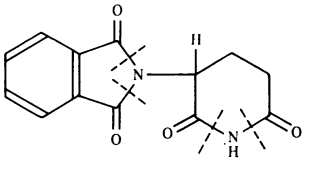
Gut, 1972, **13**, 579-585

Progress report

Hepatic metabolism of drugs

When drugs get into the body they could undergo three possible fates, namely, they could be metabolized by enzymes; they could change spontaneously into other substances without the intervention of enzymes; or they could be excreted unchanged. The majority of drugs undergo the first fate and this will be the main concern of this report. But before dealing with this main aspect, a few remarks should be made about the other two possibilities.

Some drugs when they get into the body change spontaneously into other compounds simply because they meet the right conditions of *p*H for spontaneous breakdown or because they can react chemically with certain compounds or groups in macromolecules which occur normally in the body. One of the best examples of a drug which breaks down spontaneously in the body is thalidomide. At *p*H 7·4 in aqueous solution thalidomide decomposes by spontaneous hydrolysis into some 12 other compounds. It has a half-life of about five hours at 37° and *p*H 7·4, and this instability is probably associated with its teratogenicity since none of its breakdown products are teratogenic.[1]



Thalidomide
spontaneous hydrolysis occurs at the dotted lines

Fig. 1

As we shall see later, the metabolism of drugs usually tends to make lipid-soluble substances more polar and water-soluble and therefore more easily excreted by the kidney. If a drug is already highly polar, then, on these grounds, one would not expect them to be readily metabolized. Many, but not all, of the drugs which are not readily metabolized are usually highly polar. Examples are decamethonium, the neuromuscular blocking agent, arsenilic acid, which was used as its Na salt under the name Atoxyl for trypanosomiasis and is now used in medicated feeds for poultry and swine,[2] and the sweetening agent, cyclamate.[3]

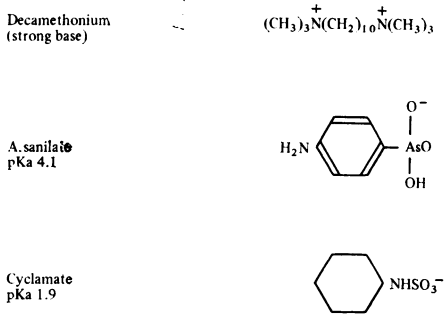


Fig. 2

Fig. 1 *Breakdown of thalidomide in the body.*

Fig. 2 *Examples of highly polar drugs which are not readily metabolized in the body.*

Sites of Drug Metabolism

There are many tissues which can metabolize drugs, but by far the most active tissue per unit weight is the liver (Tables I and II). Table I shows the relative ability of five different tissues to metabolize phenobarbitone and thiopentone. In the case of phenobarbitone only the liver shows ability to metabolize the drug but with the more lipid-soluble thiopentone, the kidney, brain, and heart show activity. The kidney, intestinal tissue, and lung have some activity and occasionally can be more active than the liver with certain drugs. Table II shows the ability of various tissues to methylate phenol to anisole and *N*-acetylserotonin to melatonin (*N*-acetyl-5-methoxytryptamine). The methylation of phenol occurs in many tissues and in this case the lung per unit weight appears to be slightly more active than the liver. The methylation of *N*-acetylserotonin seems to be limited to liver although it is known that the pineal gland can carry out this reaction. The gut flora can also metabolize drugs in certain circumstances[4,5]

Tissue	*Relative Ability to Metabolize (unit wt/unit time)* [1]	
	Phenobarbitone	*Thiopentone*
Liver	100	100
Kidney	0	52
Brain	0	24
Heart	0	19
Skeletal muscle	0	0

Table I In-vitro *drug metabolizing activity of various tissues*[1]

Rabbit tissue homogenates
Liver = 100
[1]Calculated from data of Cooper and Brodie[18]

Tissue	*O-Methylation of*	
	Phenol[1]	*N-Acetylserotonin*[2]
Liver	100	100
Kidney	48	0
Small intestine	3	0
Testis	6	0
Spleen	22	0
Lung	110	0
Heart	0	0
Adrenal	13	0
Brain	3	—
Muscle	3	—

Table II In-vitro *drug metabolizing activity of various tissues*

Activity of liver taken as 100
[1]Guinea pig tissue homogenates calculated from data of Axelrod and Daly[19]
[2]Rabbit tissue homogenates calculated from data of Axelrod *et al*[20]

Other tissues, which include the adrenal, brain, heart, muscle, skin, spleen, and testis, are not very active but show minor activity towards certain drugs. When the size of the liver and the rate of blood flow through it are taken into account, the predominance of the liver in drug metabolism is easily appreciated.

The Location of Drug Metabolism in the Liver

The majority of the reactions of drug metabolism are carried out in the liver

by enzymes which are located mainly in the smooth endoplasmic reticulum of the hepatic cells.[6] When the liver is homogenized, the endoplasmic reticulum is disrupted giving rise to small vesicles which can be separated from the homogenate by high-speed centrifugation to give the fraction called microsomes. With this fraction, under the appropriate conditions, drug metabolism can be studied in the test tube.

Table III shows the relative ability of the various fractions of liver homogenates to carry out two reactions, namely, the oxidative de-ethylation of phenacetin to panadol, ie, *p*-ethoxyacetanilide → *p*-hydroxyacetanilide, and the oxidative demethylation of codeine to morphine, ie, 3-methylmorphine → morphine. It is to be noted from Table III that, apart from the whole homogenate, the most active fraction is that containing the microsomes plus the cell sap or cytosol. The microsomes contain the drug-metabolizing enzymes and the cell sap, the cofactors necessary for activity of the enzymes. The main cofactor in the cytosol for this purpose is NADPH (reduced nicotinamide-adenine-dinucleotide phosphate). Some activity is shown by the nuclei and cytosol but this is due to incomplete separation of the microsomes.

Fraction of Liver Homogenate	*Relative Rate of*[1]	
	O-De-ethylation of Phenacetin by Rabbit Liver	*O-Demethylation of Codeine by Rat Liver*
Whole	100	100
Nuclei (crude)	8	13
Mitochondria	0	0
Microsomes	0	0
Soluble fraction (cytosol)	0	0
Nuclei + soluble	15	26
Mitochondria + soluble	8	0
Microsomes + soluble	85	75

Table III *The location of drug metabolism in the hepatic cell*

[1]Calculated from the data of Axelrod[21,22]

The drug-metabolizing system in the microsomes contains two catalysts, namely, an NADPH-oxidizing flavoprotein, NADPH-cytochrome c reductase, and a carbon monoxide-binding haemoprotein called cytochrome P-450.[7] Cytochrome P-450 is the component in the endoplasmic reticulum which binds with and metabolizes the drug. The oxidation of a drug by the hepatic microsomal system can be represented as follows:

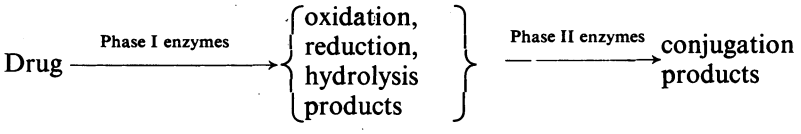
$$\text{NADPH} + \text{A} + \text{H}^+ \rightarrow \text{AH}_2 + \text{NADP}^+$$
$$\text{AH}_2 + \text{O}_2 \rightarrow \text{'active O}_2\text{'}$$
$$\text{'Active O}_2\text{'} + \text{DH} \rightarrow \text{A} + \text{DOH} + \text{H}_2\text{O}$$

In these reactions, A can be identified with cytochrome P-450, DH the drug, DOH the oxidized drug, and 'active O_2' as a complex of the oxidized form of cytochrome P-450 and the drug.

The Two-phase Metabolism of Drugs

The metabolism of drugs usually takes place in two phases. In the first phase, drugs undergo reactions which are classified as oxidations, reductions, and hydrolyses. What happens in this phase is that groups such as OH, COOH, NH_2, and SH are introduced into the drug molecule so that the product can

undergo the second phase which is that of synthesis to produce the so-called conjugation products thus:—



Not all drugs undergo the two-phase metabolism, since those which already contain suitable groupings such as OH, may undergo only a phase II reaction, eg, panadol conjugates directly with glucuronic acid in the liver. A drug such as alcohol, however, may only undergo phase I reactions since it is readily oxidized to CO_2.

Pharmacological Consequences of Phase I Reactions

The first phase of drug metabolism can alter the activity of a drug in one of three directions. (1) It can change a drug into another compound with a similar or different pharmacological activity. (2) It can convert an inactive compound into an active drug. (3) It can convert an active drug into a relatively inactive metabolite. These changes can be illustrated by the metabolism of the three drugs phenacetin, prontosil, and phenobarbitone.

The main metabolic pathway of phenacetin[8,9] is as follows (Fig. 3):—

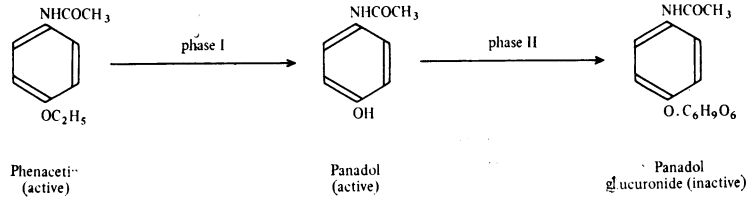


Fig. 3 *Main metabolic pathway of phenacetin.*

Phenacetin is itself an active drug, but its main activity is due to its oxidation product Panadol (Paracetamol) which is formed enzymically in the liver. Panadol then undergoes a synthesis to the inactive conjugation product *p*-acetamidophenylglucuronide which is excreted. The activity of phenacetin is thus terminated in the second phase of its metabolism.

Prontosil is a drug which is inactive *in vitro* but active *in vivo*. It is converted by reduction in the liver to sulphanilamide, an active antibacterial agent.[10,11,12] In the second phase of metabolism, sulphanilamide is acetylated and thereby inactivated (Fig. 4).

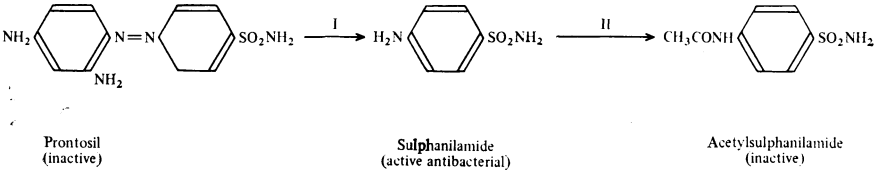
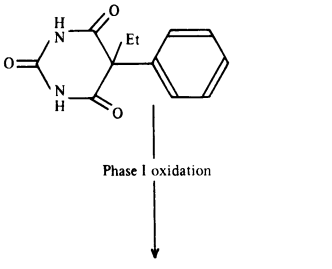


Fig. 4 *Phases of metabolism of prontosil.*

The knowledge that Prontosil was converted in the body to sulphanilamide, the active agent, led to the large number of successful sulpha drugs, some of which are still in use today.

Phenobarbitone is a long-acting hypnotic drug and in man it is partly metabolized and partly excreted unchanged.[13] That part of phenobarbitone which is metabolized undergoes the following two-phase process (Fig. 5).



Phenobarbitone is inactivated in the first phase and the relatively inactive hydroxyphenobarbitone produced undergoes a synthesis in the second phase to form a glucuronide or an ethereal sulphate which is an inactive excretory product.

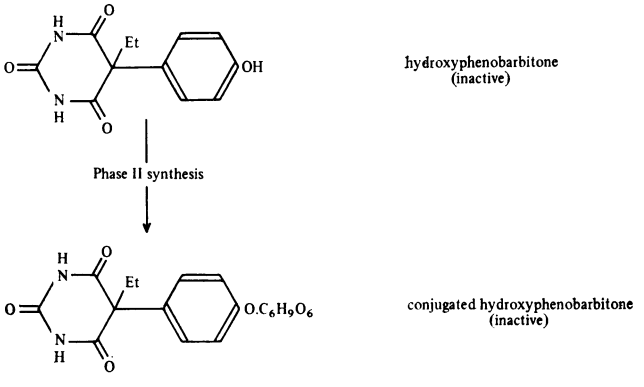


Fig. 5 *Two-phase process by which part of phenobarbitone is metabolized in the body.*

Conjugation Reactions

Most phase II reactions[14] inactivate drugs and any of their active phase I metabolites. They include the formation of glucuronides, ethereal sulphates, and amino acid conjugates containing glycine (eg, hippuric acid), glutamine, or cysteine. Methylation and acetylation of drugs also occur as phase II reactions. The cyanide ion (CN^-) has a phase II reaction of its own for it is converted enzymically in the body to the thiocyanate ion (SCN^-) with a 200-fold reduction in toxicity.

Conversion of Lipid-soluble Drugs to Water-soluble Metabolites

It would appear that what is happening in the liver is that lipid-soluble drugs which are reabsorbed by the kidney are converted into water-soluble, polar metabolites which are then readily excreted by the kidney. In each phase of metabolism the compound is made more polar and in the first phase the drug

is converted into a form suitable for undergoing the second phase by the addition of chemical groups capable of being conjugated. This is well illustrated by the main metabolic route of benzene, a simple aromatic compound once used in the treatment of leukaemia. Benzene is first oxidized enzymically in the liver to phenol which contains an OH group and is a weak acid. In the second phase the phenol is converted enzymically (the enzyme is glucuronyl transferase) into the strong acid phenylglucuronide which is virtually completely ionized at physiological *p*H values.

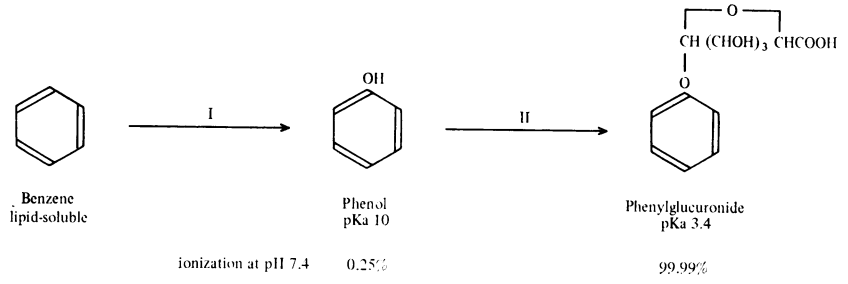


Fig. 6 *The main metabolic route of benzene in the body.*

Factors Affecting Drug Metabolism

The activity of the liver in metabolizing drugs can be influenced by a number of factors which in effect alter the activity of the drug-metabolizing enzymes. Table IV gives a list of these factors, some of which are more important than others. In Table IV those factors which are regarded as the more important

Species	Sex (mainly in rats)
Strain	Stress
Age	Temperature
Chronic administration	Time of day
Other drugs or foreign compounds	Season
Route of administration	Biliary excretion and enterohepatic circulation
Disease	Gut flora
Diet	Altitude

Table IV *Factors affecting drug metabolism*

are listed on the left and these are now being extensively studied. Species variations are often quite marked, [15] and are important in the problems of drug testing. The study of strain variations in drug metabolism has now developed into the subject of pharmacogenetics[16]. In these days of polypharmacy, the effect of one drug upon the metabolism of another [17] can have important therapeutic consequences and this is probably one of the most intensely studied aspects of drug metabolism today.

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