Chapter 3

Types of Exposure and Response

Types of Exposure

There are two basic exposure conditions for toxic compounds: acute and chronic exposure. Acute exposure applies to a single episode where a particular amount of a substance such as with an overdose of a drug, enters the organism. Chronic exposure applies to repeated exposure to a substance which may then accumulate or cause a cumulative toxic effect.

Acute toxicity usually applies to a toxic event which occurs soon after acute or limited exposure; chronic toxicity may apply to an event which occurs many weeks, months or years after exposure to either repeated doses or possibly after an acute exposure to a particular toxic substance.

Route of Exposure

Routes of exposure have already been discussed in Chapter 2 and so only brief mention will be made here. Exposure via the gastrointestinal tract is the most important route for most drugs, food additives and contaminants, natural products, and other potentially toxic substances. Inhalation is particularly important in an industrial environment both inside and outside the factory and pesticides may also be taken in this way during spraying. Absorption via the skin is also important in an industrial and agricultural setting.

The site and route of absorption is important from two points of view:

1. the route may influence the eventual systemic toxicity as already indicated in Chapter 2;
2. the site may be important if there is local toxicity at the point of absorption.

For example, substances which are irritant may cause inflammation at the site of absorption and this may depend on the conditions at this site. Particles such as asbestos will cause damage to the cells of the lung by being taken up into them,

but will not particularly damage the skin. The skin will tend to be more resistant because of the outer layer of keratinized cells and its poor absorptive properties.

Drugs may also gain access to the body by routes other than those mentioned, in particular intravenous and intramuscular injection are employed in human medicine while intraperitoneal and subcutaneous administration are commonly used in experimental animals. Intravenous and intraperitoneal injection lead to rapid distribution to most parts of the body whereas subcutaneous and intramuscular injection usually lead to slow absorption.

Types of Toxic Response

A biological system may respond in many different ways to a toxic compound. As already mentioned in the section on the dose response relationship death of the cell or of the whole organism is only one response and there are many specific causes of this. We will briefly consider the types of response here and examples will be considered in more detail in later chapters.

The major toxic responses observed are as follows: tissue damage and other pathological changes; biochemical lesions; pharmacological responses or physiological changes; reproductive or teratogenic effects; mutagenicity; carcinogenicity; irritation and corrosive effects; allergic reactions. Clearly there is overlap between some of these responses. For example, biochemical effects can lead to tissue damage or some other pathological lesion. (See paracetamol, Chapter 4 and snake venoms, Chapter 9.)

Direct tissue damage is usually the result of cellular destruction. This may have a biochemical or immunological basis but many pathological lesions are of unknown mechanism, particularly as regards the intermediate stages between the interaction of the toxin or its metabolite with cellular constituents and the start of the final degenerative changes leading to cell death. Highly reactive compounds may react with cell membranes and cause instant cell death by damaging the cell membrane sufficiently to allow rapid loss of contents and influx of external ions and substances. Some toxic compounds interfere directly with vital cellular functions such as respiration which usually leads to rapid cell death. Not all toxic compounds act in this way, however, and some cause cell death to occur more slowly. (See lead, Chapter 8.)

Biochemical lesions may lead to the development of a pathological change such as cell degeneration but they may also simply cause death of the whole organism by interfering with some vital function such as respiration. For example, cyanide causes death of cells by interfering with the electron transport chain in the mitochondria such that oxygen cannot be utilized leading to the death of cells in vital organs so that the whole organism dies. Some biochemical effects are reversible, such as the binding of carbon monoxide to haemoglobin which may be insufficient to cause death of either cells or the whole organism and generally will not result in a pathological lesion (see carbon monoxide and also ethylene glycol, Chapter 10).

Pharmacological and physiological responses are those where a particular bodily function is affected. For example, some compounds cause a change in

blood pressure by affecting ß-adrenoceptors or by causing vascular dilatation or constriction. These clearly are toxic reactions if extreme and directly life threatening or when they occur in workers occupationally exposed to the drug for example. Alternatively, a drop in blood pressure may be sufficient to initiate another response such as ischaemic tissue damage due to insufficient blood flow. (See debrisoquine and succinyl choline, Chapter 4 and tetrodotoxin and botulinum toxin, Chapter 9.)

Allergic reactions are those that occur when the immune system of the body is stimulated to react in a particular way. This may be the result of a toxic molecule being sufficiently large to be regarded as foreign by the immune system and so act as an antigen. More commonly the foreign compound (or hapten as it is called) interacts with an endogenous macromolecule (usually a protein) and the product, often a conjugate of the hapten and protein, is antigenie (Figure 3.1). An immunological reaction takes one of several forms including stimulation of a physiological response such as bronchoconstriction or cellular destruction by complement. An immunologically mediated reaction may underly a rare, idiosyncratic, response after exposure to a toxic compound,

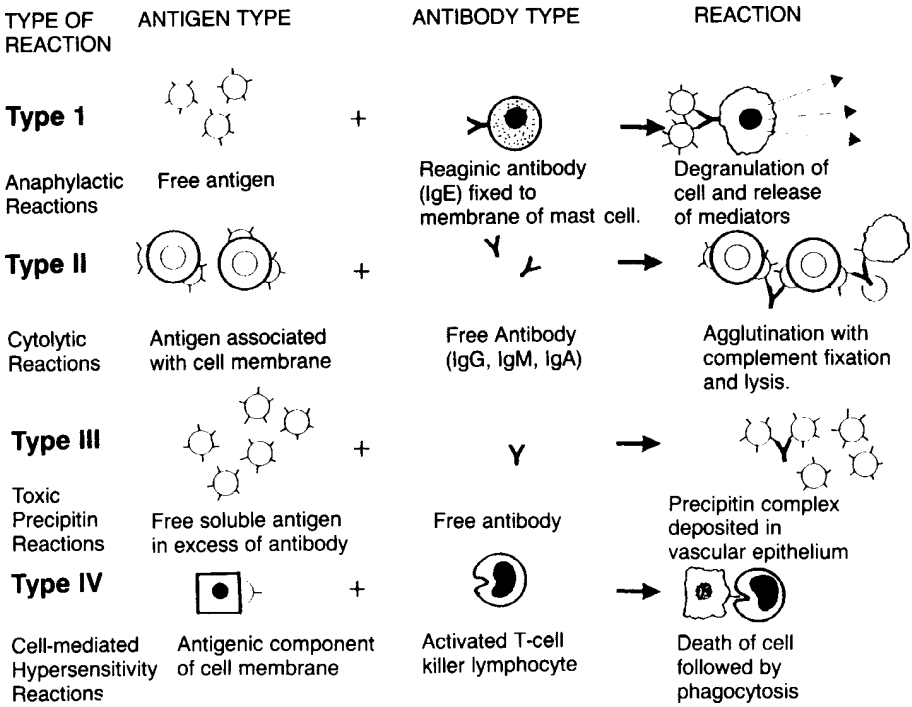

Figure 3.1. Mechanisms for the stimulation of an immune response. The antigen is usually a foreign macromolecule such as a protein or an altered cell membrane as in Type IV reactions. Most foreign compounds are of low molecular weight and are not directly antigenic. They may act as haptens and so cause immune reactions by reacting with and thereby altering endogenous proteins or cell membrane components.
Adapted from Bowman, W.C. and Rand, M.J., *Textbook of Pharmacology,* 2nd edition, Blackwells Scientific Publishers, Oxford.

such as halothane (see Chapter 4) or it may be cause a more common adverse effect to a drug such as hydralazine (see Chapter 4; also see vinyl chloride Chapter 5). It should be noted that there may be other causes of rare, idiosyncratic, reactions to foreign compounds such as a reduced ability to metabolize a compound (see debrisoquine, Chapter 4).

There are four different types of allergic or hypersensitivity reactions but these will not be discussed in detail in this book. Type I reactions (anaphylaxis) may be elicited by chemicals such as toluene di-isocyanate, an industrial chemical. Sensitization occurs after the initial exposure and then subsequent exposures cause the anaphylactic reaction resulting in bronchoconstriction and asthma. Penicillin may also cause this type of reaction. Type IV reactions underly contact dermatitis which is a major industrial problem associated with exposure to nickel and cadmium.

Most chemical induced adverse skin reactions are probably associated with irritation, and skin disease is the most common injury to industrial chemicals. After a single insult to the epidermis, the primary response is a local inflammatory reaction. Acute inflammation is the immediate response to irritant chemicals and it is characterized by dilation of blood vessels, increased blood flow, accumulation of fluid in the tissues and invasion of white blood cells. These changes give rise to redness, heat, pain and swelling.

Corrosive chemicals such as sodium hydroxide, cause destruction of tissue (see Chapter 10).

Teratogenicity is a very specific type of toxic response whereby the development of the embryo or foetus is affected. This may lead to a functional and/or structural abnormality of the foetus and of the resulting animal. In many cases this is the result of a perturbation in the development of the organism rather than direct damage to the embryo or foetus as the latter usually results in death and abortion. Teratogens are often relatively non-toxic to the mother but interfere in some specific way with the development of a particular stage of the embryo. The timing of the exposure or dosing with a teratogen relative to the stages of pregnancy is therefore crucial (Figure 3.2; see thalidomide, Chapter 4).

Mutagenicity is a toxic effect which specifically damages the genetic material in the cell. The DNA or chromosome is damaged in such a way that an error is transferred to the daughter cell or next generation. Damage to the chromosomes is known as clastogenicity. There are many ways in which a compound may cause a mutation and consequently many different types of foreign compound have been found to be mutagenic. Thus, chemically reactive compounds, such as alkylating agents, may react directly with the DNA in the cell nucleus, or a compound, such as bromouracil, may be incorporated into the DNA during cell replication. This may then lead to mistakes occurring in the new DNA. Some compounds such as the naturally occurring vinca alkaloids interfere with the processes of mitosis or meiosis so that incorrect cell division results. In mammals mutations in the germ cells can lead to birth defects. Mutations in somatic cells are also believed to underlie the development of cancer in most instances (see below).

The majority of human cancers are probably caused by chemical carcinogens

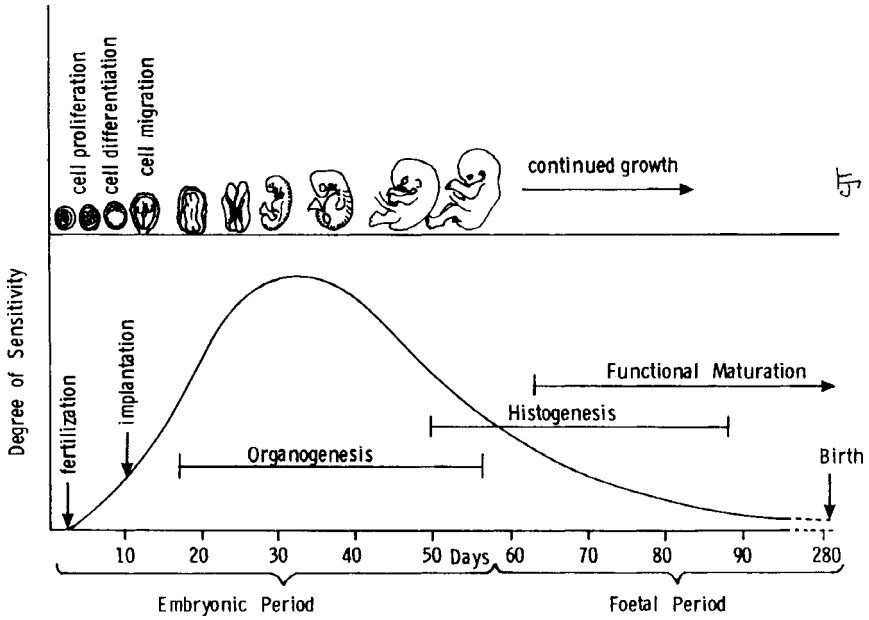

Figure 3.2. The stages of mammalian embryogenesis indicating the periods of greatest susceptibility to teratogens.
From Timbrell, J.A., Principles of Biochemical Toxicology, Taylor & Francis, London, 1991.

and although this is still a contentious issue, there are now many examples of chemicals which will reproducibly cause cancer in experimental animals. Carcinogenicity is a specific toxic effect which leads to the uncontrolled proliferation of tissue. It comes in many different forms, differing in malignancy and type of tissue affected. Cancer induction is now believed to be a multi-stage process which in simple terms requires initiation followed by promotion. Thus, toxic compounds may be carcinogenic by interfering with the genetic control of cellular processes via a mutation, such as the chemically reactive alkylating agents, vinyl chloride and aflatoxins (see Chapter 5 and Chapter 9 respectively). This initiating event is then followed by promotion either by the same compound or some other substance to which the animal is exposed. For example, tumours of mouse skin may be caused by application of a polycyclic hydrocarbon such as benzpyrene (initiator) followed by a phorbol ester (promoter). However, not all carcinogens are mutagens, for example ethionine and asbestos (see Chapter 5). Therefore, mechanisms which do not involve a mutagenic event (epigenetic mechanisms) must be invoked to explain the causation of cancer by such compounds. Also, not all mutagens are carcinogens, although there is a sufficiently good correlation between mutagenicity and carcinogenicity for mutagenicity tests to be regarded as predictive of at least potential carcinogenicity (see Chapter 11). Mutagenicity tests are also of use for prediction of germ cell defects and hence of damage which is heritable.

Detection of Toxic Responses

Some of the toxic effects described may be detected by gross pathological examination in the post mortem or histopathological examination after toxicity studies have been carried out. Some may also be detected using clinical chemical analysis of body fluids, as will be discussed briefly in Chapter 11. The detection of other toxic effects such as mutagenicity may require special techniques.

Thus, toxic responses may be detected in a variety of ways and there is increasing interest in this field of biomarkers. The term biomarkers covers both indicators of effect and exposure. Exposure markers will include the metabolites of the compound in question and conjugates between metabolites and macromolecules such as proteins. There is a wide range of markers of effect such as enzymes released into the blood by damaged tissue, induction of enzyme synthesis or stress proteins and changed synthesis or increased release of various intermediary metabolites. There are also indirect markers of effect such as changes in the immune system or changes in populations resulting from effects on the reproductive cycle of the organism.

Question

1. There are several different types of toxic response which may be caused by chemicals. Describe them and indicate how they can be detected.

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