DEVELOPMENT OF COMPARTMENTAL CONCEPTS

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HISTORICAL INTRODUCTION TO COMPARTMENTAL ANALYSIS

The first compartmental models were used in Physics for the description of radioactive decay. After Becquerel (1896) discovered the radioactivity, Rutherford and Soddy (1902) found experimentally that Thorium X decays in time according to an exponential law, i.e. that the number of radioactive atoms decaying per unit time is proportional to the number of radioactive atoms present. If X(t₀) and X(t) are the quantities of radioactive substance present at time t₀ and t respectively, the law of radioactive decay is

\[ \frac{dX}{dt} = -KX, \]

whose integral is

\[ X(t) = X(t₀) \cdot \exp(-K(t-t₀)). \]

Later Rutherford (1904) developed the theory of successive radioactive transformations. If A is transformed into B, B is transformed into C, and so forth, call Xₐ, Xₐ, Xₜ, ..., the amounts of A, B, C, ..., present at any given time; call also Kₐ, Kₚ, Kₜ the rates of such transformations. He wrote, in analogy with equation (1),

\[
\begin{align*}
\frac{dXₐ}{dt} &= -KₐXₐ, \\
\frac{dXₚ}{dt} &= +KₐXₐ - KₚXₚ, \\
\frac{dXₜ}{dt} &= +KₚXₚ - KₜXₜ, \\
\end{align*}
\]

and by integration,
\[ X_a(t) = X_a(t_0) \cdot \exp(-K_a(t-t_0)), \]
\[ X_b(t) = \frac{K_a}{K_b-K_a} \cdot X_a(t_0) \cdot \exp(-K_a(t-t_0)) + \]
\[ + \frac{(K_b-K_a)X_b(t_0)-K_aX_a(t_0)}{(K_b-K_a)} \cdot \exp(-K_b(t-t_0)), \]
and so forth.

Many experimental observations have shown that this compartmental model is consistent with the behavior of all known radioactive substances, thus confirming the hypothesis incorporated into equations (1) and (2), i.e., that radioactive decay is a first order process.

The first quantitative analysis in pharmacokinetics was made by Widmark (1920) who studied both theoretically and experimentally the kinetics of distribution of several narcotics, in particular acetone. He studied the concentration curve of acetone in the blood after a single dose administration, and assumed that the fall of the curve was due principally to elimination from the lungs and chemical metabolism. The mathematical model used by Widmark was

\[
\begin{align*}
\frac{dx}{dt} &= -ax - bx \\
\frac{dy}{dt} &= ax \\
\frac{dz}{dt} &= bx
\end{align*}
\]

where \( x, y, z \) are the amounts of acetone in the body, exhaled, and metabolized, respectively, and \( x_0 \) is the amount administered initially. From the knowledge of the time behavior of the concentration \( c(t) \) of the acetone in the blood and of the so-called "reduced body volume" \( m \), where \( m = x/c \), Widmark computed the time behavior of \( x, y, z \) in several experimental conditions.

Later Widmark and Tandberg (1924) derived the equation of a model where there is a constant rate administration, and also when the drug is administered with rapid intravenous injections repeated at uniform intervals of time.

Another important contribution has been given by Gehlen (1933) who derived some theoretical expressions for what we would now call a two-compartment model.

Widmark (1932) studied also the elimination of ethanol and developed in this context what we would now call a zero-order compartment model.

The first systematic study of the kinetics of drugs introduced into the mammalian body in various ways was performed by Teorell (1937). As in the dynamical analysis of exchange of inert gases and of distribution of narcotics, the assumptions about the transport and the definition of the regions or compartments wherein measurements are to be made, lead to a set of linear differential equations with constant coefficients. Beyond that, however, two other interesting considerations appeared in these papers. One is the idea of a