cannabidiol. Cannabichromene is a relatively unstable molecule and decomposes quite readily when exposed to heat, light, and acidic and basic conditions (9). Combined (−)-Δ^9-*trans*-tetrahydrocannabidivarin and cannabicyclol was constant until Day 20. It then declined very little and very slowly. Cannabigerol, although not shown in Fig. 2 due to its small concentration, was very stable.

The data in Fig. 2 cannot be easily explained. Certain phenomena have been reported (9) regarding the ambiguity of cannabichromene decomposing to cannabicyclol. Other than a solvent effect and a "biophysical" parameter not yet defined, this group can offer no explanation of most intrinsic data in Fig. 2.

Individual synthetic cannabinoids and a mixture of synthetic cannabinoids are stable in chloroform and do not decompose in these laboratories, as Parker *et al.* (2) reported for cannabidiol. The instability reported by Parker could be due to impure solvents. We have observed unusual stability problems with certain batches of chloroform. These problems were circumvented by using nanograde and certain brands of spectrograde chloroform[5]. Thus, our data indicate cannabinoids, synthetic or naturally occurring, to be stable in chloroform within experimental error for much longer time periods than are required in a routine analysis. We do, however, agree with Parker *et al.* that cannabinoids should not be stored in chloroform for a prolonged period. Therefore, from published data (1) and data contained within, chloroform remains the solvent of choice for extracting cannabinoids from *Cannabis* preparations.

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Voucher specimens are located in the *Cannabis sativa* L. Herbarium of the School of Pharmacy, University of Mississippi.

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[5] Mallinckrodt and Analabs solvents have given consistently good performance in our laboratory.

Disposition of *N,N*-Bis(phenylcarbamoylmethyl)dimethyl Ammonium Chloride in the Rat: An Interesting Example of First-Pass Metabolism

Keyphrases □ *N,N*-Bis(phenylcarbamoylmethyl)dimethyl ammonium chloride—disposition in rat, first-pass metabolism □ Metabolism, first pass—*N,N*-bis(phenylcarbamoylmethyl)dimethyl ammonium chloride in rat □ Lidocaine derivatives—disposition of *N,N*-bis(phenylcarbamoylmethyl)dimethyl ammonium chloride in rat, first-pass metabolism

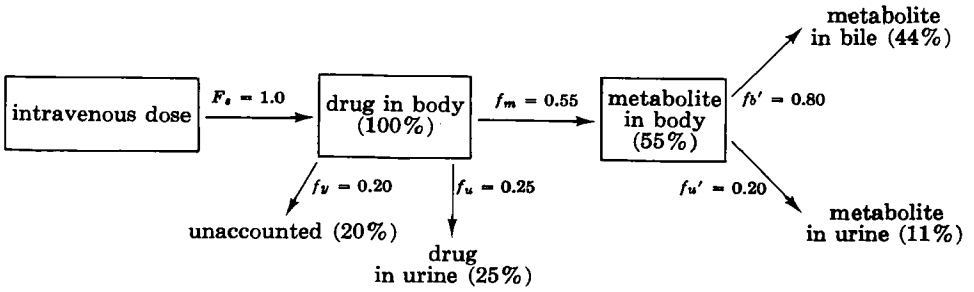
To the Editor:

It has recently been demonstrated that the disposition of *N,N*-bis(phenylcarbamoylmethyl)dimethyl ammonium chloride (I), a quaternized lidocaine derivative with antiarrhythmic activity, is dependent on the route of administration in the rat (1). The present report is concerned with a quantitative estimate of the degree to which I is subjected to a first-pass effect in the rat and with a quantitative comparison of the predicted *versus* the observed disposition of the drug after intraperitoneal administration.

After an intravenous (tail vein) dose of 2.5 mg of ^{3}H-I to Sprague–Dawley rats, 35% of the administered radioactivity was ultimately excreted in the urine in the form of I and a carboxylic acid metabolite (II). Radiochromatogram scans of urine samples subjected to high voltage electrophoresis, in addition to reverse isotope dilution data, indicated that about 70% of the total radioactivity in the urine could be accounted for by I.

With intravenous administration of an equal dose to rats with ligated bile ducts, 80% of the radioactive dose was found in the urine. Since the observed increase in urinary excretion of tritium in bile duct-ligated rats may be attributed to "spill over" into the urine of drug and/or metabolite normally excreted in bile, it was estimated that in normal rats 45% of the administered radioactivity is excreted in the bile. Reverse isotope dilution of bile samples revealed less than 5% intact drug (I), while radiochromatogram scans of electrophoregrams of bile samples indicated that a single compound (II) accounted for about 80% of the total radioactivity in the bile. The data are reasonably consistent with Scheme I, where F_s indicates the fraction of administered radioactivity reaching the systemic circulation; f_m, f_u, and f_y represent the fractions of intact drug reaching the systemic circulation that are converted to metabolite, excreted as such, and unaccounted for, respectively; and f_b' and f_u' denote the fractions of the total amount of formed metabolite that undergo biliary and urinary excretion, respectively. The parenthetical values represent percent of administered radioactivity.

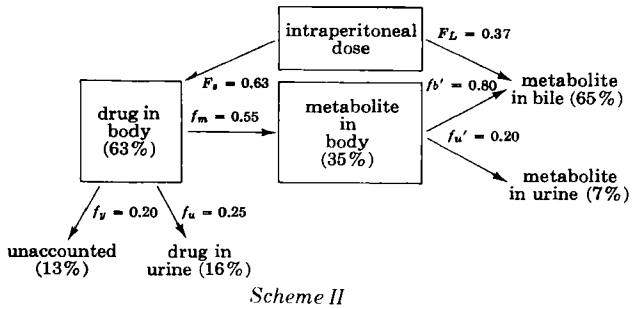
Upon intraperitoneal injection of a 2.5-mg dose of ^{3}H-I to normal Sprague–Dawley rats, one finds significantly less tritium ultimately excreted in the urine than is observed after tail vein injection (22%



Scheme I

versus 35%, $p < 0.01$). This observation raised the possibility that after intraperitoneal administration the drug undergoes a first-pass phenomenon, leading to a biliary shunt. Confirmation of this hypothesis was obtained by finding comparable total urinary recovery after either intravenous or intraperitoneal administration to rats with ligated bile ducts. A number of previous studies (2–5) with drugs manifesting first-pass metabolism consistently showed that the ratio of metabolite to unchanged drug in the urine is significantly greater after "hepatic" (intraperitoneal, oral, *etc.*) administration than after "systemic" (intravenous, intramuscular, *etc.*) administration. Surprisingly, this was not the case with I. Irrespective of the route of administration, about 70% of the total radioactivity in the urine represented intact drug while the metabolite (II) accounted for the balance; essentially no intact drug was found in the bile.

The data suggest that, during passage of drug through the liver after intraperitoneal administration, a portion of the dose is irreversibly lost by metabolic conversion and subsequent biliary excretion while the balance of the dose reaches the systemic circulation. The fraction of the dose reaching the systemic circulation after intraperitoneal administration is calculable directly from the ratio of total radioactivity excreted in the urine after intraperitoneal and intravenous dosing, *i.e.*, 22/35 = 0.63. Accordingly, Scheme I was modified to take into consideration the first-pass effect and a quantitative metabolic scheme for drug disposition after intraperitoneal administration was devised (Scheme II), where F_L is the fraction of the dose undergoing first-pass metabolism. It is assumed that all of the metabolite formed during the first pass is quantitatively excreted in the bile. All other symbols and notations are as defined in Scheme I.



Scheme II

Scheme II is in remarkably good agreement with experimental observations in the rat after intraperitoneal administration. As noted, 22% of the intraperitoneal dose of ^{3}H-I was excreted in the urine, whereas Scheme II predicts 23% (16% I and 7% II). After intraperitoneal administration of I to rats with ligated bile ducts, 14% of the total radioactivity could not be accounted for in the urine. Scheme II predicts that 13% of the dose would be unaccountable. The difference between the urinary excretion of total tritium after intraperitoneal administration to rats with ligated and patent bile ducts indicates that, in normal rats, 64% of the radioactive dose is ultimately excreted in the bile. Biliary excretion of total radioactivity 24 hr after intraperitoneal administration of ^{3}H-I to bile duct-cannulated rats accounted for 48% of the dose. Extrapolation of these data to 72 hr after drug administration to estimate total biliary excretion yields a value of 59%. Both estimates of total biliary excretion of tritium are in excellent agreement with the value of 65% calculated in Scheme II.

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