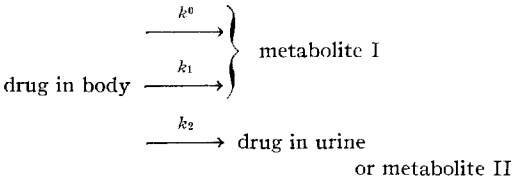
Possibility of Simultaneous Apparent Zero- and First-Order Kinetics in the *In Vivo* Formation of a Single Drug Metabolite

Sir:

The biotransformation of many drugs is describable by first-order kinetics and most of the theoretical models in pharmacokinetics have been developed on that basis (1, 2). It is now known that several important biotransformation processes have a limited capacity (3, 4) and proceed by apparent zero-order kinetics in the therapeutic dose range (4). The purpose of this communication is to propose the possibility that a single biotransformation product may be formed by a combination of simultaneously occurring apparent zero- and first-order processes.

Many biotransformation processes are known to occur in more than one tissue. For example, significant enzymic transformation of phenol to phenol sulfate has been demonstrated in human liver, adrenals, kidneys, and small intestine (5). These tissues differ in intrinsic (maximum rate per unit weight of tissue) and absolute capacity for this process. Therefore, it is likely that, at a sufficiently high drug concentration in body fluids, biotransformation in one tissue proceeds at a maximum rate while the same process in another tissue follows apparent first-order kinetics.

Such mixed kinetics in the formation of a single metabolite (metabolite I) might involve, for example, one apparent zero-order process[1] in parallel with one or more apparent first-order processes which do not reach "saturation" at any reasonable drug concentration. If the drug is also eliminated partly by renal excretion or by apparent first-order formation of another metabolite (metabolite II), the following model will apply:



where k^0 and k_1 are apparent zero- and first-order rate constants, respectively, for the formation of metabolite I, and k_2 is the apparent first-order rate constant for renal excretion of unchanged drug or for formation of metabolite II. Under these conditions, the fraction of the dose which is excreted as metabolite I will decrease with increasing dose. However, unlike the case where one of the metabolites is formed *solely* by apparent zero-order kinetics, the fraction of the dose excreted as metabolite I will approach a relatively constant value at high doses. This is so because the contribution of the apparent zero-order process to the total elimination process will become negligible at sufficiently high doses. At these high doses, the fraction of the total excreted drug which is metabolite I will approach the value $k_1/(k_1 + k_2)$ as in apparent first-order kinetics (6). The dose range where this occurs will depend on the values of k^0 and k_1.

[1] It is assumed as a matter of convenience that the capacity of this process is so low that a maximum rate is reached with very low doses.

(1) Dost, F. H., "Der Blutspiegel," Georg Thieme, Leipzig, Germany, 1953.
(2) Nelson, E., *J. Pharm. Sci.*, **50**, 181(1961).
(3) Levy, G., and Matsuzawa, T., *ibid.*, **55**, 222(1966).
(4) Levy, G., *ibid.*, **54**, 959(1965).
(5) Boström, H., *Scand. J. Clin. Invest.*, **17**, 33(1966).
(6) Nelson, E., and O'Reilly, I., *J. Pharmacol. Exptl. Therap.*, **129**, 368(1960).

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