of catecholamines on free fatty acid mobilization was observed in the rat by Jelinkova & Hruza (1963, 1964).

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Estimation of drug metabolite elimination kinetics in man by the synthesis-blocking method

It is often necessary for the complete characterization of the pharmacokinetics of a drug (Levy, Amsel & Elliot, 1969) and for drug biotransformation interactions (Amsel & Levy, 1969; Amsel & Levy, 1970) to measure the elimination (or excretion) rate constants of drug metabolites. Many drug metabolites are not readily synthesized or available commercially; they may be unstable in or not well absorbed from the gastrointestinal tract (Levy, Amsel & Elliott, 1969; Levy, Weintraub & others, 1966) and unsuitable for parenteral administration. The elimination rate constants of such metabolites, which include most glucuronides and sulphates, cannot be determined by administering the metabolite as such. Some mathematical techniques have been developed to estimate the rate constants indirectly from the urinary excretion rates of free drug and metabolites (Cummings, Martin & Park, 1967; Martin, 1967) but these estimations are difficult or impossible if little or no drug is excreted in non-metabolized form (Cummings, King & Martin, 1967).

Another approach to this problem is to administer the drug, block the synthesis of metabolite soon thereafter, and follow as a function of time the decline in the plasma concentration or urinary excretion rate of the quantity of metabolite present in the body when further synthesis was blocked (Levy & others, 1969; Amsel & Levy, 1969; 1970). Blocking the synthesis of a drug metabolite may be accomplished by administering a competitive inhibitor such as benzoate which blocks the synthesis of salicylurate from salicylate (Levy, & others, 1969), or salicylamide, which blocks the formation of salicylic glucuronides (Levy & Procknal, 1968). The formation of acetaminophen sulphate (APAPS) from acetaminophen (APAP) can also be blocked by salicylamide, which competes with APAP for sulphate (Levy & Yamada, 1970).

The elimination rate constant of APAPS has been measured in three healthy adult male volunteers who received 1 g APAP orally followed 1·5 h later by 1 g salicylamide in aqueous solution. Urine was collected every 15 min and assayed for APAPS (Levy & Yamada, 1970). Semilogarithmic plots of APAPS excretion rate versus time after salicylamide administration were linear for about 2 h and permitted the calculation of elimination half-life ($t_{\frac{1}{2}}$) and elimination rate constant ($0{\cdot}693/t_{\frac{1}{2}}$). The three subjects yielded elimination rate constants of 1·0, 0·9, and 1·0 h^{-1} respectively, equivalent to half-lives of 0·7, 0·8, and 0·7 h. Repetition of the experiment in the first subject, but with 2 g rather than 1 g salicylamide to make sure that APAPS formation had been blocked completely, yielded a rate constant of 0·9 h^{-1}.

The APAPS elimination rate constants thus obtained are in good agreement with the results of Cummings, King & Martin (1967) who determined these constants indirectly by pharmacokinetic analysis based on the excretion rates of APAP and APAPS after APAP administration. These investigators reported values ranging from 0·8 to 1·5 h^{-1} in four subjects, compared with 0·9 to 1·0 h^{-1} found in our experiments.

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