methasone was found, at each time interval, to exceed the amount of steroid released from either 0.1% of dexamethasone or betamethasone alone. It would appear that this principle could be extended to more than two drugs and that the rate of release could be extended indefinitely until the drug mixture forms a solid solution.

Obviously only *in vivo* trials can determine if the *in vitro* advantages carry over, but the data presented do indicate that such trials merit serious consideration.

ARNOLD D. MARCUS
ROBERT E DEMPSKI
TAKERU HIGUCHI
JOSEPH D. DEMARCO

Merck Sharp and Dohme Research Laboratories
West Point, Pa.

University of Wisconsin
Madison

Received November 23, 1964.
Accepted for publication December 30, 1964.

## Salicylurate Formation—Demonstration of Michaelis-Menten Kinetics in Man

*Sir:*

A detailed study of the pharmacokinetics of salicylate elimination in man has established, among other findings, that the formation of salicyluric acid from salicylic acid reaches a maximal rate when the body content of salicylate exceeds about 2 mmoles (approximately 300 mg. salicylic acid) in the normal human adult (1). It was found also that the renal excretion of salicylurate after administration of salicylate is rate limited by the rate of formation of salicylurate from salicylate and glycine (1). These characteristics of salicylate elimination made it possible to determine rates of salicylurate formation as a function of body salicylate content over an appreciable range.

Suitable doses of aspirin were administered orally to test subjects, total urine was collected at frequent and known intervals, and aliquots of urine were analyzed for salicylurate and total salicylate as described previously (1). The results of these experiments are describable by Michaelis-Menten kinetics (2) and yield satisfactory Lineweaver-Burk plots (3). Representative examples of the experimental results are shown in Fig. 1; the data points for subject *1* (male, 22 years old) were obtained in the period of 16 to 24 hr. after administration of 1.5 Gm. aspirin, while the data points for subject *2* (male, 36 years old) represent the period of 15 to 27 hr. after oral administration of 2.0 Gm. aspirin. The theoretical maximal velocity of salicylurate formation obtained from the Lineweaver-Burk plots is about twice as high as the maximal rate found experimentally (about 400 μm. per hour). This appears to be due to a depression by salicylate (when in sufficiently high concentration) of the glycine conjugative system, as has been observed previously with tissue slice preparations from the dog, rat, and rabbit (4).

The present findings are considered to be of unusual interest since they represent (*a*) a case of zero-order metabolism of a drug administered in usual therapeutic doses,[1] and (*b*) a demonstration of Michaelis-Menten kinetics (with respect to the metabolism of a drug) by means of data obtained from experiments with intact humans (rather than from experiments with tissue slices, cell fractions, or purified enzymes). Apparently, similar observations in humans have so far been made only with ethanol (5).

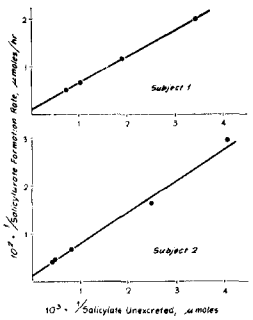


Fig. 1.—Plot of the reciprocal of salicylurate formation rate *vs.* the reciprocal of the amount of salicylate in the body.

(1) Levy, G., unpublished data.
(2) Michaelis, L., and Menten, M. L., *Biochem. Z.*, **49**, 333 (1913).
(3) Lineweaver, H., and Burk, D., *J. Am. Chem. Soc.*, **56**, 658(1934).
(4) Little, J. M., Angell, E. A., and Morgan, A. M., *Arch. Intern. Pharmacodyn.*, **111**, 259(1957).
(5) Lundquist, F., and Wolthers, H., *Acta Pharmacol. Toxicol.*, **14**, 265(1958).

GERHARD LEVY

Biopharmaceutics Laboratory
School of Pharmacy
State University of New York at Buffalo

Received December 8, 1964.
Accepted for publication January 6, 1965.
This investigation was supported in part by grant G-64-UB-1 from the United Health Foundation of Western New York.

[1] Salicylate elimination occurs mainly by salicylurate formation, ester and ether glucuronide formation, and renal excretion of unchanged drug. Zero-order kinetics have only been observed with respect to the first of these processes; the other processes are usually describable by first-order kinetics (1).