THE FATE OF FOREIGN COMPOUNDS IN MAN AND ANIMALS

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INTRODUCTION

There occur in our environment today a large number of compounds which are normally regarded as foreign to the body. Many of these get into the body in various ways and therefore it is important to know how they affect our health and how the body deals with them. These chemicals may appear in the body because they have been deliberately put there as in the case of drugs, deliberate food additives and contraceptive pills, or because they have entered the body accidentally as contaminants of food, drink and air. These contaminants may be pesticide residues, industrial chemicals in factories, products from the preparation and packaging of food, and foreign substances which occur naturally in food but have no nutrient function. The animal body has therefore to deal constantly with small quantities of thousands of compounds of very diverse chemical structures (see *Table 1*). Many of these chemicals are toxic and man is therefore living in a toxic environment. In view of the increasing use of drugs, pesticides and food additives, there is little doubt that we are existing in an increasingly toxic environment. Even before the modern era of drugs, food additives and pesticides, the human body had to cope with a large number of toxic substances which occur naturally in food[1]. The fact that our environment is becoming increasingly toxic raises the problem of what is the limit

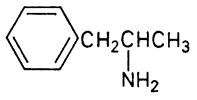
Table 1. Chemicals in the environment

Type	*Sphere of utilization*
(a) DELIBERATELY CONTRIBUTED TO THE BODY	
Drugs	Health
Cosmetics	Beauty
Detergents	Health, cleanliness
Contraceptives	Population control
Food additives	Food, health
(b) CONTAMINANTS OF FOOD AND AIR	
Toxicants occurring naturally	Agriculture, Food, Industry
Pesticides	
Packaging materials	
Industrial solvents	
Processing aids	
Growth stimulants	
Industrial and automobile fumes	

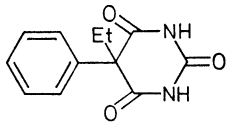
of intake of environmental toxic agents that the body can withstand. Does adaption occur? Can we keep on adding new chemicals to those already existing in the environment or must we now take account of what already occurs and become cautious and selective regarding the future use of environmental chemicals. There is evidence that man can adapt to some extent to toxic chemicals, but this is no reason for being complacent about the increasing levels of ambient toxicity.

The answers to the above questions lie in our knowledge of the extent to which the body can detoxicate and eliminate foreign chemicals. The diversity of chemical structures which the body has to deal with is illustrated in *Table 2* which gives a selection of the structures of some of the commoner chemicals which may get into the organism in various ways.

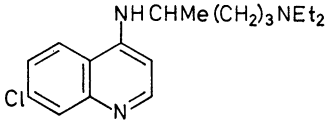
Table 2. Diversity of chemical structure of environmental chemicals



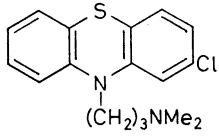
Amphetamine (stimulant)



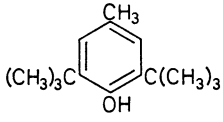
Phenobarbitone (sedative)



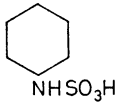
Chloroquine (antimalarial)



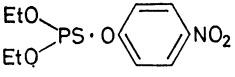
Chlorpromazine (tranquillizer)



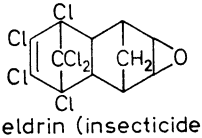
BHT
(anti-oxidant)



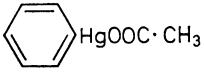
Cyclamate (sweetening agent)



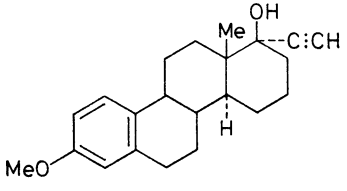
Parathion (insecticide)



Dieldrin (insecticide)

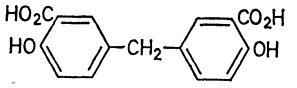


Phenylmercuric acetate
(spermicide-herbicide)



Mestranol (oral contraceptive)

The animal body, is in fact, amazingly versatile for it can metabolize almost any known chemical structure except some highly polar compounds and some chemically unreactive substances. An example of a substance which is not metabolized at all, and which was examined in my laboratory recently[2], is 5,5′-methylenedisalicylic acid (4,4′-dihydroxydiphenylmethane-3,3′-dicarboxylic acid). The bacitracin salt of this substance is used as an animal feed supplement for poultry, swine and mink. 5,5′-Methylenedisalicylic acid (see below) is excreted entirely unchanged in the rhesus monkey, dog, rabbit, guinea pig, hamster, mouse, rat and hen.



5,5′–Methylenedisalicylic acid

GENERAL ASPECTS OF DRUG METABOLISM

Much of the effort in the study of the metabolism of foreign compounds has, in the past, been devoted to drugs, and consequently this study is frequently referred to as "drug metabolism". However, the principles of drug metabolism apply equally well to any foreign compound, be it a drug, a pesticide, a food additive or an industrial chemical.

A foreign compound which gains access to the animal body encounters a large number of enzymes some of which are able to react with it and submit it to a variety of reactions which can be classified as oxidations, reductions, hydrolyses and syntheses. As a result of these processes the compound is converted into metabolites which are eliminated usually in the urine and faeces, although in some cases there may be elimination through other channels such as the expired air, skin, milk and saliva. Urinary and faecal excretion may also be preceeded by biliary excretion and entero-hepatic circulation and these, if they occur, have important consequences.

In general, the metabolism of a foreign compound occurs in two phases. In the first phase the compound undergoes reactions (asynthetic) which may be classified as oxidations, reductions or hydrolyses and in the second phase, the products of the first phase undergo reactions which are synthetic in nature, thus:

Foreign compound	phase I enzymes →	Oxidation, reduction, hydrolysis products	phase II enzymes →	Conjugation (synthetic) products

In each phase the foreign compound, which is usually lipid soluble, is made more polar, for phase I products are more polar than the initial compound and phase II products are highly polar and are frequently strongly acidic substances. The fact that the conjugation or phase II products are highly polar may be one of the reasons why highly polar foreign compounds are not metabolized or at least are only metabolized to a slight extent. The metabolism of a foreign compound thus appears to be a process aimed at

increasing its polarity rather than reducing its toxicity. As a consequence of this two-phase metabolic process, the products which may be excreted as the result of a foreign compound entering the body, are therefore, (a) the unchanged compound, (b) products of oxidation, reduction or hydrolysis, and (c) conjugation products. The proportion in which these products are excreted depends on a variety of factors, the major ones being the chemical nature of the foreign compound and the species of animal examined. These factors are considered later.

THE ENZYMES OF PHASE I REACTIONS

Each of the phases of drug metabolism is controlled by enzymes, and those of the asynthetic first phase can be broadly divided into two groups which can be called parametabolic and xenometabolic enzymes[4].

The metabolism of some foreign compounds is mediated by enzymes of normal metabolic routes and therefore such enzymes have both natural and foreign substrates. These are the parametabolic enzymes, examples of which are given in *Table 3*. The metabolism of a foreign compound by enzymes of this type can sometimes result in toxicity, a classical example of this being

Table 3. Some foreign compounds metabolized by "normal" enzymes

Foreign compound	*"Normal" enzyme acting on foreign compound*
p-Nitrobenzyl alcohol (and some other foreign alcohols)	Alcohol dehydrogenase
p-Nitrobenzaldehyde (and other foreign aldehydes)	Aldehyde dehydrogenase
α-Methyldopa	Dopa decarboxylase
Benzylamine	Monoamine oxidase
Procaine Succinylcholine	Non-specific plasma cholinesterase
8-Azaguanine	Guanase, purine nucleotide phosphorylase
Azauridine	Nucleosidase
2,6-Diaminopurine 6-Mercaptopurine 6-Thioxanthine 4-Aminopyrazolopyrimidine	Xanthine oxidase

fluoroacetic acid. The enzymes which metabolize acetic acid *via* acetylcoenzyme A to citric acid appear also to be able to metabolize fluoroacetate, and it is now accepted that the toxicity of fluoroacetate is due to its conversion by these enzymes to fluorocitrate. The latter inhibits the enzyme, aconitase, and thereby the tricarboxylic acid is jammed so that the transmission of metabolic energy to the cell is prevented[5].

The metabolism of many drugs is carried out by enzymes which occur predominantly in the endoplasmic reticulum of the liver cells. When the liver is homogenized, the endoplasmic reticulum is disrupted to form small lipoid particles called microsomes, which can be separated by centrifugation. The main drug metabolizing ability of the liver is associated with these particles, which are able to carry out a variety of oxidations, reductions and hydrolyses (see *Table 4*). These microsomal or "drug-metabolizing" enzymes[6] appear to metabolize only foreign compounds and can therefore be referred to as xenometabolic enzymes. However, the question of whether

Table 4. Examples of reactions catalysed by microsomal enzymes

Foreign Compound	*Reaction catalysed by microsomes*	*Metabolite*
Acetanilide	Aromatic hydroxylation	*p*-Acetamidophenol
4-Dimethylaminoantipyrine	*N*-demethylation	4-Aminoantipyrine
Codeine	*O*-demethylation	Morphine
Amphetamine	Deamination	Benzylmethylketone
p-Nitrotoluene	Methyl oxidation	*p*-Nitrobenzyl alcohol
Pentobarbitone	Alkyl chain oxidation	Hydroxypentobarbitone
Chlorpromazine	Oxidation of thioether	Chlorpromazine-5-oxide
Thiopental	Replacement of S by O	Pentobarbitone
Meperidine	Hydrolysis	Meperidinic acid
p-Nitrobenzoic acid	Reduction	*p*-Aminobenzoic acid
Prontosil	Reduction of azo link	Sulphanilamide

the activity of these enzymes is confined to foreign compounds is an open one, for Conney *et al.*[3] have shown that the liver microsomal enzymes which hydroxylate steroids have properties which are very similar to the xenometabolic enzymes which appear to metabolize only foreign compounds. It is possible that the property required by a compound to be a substrate of the microsomal drug metabolizing enzymes is not that it is foreign to the body, but simply that it is lipid soluble, so that it can penetrate the microsome to the sites of enzyme activity.

PHARMACOLOGICAL AND TOXICOLOGICAL CONSEQUENCES OF PHASE I REACTIONS[7,8]

When drugs and foreign compounds enter the body it is important that they should, in due course, be removed from the body. In the case of a drug it is also important that its activity should be terminated after an appropriate time, for termination of drug action in most cases is as important as the action itself. Many drugs exist in a non-polar form at physiological pH values and in this form, when they reach the kidney, they tend to be reabsorbed into the circulation by the kidney tubule. The metabolism of drugs is therefore important in the termination of their activity and in their excretion, for during this process they are converted into polar compounds which are more readily excreted by the kidney. Without these metabolic changes, some drugs would have an unreasonably long duration of action and consequently an increased toxicity and what is said about drugs also applies to any other foreign compound which may enter the body.

It is therefore of importance to examine the nature of the metabolites produced during the processes of oxidation, reduction and hydrolysis. Although these processes may convert a compound into a more polar product, they do not necessarily convert it into a product which is less active biologically. As a result of these asynthetic reactions a compound could be made (a) less active, or (b) more active, or (c) it could be converted into a compound of similar activity or different activity. These reactions are therefore not necessarily detoxication or inactivation processes. However, it can be said that in general, phase I reactions tend to produce less active or inactive products.

The production of biologically active substances by phase I reactions is of considerable interest and application, because they may lead to new drugs or new insecticides, etc. Many examples of this type of metabolic reaction are now known. Furthermore, this type of reaction explains why some substances are biologically inactive *in vitro*, but active *in vivo*. Thus phenacetin, prontosil, and chloral hydrate are pharmacologically active because they are converted in the body into active metabolites. Phenacetin is oxidatively de-ethylated *in vivo* to *p*-acetamidophenol (panadol; paracetamol), whereas chloral hydrate and prontosil are reduced to their active metabolites which are trichloroethanol and sulphanilamide, respectively. Similarly, the pesticides schradan and parathion, owe their activity to being converted *in vivo* to toxic metabolites. However, many drugs and other foreign compounds have their activity reduced by phase I reactions, common examples being the barbiturate drugs whose duration of action depends upon the rate of the inactivating metabolic reaction. A few examples of foreign compounds undergoing these reactions are shown in *Table 5.*

Table 5. Examples of activation and inactivation of foreign compounds

(a) Compounds with biologically active phase I metabolites	
Phenacetin (analgesic)	Parathion (insecticide)
Chloral hydrate (hypnotic)	β-Naphthylamine (carcinogen)
Prontosil (antibacterial)	Tetraethyltin (neurotoxic agent)
Proguanil (antimalarial)	Trichloroethylene (anaesthetic)
Schradan (insecticide)	Imipramine (anti-depressant)
(b) Drugs or toxic substances with inactive phase I metabolites	
Phenobarbitone (hypnotic, long acting)	Malaoxon (insecticide)
Hexobarbitone (hypnotic, short acting)	Tetraethyl pyrophosphate (insecticide)
Meprobamate (tranquillizer)	D.D.T. (insecticide)
Antipyrine (analgesic)	

PHASE II REACTIONS OR CONJUGATIONS[9]

As already pointed out the first phase of drug metabolism does not necessarily lead to detoxication, but in the second phase the large majority of foreign compounds are converted into water-soluble and non-toxic substances which are readily excreted in the urine. This synthetic phase leads to the formation of strong organic acids such as glucuronides, ethereal sulphates, mercapturic acids and amino acid conjugates such as hippuric acids. A list of these conjugation processes is given in *Table 6.*

Table 6. A list of detoxication mechanisms

Mechanism	*Metabolite*	*Type of compound detoxicated*
Glucuronic acid conjugation	β-Glucuronides	Hydroxy compounds
Glycine conjugation	Hippuric acids	Aromatic acids
Cysteine conjugation	Mercapturic acids	Alkyl halides, chlorinated aromatic hydrocarbons
Glutamine conjugation	Aroylglutamines	Phenylacetic acid
Ornithine conjugation	Ornithuric acids	Aromatic acids in birds and reptiles
Sulphate conjugation	Ester sulphates	Phenols
Thiocyanate formation	Thiocyanate	HCN
Methylation	*N*-,*S*- or *O*-methyl-derivatives	Phenol acids, some *N*-heterocycles
Acetylation	*N*-acetyl derivatives	Aromatic amines

These reactions are biosyntheses involving a foreign compound or its phase I metabolites and a substance provided by the body which is referred to as a conjugating agent. This latter substance is derived largely from carbohydrate or protein sources and the syntheses are catalysed by specific enzymes which require certain intermediate nucleotides for their activity. There are two kinds of conjugating reactions and these differ in the nature of the intermediate nucleotide, for in one kind the intermediate nucleotide contains the conjugating agent and in the other it contains the foreign compound or its phase I metabolite. These two types of conjugation reactions can be represented as follows:

(1) Conjugating agent $\xrightarrow{\text{energy source}}$ Activated conjugating agent nucleotide $\xrightarrow[+\text{ transferase}]{\text{foreign compound}}$ Conjugated product

(2) Foreign compound $\xrightarrow{\text{energy source}}$ Activated foreign compound nucleotide $\xrightarrow[+\text{ transferase}]{\text{conjugating agent}}$ Conjugated product

The energy source in these reactions is adenosine triphosphate (ATP). An example of the first type of reaction is glucuronide synthesis, the conjugating agent being glucuronic acid, the intermediate nucleotide, uridine diphosphate glucuronic acid (UDPGA) and the transferase, glucuronyl transferase. Other examples are ethereal sulphate synthesis, methylation and acetylation. The second type is illustrated by the hippuric acid synthesis, the foreign compound being an aromatic acid, *e.g.* benzoic acid, the intermediate nucleotide, benzoyl CoA (aroyl CoA), the conjugating agent, glycine, and the transferase, glycine *N*-acylase. Other examples are the ornithuric acid synthesis and glutamine conjugation of arylacetic acids. Defects in these detoxications can arise as a result of improper formation of the intermediate nucleotide, lack of conjugating agent or a defective transferase.

FACTORS AFFECTING THE METABOLISM OF FOREIGN COMPOUNDS

[2]It is now clear that various phases of drug metabolism are controlled by enzymes, and any factor which affects these enzymes affects the metabolism of the compound and consequently its toxicity and pharmacological activity.

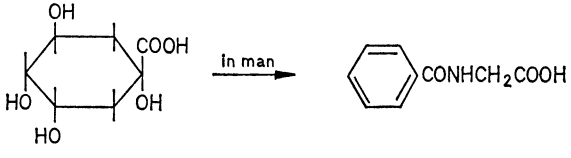
There are many factors which affect the metabolism of a drug and these can be listed as follows: species, sex, strain (genetic factors), age, diet, stress, temperature, chronic administration, disease, and the presence of other chemicals. Recently it has become clear also that biliary excretion may be important, because this introduces the question of the metabolism of foreign compounds by gut bacteria. It is possible that gut bacteria play a greater role in drug metabolism than has been hitherto realised.

It is not possible within the time allotted to this lecture to deal with all the factors which may modify the metabolism of a foreign compound and consequently its toxicity and pharmacological activity. Therefore, I shall confine my remarks to three of these, namely the species factor which is also related to the factor of biliary excretion, and the problem of the effect one chemical has upon the metabolism of another.

SPECIES DIFFERENCES IN DRUG METABOLISM[4]

The safety of drugs and other chemicals for use in man is determined by tests on laboratory animals, but the activity and toxicity of these chemicals are not always the same in animals as they are in man. One reason for these differences is that the metabolism of a compound in laboratory animals often differs from that in man, both qualitatively and quantitatively. Species differences in drug metabolism depend mainly upon differences in the enzymes which control phase I and phase II reactions. These differences in enzyme activity can be due to several causes such as the following: (a) the absolute amount of an enzyme may vary with species; (b) the amount of a natural inhibitor of an enzyme may vary; (c) the amount of an enzyme reversing a reaction may vary; and (d) there may be a species variation in the enzymic control of reactions competing for the same substrate. Examples of all these possibilities are known, but it is not possible to deal with all of them here.

A striking example of a metabolic reaction which seems to be confined to a few related species of animals is the conversion of *l*-quinic acid to hippuric acid *in vivo*. Quinic acid occurs in tea, coffee, fruits and vegetables as a component of chlorogenic acid, and in man it is converted by aromatization to benzoic acid which is excreted as hippuric acid (see below). Studies in my laboratory have shown that this reaction is confined to man and the Old



Quinic acid Hippuric acid

World Monkeys, and it does not occur to any large extent in New World Monkeys and common laboratory animals (see *Table 7*). This reaction suggests a close correlation between man and the Old World Monkeys. The reaction itself is a remarkable one and its mechanism is unknown. However,

Table 7. Aromatization of quinic acid *in vivo*
(Dose of quinic acid = 0·3 g/kg orally)

Order	*Species*	*Per cent of dose aromatized*
	Man	64
Old World Monkeys	Rhesus monkey	60
	Baboon	49
	Green monkey	45
New World Monkeys	Squirrel monkey	0
	Capuchin	0
Lemurs	Giant bushbaby	6
	Slow loris	1
	Tree shrew	0
Carnivora	Dog	1
	Cat	0
	Ferret	0
Rodents	Rabbit	4
	Guinea pig	0
	Lemming	0
	Hamster	0
	Rat	5
	Mouse	0
Birds	Pigeon	2

we have obtained results very recently to show that the reaction may be carried out by gut bacteria, for if the rhesus monkey is given 2 g of neomycin daily by mouth for six days, the aromatization of quinic acid is abolished in this animal. Aromatization does not occur if quinic acid is injected intraperitoneally.

Another interesting example is amphetamine. In the rat, this compound is mainly hydroxylated to *p*-hydroxyamphetamine, whereas in the rabbit it is mainly deaminated and converted to hippuric acid. The extent of hydroxylation of amphetamine in various species is shown in *Table 8* which suggests

Table 8. Species variation in the hydroxylation of amphetamine

Species	*Per cent of dose hydroxylated*
Man	0·5–9
Rhesus monkey	0–11
Squirrel monkey	2–3
Beagle dog	11–17
Greyhound	5–7
Rabbit	7
Guinea pig	0–2
Mouse	10–19
Rat	50–60

that the hydroxylation of amphetamine is haphazard as far as species is concerned, although the monkeys are like man in this respect.

As far as conjugation mechanisms are concerned, we again find species variation. In fact, some species are defective in some of the conjugations which occur in man. Thus the cat is defective in glucuronide synthesis, the dog cannot acetylate aromatic amines, the pig is said to be defective in sulphate conjugation and the hen does not conjugate aromatic acids with glycine. Man himself does not readily form mercapturic acids.

Glucuronide formation is one of the most widespread and versatile of the conjugation mechanisms, for glucuronides can be formed with compounds containing OH, COOH, NH_2, NH, SH and CSSH groups[10]. It occurs widely in species from amphibians to man, but is defective in cats and is replaced in insects by glucoside conjugation.

Recently a remarkable species difference in glucuronide formation was discovered in my laboratory which again shows that monkeys are similar to man in many of the reactions of foreign compounds. This was in connection with the formation of *N*-glucuronides. It has been shown that there are four types of *N*-glucuronide formed *in vivo*. These are,

(1) the aromatic amine glucuronide, $ArNH.C_6H_9O_6$,

(2) the carbamate glucuronide, $—O.CONH.C_6H_9O_6$,

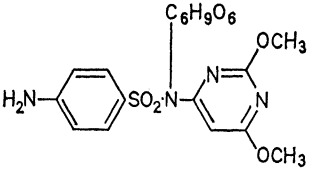
(3) the sulphonimide glucuronide, $—SO_2\underset{|}{N}.C_6H_9O_6$, and

(4) the heterocyclic *N*-glucuronide, $\diagup\!\!>N.C_6H_9O_6$.

The drug sulphadimethoxine (madribon) forms a sulphonimide glucuronide as a major metabolite in primates including man, the monkeys, and the lemurs, but not in common laboratory animals[11] (see *Table 9*).

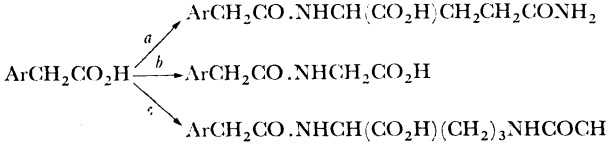
Table 9. N^1-Glucuronide formation from sulphadimethoxine (Dose of sulphadimethoxine, 0·1 g/kg orally)

	Species	% *of 24 h excretion as* N^1*-glucuronide*
	Man	70
Old World Monkeys	Rhesus monkey	70
	Green monkey	30
	Baboon	72
New World Monkeys	Squirrel monkey	51
	Capuchin	48
Lemurs	Giant bushbaby	48
	Slow loris	62
	Tree shrew	52
Carnivore	Dog	19
Rodents	Rabbit	0
	Guinea pig	5
	Rat	7



Sulphadimethoxine N^1–glucuronide

Another reaction which indicates a close relationship between man and sub-human primates is the conjugation of arylacetic acids (*e.g.* phenylacetic and indolylacetic acids) with glutamine[4, 9]. This conjugation occurs in man and Old World Monkeys (reaction *a* below) but not in the lemurs and common laboratory animals which form glycine conjugates with this type of acid (reaction *b*). In hens arylacetic acids are converted into ornithine conjugates (reaction *c*).



BILIARY EXCRETION AND DRUG METABOLISM[12,13]

The bile can be an important channel of elimination of some foreign compounds, and such elimination can have important consequences. As a result of biliary excretion a compound despite being readily absorbed from the intestine could be excreted largely in the faeces. It could also undergo entero-hepatic circulation and be extensively degraded by gut bacteria. Recent work in my laboratory has shown that the biliary excretion of a compound depends upon molecular weight and upon species. The ability to form conjugates, particularly glucuronic acid conjugates, may also be important in biliary excretion.

Compounds with small molecular weights, *i.e.* up to about 200–250, are not extensively excreted in the bile in any species[14], but as the molecular weight increases above this value biliary excretion tends to increase. This molecular weight effect is particularly marked in the rat, dog and hen, but less so in the cat and sheep. In the rabbit and guinea pig the molecular weight effect is present but it is not very marked. Thus a compound of low molecular weight such as benzoic acid (mol. wt. 122) is excreted in the bile only to the extent of 1–2 per cent mainly as its conjugates in all the species examined, including the dog, cat, rat, hen, guinea pig and rabbit. However, the large molecule succinylsulphathiazole (mol. wt. 355) has a biliary excretion of 20–30 per cent in the rat, dog and hen, 7–12 per cent in the cat and sheep and only 1 per cent of the dose in the rabbit and guinea pig. The rhesus monkey is also a poor biliary excretor and behaves like the rabbit and guinea pig in this respect[15].

The reasons for the differences in the extent of biliary excretion in these species are not yet clear, but it appears that compounds which are readily

excreted in the bile in the rat also penetrate easily into the liver, whereas in the rabbit penetration into the liver does not occur readily[16].

THE INFLUENCE OF ONE COMPOUND ON THE METABOLISM OF ANOTHER

It is now known that one foreign compound can influence the metabolism of another. Since a large number of foreign compounds occur in the environment, it is important to know which ones interact, especially those where interaction causes increased toxicity or, in the case of drugs, an altered therapeutic efficiency. One compound can affect the metabolism of another in two ways, namely by inhibiting its metabolism or by accelerating its metabolism[8]. If this occurs then four situations can arise as illustrated in *Table 10.*

Table 10. The effect of one compound upon the metabolism and toxicity of another

	Effect on toxicity of A
1. COMPOUND B INHIBITS THE ENZYME METABOLIZING COMPOUND A	
(a) A (non-toxic) —B inhibits enzyme→ C (toxic metabolite)	Diminished
(b) A (toxic) —B inhibits enzyme→ C (non-toxic metabolite)	Increased
2. COMPOUND B ACTIVATES THE ENZYME METABOLIZING COMPOUND A	
(c) A (non-toxic) —B activates enzyme→ C (toxic)	Increased
(d) A (toxic) —B activates enzyme→ C (non-toxic)	Diminished

In *Table 10*, A is the parent compound, C is its metabolite and B is a second foreign compound or drug. If B inhibits the enzyme which converts A to C, then the biological activity of A is diminished if C is an active or toxic metabolite [see (a) *Table 10*], but if A is an active or toxic compound and its metabolite C is inactive, then B will increase the activity or toxicity of A [see (b) in *Table 10*]. The reverse situations occur [see (c) and (d) in *Table 10*] if B activates the enzyme which converts A to C.

Many examples of these situations have been found to occur in practice especially where mixtures of drugs or of pesticides have been used[17]. It follows also from the situations listed in *Table 10* that pesticides and food additives could affect the metabolism of drugs and consequently their therapeutic activity. The reverse should also be true that drugs could affect the toxicity of other chemicals in the environment. Several examples of drugs affecting each other's activity through the activation of drug metabolizing enzymes are now known, such as the lowering of the anticoagulant activity of warfarin and dicoumarol by phenobarbitone. The chlorinated

insecticides chlordane, dieldrin and DDT are known to stimulate drug-metabolizing enzymes and therefore can affect the activity of drugs. The reported resistance of rats to warfarin in some areas may be due to their exposure to insecticides in the countryside. The toxicity of certain foodstuffs, such as cheese, to patients receiving antidepressant drugs, such as tranylcypromine, is due to the drug inhibiting the enzyme which detoxicates pressor amines occurring naturally in food.

The study of the fate of foreign compounds in man and animals plays an increasingly important role in the assessment of the safety of drugs and other chemicals in the environment. Furthermore, such a study helps to increase our understanding of the mode of toxic action of such substances and should lead the way to producing more effective and less toxic materials for human use.

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