Role of Drug Metabolism in Drug Research and Development: View of a Medicinal Chemist

FRANK H. CLARKE

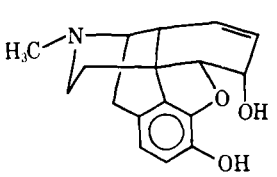
Abstract □ This short review is an attempt to illustrate, with a few specific examples, how useful the results of drug metabolism studies are to the medicinal chemist who is seeking to improve the physiological properties of a potential new medicinal agent. The medicinal chemist must keep abreast of the studies of his associates who are evaluating his new compound as a potential drug. Only with close cooperation and teamwork among all concerned will the full potential of the new discoveries of medicinal chemistry be realized.

Keyphrases □ Drug metabolism—role in drug research and development, symposium □ Medicinal chemists—use of drug metabolism studies to design and synthesize potential new drugs □ Development of new drugs—use of drug metabolism studies by medicinal chemists

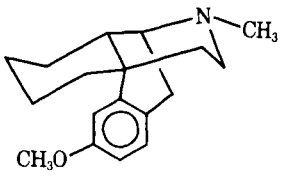
It is the responsibility of the medicinal chemist to design and synthesize potential new drugs. Usually he seeks a lead to a new chemical class of medicinal agents and then develops this lead until a compound is selected for clinical evaluation. Attention will be focused here on how a knowledge of drug metabolism assists the chemist in the design of the lead compound and in its development toward a selected clinical candidate.

FINDING THE LEAD COMPOUND

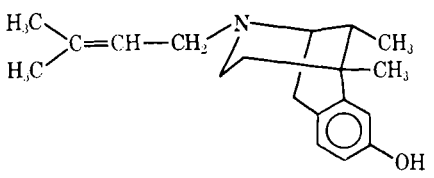
Let us first consider how the new lead is discovered. In many areas of medicinal research, a natural product was modified to find a new and more useful drug. Morphine (I), from the opium poppy, has been modified to provide the antitussive dextromethorphan (II) and, more recently, the analgesic pentazocine (III), each with superior properties. Penicillin (IV) was found to be a superb antibiotic but was ineffective against staphylococcal infections because of hydrolytic inactivation by the penicillinases. A knowledge of this metabolic inactivation led to the development of methicillin (V) which can be used to treat penicillin-resistant infections. Modification of the tetracycline (VI) antibiotics led to methacycline (VII) and doxycycline (VIII) which retain activity and are better absorbed from the GI tract because of enhanced lipid solubility.



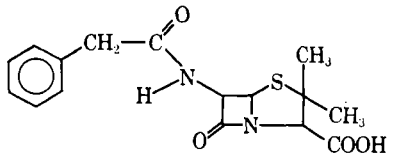
morphine
I



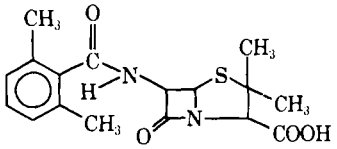
dextromethorphan
II



pentazocine
III



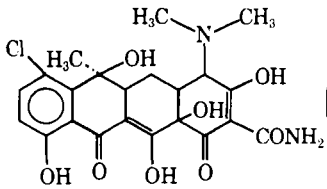
penicillin G
IV



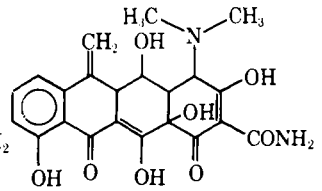
methicillin
V

Although the origins of many other drugs, such as the steroid hormones, the glucocorticoids, the amphetamines, and even aspirin, can be traced to natural products, a surprising number of useful drugs owe their discovery to serendipity—often in the clinic. The tranquilizers and antidepressants such as chlorpromazine (IX), perphenazine (X), imipramine (XI), and amitriptyline (XII) fall into this category. Of course, it should be made clear that although the discovery of the exciting clinical usefulness of these drugs was serendipitous, there was initially a rational basis for the testing of these compounds in man. Thus, the phenothiazines and iminodibenzyl derivatives were first studied as potential antihistamines to which they bear a strong structural resemblance. With the initial drugs as leads, medicinal chemists were soon able to provide congeners with enhanced potency and with new spectra of therapeutic effectiveness.

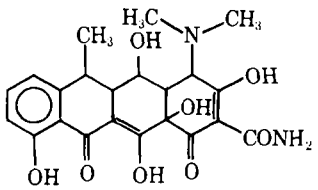
Every medicinal chemist dreams of becoming the discoverer of a completely new chemical class of drugs. In this respect, few are as fortunate as Dr. Sternbach of Hoffmann-La Roche who first prepared chlordiazepoxide (XIII) and diazepam (XIV).



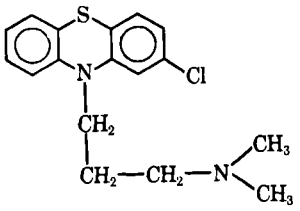
chlortetracycline
VI



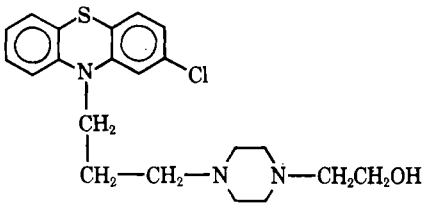
methacycline
VII



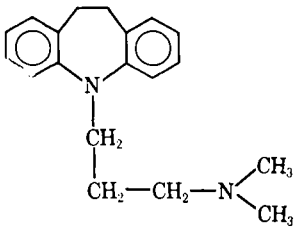
doxycycline
VIII



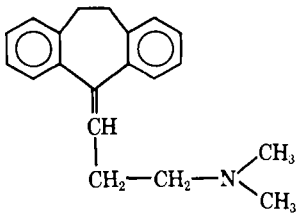
chlorpromazine
IX



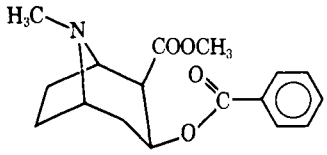
perphenazine
X



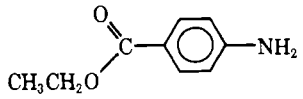
imipramine
XI



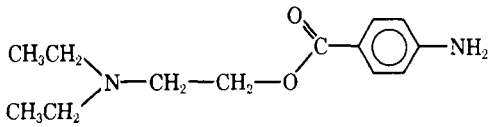
amitriptyline
XII



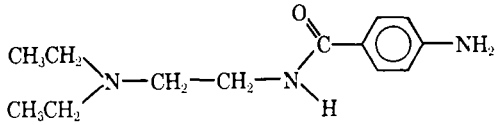
cocaine
XV



benzocaine
XVI



procaine
XVII



procainamide
XVIII

Nevertheless, much exploratory research is carried out with new classes of chemical compounds in the search for useful activity. We all know of medicinal chemists who believe they have found the perfect drug--all that must be done now is to discover a disease it will cure.

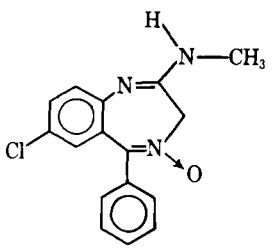
New discoveries such as those of chlordiazepoxide and diazepam are few and far between. In the meantime, there is a growing body of knowledge concerning the nature of disease and the biochemical reasons for abnormal function. As biochemistry and even biology provide explanations at the molecular level, it may one day be possible to point to an ideal example of a drug that was the result of rational design. Today, however, there are many approaches to rational design in which the medicinal chemist may use his intuition and his knowledge of what is wrong with existing therapy and design new compounds that will be superior to the best drugs now in use.

DEVELOPING THE LEAD

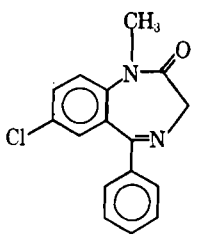
Let us first look at the discovery of some typical drugs.

The discovery of the local anesthetic properties of the alkaloid cocaine (XV) (1) led to the elucidation of its structure and the synthesis and testing of simplified versions of the molecule. Eventually these led to benzocaine (XVI) which was effective topically but was too insoluble to be useful by injection. Further studies led to procaine (XVII), which became the leading local anesthetic for 50 years. In 1936 the antiarrhythmic action of procaine was discovered (2) and a search was begun for an analog that would be longer lasting and not so readily hydrolyzed by esterases in the body. The result was the discovery of procainamide (XVIII), a very effective antiarrhythmic agent that is stable and has a prolonged duration of action.

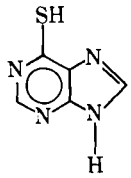
In a rational approach to chemotherapy, Hitchings and Elion (3) looked for compounds that would act as antimetabolites and interfere selectively with nucleic acid biosynthesis in parasitic microorganisms. Their search led to the useful antileukemic agent, 6-mercaptopurine (XIX). This drug had a major fault, however, because most of the drug is rapidly destroyed in the body and excreted as inactive products. Hitchings and Elion reasoned that it might be possible to attach a removable group to the drug, one that would be labile in the leukemic cell. Azathioprine (XX) was selected as a derivative with the right properties; but as an antileukemic, it proved to be no better than 6-mercaptopurine. Later, the immunosuppressive properties of 6-mercaptopurine were discovered by Schwartz and Dameshek (4); and when azathioprine was tested, it was found to be much more effective in the prevention of immunological rejection of organ transplants. In its first 7 years of use, azathioprine was the basic component in the immunosuppressive regimen of most of the kidney transplant and heart transplant subjects (4).



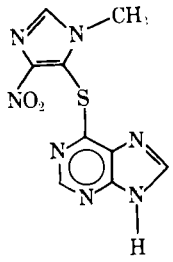
chlordiazepoxide
XIII



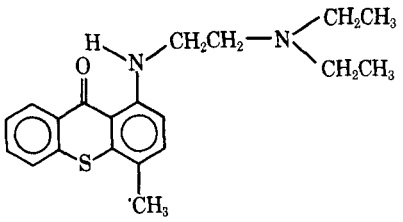
diazepam
XIV



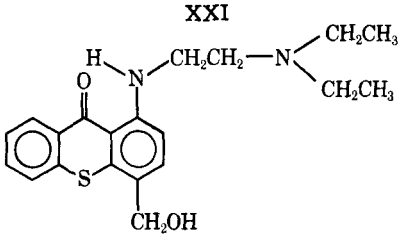
6-mercaptopurine
XIX



azathioprine
XX



lucanthone
XXI



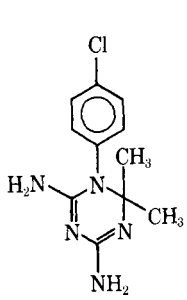
hycanthone
XXII

Lucanthone (XXI) is an orally effective schistosomicidal agent that is not active by injection (5). The reason for this puzzling observation was found by scientists at Sterling-Winthrop Research Institute; they discovered that following oral administration in primates, lucanthone is converted to the active metabolite hycanthone (XXII). It is known that the bloodstream into which drugs are absorbed from the small intestine goes first to the liver where metabolism occurs. On the other hand, compounds absorbed from muscular injection sites may be carried to all parts of the body without prior metabolism in the liver. The discovery that hycanthone was the effective agent led Sterling-Winthrop to widespread clinical trials with a "one-shot" injectable cure for schistosomiasis.

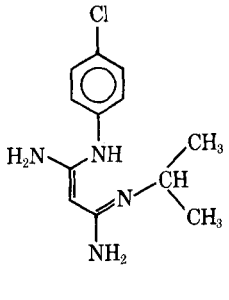
With procainamide, azathioprine, and hycanthone as examples, it is easy to see that the medicinal chemist must keep the results of drug metabolism studies in mind when he is exploring new series of potential medicinal agents.

ROLE OF PHYSICAL PROPERTIES

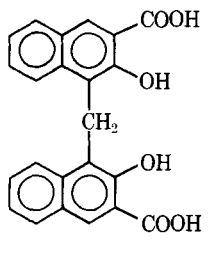
It may seem obvious that a drug must dissolve in an aqueous medium of the GI tract before it can be absorbed into the circulation. In a review of the absorption of drugs from the GI tract, Brodie (6) pointed out that the intestinal wall acts as a lipid barrier so that some lipid solubility is also required. In many cases the ratio of lipid to aqueous solubility is a very important factor in drug action. In fact, Mautner and Clemson (7) concluded that physical characteristics such as these rather than three-dimensional structures are responsible for the physiological activity of the barbiturates. The amount of administered drug that gains access to the CNS depends on lipid solubility; for an acidic or a basic drug that is largely ionized at physiological pH, increased lipophilicity can be provided not only by increasing the part of the molecule that is nonpolar but by altering its pKa. For the narcotic analgesics (8) and the barbiturates (7), the concentration of drug that enters the CNS appears to be correlated with organic solvent–aqueous buffer partition ratios. Brodie (6) showed that similar considerations must be taken into account for absorption into the bloodstream from the GI tract.



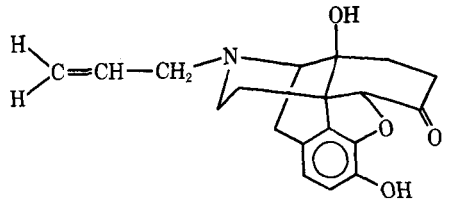
cycloguanil
XXIII



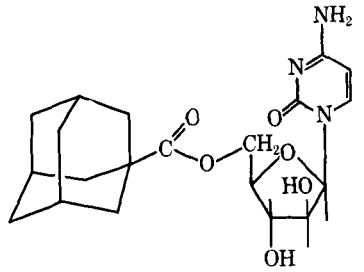
chlorguanide
XXIV



pamoic acid
XXV



naloxone
XXVI



5′-adamantoyl cytosine arabinoside
XXVII

In considering the solubility properties of a potential drug, it is important to remember that it is the rate of solution and not the equilibrium solubility that is important for oral absorption (6). The drug only remains in a particular portion of the GI tract for a short time, and laboratory measurements of solubility must take this fact into consideration. Although the drug first encounters the strongly acidic medium of the stomach, our own experience has shown that it is a mistake to believe that if the hydrochloride salt of a potential drug is not soluble, other salts or even the base should not be studied. The chemist tests for aqueous solubility under simplified conditions. Thus, a water-soluble methanesulfonic acid salt may precipitate as an insoluble hydrochloride with the addition of hydrochloric acid in the test tube. However, the same salt may remain as a supersaturated solution in the stomach for a time and become absorbed later from the intestine where the pH is closer to 7.

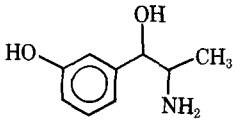
Although most often the medicinal chemist is concerned that his new compound will not be well absorbed, there are many instances in which slow absorption is a distinct advantage. Cycloguanil (XXIII) is a case in point (9). It is well known that after the introduction of chlorguanide (XXIV) hydrochloride for the chemotherapy of malaria, it was discovered that the parent compound was inactive *per se* and cycloguanil was the active metabolite. However, cycloguanil hydrochloride is rapidly excreted in the urine and a large number of less soluble salts were studied in the search for an effective depot formulation. The study culminated in the selection of the pamoic acid (XXV) salt for large-scale clinical evaluation, and it was found that single intramuscular injections afforded protection for 8–12 months against susceptible strains of Plasmodium.

An interesting and more recent application of a pamoate salt was described (10) for naloxone (XXVI), which is a short-acting narcotic antagonist. The new salt is under study for the treatment of physical dependence on heroin. An injection of the pamoate salt provides a much longer pharmacological effect, and clinical studies are planned by Endo Laboratories.

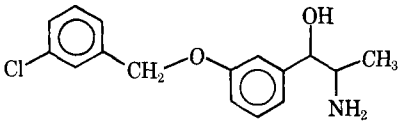
Other methods of prolonging drug action are also under study. Repository implants of silicone rubber (silastic) containing the antimalarial drug pyrimethamine were found to offer protection against Plasmodium in mice (9). Other studies are in progress concerning the slow release of progesterone from a small membrane-enclosed drug reservoir placed in the uterus to prevent implantation (11). A new product, expected to be marketed in 1972, will have pilocarpine imbedded in a plastic film device that is placed under the eyelid to treat glaucoma (11). Even more revolutionary are studies of drug delivery systems in which the drug is released from a bandage directly into the bloodstream after slow absorption through the skin (11).

ROLE OF DRUG METABOLISM

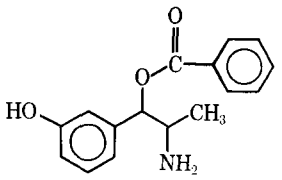
Important as delivery systems are, the chemist must first find the useful new medicinal agent. He will find it helpful to know something of drug metabolism to design his compound to survive the



metaraminol
XXVIII



metaraminol *m*-chlorobenzyl ether
XXIX



metaraminol side-chain ester
XXX

body's metabolic defenses while avoiding toxic side effects. It is not practical in this presentation to review the many metabolic pathways known to affect drugs, but it may be of interest to discuss some of the useful features of these pathways with some specific examples.

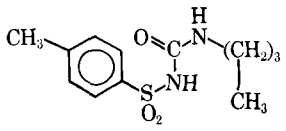
Metabolism usually converts the drug to a more polar compound which is more easily eliminated from the body. This appears to be the general rule but there are many exceptions, some of which we shall discuss later. Compounds with phenolic or alcoholic hydroxy groups are converted to conjugates such as glucuronides or sulfate esters (12) which have a much lower lipid–water partition coefficient and are often excreted in the urine after passage through the kidney. On the other hand, other glucuronides pass from the liver to the bile and enter the GI tract. Here they may be hydrolyzed and reabsorbed from the intestine, thus providing the bloodstream with a new increase in the drug concentration. This appears to be the case with many of the narcotic analgesics (8).

E. J. Ariens' (13, 14) reviews are very useful to the medicinal chemist who is seeking to apply metabolic studies to the design of new medicinal agents. A glance at recent issues of the *Journal of Medicinal Chemistry* reveals that many medicinal chemists are using these principles in their syntheses of potential new medicinal agents. Let us look at only a few typical examples.

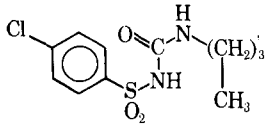
As already mentioned, procainamide was designed to be longer acting by delaying its inactivation through hydrolysis. Metabolic inactivation may often be slowed down considerably by formation of a stable ester. Thus, the duration of action of the immunosuppressive and antileukemic agent cytarabine was lengthened considerably by formation of its 5′-ester (XXVII) with adamantoyl carboxylic acid (15). This and other esters are cleaved by esterases in human serum to provide the biologically active cytarabine. It is well known that less soluble esters of estrogens and androgens provide depot forms of these hormonal steroids.

Metaraminol (XXVIII) has shown significant antihypertensive activity in man, but it can also produce acute pressor effects which are undesirable (16). Saari *et al.* (17) reported that the *m*-chlorobenzyl ether (XXIX) is slowly dealkylated metabolically to metaraminol and that in dogs, at least, its administration is not accompanied by the pressor response seen when metaraminol itself is administered. On the other hand, esters of the side-chain alcohol of metaraminol (XXX) either showed greatly diminished activity (as judged by norepinephrine depletion) or also provided a pressor response (16).

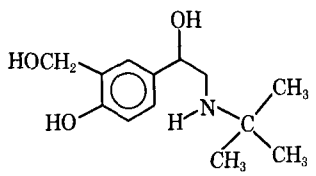
There are other ways in which metabolism may be modified to increase the plasma half-life of a drug. Thus, the half-life of the oral antidiabetic tolbutamide (XXXI) was increased from 5.7 to 33 hr. by replacing the metabolically labile methyl group with a chloro substituent (XXXII) (18). The new β-blocking agent salbutamol (XXXIII) has a hydroxymethyl substituent and a tertiary butyl group which, in contrast to isoprenaline (XXXIV), render



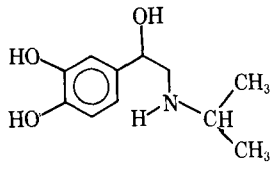
tolbutamide
XXXI



chlorpropamide
XXXII



salbutamol
XXXIII

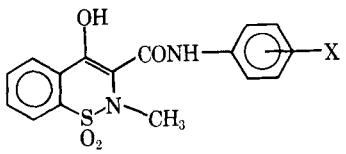


isoprenaline
XXXIV

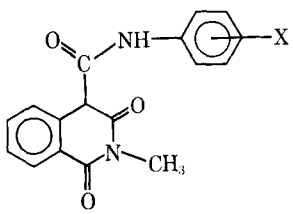
this compound resistant to the metabolizing enzymes catechol *o*-methyltransferase and MAO, respectively. Accordingly, salbutamol is reported to have a longer half-life than isoprenaline (19).

It was mentioned earlier that most drug metabolites are more polar than the parent compound and, as a consequence, are eliminated more rapidly by the kidney or in the bile. A recent study by Chionini *et al.* (20) suggested that this is not always the case. Usually, hydroxylation of a phenyl ring is believed to provide a route for the body to form a glucuronide or sulfate ester prior to elimination of the drug. However, these investigators reported that in the case of the acidic anti-inflammatory 1,2-benzothiazine-3-carboxanilide (XXXV) the parent compound has a shorter half-life (21 hr.) in man than that of its metabolite (XXXVI) (37 hr.). Similarly the half-life of the related drug (XXXVII) (8.5 hr.) is shorter than that of its metabolite (XXXVIII) (15 hr.) (21). One must use caution, therefore, in the application of metabolic results to the design of new medicinal agents, and there is still no generalization that is a sure substitute for the actual experiment.

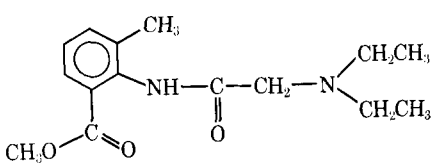
In some cases, it may be desirable to provide a drug with a shorter duration of action to avoid toxic effects and to provide greater control over the action of the drug. An interesting case, referred to by Ariens (13), is baycaine (XXXIX), a short-acting local anesthetic which is readily hydrolyzed by plasma and liver esterase and is thus devoid of systemic toxicity.



XXXV: X = H
XXXVI: X = OH



XXXVII: X = H
XXXVIII: X = OH



baycaine
XXXIX

REFERENCES

(1) B. H. Takman and G. Camougis, in "Medicinal Chemistry," 3rd ed., A. Burger, Ed., Wiley, New York, N. Y., 1970, p. 1607.

(2) C. S. Davis and R. P. Halliday, in *ibid.*, p. 1083.

(3) G. H. Hitchings and G. B. Elion, *Accounts Chem. Res.*, **2,** 202(1969).

(4) G. H. Hitchings, in "Progress in Drug Research," P.M.A. Res. Symposium, Washington, D. C., Mar. 1969, p. 16.

(5) S. Archer, in *ibid.*, p. 31.

(6) B. B. Brodie, in "The Physiological Equivalence of Drug Dosage Forms," Food and Drug Directorate Symposium, Ottawa, Canada, June 1969, p. 5.

(7) H. G. Mautner and H. C. Clemson, in "Medicinal Chemistry" 3rd ed., A. Burger, Ed., Wiley, New York, N. Y., 1970, p. 1365.

(8) S. J. Mule, in "Narcotic Drugs: Biochemical Pharmacology," D. H. Clouet, Ed., Plenum, New York, N. Y., 1971, p. 99.

(9) E. F. Elslager, in "Progress in Drug Research," vol. 13, E. Jucker, Ed., Birkhäuser Verlag, Basel, Switzerland, 1969, p. 170.

(10) *P.M.A. Newsletter 13*, No. 47 (Nov. 26, 1971).

(11) *Chem. Eng. News*, 20 (Sept. 6, 1971).

(12) L. B. Mellet, in "Progress in Drug Research," vol. 13, E. Jucker, Ed., Birkhäuser Verlag, Basel, Switzerland, 1969, p. 136.

(13) E. J. Ariens, in "The Physiological Equivalence of Drug Dosage Forms," Food and Drug Directorate Symposium, Ottawa, Canada, June 1969, p. 23.

(14) E. J. Ariens, in "Progress in Drug Research," vol. 14, E. Jucker, Ed., Birkhäuser Verlag, Basel, Switzerland, 1970, p. 11.

(15) D. T. Gish, R. C. Kelly, G. W. Camiener, and W. J. Wechter, *J. Med. Chem.*, **14,** 1159(1971).

(16) W. S. Saari, A. W. Raab, C. S. Miller, W. F. Hoffman, and E. L. Engelhardt, *ibid.*, **14,** 1230(1971).

(17) W. S. Saari, A. W. Raab, C. S. Miller, W. H. Staas, M. L. Torchiana, C. C. Porter, and C. A. Stone, *ibid.*, **13,** 1057(1970).

(18) F. G. McMahon, in "Molecular Modification in Drug Design," p. 102; R. F. Gould, "Advances in Chemistry Series 45," American Chemical Society, Washington, D. C., 1964.

(19) F. J. Prime, *Drugs*, **1,** 269(1971).

(20) J. Chionini, E. H. Wiseman, and J. G. Lombardino, *J. Med. Chem.*, **14,** 1175(1971).

(21) E. H. Wiseman, E. J. Gralla, J. Chiaini, J. R. Migliardi, and Y.-H. Chang, *J. Pharmacol. Exp. Ther.*, **172,** 138(1970).

ACKNOWLEDGMENTS AND ADDRESSES

Received from the *Research Department, Pharmaceuticals Division, Ciba-Geigy Corporation, Ardsley, NY 10502*

Role of Drug Metabolism in Drug Research and Development: Factors Affecting Metabolism of Drugs and Their Pharmacological and Toxicological Activity

BITTEN STRIPP▲ and JAMES R. GILLETTE

Abstract □ Drug effects are influenced by binding to target sites, by inhibition or induction of hepatic drug-metabolizing enzymes by various agents, and by the formation of physiologically active metabolites in the liver as well as in extrahepatic tissue. Knowledge of the principles involved provides a better understanding of the pharmacological action of a drug and helps in the design of less toxic drugs.

Keyphrases □ Drug metabolism—role in drug research and development, symposium □ Pharmacological, toxicological activity—effects of binding, hepatic drug-metabolizing enzymes, formation of active metabolites □ Toxicological activity of drugs—effects of binding, hepatic drug-metabolizing enzymes, formation of active metabolites □ Metabolizing enzymes, drug—inhibition, induction, effect on drug metabolism □ Metabolite formation—effect on drug metabolism

Although the pharmacological effect of a drug is determined by a number of factors, such as absorption, distribution, excretion, and metabolism, it is generally terminated by the conversion of the therapeutic agent into nonactive metabolites. Sometimes a change in metabolism may affect the pharmacological activity in a predictable way, and plasma levels of a drug can be directly related to the effect of the drug. But when a compound has to be converted to an active metabolite to exert its activity, as is seen with imipramine and a number of cholinesterase inhibitors of the phosphorothionate type, a correlation between plasma levels of the drug and its activity is usually not observed. Moreover, some drugs during their metabolism can be irreversibly or pseudoirreversibly bound to the target organ and exert their activity long after they are undetected in plasma. This occurs with cholinesterase inhibitors and reserpine. In these cases the complex interplay of the above-mentioned factors that determine the effect of a drug will quite often make it impossible to predict the effects of inhibitors or inducers of drug metabolism on the pharmacological effect of the drug. There are general principles, however, regarding the effects of inhibitors or inducers of drug-metabolizing enzymes on drug action; these principles can be helpful to the pharmacologist who is evaluating a new drug.