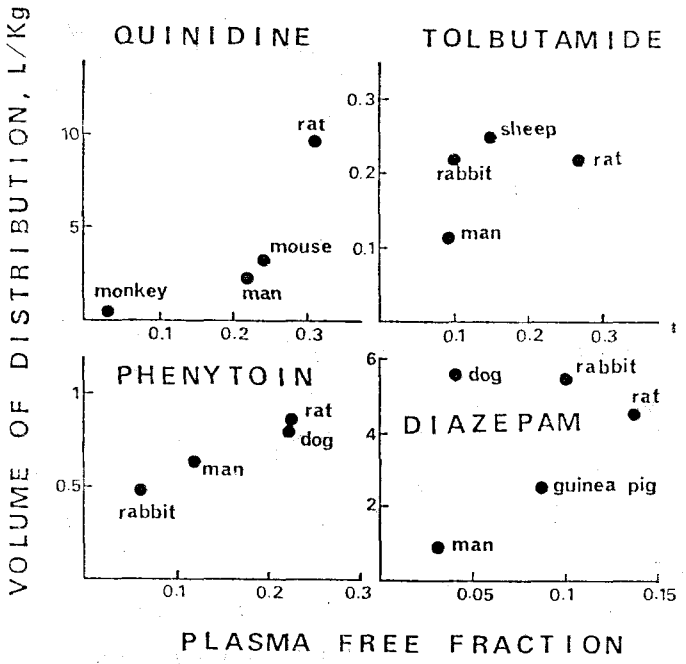


Figure 16—Plasma free fraction and distribution volume.

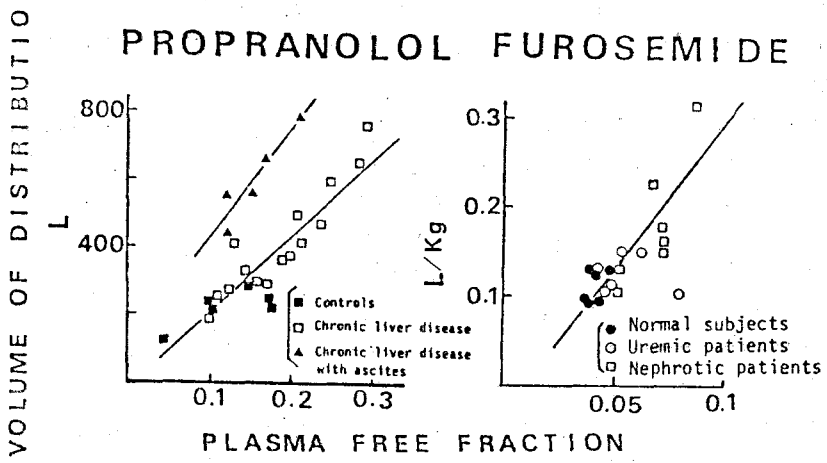


Figure 17—Plasma free fraction and distribution volume in disease states.

Fig. 17 is the result of calculation for the same correlation in the case of human disease. The increased free fraction in liver disease is thought to be caused by the decrease of the plasma albumin, the increase of plasma free fatty acid, and also the increase of the bile dyes in the circulating plasma.

In these four drugs show in Fig. 18, however, the volumes of distribution are not varied with the liver disease though the plasma free fractions are increased. A weak effect of free fraction on the volume of distribution can be described in such a drug

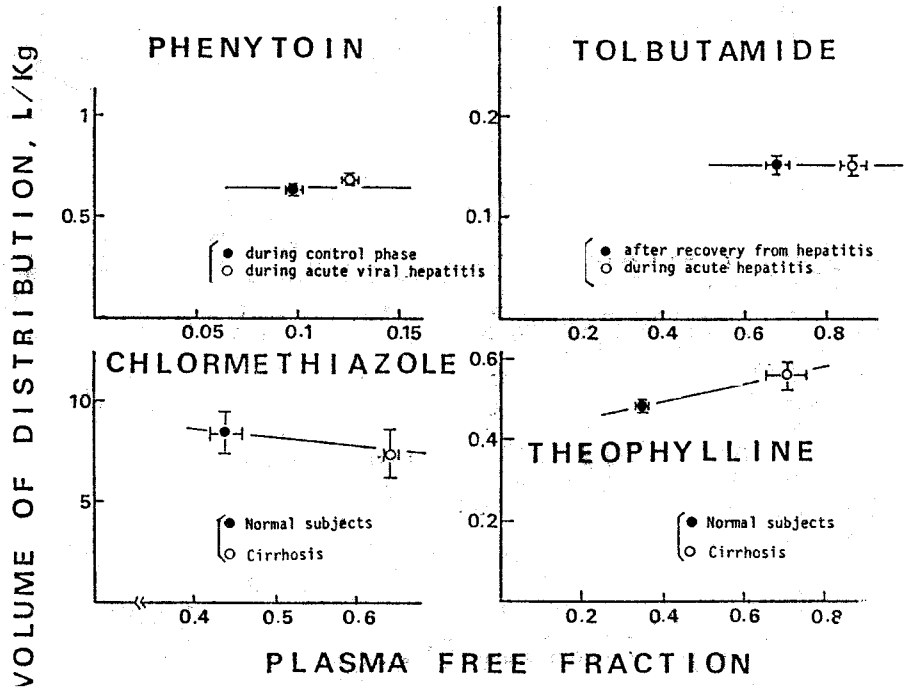


Figure 18—Plasma free fraction and distribution volume in disease state.

as it distributes almost completely in plasma and does not in tissue cell. The volumes of distribution of these four drugs, however, are not specially smaller than the drugs which have the good correlation.

The drug interactions which cause the increase of plasma free fraction are famous. A drug bound to plasma albumine is competitively released by another drug. Fig. 19 is example of such drug interaction. The volumes of distribution are increased with increasing the plasma free fraction by the interaction.

As shown in Fig. 20, in case of warfarin, however, the increase of distribution volume is dismissed with alternation of displacing drug from clofibrate to phenylbutazon though the plasma free fraction of warfarin is equally increased. In the case of tolbutamide, the increase of volume is found in rat, but not found in rabbit and sheep by the same displacing drug, though the increases of free fraction are found in all cases. From the theoretical point of view, the distribution volume can not be varied if the displacing drug releases the drug from not only plasma albumine but also constituents in the cell. In this case, the partition coefficient keeps almost constant by the displacing effect balanced on plasma and cell. The actual mechanisms of both drugs seen here are not known yet.

The left side in Fig. 21 shows the comparison on the volume of distribution per body weight between human and animal. We tried to predict the volume of distribution in human from animal studies considering the correlation between the distribution volume and the plasma free fraction found in many drugs. At first, the distribution volume

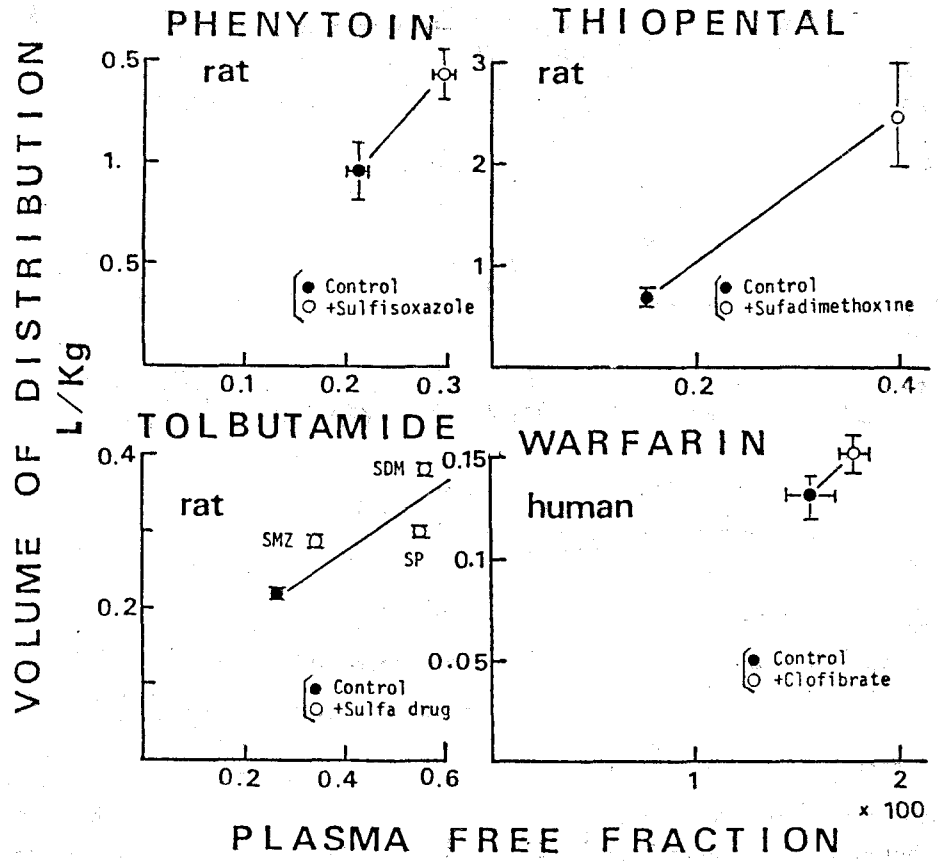


Figure 19—Plasma free fraction and distribution volume in combination administration.

is reduced by the real plasma volume in order to estimate the volume outside plasma. This volume of animal is converted to human using the ratio on the plasma free fraction between human and animal. Finally, the predicted volume outside plasma is added to human plasma volume that is 0.08 *l*/kg weight. The right side in this graph shows the comparison between the predicted distribution volumes from various animals and the reported values. In many cases, the prediction is successful. Though the prediction from only an animal will be risky, the mean of predicted values from several animals is thought to give us the good approximation of human value. This procedure needs the measurement of plasma free fraction in human. This measurement can be easily done by an in vitro experiment. In this method of prediction, we assumed uniformity of free fraction in tissue among animals. We should again emphasize that the data used in this investigation are gathered from the different experiments. The standardization of measurements for the plasma free fraction will hopefully bring us a progress of the prediction.

In Table II, the tissue free fractions of seven drugs in rat are listed. The fractions are largely different with drugs. Though the over unity of fraction given in tolbutamide might look peculiar, this is a reflection of partial distribution of free tolbutamide

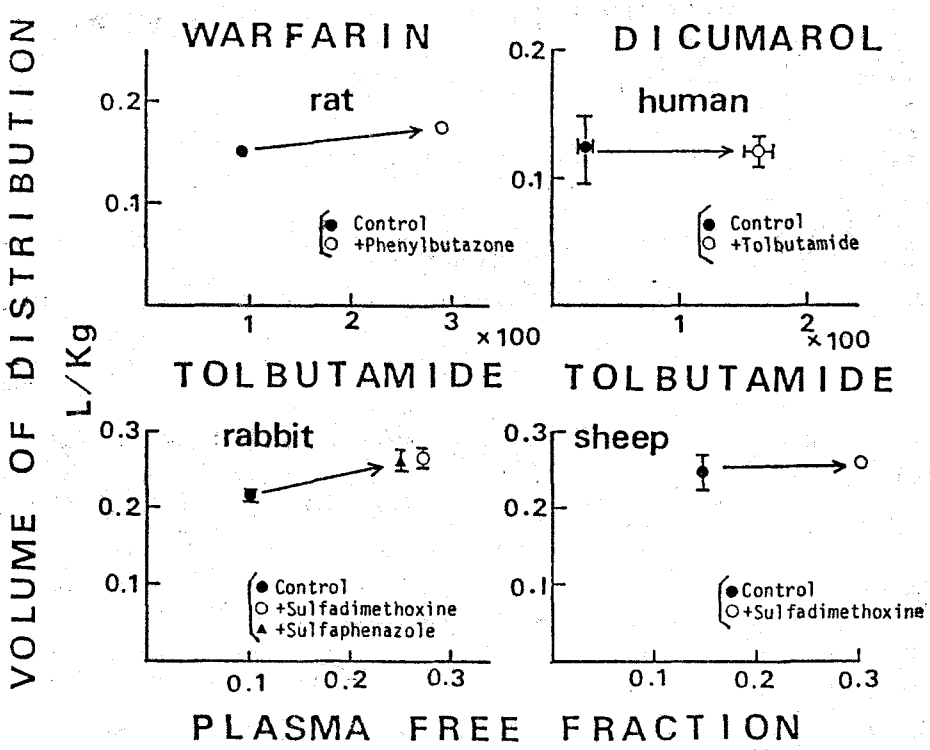


Figure 20—Plasma free fraction and distribution volume in combination administration.

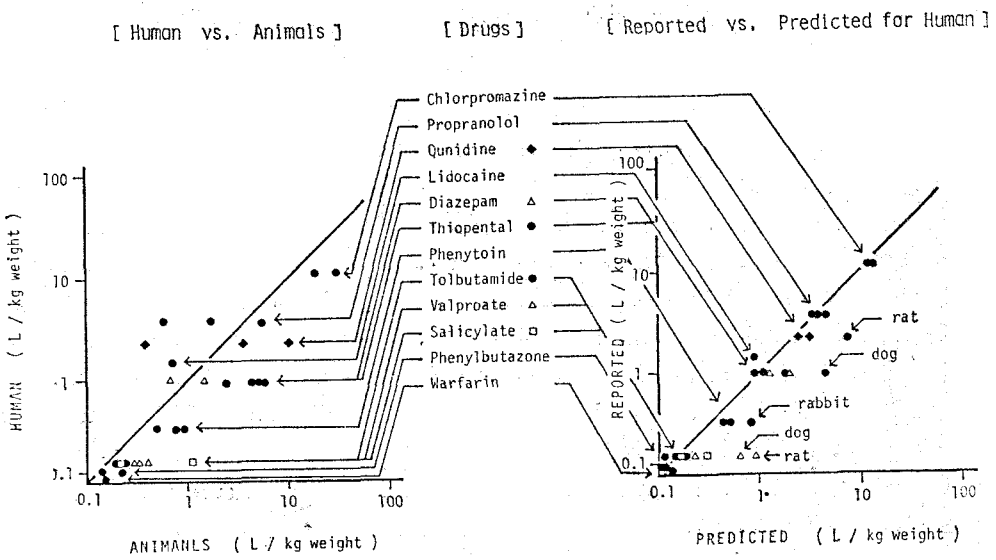


Figure 21—Distribution volumes of various drugs.

molecule into tissue cell. When the concentration of free drug in plasma is larger than that in cell, the calculated free fraction shows over unity, because the equal concentration of free drug in palsma and cell fluid is assumed in the calculation.

Using these data of rat, we can predict not only the plasma concentration profiles, but also the tissue concentrations in various animals. We have reported the successes of prediction in the case of ethoxybenzamide and tolbutamide in rabbit.

Table II—Tissue Free Fractions of Various Drugs in Rat

	Diphenyl-hydantoin	Tolbutamide	Phenyl-butazone	Thiopental	Pheno-barbital	Hexobarbi-tal	Warfarin
G.I.	0.201	3.17	0.192	0.142	0.970	0.268	0.046
Lung	0.300	0.98	0.136	0.161	0.671	0.533	—
Brain	0.286	6.54	0.703	0.212	0.796	0.533	—
Heart	0.312	1.13	—	0.155	0.431	0.465	—
Liver	0.132	1.82	0.086	0.064	0.465	0.491	1.080[b]
Kidney	0.206	1.89	0.128	0.140	0.990	0.412	0.023
Muscle	0.371	2.95	0.325	0.249	0.735	0.990	0.183
Skin	0.288	1.28	0.211	0.085	0.603	0.681	0.040
Adipose	0.214	3.31	—	0.058	0.318	0.377	—
Pancreas	—[a]	1.78	—	—	—	—	—
Spleen	—	2.45	—	—	—	—	—
Lymph	—	0.47[b]	—	—	—	—	—
C_P/C_B	1.01	1.33	1.067[c]	1.085	1.110	1.000	1.770[d]

a) not determined, b) Kp values, c) oxyphenbutazone, d) C_{blc}, cell=0 (

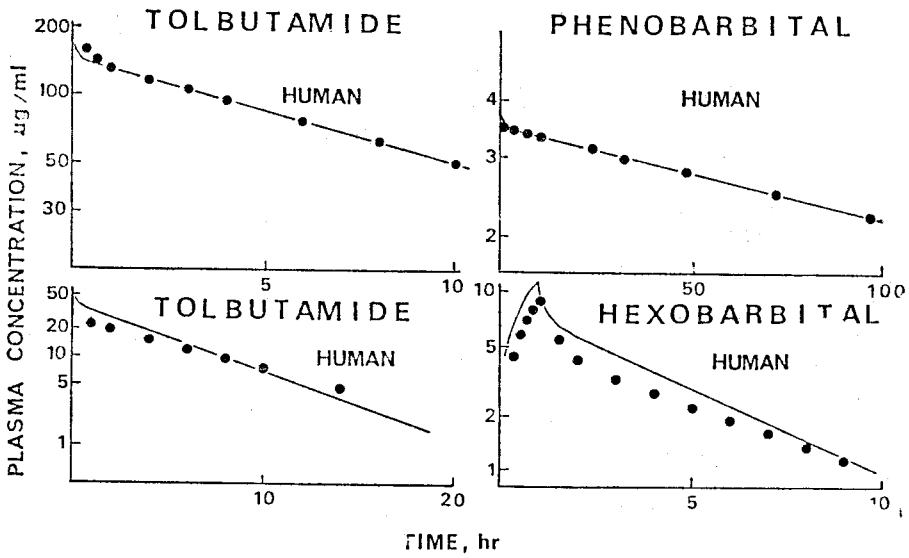


Figure 22—Plasma concentrations of various drugs.

Fig. 22 is the result of our calculation about the time courses of human plasma concentration of three drugs. The free fractions in tissues used in this calculations are the rat values. The plasma free fraction and the total clearance are the value of human. The time courses are calculated by the method of physiological pharmacokinetics using a digital computer. The concentration of drug in tissue calculated simultaneously with that in plasma is not shown here because of lack of measured data for the comparison. In the cases of two different dose of tolbutamide, phenobarbital and hexobarbital, the predicted plasma concentration shown by the solid line agrees closely with the measured values shown by the circles. In this result, we should point out that the area under curve must always show the agreement between the predicted value and the reported, since the total clearances from real measurement are used for the calculations. Usefulness of this method, however, is clearly indicated by the consistent half lives of the predicted plasma concentration with that reported.

The plasma concentration profile of thiopental interacted by sulfadimetoxin is simulated as follows. The tissue free fractions are assumed to be the same of data from

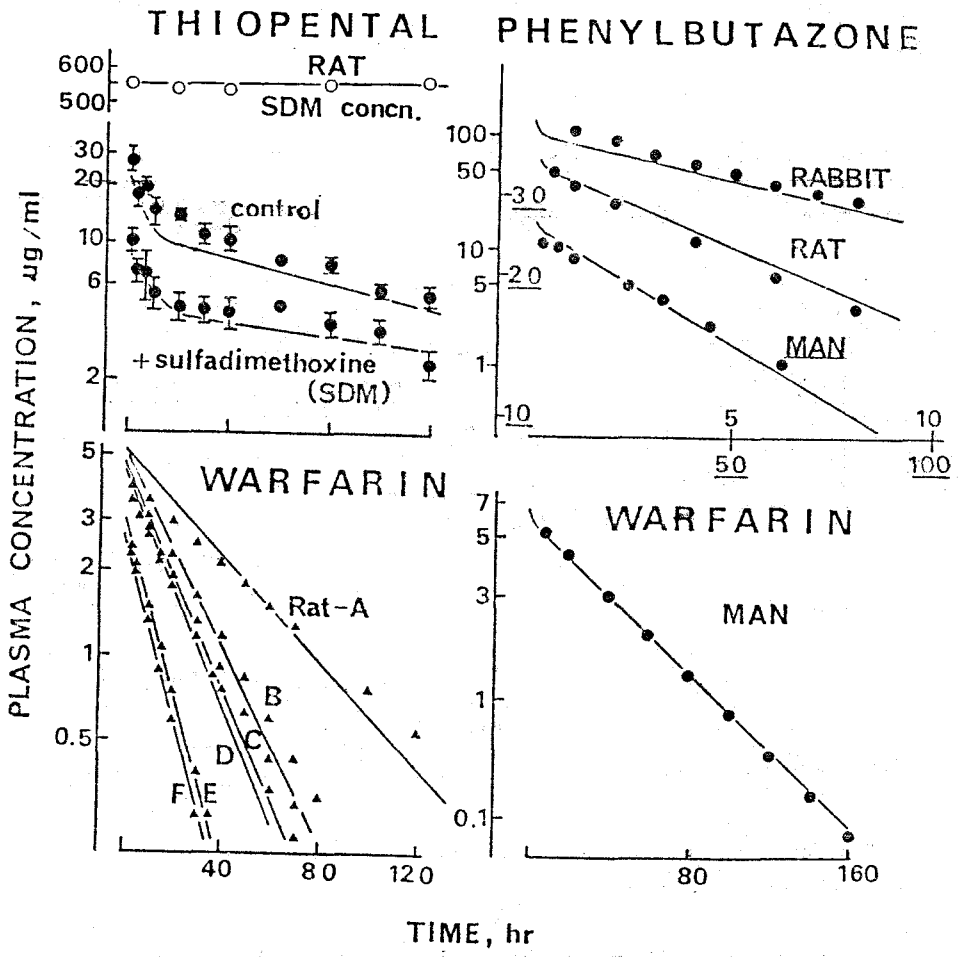


Figure 23—Plasma concentrations of various drugs in man and animals.

a single ingestion of thiopental to rat. The plasma free fraction is corrected by the data concerning the displacement of sulfa drug to thiopental obtained from the in vitro study. The total clearance is really measured by the in study of the combined ingestion. The profiles of phenylbutazon in human and rabbit are simulated using the tissue free fractions of rat, the real plasma free fraction of each species, and the real values of total clearance. The warfarin profiles of individual rat are simulated assuming uniformity of free fraction in tissue at each rat. The individual variation, therefore, is assumed to be brought only from the plasma free fraction and the total clearance. The human plasma profile of warfarin is simulated from the tissue free fractions of rat, the plasma free fraction of human, and real total clearance. In every simulation shown in this graph (Fig.23) agreement between the predicted and reported values is satisfactory.

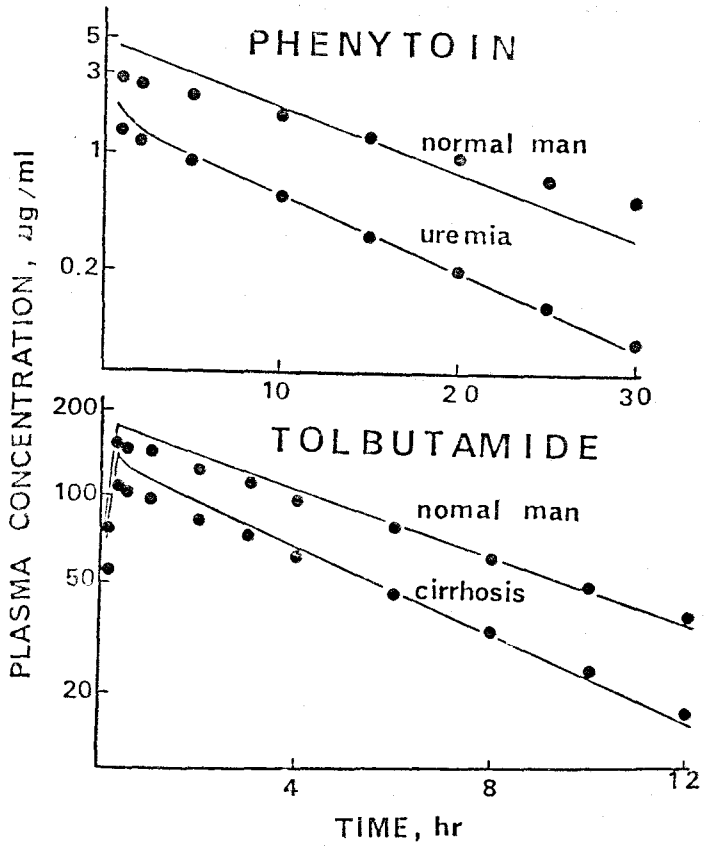


Figure 24—Plasma concentrations of phenytoin and tolbutamide in normal and disease states.

Fig.24 shows the results of simulation in diseases. The tissue free fractions obtained from rat are also used for the simulation and the plasma free fraction and the total clearance are real values in disease. Close agreements between the predicted and reported values are also found in both of phenytoin and tolbutamide.

The uses of predicted total clearances instead of the real values will bring us variance of simulation. Individual differences are sometimes large in the plasma concentration profiles of most drugs. Usefulness of this method will be sufficient enough for the practical use in spite of the variance. Until the present day, however, we can not have any sufficient way for general system of prediction on the drug clearance, especially the metabolic clearance. More development is wanted for the method of prediction of metabolic clearance based on the real mechanism, for example, on the total activities of p-450 enzyme system. We feel the insufficiency of researches concerning the pharmacokinetics and the affecting factors, for example, plasma binding properties of drugs, from the experience of the present investigation. Some people are arguing today the worthlessness of animal studies because of the unexpected difference from human but I would like to emphasize the importance of animal studies on the mechanism of pharmacokinetics in details.