

## *Metabolism of foreign compounds*

### *Chapter outline*

From this chapter you will learn about the metabolic fate of chemicals in biological systems and the importance to toxicity:

- The overall purpose of metabolism
- The consequences of metabolism
- Phase 1 reactions – cytochrome P450 and its role in oxidation reactions
- Phase 1 reactions – types of oxidation, reduction and hydrolysis reactions
- Phase 2 reactions – conjugation with glucuronic acid, sulphate, glutathione, amino acids and acetyl groups
- Toxication and detoxication reactions
- Factors affecting toxic responses: species, strain, sex, genetic factors, enzyme induction and inhibition

As we have seen, foreign compounds absorbed into a biological system by passive diffusion are generally lipid soluble and consequently not ideally suited for excretion. For example, very lipophilic substances such as **DDT** (Figure 8.1) and the **polychlorinated biphenyls** are very poorly excreted and hence remain in the animal's body for many years.

After a foreign compound has been absorbed into a biological system it may undergo metabolism (also known as **biotransformation**). The metabolic fate of the compound can have an important bearing on its toxic potential, disposition in the body and its excretion. The products of metabolism are usually more water soluble than the original compound. Indeed, in animals biotransformation seems directed at increasing water solubility and hence excretion. Facilitating the excretion of a compound means that its **biological half-life** is *reduced* and hence its potential **toxicity** is kept to a *minimum*. Metabolism may

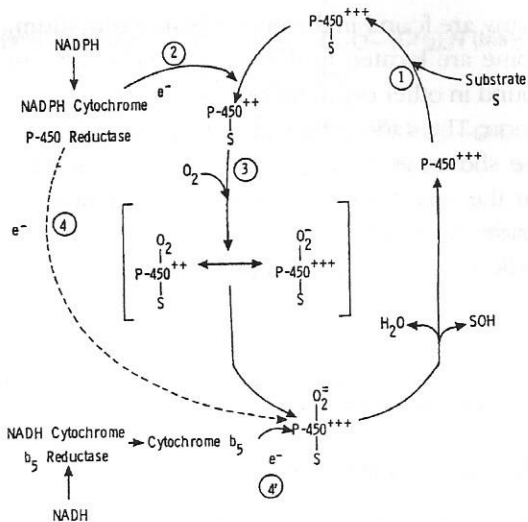


FIGURE 3.4 The cytochrome P450 mono-oxygenase system which catalyzes the phase 1 metabolism of many foreign compounds.

From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

- 1 addition of **substrate** to the enzyme;
- 2 donation of an **electron**;
- 3 addition of **oxygen** and rearrangement;
- 4 donation of a **second electron** and loss of water.

## Cytochrome P450

The cytochrome P450 mono-oxygenase system is actually a collection of isoenzymes (at least forty in humans) based on a haem protein, at the centre of which is an iron atom. The system also requires another enzyme, **NADPH cytochrome P450 reductase**, which donates electrons to the cytochrome P450. Although the enzyme is mainly located in the SER other organelles such as the nucleus also have some activity. There are at least twenty-seven gene families in the cytochrome P450 gene superfamily. The enzyme protein is designated CYP and

there are three families especially involved with the metabolism of xenobiotics, CYP 1, CYP 2 and CYP 3. CYP 4 is responsible for the metabolism of fatty acids but may also be involved in the metabolism of xenobiotics. A number of the isozymes show **genetic polymorphisms** which influence the metabolism of drugs and other chemicals (see later). The proportions of isoenzymes varies between different tissues in the same animal and between different species of animal. There may also be differences between different sexes and other factors such as exposure to xenobiotics which may induce particular isozymes.

Cytochrome P450 carries out about sixty different types of reaction and the isozymes have broad and overlapping substrate specificity.

Although there is a large variety of types of substrate for cytochrome P450, one factor in common is that most are lipophilic. There is indeed a correlation between the metabolism and lipophilicity of chemicals metabolized by the enzyme with the more lipophilic being better substrates.

Cytochrome P450 shows a number of polymorphisms which may affect the metabolism of drugs and other chemicals. Thus there may be considerable differences between individual humans in terms of their ability to metabolize drugs and other chemicals. (See below under genetic factors.) These catalyze different types of oxidation reactions and under certain circumstances catalyze other types of reaction.

Let us look at the major types of oxidation reaction catalyzed by the cytochrome P450 system.

**Aromatic hydroxylation**, such as occurs with benzene (Figure 3.3) and **aliphatic hydroxylation** such as with **vinyl chloride** (Figure 3.5) involves adding oxygen across a double bond. Hydroxylation of the aliphatic moiety in **propylbenzene** may occur at one of three positions (Figure 3.6). **Alicyclic** and **heterocyclic** rings may also undergo hydroxylation.

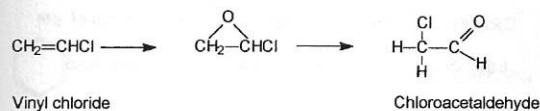


FIGURE 3.5 Epoxidation of vinyl chloride.  
From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

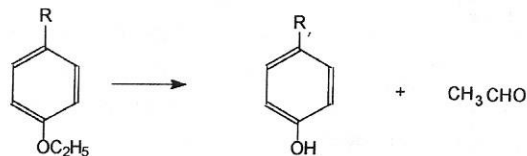


FIGURE 3.7 Dealkylation reactions.  
From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

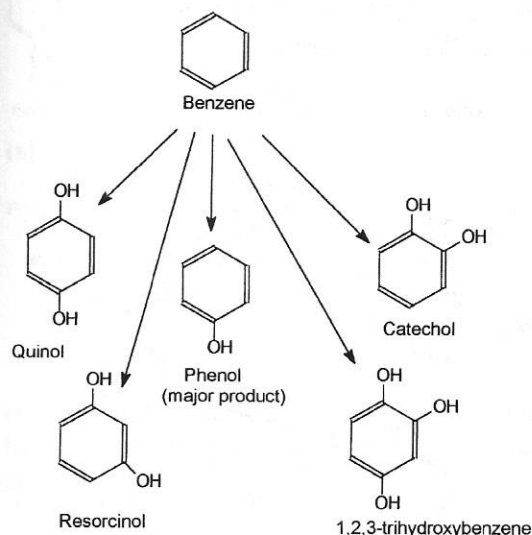


FIGURE 3.6 Oxidation of *n*-propylbenzene.  
From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

Alkyl groups attached to N, O or S atoms may be removed by **dealkylation** reactions which involve oxidation of the alkyl group and then rearrangement and loss as the respective **aldehyde** (Figure 3.7). Nitrogen and sulphur atoms in xenobiotics may be oxidized by the microsomal enzymes (Figure 3.8) and sulphur and halogen atoms may be removed oxidatively (Figures 3.9 and 3.10).

Certain oxidation reactions are catalyzed by other enzymes such as **alcohol dehydrogenase** (Figure 3.11), **xanthine oxidase**, **microsomal amine oxidase**, **monoamine** and **diamine oxidases**.

Another important group of enzymes which catalyze oxidation reactions for foreign compounds are the **peroxidases**. For example, the toxic solvent benzene, which causes **aplastic anaemia**, is believed to be metabolized by peroxidases in the bone marrow. The drug **hydralazine** is also believed to be metabolized by this enzyme system (see Chapter 5).

### Reduction reactions

These reactions may be catalyzed by either microsomal or cytosolic **reductases** and by the **gut bacteria**, which also possess reductases. The most commonly encountered type of reductive reaction is the reduction of **nitro** and **azo** groups such as those present in the food colour **tartrazine** (Figure 3.12). Less common reduction reactions include reduction of

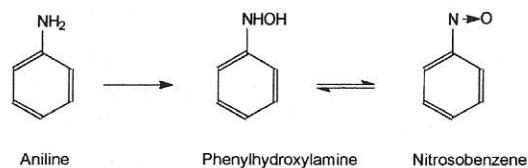


FIGURE 3.8 *N*-hydroxylation of an aromatic amino group.  
From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

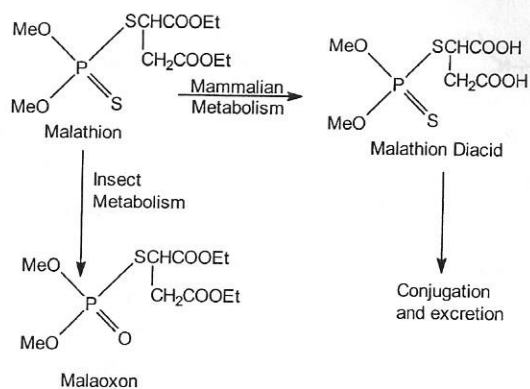


FIGURE 3.9 Metabolism of the insecticide malathion. From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

aldehyde and keto groups, epoxides and double bonds.

Reductive dehalogenation, catalyzed by the microsomal enzyme system is an important route of metabolism for anaesthetics such as halothane (Figure 3.10) (see Chapter 5).

Reductive dechlorination is involved in the toxicity of carbon tetrachloride.

## Hydrolysis

Esters and amides are hydrolyzed by esterases and amidases respectively, and there are a number of these enzymes, which are usually found in the cytosol of cells in a variety of tissues. Some are also found in the plasma. Microsomal esterases have also been described. Typical esterase and amidase reactions are shown in Figure 3.13. An example of esterase

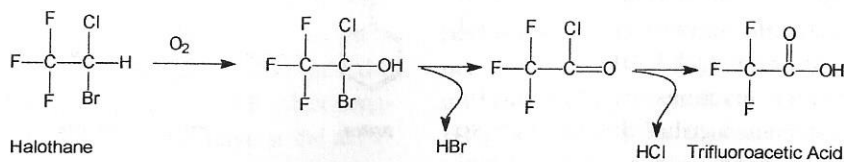


FIGURE 3.10 The metabolism of the anaesthetic halothane showing the oxidative pathway. The penultimate product, trifluoroacetyl chloride is believed to be the reactive intermediate which acylates liver proteins.

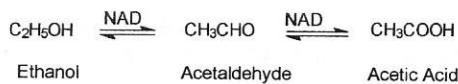


FIGURE 3.11 Oxidation of the primary alcohol ethanol. From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

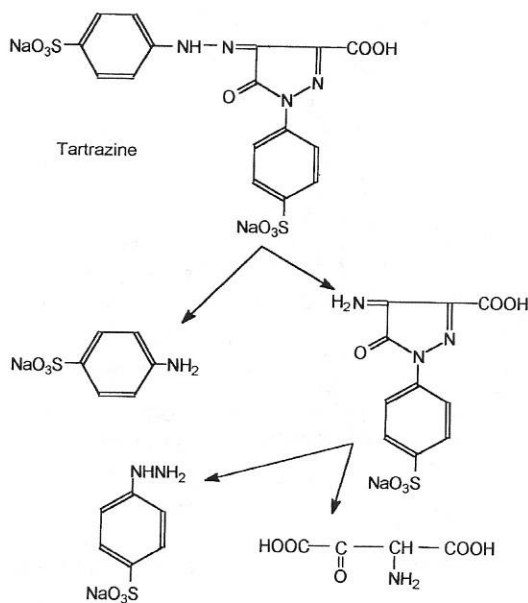


FIGURE 3.12 Metabolic reduction of the food-colouring agent tartrazine.

action which is *toxicologically* important is that of the hydrolysis of the drug succinyl choline. The very short duration of action of this compound is due to it being very rapidly hydrolyzed in the plasma (see Chapter 5). Amidases have an important role in the toxicity

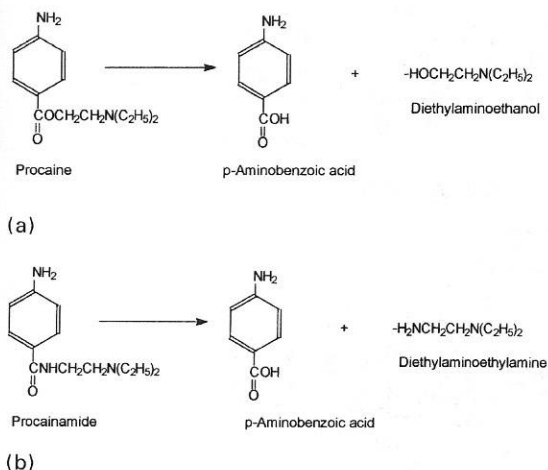


FIGURE 3.13 Hydrolysis of an ester (the drug procaine) and an amide (the drug procainamide). From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

of the drugs **isoniazid** and **phenacetin**, where hydrolysis is an important step in the metabolic activation.

### Hydration

**Epoxides**, which can be stable metabolic intermediates, may undergo hydration catalyzed by the enzyme **epoxide hydrolase** located in the microsomal fraction. This is usually a *detoxication* reaction as the dihydrodiol products are normally much less chemically reactive than the epoxide.

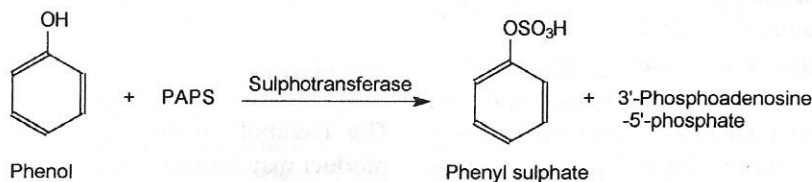


FIGURE 3.14 Conjugation of a phenol and an aliphatic alcohol with sulphate. PAPS is the sulphate donor, phosphoadenosinephosphosulphate. From Timbrell, J. A., Principles of Biochemical Toxicology, Taylor & Francis, London, 2000.

## PHASE 2 REACTIONS

These reactions, also known as **conjugation** reactions, involve the addition of a **polar group** to the foreign molecule. This polar group is either conjugated to an existing group or to one added in a phase 1 reaction, such as a hydroxyl group. The polar group renders the foreign molecule *more water soluble* and so more readily cleared from the body and less likely to exert a toxic effect. The groups donated in phase 2 reactions are commonly those involved in intermediary metabolism. Conjugation reactions are considered below.

### Sulphation

The addition of the sulphate moiety to a **hydroxyl** group is a major route of conjugation for foreign compounds. It is catalyzed by a cytosolic **sulphotransferase** enzyme and utilizes the coenzyme **phosphoadenosine phosphosulphate**. The product is an ester which is very polar and water soluble. Both aromatic and aliphatic hydroxyl groups may be conjugated with sulphate as may N-hydroxy groups and amino groups (Figure 3.14).

### Glucuronidation

Glucuronic acid is a polar and water soluble carbohydrate molecule which may be added to **hydroxyl** groups, **carboxylic acid** groups, **amino** groups and **thiols** (Figure 3.15). This

The **carboxylic acid** group first reacts with **Coenzyme A** and then with the particular amino acid. The **acylase** enzyme catalyzing the reaction is found in the mitochondria.

### Methylation

**Hydroxyl, amino and thiol** groups in molecules may be methylated by one of a series of **methyltransferases**. This occurs particularly with endogenous compounds but xenobiotics may also be substrates. As with acetylation this reaction tends to *decrease* rather than increase **water solubility**.

An important *toxicological* example is the methylation of heavy metals such as **mercury**. This may be carried out by micro-organisms in the environment (see Chapter 9). The importance is that this *changes* the **physico-chemical characteristics** of mercury from a **water-soluble** inorganic ion, to a **lipid-soluble** organic compound. There is also a corresponding *change* in the **toxicity** of mercury with mercuric ion being toxic to the **kidney** in contrast to organomercury which is toxic to the **nervous system**.

There are other reactions that a foreign molecule may undergo but the interested reader should consult one of the texts or reviews given in the bibliography. One important point to remember, however, is that although a molecule is *foreign* to a living organism, it may still be a substrate for an enzyme involved in *normal* metabolic pathways, provided its chemical structure is appropriate, and so this widens the scope of potential metabolic reactions. Foreign compounds can be metabolized by a number of different enzymes simultaneously in the same animal and so there may be many different metabolic routes and metabolites. The balance between these routes can often determine the toxicity of the compound.

### TOXICATION VERSUS DETOXICATION

The metabolism of foreign compounds has been termed detoxication because in general it converts these compounds into more water-soluble, readily excreted substances and *decreases* the **toxicity**. However, in some cases the reverse occurs and a metabolite is produced which is *more toxic* than the parent compound. A prime example of this is the drug **paracetamol** (acetaminophen) which is discussed in more detail in Chapter 5. However, in this case there are several pathways of metabolism that compete. Consequently, factors that alter the balance between these pathways will alter the eventual toxicity. This *balance* between **toxication** and **detoxication** pathways (Figure 3.18) is very important in toxicology and underlies some of the factors that affect toxicity. These will be discussed later in this chapter.

### Factors affecting toxic responses

As already indicated, metabolism is a major factor in determining the toxicity of a com-

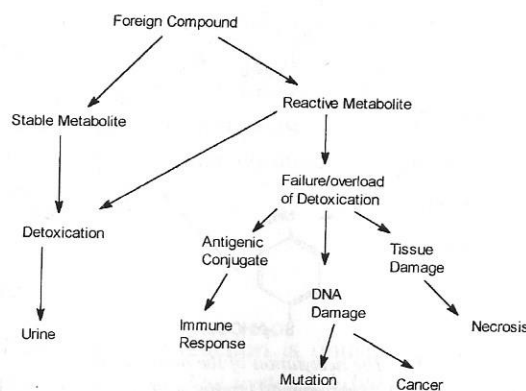


FIGURE 3.18 An illustration of the ways in which the metabolism of a compound may have a variety of consequences for the organism.

pound. Factors that affect the disposition will consequently affect toxicity. There are many such factors, which may be either chemical or biological. Chemical factors include the physico-chemical characteristics (**pK<sub>a</sub>**, **lipophilicity**, **size**, **shape**) and **chirality** (various types of isomers). Biological factors are more numerous and include **species**, **genetics**, **diet**, **age**, **sex**, **pathological state**. Many of these factors affect metabolism and so may influence the toxicity of the compound. For example, different isomers may be metabolized differently and hence show different biological activity. In humans, genetic differences may affect metabolism and consequently toxicity. Different species will have different metabolic capabilities and, therefore, may be more or less susceptible to the toxic effects of some compounds. Dietary constituents may influence metabolic pathways or rate of metabolism and, therefore, whether or not a compound is toxic. However, many of these factors will be discussed and highlighted in examples in later chapters and so will not be discussed in detail here.

### SPECIES

Species often vary widely in their responses to toxic compounds and this may be extremely important in relation to veterinary medicine, human medicine and environmental toxicology. For example, **drugs** are tested in animals for eventual use in man. If the response in the human animal is very different from that in rats or mice problems may arise when the drug undergoes clinical trials (see Chapter 12).

Similarly, veterinary products may be used on a variety of species and if there are big differences in toxicity this may lead to fatalities or pathological damage in farm animals or pets. For example **cats** have been found to

be particularly susceptible to the toxic effects of paracetamol. This is because **paracetamol** detoxication by conjugation with glucuronic acid is deficient in the cat which therefore has to rely on sulphate conjugation, which may be easily saturated. Consequently, the cytochrome P450 mediated pathway which produces a toxic metabolite (see below Chapter 5) becomes more significant and the cat suffers liver damage more readily. In the environment very large numbers of widely different species may all be exposed to a pesticide and may react very differently. Indeed this difference in sensitivity is exploited in pesticides. Insecticides, such as **organophosphorus compounds** and **DDT** (see Chapter 8), are much more toxic to insects than to humans and other mammals; in some cases this is due to metabolic differences. For example, the insecticide **malathion** is metabolized by *hydrolysis* in mammals but is *oxidized* in the insect to malaoxon which then binds to and inhibits the enzyme **cholinesterase** (Figures 3.9 and 8.4; see also Chapter 8).

One of the problems associated with species differences in metabolism is the use of animals for the safety evaluation of drugs and other chemicals. The testing of such compounds of necessity has to be carried out in animals prior to human exposure but choosing the 'right' animal model may be difficult, especially because human metabolism of the chemical may be very different from the commonly used experimental species. Also, of course, species may vary in their response to chemicals, although this is probably less common than metabolic differences between species. (See also Chapter 12.)

There are very many species differences in metabolism and it is beyond the scope of this book to discuss them in detail. The interested reader is recommended to consult the bibliography at the end of this chapter.

### STRAIN OF ANIMAL

Just as different species may vary in their response to toxic compounds and in the way they metabolize them, different inbred strains of the same animal may also show variation. For example, different strains of mice vary widely in their ability to metabolize **barbiturates** and consequently the magnitude of the pharmacological effect varies between the strains (Table 3.2).

### SEX

Males and females can also differ in their responses due to **metabolic** and **hormonal differences**. Males in some species metabolize compounds *more rapidly* than females, although this difference is not found in all species. As well as metabolic differences there are examples of sex differences in *routes* of excretion which underlie differences in *susceptibility*. For example, **dinitrotoluene**-induced hepatic tumours occur predominantly in males due to the differences in the route of excretion. Biliary excretion of a glucuronide conjugate is favoured in males while urinary excretion predominates in females.

TABLE 3.2 *Strain differences in the duration of action of hexobarbital in mice*

Strain	Sleeping time
A/NL	48 ± 4
BALB/cAnN	41 ± 2
C57L/HeN	33 ± 3
C3HfB/HeN	22 ± 3
SWR/HeN	18 ± 4
Swiss (non-inbred)	43 ± 15

Source: G. E. Jay (1955), *Proceedings of the Society of Experimental Biology and Medicine*, 90, 378

The glucuronide conjugate is broken down in the intestine by gut bacteria and the products are reabsorbed, causing the hepatic tumours. The difference in susceptibility to **chloroform**-induced kidney damage between male and female mice is an example of a sex difference which has a metabolic basis and hormonal basis. The male mice are more susceptible but this difference can be removed by castration and restored by **androgens**. It may be that **testosterone** is influencing the microsomal enzyme-mediated *metabolism* of chloroform to give greater metabolism in males.

### GENETIC FACTORS AND HUMAN VARIABILITY IN RESPONSE

Genetic variation is particularly important in the **human** population which is genetically mixed. There are now many examples of **toxic drug reactions** which occur in individuals due to a genetic defect or genetic difference in metabolism. The best known example in man is that of the **acetylator phenotype** where the acetylation reaction (see page 46) shows genetic variations which are due to mutations giving rise to mutant alleles. This results in rapid and slow acetylators where the latter have *less functional acetyltransferase enzyme*. This is an important factor in a number of adverse drug reactions including the **hydralazine-induced lupus syndrome** discussed in Chapter 4, **procainamide**-induced lupus syndrome, **isoniazid**-induced liver damage and **isoniazid**-induced peripheral neuropathy.

The first genetic polymorphism of cytochrome P450 to be discovered and perhaps the most well characterized is that affecting **CYP2D6** which catalyses the metabolism of the drugs **debrisoquine**, **bufuralol** and **sparteine**, for example. (See also below Chapter 5 under debrisoquine.) There are two pheno-

types resulting from this polymorphism, known as poor metabolizers and extensive metabolizers. Poor metabolizers are individuals who have reduced metabolic activity towards certain substrates due to almost the complete absence of functional cytochrome P4502D6 as a result of one of a number of mutations. These mutations produce abnormal mRNA, and hence abnormal enzyme protein. Poor metabolizers may suffer increased toxicity from some drugs such as **penicillamine**, which may cause skin rashes, and **phenformin**, which may be associated with lactic acidosis. The poor metabolizer phenotype occurs in approximately 5–10 per cent of the white Caucasian population. A similar genetic polymorphism occurs with cytochrome P4502C, which is particularly common in the Japanese population.

Other enzymes involved in drug metabolism may also be subject to genetic variation such as **alcohol dehydrogenase** and **esterases**. These variations may also underlie toxic or exaggerated responses. For example, increased sensitivity to **alcohol** may result from reduced metabolism in some individuals such as **North American Indians**. This is caused by a variant of alcohol dehydrogenase that metabolizes alcohol at a slower rate in certain individuals. There are indeed a number of variants of alcohol dehydrogenase that occur in different ethnic groups and some are associated with particular reactions to alcohol exposure.

Similarly **esterases** show a number of polymorphisms. For example, the metabolism of **succinylcholine (suxamethonium)**, a muscle relaxant drug, can show considerable variation between human individuals. This in turn affects the duration of action of the drug. Thus, in most individuals, muscle relaxation after succinylcholine lasts a matter of minutes, whereas in a few individuals with a particular isoform of pseudocholinesterase, metabolism is reduced and the relaxation can last for an hour or more and may become life threatening.

Toxic responses to foreign chemicals may show large variation between human subjects and some of this variation can be ascribed to the factors mentioned. As well as genetically determined metabolic differences, there may be genetic differences in a receptor or in an immunological parameter giving rise to variation in toxicological and pharmacological responses to drugs and other foreign compounds. Several examples will be discussed later in this book. In some cases, however, rare idiosyncratic reactions of unknown origin may occur and in other cases a combination of factors may be necessary for a toxic reaction to occur (see Chapter 5; hydralazine). Unfortunately, much of the variability seen in humans is not encountered in inbred experimental animals and consequently rare but severe and life-threatening toxic reactions may not be encountered in toxicity studies in animals and may only become known after very large numbers of humans have been exposed to the particular chemical.

#### ENVIRONMENTAL FACTORS

Another factor which affects the human population is the environment, in particular the other chemical substances to which people are exposed. Thus, chemicals in the diet, air or water may all influence the toxic response to another chemical. Unlike experimental animals, humans may be under medication with several drugs when exposure to an industrial chemical occurs, for instance. These drugs can influence the way in which the body reacts to the chemical. The intake of one drug may affect the response to another. Repeated exposure of animals to chemicals may increase the *in vivo* activity of enzymes involved with the metabolism of xenobiotics. In some cases this may be the enzymes that are responsible for metabolism of the chemical itself. This phenomenon

is known as enzyme induction and is due to increased amounts of the enzyme, possibly as a result of increased synthesis. There are a number of enzymes involved with xenobiotic metabolism which may be induced but possibly the most important is cytochrome P450. Phase 2 enzymes may also be induced such as glucuronosyl transferase. The **induction** of these enzymes can lead to either increased or decreased toxicity of a compound. Therefore exposure to such substances, which might be drugs or environmental chemicals, can have a significant effect on the toxicity of another substance such as a co-administered drug or another environmental chemical. For example, overdoses of **paracetamol** are more likely to cause serious liver damage if the victim is also exposed to large amounts of **alcohol** or **barbiturate**, both of which *induce* drug metabolizing enzymes and thereby **increase** the *in vivo* activity.

Enzyme induction may also alter endogenous metabolic pathways such as the synthesis of steroids.

Conversely, some chemicals can act as enzyme inhibitors and thereby alter the metabolism of other chemicals and possibly increase their toxicity. Enzyme inhibitors could be drugs or industrial chemicals. Unlike enzyme inducers, **inhibitors** usually act after a single exposure. Both enzyme inducers and inhibitors may be natural constituents of the diet or regularly used drugs such as alcohol or tobacco. **Alcohol** is especially important as an enzyme inducer in relation to drug use and abuse.

A recent example of a naturally occurring inhibitor is a flavonoid found in **grapefruit juice** which is a potent inhibitor of cytochrome P450 3A4.

Compounds which inhibit metabolic pathways by blocking particular enzymes may also be factors in toxic responses. For example, workers exposed to the solvent **dimethylformamide** seem more likely to suffer alcohol-

induced flushes than those not exposed, possibly due to the *inhibition* of alcohol metabolism. The diet contains many substances which may influence the enzymes of drug metabolism such as the microsomal enzyme inducer  **$\beta$ -naphthoflavone** found in certain vegetables. **Cigarette smoking** and **alcohol** intake also are known to affect drug metabolism and pharmacological and toxicological responses.

Although enzyme induction and inhibition can be important with regard to the disposition and toxicity of environmental chemicals, it is probably more often a significant problem with drugs. This is because drugs are commonly administered together, possibly for extended periods and at higher concentrations than those of environmental chemicals to which we are exposed.

#### PATHOLOGICAL STATE

The influence of disease states on metabolism and toxicity has not been well explored. Diseases of the **liver** will clearly affect metabolism but different liver diseases can influence metabolism differently. Disease states such as **influenza** are also known to affect drug metabolizing enzymes, possibly via the production of **interferon**.

### *Summary and learning objectives*

This chapter has been concerned with **metabolism or biotransformation** of chemicals, the enzyme catalyzed conversion of the molecule into products with altered, physico-chemical and biological properties. These are usually **more water soluble, less lipid soluble** and often of greater molecular weight. Therefore

the *consequences of metabolism* are increased excretion, shortened half-life and reduced accumulation and exposure of the biological system to potentially toxic compounds. Metabolism of a chemical is determined by its structure, properties and available enzymes. It can be divided into two phases: *phase 1* predominantly *oxidation* but also *reduction* and *hydrolysis*; *phase 2*, *conjugation*. Phase 1 results in the generation of a functional group; phase 2 involves addition of an endogenous moiety to that functional group to increase water solubility. The most important enzyme involved in phase 1 oxidation reactions is the *cytochrome P450 system* (27 gene families; 3–4 involved with chemical metabolism), of which there are many isoforms and it is located in the smooth endoplasmic reticulum. Some of the isoforms show genetic polymorphisms. Other oxidative enzymes include alcohol dehydrogenase, xanthine oxidase, microsomal amine oxidase, monoamine and diamine oxidases and peroxidases. *Reduction* is commonly catalyzed by reductases (azo- and nitro-) in gut bacteria. *Hydrolysis* (ester and amide) is catalyzed by esterases. Hydration of epoxides, a detoxication reaction, is catalyzed by a microsomal epoxide hydrolase.

The main phase 2 reactions are addition of *glucuronic acid*, *sulphate*, *glutathione*, *amino acids* and *acetylation* catalyzed by transferases. Glutathione conjugation is an important detoxication reaction.

The *balance* of metabolic pathways may determine whether a compound undergoes *toxication* or *detoxication*.

Metabolism may be affected by chemical, biological and environmental factors. Physico-chemical factors such as chirality, size, shape, lipophilicity are important. Biological factors include *species and strain*, *genetic differences in humans*, *age*, *sex*, *disease* and *diet/nutrition*. Species differences are important for drug safety testing and pesticide design. Genetic fac-

tors are important in human response. Disease may reduce metabolism. Environmental factors include the influence of other drugs, food constituents or environmental contaminants as *inducers* or *inhibitors*.

## Questions

- Q1. Choose one answer which you think is the most appropriate.  
Metabolism of a foreign chemical will lead to:
- accumulation of the chemical in the tissues
  - increased excretion in urine
  - decreased toxicity
  - altered chemical structure
  - increased toxicity.
- Q2. Indicate which of the following statements is true and which is false.  
Cytochrome P450 is an enzyme which:
- is found in lysosomes
  - is responsible for the conjugation of drugs
  - is a central part of the drug metabolizing system
  - is one of the enzymes in the mitochondrial electron transport chain
  - c and d are correct.
- Q3. Choose one answer which you think is the most appropriate.  
Phase 2 metabolism usually involves:
- microsomal enzymes
  - decreasing the polarity of a chemical
  - increasing the toxicity of compounds
  - the addition of an endogenous moiety
  - hydrolysis.

Q4. Indicate which of the following is true and which false:  
Glutathione is:

- a a protein
- b a tripeptide
- c an enzyme involved in detoxication
- d a substance found in the kidneys
- e a vitamin.

Q5. Answer a if the statement is true and b if the statement is false.

Cytochrome P450 mainly catalyses the phase 1 metabolism of chemicals.

Q6. Select A if 1, 2 and 3 are correct  
Select B if 1 and 3 are correct  
Select C if 2 and 4 are correct  
Select D if only 4 is correct  
Select E if all four are correct

The microsomal enzyme system is responsible for the metabolism of foreign compounds. Which of the following are essential aspects of this system?

- 1 magnesium ions
- 2 the addition of two electrons
- 3 molecular oxygen
- 4 the substrate is bound to an iron atom in the active site.

Q7. Indicate which of the following is true and which false:

The acetylator phenotype is:

- a not found in dogs
- b found exclusively in Orientals
- c responsible for the toxicity of amines
- d an inherited trait affecting a particular metabolic reaction
- e associated with the HLA type.

Q8. Choose one answer which you think is the most appropriate.

The phenomenon of enzyme induction involves:

- a an increase in the synthesis of the enzyme
- b an increase in the activity of the enzyme
- c an increase in liver weight
- d a change in the substrate specificity of the enzyme
- e an increase in bile flow.

#### SHORT ANSWER QUESTIONS

Q9. Write short notes on three of the following:

- a enzyme-mediated dealkylation
- b alcohol dehydrogenase
- c glucuronic acid conjugation
- d phase 1 and 2 metabolism.

Q10. Write notes on the role of three of the following in drug toxicity:

- a ethnic origin
- b cytochrome P450 isozymes
- c enzyme induction
- d acetylator phenotype.

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