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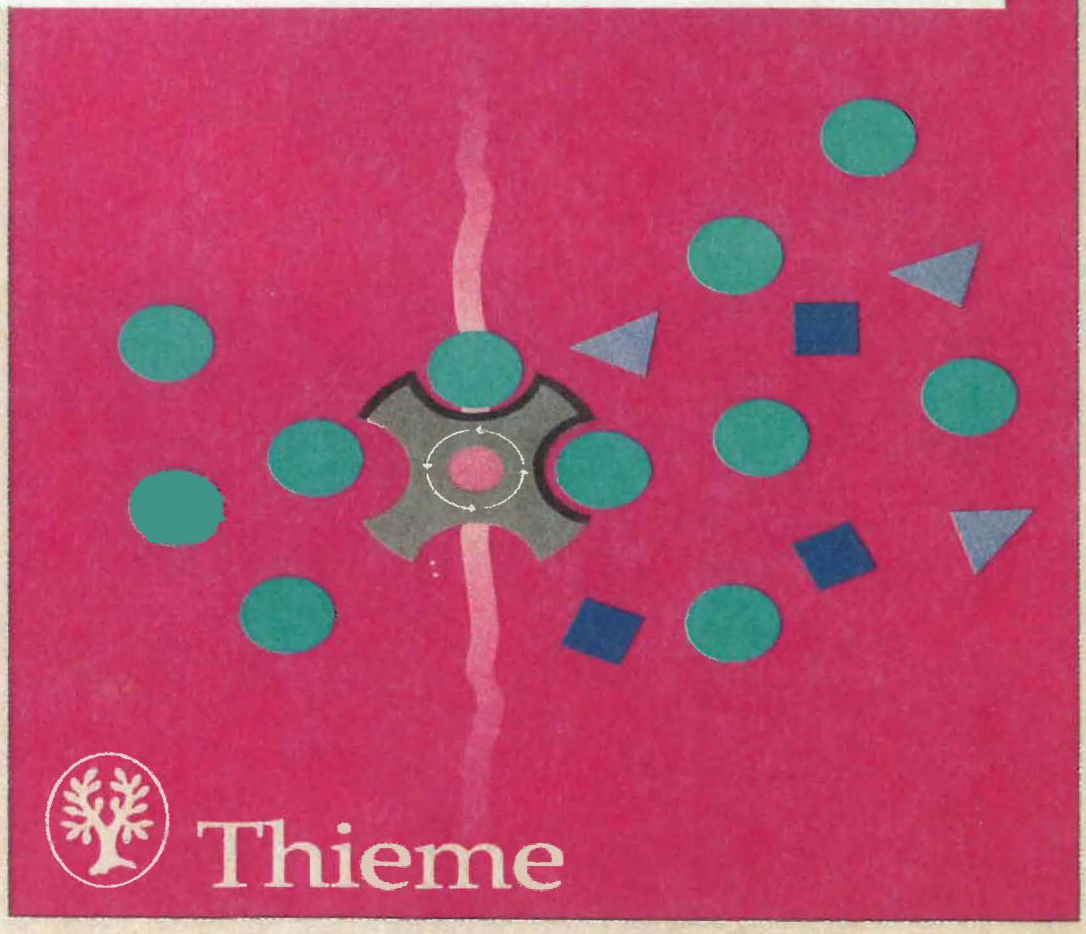
Color Atlas of Pharmacology



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Drug Concentration in the Body as a Function of Time. First-Order (Exponential) Rate Processes

Processes such as drug absorption and elimination display exponential characteristics. As regards the former, this follows from the simple fact that the amount of drug being moved per unit of time depends on the concentration difference (gradient) between two body compartments (Fick's Law). In drug absorption from the alimentary tract, the intestinal contents and the blood would represent the compartments containing an initially high and low concentration, respectively. In drug elimination via the kidney, excretion often depends on glomerular filtration, i.e., the filtered amount of drug present in primary urine. As the blood concentration falls, the amount of drug filtered per unit of time diminishes. The resulting exponential decline is illustrated in **(A)**. The exponential time course implies constancy of the interval during which the concentration decreases by one-half. This interval represents the half-life ($t^1/_2$) and is related to the elimination rate constant k by the equation $t^1/_2 = \ln 2/k$. The two parameters, together with the initial concentration c_o, describe a first-order (exponential) rate process.

The constancy of the process permits calculation of the plasma volume that would be cleared of drug, if the remaining drug were not to assume a homogeneous distribution in the total volume (a condition not met in reality). The **notional plasma volume freed of drug per unit of time** is termed the **clearance.** Depending on whether plasma concentration falls as a result of urinary excretion or of metabolic alteration, clearance is considered to be renal or hepatic. Renal and hepatic clearances add up to total clearance (Cl_{tot}) in the case of drugs that are eliminated unchanged via the kidney and biotransformed in the liver. Cl_{tot} represents the sum of all processes contributing to elimination; it is related to the half-life ($t^1/_2$) and the apparent volume of distribution V_{app} (p. 28) by the equation:

$$t^1/_2 = \ln 2 \cdot \frac{V_{app}}{Cl_{tot}}$$

The smaller the volume of distribution or the larger the total clearance, the shorter is the half-life.

In the case of drugs renally eliminated in unchanged form, the half-life of elimination can be calculated from the cumulative excretion in urine; the final total amount eliminated corresponds to the amount absorbed.

Hepatic elimination obeys exponential kinetics because metabolizing enzymes operate in the quasilinear region of their concentration–activity curve, and hence the amount of drug metabolized per unit of time diminishes with decreasing blood concentration.

The best-known exception to exponential kinetics is the elimination of alcohol (ethanol), which obeys a linear time course (zero-order kinetics), at least at blood concentrations $>$ 0.02%. It does so because the rate-limiting enzyme, alcohol dehydrogenase, achieves half saturation at very low substrate concentrations, i.e., at about 80 mg/L (0.008%). Thus, reaction velocity reaches a plateau at blood ethanol concentrations of about 0.02%, and the amount of drug eliminated per unit of time remains constant at concentrations above this level.

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