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Torsten Teorell, the Father of Pharmacokinetics

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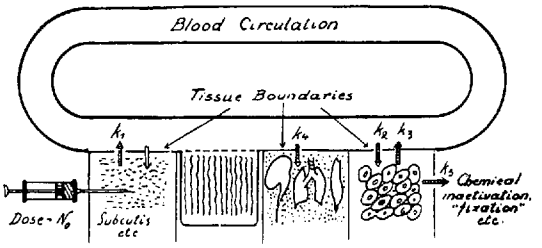
During the summer of 1937 Torsten Teorell submitted two scientific papers (1,2) for publication which appeared in Archives Internationales et Pharmacodynamie et de Thérapie in October in the same year. More than 30 years later these two articles came to be considered as two of the most important contributions to drug research and led to Teorell being characterized as the father of pharmacokinetics.

Both these papers had the same title, "Kinetics of distribution of substances administered to the body", and the first one dealt with extravascular modes of administration (1), while the second one discussed the intravascular modes (2). In the introduction to the first paper Teorell pointed out that at that time the interest of the physician or the physiologist was focused more on practical points such as testing the proper dosage or suitable ways of administration, or on the finer mechanism involved in the effects produced by the drug, whereas very little work seemed to have been devoted to the *kinetics*, i.e. the time relations of drug action. The objectives of the two papers by Teorell were to derive "general mathematical relations from which it is possible, at least for practical purposes, to describe the kinetics of distribution of substances in the body" and to present time-concentration curves as illustrations of the relations derived.

To describe what happens to a drug in the body when it is administered by an extravascular mode, e.g. by the subcutaneous route, Teorell made a simplified model of the body as illustrated in Fig. 1.

Blood is circulated throughout the body and can be illustrated

by a circle of as water pipeline in contact with the tissues of the body. Each tissue has a certain volume, and as seen in the figure a drug is transported by diffusion from the subcutaneous tissue to the blood (absorption process with the rate constant k_1) and then circulated throughout the body. The processes of transport from the blood to the different tissues are described by the rate constant into the tissue and by another rate constant out of it. Some organs, such as the liver and the kidney, have the capacity to eliminate the drug and they are illustrated by one rate constant out from the blood (Fig. 1).



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	–	V_3	–
Concentration	x/V_1	y/V_2	–	z/V_3	–
Perm. coeff	k_1'	–	k_4'	k_2'	–
Velocity constant out	$k_1 = k_1'/V_1$	–	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_2$	k_5
Velocity constant in	neglected	–	not existing	$k_2 = k_2'/V_3$	–
Name of process	Resorption	–	Elimination	Tissue take up -m- output	Inactivation

FIG. 1

Scheme of the Concept of Drug Distribution used in this paper.
Instead the *injection* pictured in the figure, the administration of the drug depot can be made *per os*, *per rectum*, *by inhalation*, etc.

Fig. 1. From Torsten Teorell ref. 1.

Teorell then derived the differential equations for these processes and presented their solutions. By giving the rate constants and volumes certain possible values, he calculated the time course of drug amounts in the body, expressed as per cent of the dose, as illustrated in Fig. 2.
As seen in this figure, the rapid absorption after a subcutaneous dose produces a peak concentration in the blood

that declines exponentially over time, while the concentration in the tissue, which most probably includes the site of action, peaks later than that in the blood but then declines in parallel with the concentration in the blood. The elimination curve and the amount of drug in the subcutaneous depot are also illustrated in Fig. 2.

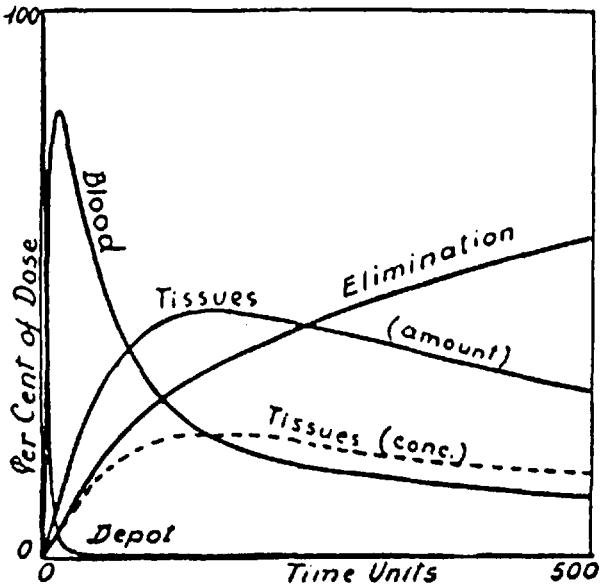


FIG. 3

Typical Case of Extravascular Administration in the absence of tissue inactivation.

($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.005$; i.e. " blood " volume/" tissue " volume is 1 : 2; $k_4 = 0.005$; $k_5 = 0$).

Fig. 2. From Torsten Teorell ref. 1.

Furthermore, by performing several numerical calculations, Teorell emphasized that a marked change in the absorption

properties may bring about a marked change in the magnitude and duration of the blood and tissue concentration curves, and states that "these and other conclusions may have bearings upon practical pharmacology and therapeutics".
These conclusions may today seem self-evident, but one has to recall that at that time nobody had really thought that we could treat the distribution of drugs in the body in such a simplistic and clear way. All the conclusions presented by Teorell are certainly still valid and at that time they should have been an eye-opener to those who were using drugs but who clearly were unaware of what can happen to a drug in the body.
However, these two papers of Teorell produced the opposite effect and the reviewers of the applications for the chair in physiology, which Teorell obtained in 1940, rather considered these two papers more as a burden than a merit. Consequently, they were forgotten and nothing really happened for more than 25 years, when German and especially U.S. scientists rediscovered Teorell´s work.

The word pharmacokinetics was introduced by the German professor F.H. Dost in 1953 and in a review article (3) by John G. Wagner (1981) on the history of pharmacokinetics we can read the following: "In 1937, Teorell, a Swedish physiologist and biophysicist, published two remarkable articles which many now attribute as being the foundations of modern pharmacokinetics". Thanks to the work of various groups, for example Sidney Riegelman, Bernard B. Brodie, Eino Nelson, Gerhard Levy, John Wagner and others in the U.S.A., and by Europeans such as Ekkehard Krüger-Thiemer, E.J. Ariëns and Jacques van Rossum, pharmacokinetics quickly developed during the 1960´s. One important contributory factor was the rapid advances in bioanalytical techniques, which made it possible to analyse minute drug concentrations in plasma, urine and other tissues. During this period the so-called compartmental models were used for the mathematical interpretation of data. The main drawback of this approach was apparent at least to those who were going to utilize the findings, i.e. the physicans, who had difficulties in understanding the meaning of the information produced.

In the beginning of the 1970´s a new era of pharmacokinetics began when the research became more oriented towards a physiological approach. With the introduction of the clearance concept by Rowland et al. (1973), a better understanding of physiological factors such as blood flow, hepatic metabolic capacity and plasma protein binding was achieved (4).

During about the same time period, another type of pharmacokinetic model appeared in the literature. Bischoff and Dedrick (1968) described what they called a physiological flow model, which took into account the influence of the blood flow and binding of drugs in different tissues of the body (5). The elegant thing about these models was that it was possible to scale them up from animals to humans by changing, for example, the magnitude of animal tissue blood flows and the elimination capacity to that found in man. By this way the human situation could be predicted from the outcome of an animal experiment. Once again Torsten Teorell´s work was rediscovered, since it was obvious that the model Teorell had used was also the first physiological model, and in his honour a conference was arranged in 1972 at the Fogerty International Center at NIH in Bethesda, which he attended and where his achievements were recognized (6).

During the last two decades pharmacokinetics has advanced explosively and today it is one of the most quickly developing branches of science, especially of the pharmaceutical sciences, and it provides us with a fundamental knowledge upon which modern drug therapy rests.

Personally, I know that Teorell was pleased with the fact that Uppsala University became the first university in the Nordic countries that established a chair in pharmacokinetics. It has always been a privilege and an honour for me to hold this position at a university that is known all over the world as the place at which Torsten Teorell, the father of pharmacokinetics, was working. There is no risk that his name will be forgotten.

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