Role of Drug Metabolism in Drug Research and Development: Importance of Drug Metabolism in Clinical Pharmacological Evaluation of New Drugs

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Abstract □ Since man is characterized by marked individual variations in the disposition and metabolism of drugs, proper evaluation of a new drug requires the inclusion of pharmacokinetic parameters in efficacy studies. Later phases of clinical evaluation should not overlook interactions between a new drug and other therapeutic agents, normal body constituents, or naturally occurring compounds in the diet.

Key phrases □ Drug metabolism—role in drug research and development, symposium □ Clinical pharmacologists—evaluation of new drugs □ Development of new drugs—evaluation of metabolism, bioavailability, drug interactions, role of clinical pharmacology

Drug metabolism plays an important role in the various stages of the research and development of potential new drugs. Recognition of its great importance has led governmental regulatory agencies to require a multitude of information on the bioavailability, pharmacokinetics, pathways of metabolism, and excretory patterns of a compound before it is given consideration as a new drug. Prior knowledge of these parameters from animal studies is important; however, the ultimate decision regarding a new drug's safety and potential use can only be obtained after the drug has been administered to man. When a compound has been found to be safe and efficacious in animal studies and the decision has been made to study its effects in humans, an investigational new drug application must be filed with the Food and Drug Administration (FDA).

The clinical investigation of a new drug has been divided into several phases. Phase I is essentially a pilot study conducted by well-trained clinical pharmacologists. The drug is cautiously administered to a small number of healthy volunteers, with the major objective being a confirmation of the animal data on safety and lack of toxicity. Initially, the drug is administered in a dose that is not expected to produce any pharmacological effect. This initial dose must be a fraction of the maximum tolerated dose administered to the most sensitive species. This information is obtained from the subacute animal toxicity studies. The dose in man is then cautiously, gradually increased. During this phase, information about the bioavailability, pharmacokinetics, transformation, and excretion of the drug is obtained.

If the compound is shown to be safe in doses at which a desired pharmacological effect might be anticipated, the drug is then subjected to the second phase. Primarily, Phase II studies are designed to evaluate the therapeutic efficacy of the new drug, *i.e.*, its usefulness in the treatment and prevention of the disease state for which it has been designed. Other objectives of this phase are to confirm the continued safety of the drug in man, to obtain information that might elucidate its mechanism of action, and to study further its metabolism in man.

If the drug appears to be both safe and efficacious, or if the benefit from its use would be greater than the risk involved, the drug may enter Phase III, or the broad clinical trial. During this phase, extensive clinical trials are performed by a greater number of physicians for the further accumulation of data about the drug's safety and efficacy in a larger patient population. If the new compound passes the criteria of usefulness and relative safety in rather broad use, a new drug application is submitted to the FDA, at which time a decision is made whether or not the drug should be marketed.

ROLE OF DRUG METABOLISM

An interdisciplinary approach is essential for the research and development of a new drug. The techniques and methodology employed are in part the same as those used in preclinical studies, *i.e.*, analysis of plasma, urine, feces, and other biological fluids. However, many important restrictions apply to man, such as limited availability of time and manpower for analysis, limited numbers and specific types of subjects required, and the need for use of noninvasive techniques.

PHARMACOKINETICS AND BIOAVAILABILITY

Major advances in drug evaluation and mechanistic studies have been made in the field of clinical pharmacology as a result of the availability and utilization of more precise analytical, chemical, radiochemical, and immunological methods. The need for a sensitive assay method for determining drug levels in biological fluids early in the course of a Phase I study is essential for the initial bioavailability and pharmacokinetic studies.

Interest has increased recently in the metabolism of Δ^9-tetrahydrocannabinol, the active constituent of *Cannabis sativa* or marijuana. This drug was officially recognized in the USP several decades ago and is now being evaluated by several research groups as a possible antidepressant. There are interesting differences relating to the route and manner of administration of Δ^9-tetrahydrocannabinol (1–3). In general, for most other drugs the oral route is the most common route of administration in man. After this route, the compound must first be absorbed from the GI tract to exert its effects systemically. To establish the bioavailability of a drug, *i.e.*, the percentage of the drug that is absorbed and made available to the organism, levels of drug in biological fluids are examined. One approach to studying the bioavailability of a drug administered by the oral route is exemplified by studies done with radiolabeled tetrahydrocannabinol. When ^{14}C-Δ^9-tetrahydrocannabinol is administered intravenously, no unchanged drug is excreted in feces or urine, indicating its complete metabolism *in vivo* (3, 4). However, after oral administration, about 5–10% of unchanged Δ^9-tetrahydrocannabinol is excreted in the feces, indicating that 90–95% of the dose is absorbed from the GI tract (3).

Plasma levels of ^{14}C-Δ^9-tetrahydrocannabinol and its metabolites after oral, intravenous, and inhaled administration are depicted in

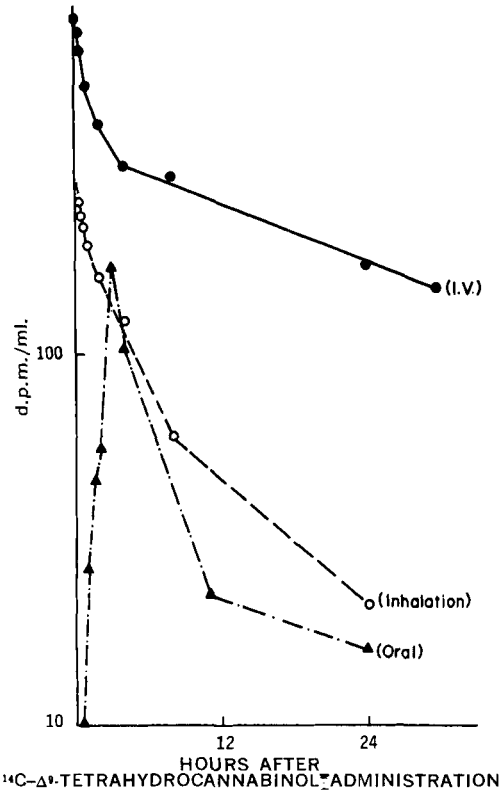


Figure 1—*Plasma levels of ^{14}C-Δ^9-tetrahydrocannabinol and its metabolites after oral and intravenous administration or after inhalation of ^{14}C-Δ^9-tetrahydrocannabinol to man. Each curve represents a typical subject.*

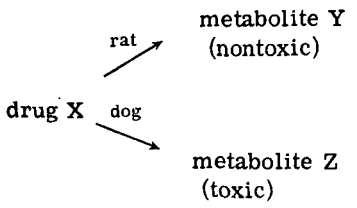
Fig. 1. After the oral administration of this drug, dissolved in an alcoholic solution and suspended in cherry syrup, the plasma levels of radioactivity increased gradually, peaking at 3 hr. When this vehicle was used, the pharmacological effects were described as pleasant. Administration of this drug in gelatin capsules in a solution of sesame oil or glycocholic acid results in more rapid absorption, higher plasma levels, and an intense, unpleasant pharmacological effect[1]. Information of this type allows the pharmaceutical chemist to modify the formulation if necessary and allows the clinician to adjust the dosage based on the knowledge derived from the plasma levels.

Although there are several important exceptions, in general the pharmacological effects of a drug can be correlated with its plasma concentration. With a method capable of determining plasma levels of a drug, one can often demonstrate the range of plasma levels required to give the desired pharmacological effect. This has been best exemplified by studies in the field of cardiac antiarrhythmia agents which have demonstrated that the drug will be ineffective at plasma levels below the ideal level while those beyond this optimum level will result in undesired effects (5, 6).

Since man is a heterogeneous species, plasma levels of a drug may vary markedly between individuals due to genetic and/or environmental factors. Hammer and Sjöqvist (7) administered a uniform dose of the antidepressant desipramine (25 mg. three times daily) to a series of subjects until their plasma drug levels were at a steady state. These investigators found a marked variation in the plasma levels of desipramine as well as in the therapeutic response of the subjects. The knowledge of the plasma levels of drugs in the area of CNS pharmacology is of great importance since, in most cases, only subjective effects can be measured in the evaluation of a new drug. Thus, a drug that appears to be a therapeutic failure may in fact not have been given a fair trial since the drug may not have been administered in sufficient doses. Likewise, a drug that in the initial studies appears to have intolerable side effects in a few patients may actually be the result of excessive levels and, after readjustment of the dose, may prove to be an effective, well-tolerated, therapeutic agent. In the efficacy Phase II studies, plasma drug levels should be measured, whenever feasible, to avoid discarding potential new drugs.

The bioavailability of new formulations or routes of administration should be assessed during all phases of clinical pharmacology. The investigation of timed-release preparations or other dosage forms of an investigational new drug or a marketed drug should be accompanied whenever possible by data that, in fact, the drug is absorbed and that the plasma levels and pharmacological effects are what would be expected. (For example, after timed-release medication, the plasma levels and pharmacological effects should be maintained for a longer duration.) Again, information of this type obtained from clinical studies enables the pharmaceutical chemist to modify the formulation, if necessary, to deliver the desired dose over the desired duration.

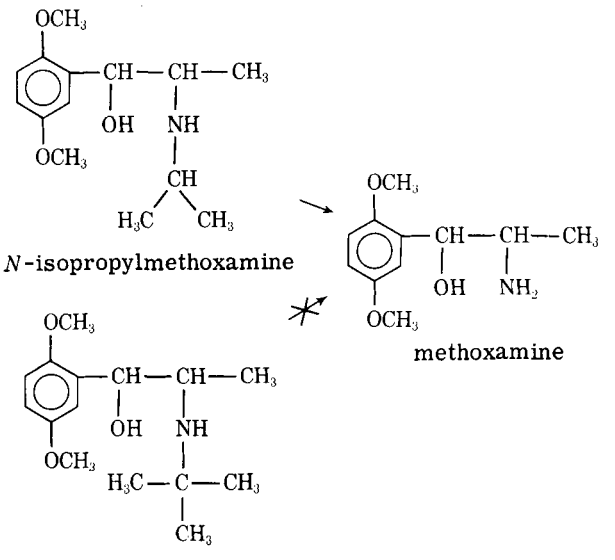
[1]M. Perez-Reyes, M. A. Lipton, and M. E. Wall, unpublished observations, 1971.



Scheme I—Hypothetical example of species variation in drug metabolism

METABOLISM

The importance of drug metabolism studies in man is obvious since species variation in the metabolism of drugs is not uncommon. Preclinical studies may reveal that a potentially useful drug is metabolized *via* different routes in different species. Considering a hypothetical case (Scheme I), Drug X is metabolized in the rat to Y, a nontoxic metabolite, while in the dog Drug X is metabolized *via* a different pathway to metabolite Z, which shows marked toxicity. It is then essential that in early Phase I studies, metabolic studies using radiolabeled drug (or, alternatively, nonradiolabeled drug if the assay method is sensitive enough) be undertaken to determine what the metabolic pathway is in man. In fact, in this case it is the responsibility of the investigator in early Phase I to be sure that the toxic metabolites are not formed in substantial quantities since, in



Scheme II—Structures and metabolic interrelationships between N-isopropylmethoxamine and butoxamine (N-tert-butylmethoxamine) and methoxamine

certain individuals, this latter pathway might be predominant and may lead to marked toxicity.

Knowledge of the metabolic pathway of a drug can be of value to medicinal chemists when structurally altering a drug in an attempt either to retard its metabolism, thereby prolonging its pharmacologic effect, or to prevent the formation of undesirable metabolites which may be associated with untoward side effects. *N*-Isopropylmethoxamine, an analog of methoxamine (Scheme II), was studied clinically as an agent that would lower plasma free fatty acids. This drug was effective in its desired therapeutic effect; however, it produced marked side effects including hypertension and reflex bradycardia. Metabolic studies revealed that in animals a significant percentage of the drug is *N*-dealkylated to methoxamine, a potent pressor drug[2] (8). The substitution of an *N-tert*-butyl group for the *N*-isopropyl group prevented this dealkylation and butoxamine, the resulting compound, was then extensively studied in man (9, 10).

The importance of drug metabolism in the development of new drugs cannot be overemphasized if one considers that a potentially active drug may be only a precursor and may, in fact, be converted to the active form *in vivo*. After the oral administration of Δ^9-tetrahydrocannabinol (11), a relatively low concentration of the parent drug is found in plasma (Fig. 2). The majority of the material is present in the form of metabolites which show a good temporal relationship to the psychological effects of Δ^9-tetrahydrocannabinol. From the standpoint of drug development, it would be beneficial to know if an active metabolite were formed so that this compound might be clinically evaluated.

The metabolism of levodopa, the antiparkinson drug, depicts an example of the clinical usefulness of data obtained from basic metabolic studies. Levodopa is metabolized by the ubiquitous enzyme dopa decarboxylase. In early clinical trials (12), large doses had to be employed to achieve the desired therapeutic effect. However, with these large doses, marked side effects were in evidence due to decarboxylation of the drug in peripheral tissues, and excess doses were required to get sufficient quantity of material to the site of action (the brain). Knowledge of levodopa metabolism led to clinical trials of dopa with specific peripheral decarboxylase inhibitors, allowing the dopa to enter brain tissue where it was subsequently decarboxylated to dopamine. As a result, the dose of dopa was reduced severalfold and many of the side effects were diminished (13–15).

Species differences in drug metabolism play a significant role in drug interactions. Amphetamine is metabolized primarily by parahydroxylation in rats, while in man the major route is by deamination (Scheme III) (16). In rats the half-life of amphetamine in brain

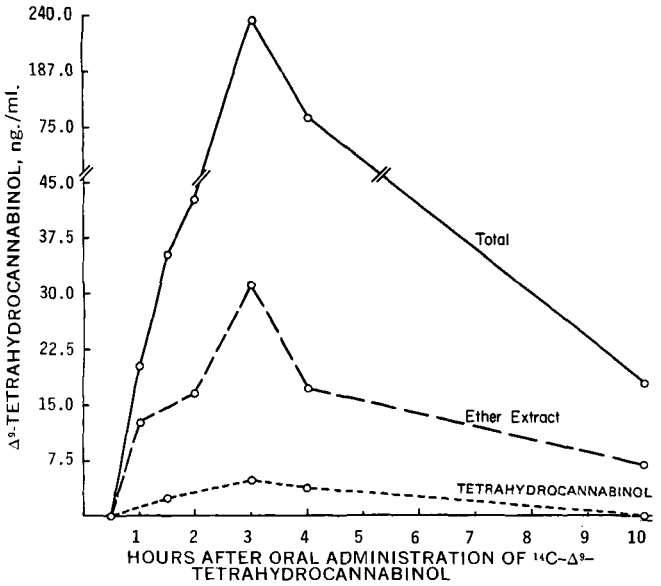


Figure 2—*Plasma levels of* ^{14}C-Δ^9-*tetrahydrocannabinol, total radioactivity, and ether-extractable radioactivity after the oral administration of* ^{14}C-Δ^9-*tetrahydrocannabinol to man.*

[2] A. Klutch, A. H. Conney, and J. J. Burns, unpublished observations.

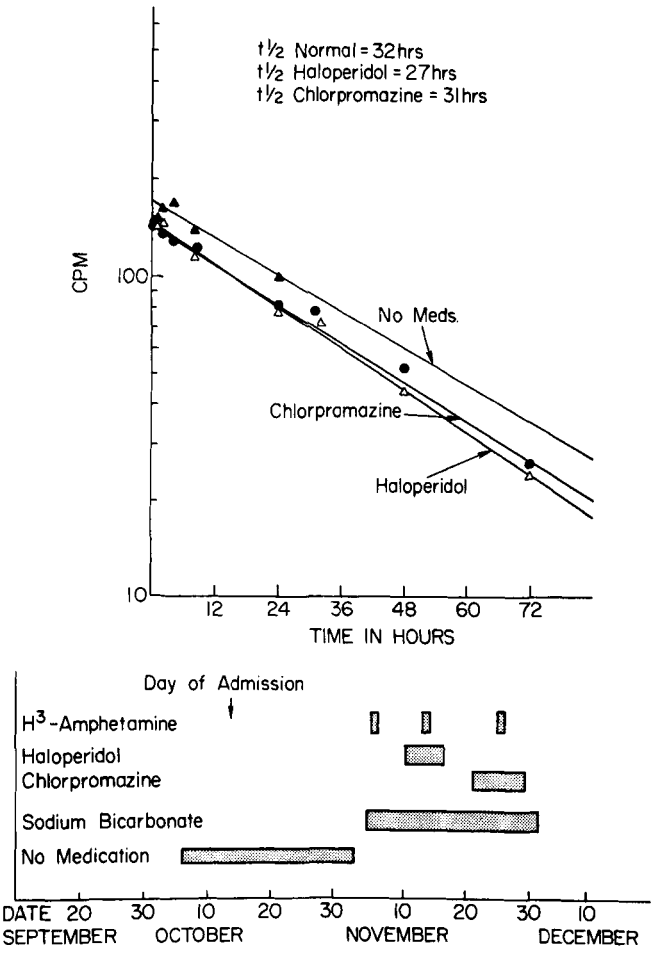


Figure 3—*Plasma levels of* ^3H-*amphetamine in a subject after pretreatment with haloperidol, or chlorpromazine, or without any premedication. Subjects were given sodium bicarbonate to maintain urine at an alkaline pH (Lemberger and Davis, unpublished observations).*

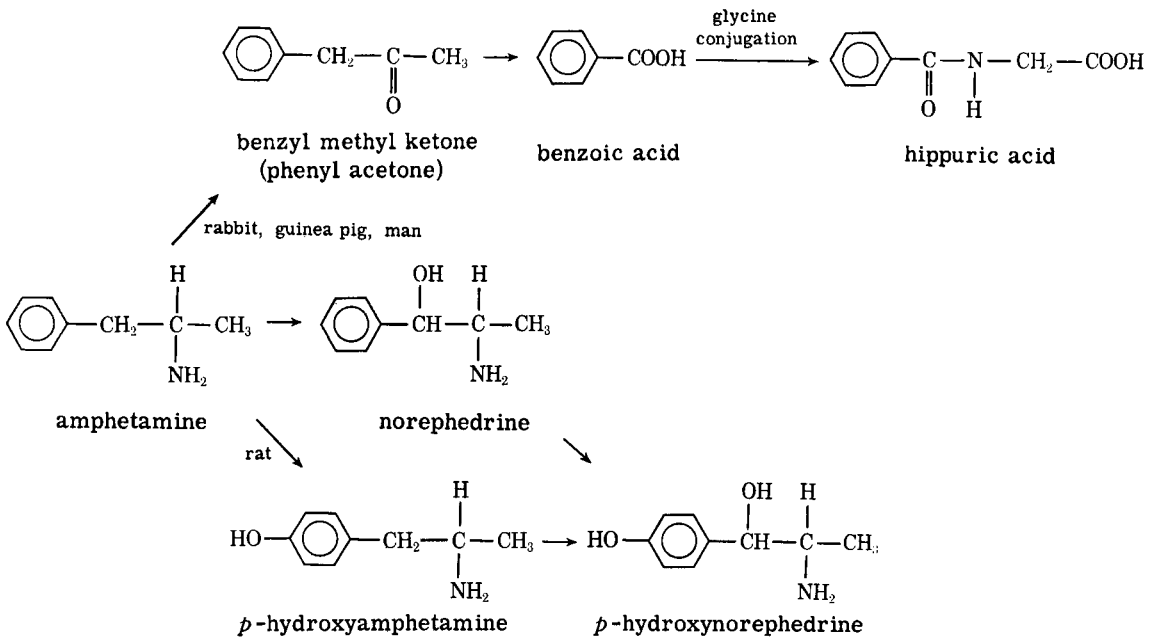
and whole body can be increased by pretreatment with chlorpromazine (17). In contrast, chlorpromazine had no significant effect on the plasma half-life of human subjects whose urine was maintained at an alkaline pH (Fig. 3). Thus, before drawing conclusions concerning the interactions of drugs, the studies must ultimately be done in man.

EXCRETION

The excretion of a drug by the kidney or liver may play an important role in the plasma levels of the drug and on its therapeutic or toxic effects. Using Δ^9-tetrahydrocannabinol as an example, Agurell *et al.* (18) showed that the rabbit rapidly excretes Δ^9-tetrahydrocannabinol in the urine (Fig. 4). This is reflected by the shorter plasma half-life in this species than in either man (4) or rat (19) who excrete the drug primarily in the bile.

The importance of urinary pH on the excretion and metabolism of amphetamine has been studied in several laboratories (20, 21). Since most drugs are either weak anions or cations, their plasma levels and the duration of pharmacological effects can be indirectly influenced by the urinary pH. These principles are used in the treatment of overdosages by agents such as amphetamines or barbiturates.

An example of the importance of renal function in drug evaluation in man is seen in the development of new antibiotics since, in high concentrations, they may be toxic to the host as well as to the parasite. It is, therefore, important to attempt to monitor plasma levels of the drug either chemically or by bioassay techniques. This is especially true of individuals with advanced renal disease who re-



Scheme III—Metabolic pathways for amphetamine in man and several animal species

quire chemotherapy for Gram-negative infections for which a new antibiotic is being evaluated.

DRUG INTERACTIONS

In the latter phase of clinical evaluation of potential therapeutic agents, the need exists to determine if there will be any significant drug interactions with other known agents frequently used concurrently for a specific disease state. The best known example of this is the interaction of the coumarin anticoagulants with other drugs (22). In this instance, the mechanism of the interaction has been extensively studied and can be secondary to the displacement of these anticoagulants from plasma protein or secondary to an effect on their metabolism. Another type of drug interaction is simply of chemical or physical nature. Interactions of this type may occur due to ingredients in a new formulation or from the simultaneous administration of incompatible drugs—the well-known example of tetracyclines with certain antacids.

In addition to interactions with other drugs, interactions with normal body constituents or naturally occurring compounds such as foods may be of importance. For example, certain cheeses and other foods are rich in the biogenic amine tyramine. This amine is normally metabolized in the liver by the enzyme MAO. In several instances, patients being treated for depression or hypertension with MAO inhibitors ingested cheese and evidenced severe hypertensive crises, resulting sometimes in death. An awareness of possible drug interactions is essential to avoid catastrophic toxic effects resulting in the liquidation of potentially useful drugs during their development or after they have been marketed.

The effect of drugs on laboratory tests has also been of concern to clinical investigators. In some instances, the administration of certain drugs can result in artifactual laboratory values which can be frightening to the uninitiated or unaware investigator.

During efficacy studies, in those cases where the test drug is given on a long-term basis as in the treatment of hypertension, epilepsy, or psychotic states, it is important to substantiate by plasma levels if the drug is inducing its own metabolism with the resultant de-

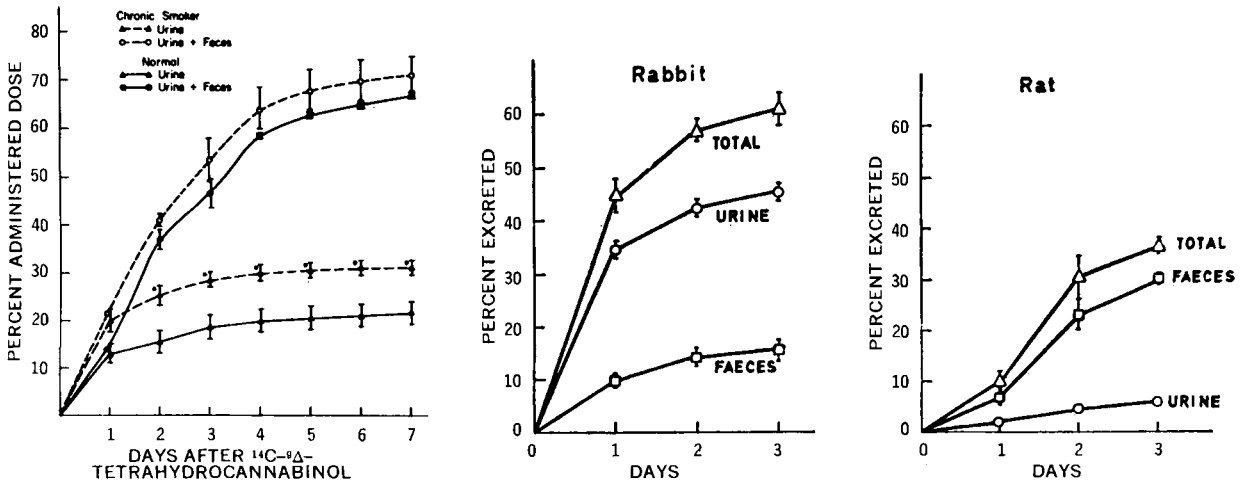


Figure 4—*Excretion patterns of radioactivity in man, rabbit, and rat after the administration of radiolabeled Δ⁹-tetrahydrocannabinol. (Left) Comparison of the cumulative excretion of radioactivity in chronic marijuana users and nonusers after the intravenous injection of ¹⁴C-Δ⁹-tetrahydrocannabinol. (Center) Cumulative excretion of radioactivity in the rabbit after the intravenous administration of ¹⁴C-Δ⁹-tetrahydrocannabinol (18). (Right) Cumulative excretion of radioactivity in the rat after the intravenous administration of ¹⁴C-Δ⁹-tetrahydrocannabinol (19).*

crease in therapeutic effect. The monitoring of plasma drug levels provides the clinical pharmacologist with analytical data, allowing him to increase the dosage to achieve and maintain the optimum plasma level for producing sustained therapeutic effects.

In conclusion, the role of drug metabolism and drug development at the stage of the clinical trial is as essential, if not more essential than, during the early stage of a drug's development. Perhaps the major reason for clinical pharmacology having obtained recognition as a clinical science has been its close collaboration and interaction with analytical chemistry, medicinal chemistry, toxicology, pharmaceutical chemistry, and biochemical pharmacology.

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ACKNOWLEDGMENTS AND ADDRESSES

Received from *Lilly Laboratory for Clinical Research, Marion County General Hospital, Indianapolis, IN 46202*