CRC

TARGET ORGAN TOXICITY

Volume I

Gerald M. Cohen

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Editor

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INTRODUCTION

The specificity of certain chemicals to induce a wide variety of differing toxicities, including hepatotoxicity, neurotoxicity, pulmonary toxicity, nephrotoxicity, ototoxicity, and cancer in particular organs is a fascinating problem currently under active investigation in many laboratories.

The purpose of these volumes is to provide a valuable reference for established investigators and postgraduate students in toxicology. Essential information on the general principles of target organ toxicity is provided in the first seven chapters in Volume I. Included are the importance of pharmacokinetics, metabolic activation and key defense mechanisms, excretion, species variation, and tissue-specific biochemistry. Next these general principles are illustrated by dealing with specific examples of toxicity to different target organs and systems. Volume II, Chapter 9, deals with DNA modifications and repair in tumor induction, and the final chapter discusses organ specificity in tumor initiation and complete carcinogenesis.

THE EDITOR

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To Judith, Gidon, Raffi, and Aron
For Their Encouragement and Understanding

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Chapter 1

BASIC PRINCIPLES OF TARGET ORGAN TOXICITY

Gerald M. Cohen

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I. INTRODUCTION

A baffling array of different toxicities may be induced in various organs of the body by thousands of chemicals to which we are exposed. All tissues are susceptible in varying degrees to these toxic effects, but many chemicals exhibit a marked propensity to damage specific organs; these are known as the *target organs of toxicity*. An understanding of the remarkable ability of some chemicals to cause these organ-specific lesions is the subject of this book. Some examples of specific compounds and their target organs of toxicity are given in Table 1.

In this chapter, I shall discuss the basic principles which determine the susceptibility of particular organs to the toxicity of chemicals. Several factors predispose particular organs to toxicity. Portals of entry and exit from the body will generally be exposed to high concentrations of chemicals and thus are more likely to be susceptible to toxicity. For example, the lungs are exposed to a wide variety of inhaled chemicals including atmospheric pollutants, irritants, and cigarette smoke, as well as medicinal and household aerosols. Other portals of entry include the skin and GI tract, which will be exposed to chemicals either from dermal contact or by ingestion, respectively. Similarly, in the process of excretion of chemicals from the body, the kidney and the biliary tree and intestines may be exposed to high concentrations of drugs and/or metabolites. Many xenobiotics (foreign chemicals) are lipid soluble compounds which, if not metabolized to more polar and more readily excretable metabolites, would remain in the body for long periods.[1,2] Quantitatively the major site of xenobiotic metabolism is the liver and as many chemicals are metabolized to toxic metabolites, the liver is often a target organ for toxicity. Often it is the balance in a particular tissue between activating and deactivating enzymes which determines the susceptibility of different organs to toxicity.

A. Factors Affecting Toxicity

Many factors may influence the susceptibility of specific organs to toxicity and particular consideration should be given to the distribution of toxic compounds in the body and their mechanisms of toxicity. It is self-evident that for any chemical to exert a deleterious effect on a specific organ it must first gain access to "its site of action" (Figure 1). The quantitation of the time course of distribution of a toxic chemical and its metabolites in the body is known as toxicokinetics and is dealt with in detail in Chapter 2. The response of an organ is affected by:

1. Factors affecting the disposition of the toxic compound to an organ (Figure 1 and Table 2). These include physicochemical properties of the compound, such as pKa and lipid solubility, as well as absorption, plasma protein binding, and excretion of the compound and its metabolites.
2. Metabolic fate of a chemical and its metabolites within the organ and the body, e.g., the generation and detoxication of reactive metabolites in the target tissue.
3. The ability of the organ to respond to the effects of the chemical, e.g., its ability to repair chemically induced damage.

The importance of these three factors will now be illustrated with appropriate examples.

II. DISPOSITION OF THE TOXIC CHEMICAL

The concentration of a xenobiotic or its reactive metabolite and the duration of exposure of a target organ will generally determine the severity of the toxicological response. However,

Table 1
SOME TARGET ORGANS OF TOXICITY OF CERTAIN CHEMICALS

Organ or tissue	Chemical	Toxicity
Nervous system	Acrylamide	Axonopathy
Liver	Paracetamol	Liver necrosis
Kidney	Cephaloridine	Nephrotoxicity
Respiratory system	Bleomycin	Pulmonary fibrosis
Eye	Chloroquine	Retinopathy
Ear	Streptomycin	Ototoxicity
Blood	Primaquine	Hemolytic anemia
Bone marrow	Chloramphenicol	Aplastic anaemia
Reproductive system	1,2-Dibromo-3-chloropropane	Male sterility
Heart	Adriamycin	Cardiomyopathy
Skin	Phenylbutazone	Exfoliative dermatitis
GI tract	Methotrexate	Ulceration
Fetus	Phenytoin	Congenital abnormalities (cleft palate)
Bone	Anticonvulsants	Osteomalacia
Pancreas	Alloxan	Damage to β cells

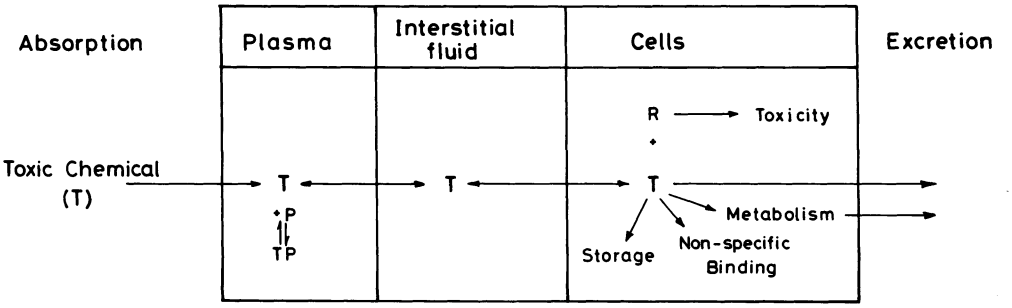

FIGURE 1. Distribution of a toxic chemical (T) in the body. Many factors such as binding to plasma proteins (P) and storage may affect the concentration of T available to interact with critical receptors (R) and elicit toxicity in the target organ.

Table 2
MAJOR FACTORS AFFECTING THE SUSCEPTIBILITY OF ORGANS TO CHEMICAL-INDUCED TOXICITY

Factor	
Tissue distribution of the compound	Physicochemical properties; pKa, lipid solubility, absorption, distribution
	Plasma protein binding and excretion of compound
	Possibility of active transport or secretion
	Dose-dependent kinetics
Metabolism	Depends whether the parent compound or a metabolite is toxic
	Tissue distribution of drug-metabolizing enzymes
	Qualitative and quantitative nature of enzymes present
	Balance of activating and deactivating enzymes in liver and/or target organ(s).
	Different enzyme inducers or inhibitors may affect these tissues differently
Individual biochemistry of different tissues	Presence of a particular biochemical pathway
	Absence or low levels of key defensive mechanisms, e.g., glutathione
Host	Ability to repair a particular damage or lesion
	Presence of impaired host function, e.g., liver or kidney disease

Table 3
TARGET ORGAN TOXICITY OF CHEMICALS WHERE TISSUE-SPECIFIC ACCUMULATION IS OF MAJOR IMPORTANCE

Chemical	Target organ of toxicity	Comments	Ref.
Paraquat	Lung	Active uptake system into type I and II alveolar epithelial cells due to structural similarity to endogenous polyamines	3 and Vol. II, Chap. 3
Streptozotocin	Pancreas	High specificity for pancreatic β cells possibly due to glucose moiety which causes specific binding to cells with glucose receptors	4
Chloroquine, chlorpromazine, and other N-substituted phenothiazines	Eye	High persistent concentrations in the pigmented eye due to avid binding to melanin	5
Kanamycin, chloroquine	Ear	Binding to melanin in ear	6
Cephaloridine	Kidney	Uptake into the kidney by anion transport system and subsequent accumulation due to presence of cationic grouping in cephaloridine preventing its excretion by the anion transport system	7
6-Hydroxydopamine	Adrenergic nerves	Taken up into adrenergic nerve terminals because of structural similarity to endogenous substrate	8

high concentrations of a toxic chemical in a particular tissue do not necessarily lead to toxicity in that tissue. For example, DDT and related insecticides accumulate in adipose tissue without exerting any apparent deleterious effect on it. However, selective accumulation of a chemical in a tissue may be a critical factor in determining the target organ of toxicity and several examples of this are given in Table 3. Further details of the nature and importance of the accumulation of paraquat and streptozotocin are given in Volume II, Chapters 3 and 8, respectively.

The normal physiological function of an organ may also predispose it to toxicity. Many chemicals are nephrotoxic due in part to their accumulation in the kidney as a result of its large blood supply but also because of particular aspects of its normal physiological functions.[9,10] Any potentially toxic chemical in the systemic circulation will be presented to the kidney in significant quantities, where it will be filtered at the glomerulus. Thus, toxic concentrations that may be reached in the tubular fluid as salt and water are reabsorbed from the glomerular filtrate. Compounds may also become particularly concentrated in tubular cells because of active secretion or reabsorption. Any chemical which is actively secreted will first be concentrated, in cells of the proximal tubule, to levels greater than those found in plasma. These cells may, therefore, be exposed to potentially toxic concentrations. High concentrations of chemicals may also be attained in the renal medulla, although this tissue only receives about 10% of total renal blood flow; medullary cells will be exposed to high concentrations of chemicals in the tubular urine as they pass through the loop of Henle and the medullary collecting duct. The countercurrent effect in the medulla may also act to concentrate chemicals. Due to normal physiological functions, certain areas of the kidney may, therefore, be exposed to excessively high concentrations of potentially toxic compounds resulting in nephrotoxicity.[9,10] These aspects are discussed in more detail in Volume II, Chapter 1.

A. Binding to a Specific Macromolecule: Melanin

Binding to specific macromolecules either intracellularly or to plasma proteins[2] may profoundly affect the body distribution of xenobiotics. Many drugs including chloroquine, phenothiazine derivatives, and aminoglycoside antibiotics bind avidly to melanin.[5] Melanin is found in the eye, the inner ear, the skin, nuclei of the brain stem, and some other tissues. Following long-term administration, these drugs accumulate in melanin-containing tissues, often resulting in toxicity. This has been best documented for the antimalarial chloroquine, which on prolonged high-dose therapy, may damage both the eye and the inner ear. The chloroquine-induced retinopathy has been related to very high concentrations in the pigmented eye and these high levels persist long after other tissues are depleted. A similar accumulation and retention of chloroquine with the melanin of the inner ear has also been observed. A high retention was found 1 year after a single administration of radiolabeled chloroquine.[6] Following administration of kanamycin, the stria vascularis, the melanin-containing region in the cochlea, was damaged to a greater extent in pigmented guinea pigs than albinos, supporting the involvement of melanin in kanamycin-induced ototoxicity.[6,11]

III. ROLE OF METABOLIC ACTIVATION IN TARGET ORGAN TOXICITY

Toxicity of a chemical may be due to the parent compound, a chemically reactive metabolite or a chemically stable metabolite. Many types of toxicity such as carcinogenesis, mutagenesis, teratogenesis, cell necrosis, and hypersensitivity reactions may be mediated by reactive metabolites.[12,13] Such toxicities often result following the metabolism of xenobiotics to reactive electrophiles which combine covalently with critical cellular macromolecules such as DNA, RNA, or proteins.[12-14]

When toxicity is mediated by a metabolite, consideration must be given to whether (1) the formation of the toxic metabolites occurs in the liver followed by transport to the target organs, (2) metabolic activation occurs in the target organ(s), or (3) the process requires a combination of both. These concepts have been recently reviewed[15-17] and are also discussed in Chapter 3. Thus, the metabolic activation of a compound in a particular organ may be a critical factor in determining its susceptibility to toxicity.

A. Toxicity Mediated by the Parent Compound

The effects of metabolism are self-evident when the parent compound is itself toxic (Figure 2). Any change in the rate of metabolism of the compound, either in the liver or in any extrahepatic tissue, will alter its effective concentration in the target organ(s) and cause a corresponding effect on toxicity.[15,17] It may also be readily appreciated from Figure 2 that any other factors that serve to increase or decrease the concentration of the toxic compound in the target tissue will have a correspondingly predictable effect on toxicity, provided, of course, that the toxicity is a dose-related phenomenon. Thus, induction of drug-metabolizing enzymes with inducing agents such as phenobarbitone or 3-methylcholanthrene results in increased metabolism of the active parent compound and therefore in decreased amounts available for pharmacological or toxicological activity.

B. Toxicity Mediated by Reactive Metabolites

The situation is more complex when toxicity is due to a metabolite. If the metabolite formed is chemically stable, then it may be formed in one organ and transported by the systemic circulation, as illustrated in Figure 3.[15,17-20] In contrast, some metabolites may be chemically reactive, i.e., their half-lives are very short.[20] Such reactive metabolites would most likely react either intracellularly, within the cell in which they were formed, or if they escaped from the cells, with constituents or blood. The extrahepatic toxicity of these metabolites will most likely be mediated by reactive intermediates generated *in situ* within their

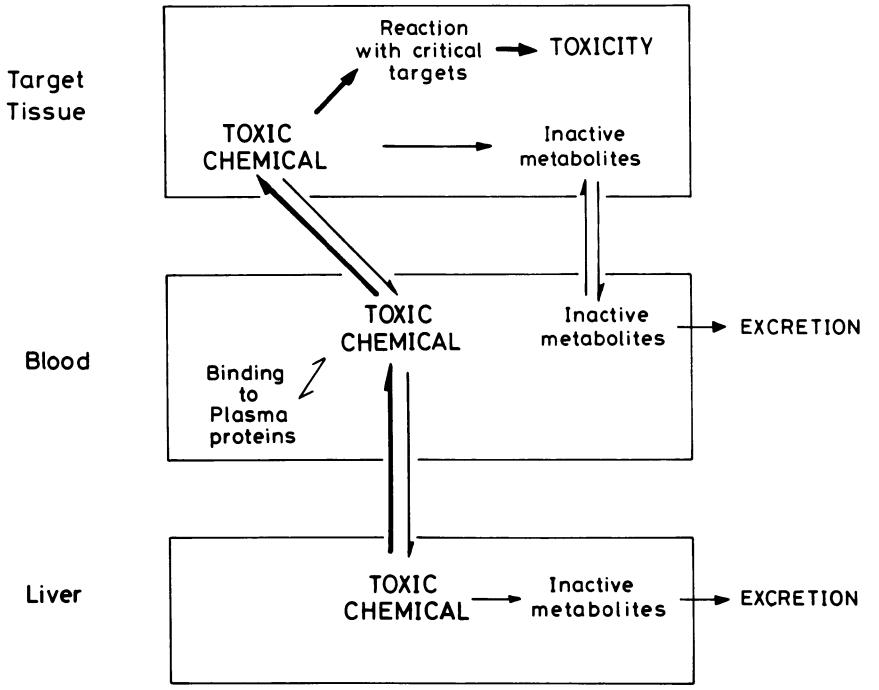

FIGURE 2. Toxicity mediated by the parent chemical. Any factor, such as plama protein binding, which affects the concentration of the toxic chemical available to interact in the target organ, will affect the toxicity of the chemical.

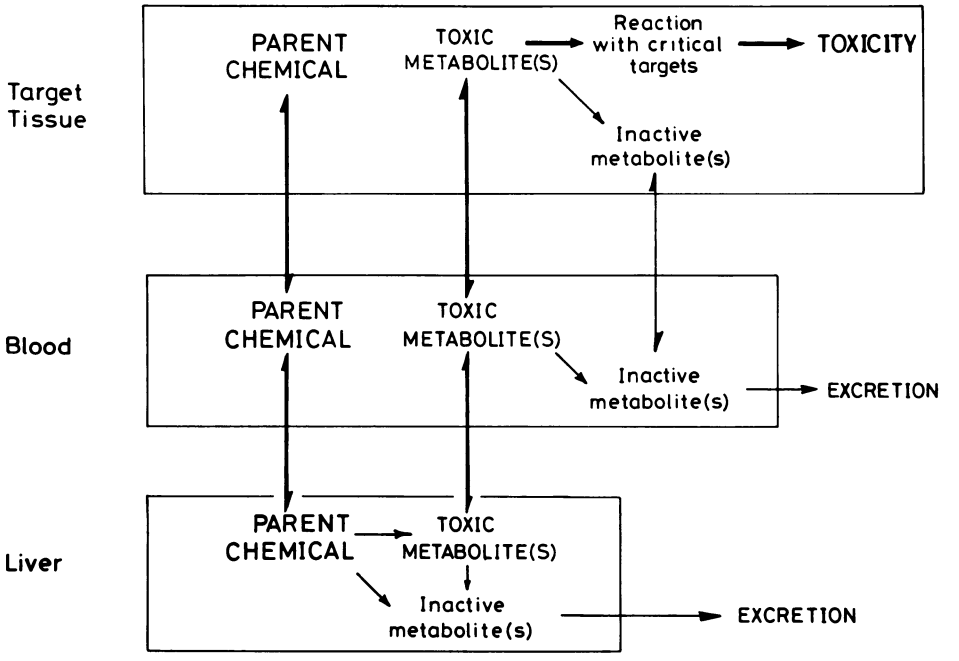

FIGURE 3. Toxicity mediated by a toxic metabolite generated in the liver and transported to the target organ. The toxic metabolite is formed in the liver and is sufficiently stable that it may then be transported via the circulation to the target organ of toxicity.

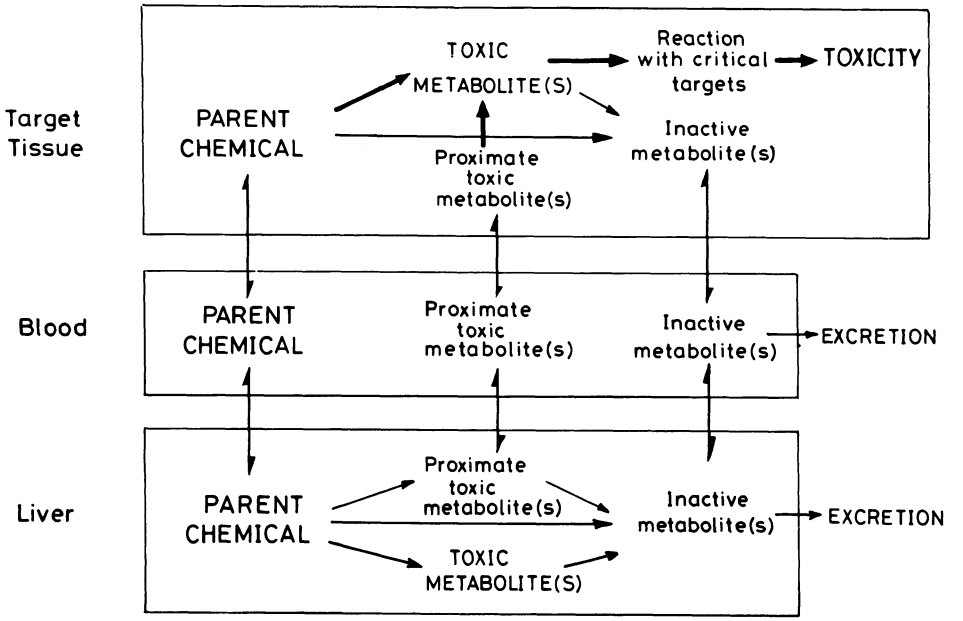

FIGURE 4. Toxicity mediated by reactive metabolites formed in the target organ either from the parent chemical or from a proximate toxic metabolite. If the toxic metabolite is chemically very reactive, it may have to be generated *in situ* in the target organ in order to exert toxicity. Depending on the metabolic capability of the tissue, the metabolic activation from the parent chemical may be completely carried out in the target organ. Alternatively, part of the metabolic activation may be carried out in other tissues, such as the liver, but the ultimate toxic metabolites are formed *in situ* in the target organ.

target organs,[15,17,20] as illustrated in Figure 4. This latter case is particularly well exemplified by the work of Boyd[21] and colleagues with 4-ipomeanol which causes specific damage to the Clara cells in a number of species (Volume I, Chapter 5 and Volume II, Chapter 3). In order to establish whether a compound is activated by either one or more of the previously discussed mechanisms, it is necessary to consider other factors, including the tissue distribution of the xenobiotic metabolizing enzymes, as illustrated in the following section.

C. Tissue Distribution of Xenobiotic Metabolizing Enzymes

While it is generally recognized that the liver is the major site of most xenobiotic metabolism, a significant amount of extrahepatic metabolism also takes place.[22] The ability of extrahepatic tissues to metabolize xenobiotics has recently received more attention. Although quantitatively the contribution of a particular extrahepatic tissue may represent only a small percentage of the overall metabolism, it may be of particular toxicological significance. The enzymes responsible for the activation of xenobiotics will often be the phase I oxidative enzymes but may in some cases be the phase II conjugating enzymes, such as the activation of *N*-hydroxyacetylaminofluorene following sulfate conjugation.[14,23] The tissue distribution of both phase I and II drug metabolizing enzymes and the relative availabilities of their various co-factors are, therefore, vital factors in determining the relative susceptibilities of different tissues to toxic chemicals (see Chapter 3).

The wide tissue distribution of some of these xenobiotic metabolizing enzymes[22,24] may be illustrated by the large number of tissues capable of metabolizing benzo(*a*)pyrene, a ubiquitous environmental carcinogen and mutagen (Table 4). This particular reaction has been extensively studied because benzo(*a*)pyrene requires metabolic activation before exerting its carcinogenic and mutagenic effects and also because some of the major metabolites (i.e., 3- and 9-hydroxybenzo(*a*)pyrene) may be measured by an extremely sensitive fluo-

Table 4
TISSUE DISTRIBUTION OF BENZO (*a*)PYRENE 3-MONOOXYGENASE

Liver	Testes
GI tract	Thyroid
Lung	Adrenal
Trachea	Spleen
Skin	Thymus
Kidney	Lymph nodes
Placenta	Bone marrow
Muscle	Lymphocytes
Aorta	Monocytes
Mammary gland	Leukocytes
Salivary gland	Ovary
Prostate	Kidney
Pancreas	Eye

rometric assay. This enzyme activity is known as benzo(*a*)pyrene 3-monooxygenase, benzo(*a*)pyrene hydroxylase, aryl hydrocarbon hydroxylase, or AHH (E.C. 1.14.14.2). A large amount of data has been accumulated over the last few years strongly implicating the formation of "bay region" diol epoxides as the ultimate carcinogens of polycyclic aromatic hydrocarbons (PAH).[25] It is readily apparent that a large number of tissues may, under appropriate conditions, metabolize foreign chemicals[22] (Table 4 and Chapter 3). It should be stressed that although such metabolism may be demonstrated in vitro, it does not mean that these tissues will necessarily metabolize these compounds in vivo; it will depend on many factors such as blood flow, the nature of the substrate and its availability, and a supply of the necessary co-factors.

Important differences in the distribution of the drug-metabolizing enzymes in any particular tissue may also predispose particular cell types in a tissue to toxicity. Even in the liver, considered a relatively homogeneous tissue, large differences in the tissue distribution of cytochrome P-450 and glutathione have been observed using quantitative cytochemistry.[26,27] Therefore, it is not surprising that in heterogeneous tissues such as the lung, with more than 40 cell types present,[28] one observes an increased concentration of drug-metabolizing enzymes such as cytochrome P-450 in certain cell types.[21,29,30] In addition to quantitative differences in the distribution of these enzymes, important differences in isoenzymes, with different substrate specificities, may be observed which may also contribute to susceptibility to target organ toxicity.[30]

Thus the Clara (nonciliated bronchiolar epithelial) cells, which constitute only 1% of the cells of the lung, contain the majority of the pulmonary cytochrome P-450.[21,29] This high intracellular enzyme concentration predisposes the Clara cells to damage from a number of agents including 4-ipomeanol, 3-methylfuran, and carbon tetrachloride.[21,30] Similarly, a number of studies suggest that the highest activities of microsomal cytochrome P-450 mixed function oxidases in the kidney are found in the S_3 cells of the proximal tubules.[31,32] The highest concentration of S_3 cells is found in the pars recta, that portion of the proximal tubule most susceptible to toxic damage.

D. Balance of Activating and Deactivating Enzymes

It is vitally important when considering the generation of reactive metabolites in any tissue, either hepatic or extrahepatic, that due attention is given to both the activating and deactivating enzymes. It is the balance of the activities of these enzymes and the availability of their respective co-factors which will ultimately determine both quantitatively and qual-

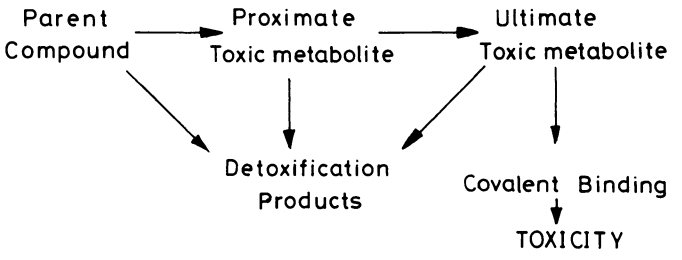

FIGURE 5. Multistep metabolic activation to generate ultimate toxic metabolite.

Table 5
CHEMICALS REQUIRING MULTISTEP METABOLIC ACTIVATION TO GENERATE THEIR ULTIMATE TOXIC METABOLITES

Benzene	Bromobenzene
Naphthalene	7,12-Dimethylbenz(*a*)anthracene
Benzo(*a*)pyrene	Hexachlorobutadiene
Benz(*a*)anthracene	2-Naphthylamine
3-Methylcholanthrene	4-Aminobiphenyl
Acetylaminofluorene	Isoniazid
Chlorobiphenyl	

itatively how much of a reactive metabolite(s) is generated in a particular tissue and, therefore, is subsequently available for interaction with critical cellular targets ultimately leading to toxicity. This has been well illustrated in studies with the carcinogenic PAHs, benzo(*a*)pyrene[33] and 7,12-dimethylbenz(*a*)anthracene,[34] when the hydrocarbon-deoxyribonucleoside adducts formed following microsomal activation of the carcinogen are markedly different to those formed either in vivo or in intact cells. This is primarily due to the fact that with microsomes there is a disruption of the normal cellular integrity, resulting in the loss of the normal balance of activating and deactivating enzymes and the formation of reactive metabolites not normally formed in vivo. Such problems would appear to be of more importance with compounds which require a multistep metabolic activation such as the PAHs, rather than with those requiring a single step activation.

E. Formation of Proximate Toxic Metabolites in the Liver and Ultimate Reactive Metabolites in the Target Tissue

Several years ago James and Elizabeth Miller,[14,35] at the McArdle Laboratory in Wisconsin, proposed the importance of proximate and ultimate carcinogens in their unifying concept of the role of metabolism in the generation of ultimate reactive electrophiles in chemical carcinogenesis (Figure 5). It is realized that several toxic chemicals, in addition to many carcinogens, require multistep metabolic activation before generating their ultimate toxic metabolites (Table 5). It is, therefore, conceivable that the initial activation to a stable proximate toxic metabolite may take place in the liver or any other tissue and this metabolite could be transported to the target organ where it is metabolized to the ultimate toxic metabolite (Figure 4). The revelation that many chemicals require such multistep activation suggests that this mechanism may be far more important than previously realized. Different enzymes may also be involved in different stages of the activation and this may be of importance in target organ toxicity. For example, a target tissue may not be able to metabolize the parent chemical to its proximate toxic metabolite but may be able to convert this to the ultimate reactive species. Much further work will be needed to verify these suggestions. Indirect support comes from recent findings that several extrahepatic tissues, while low in the activities

of cytochrome P-450 dependent mixed function oxidases, may activate xenobiotics to reactive metabolites by a variety of different enzymes and mechanisms including prostaglandin endoperoxide synthetase,[36] peroxidase,[37] xanthine oxidase,[38] tyrosinase,[39] and even by-products derived during lipid peroxidation.[40]

IV. ROLE OF THE SPECIFIC BIOCHEMISTRY OR PHYSIOLOGY OF THE TISSUE IN DETERMINING TARGET ORGAN TOXICITY

Major differences in the basic biochemistry or physiology of different tissues and cells is obviously of prime importance in determining the inherent susceptibility of different organs to toxicity. The presence of vital metabolic pathways and specific receptors in certain tissues may predispose these tissues to the toxicity of certain chemicals (Chapter 6). Undoubtedly this is one of the least documented areas of target organ toxicity because our basic knowledge of the mechanisms of toxicity of the majority of chemicals is very poor.[41] Much more is known about the factors governing both the disposition of toxic chemicals and their subsequent metabolic activation, if required, than about their interaction with cellular targets and the biochemical pathways then involved before clinical signs of toxicity are manifested.[41]

Although the factors governing the inherent susceptibility of a particular organ to toxicity are less well understood it may be useful to subdivide them into those related either to (A) organ function or (B) biochemistry of the tissue.

A. Organ Function

The normal physiology and function of the tissue may predispose it to toxicity. Thus the nephrotoxicity of many chemicals is related to their concentration in the kidney due to its normal physiological function[10] (see Volume II, Chapter 1). Similarly, the respiratory tract will be exposed to high concentrations of inhaled pollutants (Volume II, Chapter 3).

The normal function of a tissue may be impaired in certain diseased states such as liver or kidney disease. This may lead to impaired metabolism and/or excretion of compounds followed by an accumulation of toxic concentrations of the chemicals[42] and may be one of the reasons for the high incidence of adverse drug reactions observed in patients with impaired renal function. In addition to effects on the parent compound, impaired renal excretion of metabolites may also be observed leading to increased concentrations of metabolites.[42,43] The metabolites may be toxicologically active per se or they may interfere with the metabolism and/or distribution of the parent compound. This area and its clinical implications has been recently reviewed.[42,43]

Tissues with a high proportion of dividing cells such as bone marrow, GI tract, and hair follicles are more sensitive to the toxic effects of many anticancer drugs than tissues with a lower proportion of such cells.[44] Thus, treatment with anticancer drugs such as the antimetabolites or alkylating agents often results in damage to the bone marrow. Since the marrow contains stem cells, i.e., the immature precursors of the red cells, the platelets, and the white cells, this damage may result in pancytopenia, a decrease in the numbers of the three major groups of formed elements, which are circulating. If the damage is very severe the marrow may no longer proliferate, a condition known as aplastic anemia. The damage to the platelets can lead to thrombocytopenia and bleeding while damage to the leukocytes leads to an increased risk of infection in patients treated with many anticancer drugs.

A particular problem associated with the inhibition of rapidly dividing cells occurs with the fetus. Drugs which inhibit rapidly dividing fetal cells may produce developmental abnormalities and some anticancer drugs have been shown to be teratogenic.[45]

B. Organ-Specific Biochemistry

The differentiated functions of different cells endow them with specialized biochemical

pathways and enzymes. Organ-specific toxicity may result from the interaction of chemicals with enzymes or other macromolecules connected with these specialized functions. In Table 6, a number of examples are given of biochemical differences, which predispose particular tissues or organs to toxicity. These examples do not include differences due either to the presence of specific uptake mechanisms or metabolic activation by the mixed function oxidase system which have already been discussed. Our current understanding of the role of tissue-specific biochemistry in target organ toxicity is relatively poor but will increase as our understanding of the mechanism of toxicity of chemicals improves (Chapter 6).

V. FACTORS AFFECTING TARGET ORGAN TOXICITY

Numerous factors are known to affect the toxicity of chemicals.[2,54,60] In a short review one cannot consider many of these factors in detail; however, it is obvious that in many cases such factors may also affect the organ-specific toxicity of a chemical. Such variables include age, route of administration, diet, species (Chapter 5), and environment. A number of examples are given in Table 7.

VI. SUMMARY

Some basic principles of organ-specific toxicity have been discussed. For convenience these were considered together with a number of examples in three distinct, but interrelated, areas: (1) the pharmacokinetics or toxicokinetics of the compound which determines the tissue distribution of the chemical, (2) the metabolism of the compound to either toxic or inert metabolites, and (3) the individual biochemistry of different organs and their response to chemically induced damage.

Induction of toxicity in a specific organ in one species does not necessarily mean that the same organ will be affected in another species.[65] Only by understanding more about the mechanisms of toxicity and target organ toxicity will it be possible to extrapolate scientifically the meaning of toxicity data obtained in animals for man.

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Table 6
ORGAN-SPECIFIC BIOCHEMICAL DIFFERENCES PREDISPOSING PARTICULAR ORGANS TO TOXICITY

Biochemical difference	Examples	Ref.
DNA repair	Individuals with defective DNA repair, e.g., xeroderma pigmentosum, are very susceptible to skin cancer; in animals, differences in DNA repair correlate with organ-specific carcinogenicity of certain nitrosamines and nitrosamides	46, 47, and Vol. 2, Chapter 10
Neurotoxic esterase	Toxicity of certain organophosphorous esters related to their ability to combine with a specific neurotoxic esterase	48, 49
Ah locus	There are large differences in the susceptibility of different strains of mice to drug toxicity, chemical carcinogenesis, and teratogenesis, much of which is due to the presence, absence, or defects in a cytosolic receptor controlled by the Ah locus; this is responsible for the activities of a battery of different enzymes including monooxygenase activities; alterations in the receptor have been related to differing toxicities to mice of either 2,3,7,8-tetrachlorodibenz-*p*-dioxin (TCDD) or the induction of cataracts by paracetamol or naphthalene	50—52
Glucose 6-phosphate dehydrogenase deficiency	Individuals with a deficiency of this enzyme in their erythrocytes are susceptible to drug-induced hemolysis for a variety of compounds including phenylhydrazine, vitamin K, and fava beans	2, 53
Galactose metabolism	Cataracts commonly occur in congenital galactosemia associated with a deficiency of galactose-1-phosphate-uridyl transferase; rats fed a diet high in galactose develop cataracts due to reduction of galactose by aldose reductase in the lens, to galactitol; this sugar alcohol does not readily permeate membranes so the lens is subject to osmotic stress	54, 55
Dihydrodiol dehydrogenase	Naphthalene induces experimental cataracts in animals, particularly rabbits; it is metabolized in the liver to 1,2-dihydro-1,2-dihydroxynaphthalene and then conjugated with UDP-glucuronic acid; in the lens, the dihydrodiol is readily metabolized by the lens dihydrodiol dehydrogenase to 1,2-dihydroxynaphthalene; this immediately autooxidizes to the toxic 1,2-naphthoquinone	54, 56
Tyrosinase	Cells, such as melanoma cells, may be selectively destroyed by compounds activated by tyrosinase; thus, γ-L-glutaminyl-4-hydroxybenzene is metabolized in melanomas to a cytotoxic quinone	39
C-S or β-lyase	This enzyme cleaves cysteine but not glutathione of *N*-acetyl cysteine conjugates to a reactive product; high concentration of this enzyme in the kidney may be involved in the nephrotoxicity of *S*-(1,2-dichlorovinyl) cysteine and hexachloro-1-butadiene	57
Alcohol dehydrogenase	Highest concentrations in periportal area of liver results in periportal necrosis following activation of allyl alcohol to acrolein	Chapter 8
Amine oxidase	Allylamine is toxic to the cardiovascular system, most probably due to acrolein which is formed by the action of benzylamine oxidase; the activity of this enzyme is much higher in cardiovascular tissue than liver, brain, or plasma	58

Table 6 (continued)
ORGAN-SPECIFIC BIOCHEMICAL DIFFERENCES PREDISPOSING PARTICULAR ORGANS TO TOXICITY

Biochemical difference	Examples	Ref.
Oxidative defenses	Adriamycin causes a life-threatening cardiotoxicity possibly due to a decreased ability of cardiac tissue to cope with oxidative stress because of low levels of catalase and superoxide dismutase; adriamycin also decreased cardiac glutathione peroxidase	59

Table 7
FACTORS AFFECTING TARGET ORGAN TOXICITY

		Ref.
Age	CNS of children affected by organic Pb because blood brain barrier not fully developed; in adults the peripheral nervous system affected	54
	Calcium disodium ethylene diaminetetracetic acid causes liver necrosis in very young rats and severe kidney lesions in 12-week-old animals	61
Developmental stage	Teratogenic agents act selectively on developing cells	45
Route of administration and duration of exposure	Benzene on inhalation of high concentrations for a short time depress the CNS whereas chronic exposure to low levels affects the hemopoietic system	
Diet	In rats fed a normal diet, paraquat causes lung damage, but in selenium deficient animals, liver damage is observed	62
	Toxicity due to cassava is only observed in individuals with a dietary deficiency	63
	Oral administration of dimethylnitrosamine induces liver tumors to rats on a normal diet; it causes kidney tumors in animals fed a low-protein diet	64
Species	Dithizone and ethambutol cause a retinopathy in dogs and rabbits, which possess a tapetum, but not in rats and monkeys	54 and Vol. 2, Chapter 6
	Dihydrostreptomycin causes cochlear toxicity in man and patas monkey, but not in macaque monkey	
Environment	Various factors in environment, including enzyme inducing agents or inhibitors, may alter the metabolism of a chemical and thereby change its target organ of toxicity	
Chemical structure	Small variations in chemical structure can profoundly influence the target organ of toxicity; paraquat, but not structurally related diquat, damages the lung	3 and Vol. 2, Chapter 3

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