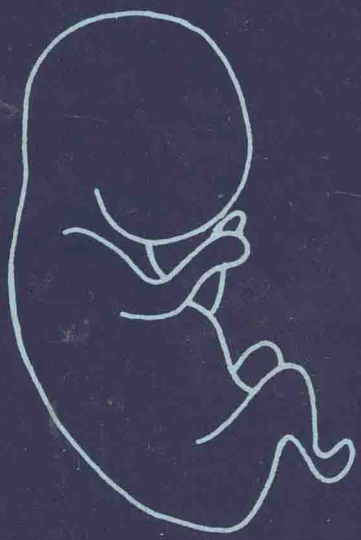
Toxicology and the newborn

S. Kacew and M.J. Reasor, editors



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TOXICOLOGY AND THE NEWBORN

edited by

Sam Kacew and Mark J. Reasor

with a Foreword by

Gabriel L. Plaa

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Foreword

The potentially adverse effect of chemical substances on the fetus and the newborn is of major concern in today's society. In the last 30 or so years, a number of drugs have been shown to be particularly toxic in immature or developing organisms. The thalidomide tragedy of the 1960s emphasized the marked susceptibility of the human fetus to exposure to certain types of chemical agents. Exposure of the fetus to diethylstilbestrol (DES) and the subsequent appearance of neoplasms in female children of women given DES is another example. The field of teratology has expanded tremendously in the last 20 years, with the result that much knowledge has been acquired of the development of the fetus. This interest in the developing fetus has followed its natural course. In the 1980s we see a newly emerging field, developmental toxicology, which follows development well beyond the fetus, through maturity, and even into senescence.

Newborn animals generally are more susceptible than adults of the same species, although some exceptions do exist. Newborn rats have been found to be 0.1 to 20 times more susceptible than adult rats to the lethal effects of drugs. The newborn infant also can be particularly susceptible to chemical agents. Many of these exaggerated responses, particularly with drugs, can be explained by altered pharmacokinetics (absorption, distribution, biotransformation, elimination) in the newborn. Chloramphenicol toxicity in the newborn is characterized by cardiovascular collapse, coma and cyanosis (grey syndrome). The neonate cannot glucuronidate this antibiotic adequately, resulting in high and prolonged plasma concentrations of chloramphenicol. Now that the mechanism is known (impaired biotransformation), this adverse reaction can be avoided by adjustment of the dosages of chloramphenicol administered to infants.

Membrane permeability can affect drug response markedly. The blood-brain barrier is not developed fully in the human neonate, and this characteristic is the explanation for the appearance of neonatal kernicterus sometimes observed following sulfonamide therapy in the newborn infant. Normally unconjugated bilirubin is bound highly to plasma protein; sulfonamides can displace the bilirubin from the

binding sites, and the unbound bilirubin passes through the immature blood-brain barrier into the central nervous system. This adverse reaction is now avoided by not administering drugs that can displace bilirubin from plasma proteins.

Drugs are not the only chemicals that can affect the newborn. During the last decade, society has become keenly aware of the numerous chemical substances present in the environment. Chemical contamination of waterways, air or soil is of major concern. A number of these substances are highly persistent. Furthermore, some may enter into the food chain because they can bioaccumulate. The potential impact of these agents on the newborn is not well known, and society rightfully is demanding that toxicologists address the issue. The questions are clear: What are the toxic manifestations in the newborn? Do they differ from those observed in mature organisms? Is the newborn at higher risk than the adult? What biological mechanisms are involved? Can the effects be predicted? What are the short- and long-term consequences? How can the effects be prevented?

The modern toxicologist must be informed about these problems. The present monograph is a welcome addition to the toxicology literature. A number of specific chemical substances are treated in detail. Furthermore, experimental approaches and their interpretation are described. This monograph will surely enhance our knowledge of toxicology and the newborn.

Gabriel L. Plaa

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Chapter 1

Development of Detoxication Mechanisms in the Neonate

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CONTENTS

I. INTRODUCTION

It is well known that the foetus and neonate are particularly susceptible to the toxic effects of drugs and other chemical substances. The treatment of infants with the newly discovered antibiotic chloramphenicol in the 1946–1947 European epidemic of infantile diarrhoea is believed to have contributed largely to the high mortality of that tragic catastrophe (Lischner et al., 1961) and confirmed the widely held opinion that infants were especially vulnerable to the toxic side-effects of drugs. Nearly 20 years later, this view was reaffirmed by the thalidomide disaster, in which thousands of babies were born deformed by foetal malformations induced as the result of the mother taking the tranquillizing drug thalidomide, which had been especially noted for its freedom from toxic side-effects in adults (Lenz, 1965). More recently, it was found that the synthetic oestrogenic drug diethylstilbestrol, given in high dosage to pregnant women to maintain their pregnancies in threatened spontaneous abortion, has been the cause of adenocarcinoma of the vagina occurring in their female offspring on reaching sexual maturity (Herbst et al.,1975). The antiseptic hexachlorophene, widely used in the bathing of young babies, had to be restricted in its use since it was found to be associated with the occurrence of convulsions and brain damage (Kimbrough, 1973); and infants exposed to polychlorinated biphenyls present as contaminants in their mother's breast milk exhibited muscular weakness and apathy (Kuwabara et al., 1979). Infant mortality, teratogenesis, transplacental carcinogenesis and infant ill-health may thus be the occasional tragic results of drug administration to neonates or the results of incautious taking of drugs, or exposure to toxic environmental chemicals, during pregnancy, the puerperium or the postnatal period of lactation. These clinical aspects of developmental pharmacology and toxicology have recently been reviewed in detail (Aranda and Stern, 1983).

Research during the past few decades has elucidated some of the reasons why the foetus and neonate are particularly vulnerable to the toxic effects of drugs and environmental chemicals. Accumulated scientific evidence has shown that the deactivation and detoxication of drugs and other chemicals are undeveloped in the foetus, and that drugs may cross the placenta from the maternal blood into the foetus, effecting damage that may result in the death or maldevelopment of the unborn infant or give rise to latent malignancy. Furthermore, it has been shown that the neonate has only limited detoxication ability, and therefore little natural protection against the toxic effects of the drugs and chemicals, which may reach the child not only by direct administration but also indirectly through secretion in the mother's milk.

II. MAMMALIAN METABOLISM OF XENOBIOTICS

When environmental chemicals, or xenobiotics, are ingested by the mammalian organism they may be rapidly excreted, if they are polar, non-lipophilic materials. If they are lipophilic, they generally undergo metabolism into more polar, water-soluble

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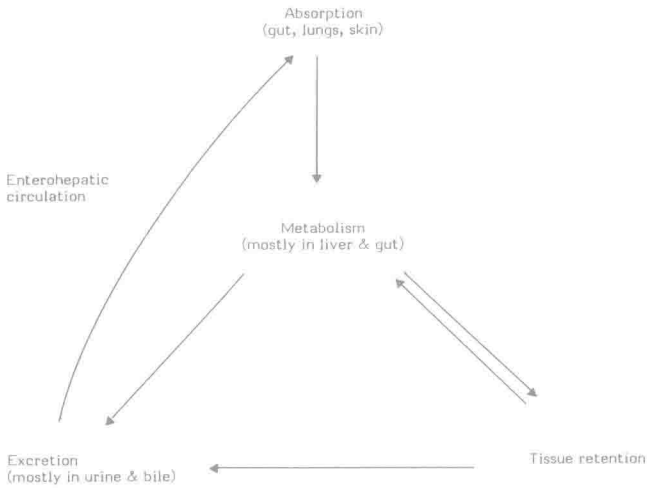


Figure 1. Disposition of xenobiotic chemicals in mammals.

compounds, which are then excreted more readily. The original chemical, or any of its metabolities, may be distributed into the tissues or excreted from the body (see Fig. 1). In this way lipophilic chemicals are made more polar and are eventually eliminated in the urine or bile. Many compounds which are excreted into the bile may undergo further metabolism in the gastrointestinal tract, be absorbed, then excreted once again in either the urine or bile, a process known as enterohepatic circulation.

However, increasing numbers of synthetic chemicals, especially halogenated compounds, are metabolised with difficulty by mammals, and only very slowly by micro-organisms, despite their being highly lipophilic. These chemicals, for example, hexachlorobenzene, hexabromobiphenyl and tetrachlorodibenzodioxin (TCDD), are thus characterized by their environmental persistence, their very long biological half-lives, and their progressive accumulation in the fatty tissues of animals exposed to these chemicals.

1. Absorption, distribution and excretion

The absorption and excretion of xenobiotic chemicals involves transfer of these compounds across the various barrier membranes of the body, such as the gastrointestinal epithelium, renal tubular epithelium, hepatic parenchyma, the skin and placental membranes. This transfer of substances across biological membranes may occur by four different mechanisms, namely: simple diffusion, filtration through aqueous pores in the lipoprotein membrane, active transport by carrier mechanisms (usually limited to nutrients), and pinocytosis. In the transfer of xenobiotics by simple diffusion only lipophilic non-ionized molecules readily pass through the membranes, so that non-electrolytes are transferred according to their lipid

solubility and electrolytes according to their degree of ionization and the lipid-solubility of the non-ionized molecules.

(a) Absorption

Absorption of xenobiotics may occur through all the body's external surfaces, including the mouth, the gastrointestinal tract, the lungs and skin, and mostly involves only simple diffusion.

Substances absorbed from the mouth are not exposed to gastrointestinal secretions, microflora or intestinal drug-metabolising enzymes, and are not so rapidly metabolised, as they are not transported directly to the liver, where most drug metabolism takes place. Absorption from the stomach depends on the pH of the gastric contents, and the dissociation constant (pK) and lipid solubility of the environmental chemical; low gastric acidity, as occurs in neonates, also predisposes to microbial overgrowth, which may lead to reductive metabolism of xenobiotics and reduction of ingested nitrate to nitrite, with the formation of nitrosamines in situ. Absorption from the intestines occurs readily for non-ionized, lipophilic chemicals and for weak acids and bases, but highly ionized compounds are absorbed only slowly.

Absorption through the skin depends on age, as the main barrier to the absorption of environmental chemicals is the keratinized outer layer, the stratum corneum, which tends to thicken with age; absorption is much greater through abraded skin and human skin is less permeable than that of most fur-covered laboratory animals. Absorption from the lungs occurs readily for lipid-soluble gases, and for lipophilic compounds with high vapour pressures, e.g., *p*-dichlorobenzene.

(b) Distribution

Once absorbed, xenobiotic chemicals may be distributed to other tissues, first to the liver when absorbed from the gastrointestinal tract, and to fat depots if highly lipophilic. The blood–brain and blood–cerebrospinal barriers are typical lipoprotein membranes and are permeable to non-ionized or ionized lipophilic molecules. The placenta similarly is permeable to lipophilic molecules, but polar molecules are transferred with difficulty.

Certain chemicals have affinity for specific tissues, e.g., tetracycline antibiotics have an affinity for bones and teeth; the herbicide, paraquat, and the toxin of mouldy sweet potatoes, 4-ipomeanol, become concentrated in lung tissue; alkylmercury and alkyllead compounds are found in high concentrations in the brain; the toxic metal, cadmium, accumulates in the kidney, and arsenic, selenium and other metals accumulate in the hair (Parke, 1982).

(c) Excretion

Excretion of xenobiotics by the kidney comprises three distinct processes, namely: glomerular filtration, passive tubular transfer (of lipophilic non-ionized molecules), and active tubular transport (secretion of highly ionized acids and bases, e.g., glucuronides, sulphate esters and tetra-alkylammonium compounds). Binding of

compounds to plasma proteins markedly impairs their renal excretion, but leads to their excretion in the bile; the rates of biliary excretion of a number of azo dyes have been shown to be functions of their binding to plasma and liver proteins (Parke, 1982).

The biliary excretion of xenobiotic chemicals varies with species and is dependent on molecular size, being negligible for compounds of a molecular weight of less than 300, e.g., 4-hydroxybiphenyl glucuronide (molecular weight, 346) is readily excreted in the bile of rats, but 4-aminophenyl glucuronide (molecular weight, 285) is not. As the molecular weight of the excretion product increases above a value of around 300, biliary excretion progressively increases, and urinary excretion correspondingly decreases. Chemicals are excreted in the bile mostly as conjugates, which may be hydrolysed by enzymes (β-glucuronidases, sulphatases, etc.) present in the bile, or subsequently by enzymes of the intestinal microflora. Biliary excreted conjugates of xenobiotics, being polar, are not reabsorbed from the gastrointestinal tract, but their hydrolysis products, if non-polar, may be reabsorbed, transported to the liver, re-conjugated, and excreted again in the bile, a process known as enterohepatic circulation.

Other routes of excretion are relatively minor, and include the secretion of bases into the stomach, the excretion of acids into the pancreatic juice and into the lumen of the intestine, the elimination of volatile compounds in the expired air, and the secretion of lipophilic materials, such as polychlorinated biphenyls and hexachlorobenzene, into the milk (Bailey et al., 1980).

2. *Metabolism*

Xenobiotic chemicals are metabolised in mammals by mammalian enzymes, which are most active in the liver and gastrointestinal tract, and also by the microbial enzymes of the gastrointestinal microflora. The mammalian enzymes have been classified into (a) phase I reactions (biotransformations) and (b) phase II reactions (conjugations).

These biotransformation and conjugation reactions may lead either to the detoxication of the chemical and the excretion of its metabolites, or to activation of the chemical into reactive intermediates, which subsequently may be detoxicated by interaction with glutathione, or may react with tissue proteins, enzymes, RNA or DNA, to result in toxic reactions (see Fig. 2). The major types of biotransformation reactions are oxidations (oxygenations), reductions, and hydrolyses, catalysed mostly by the mammalian enzymes of the endoplasmic reticulum (microsomal enzymes), and by non-microsomal enzymes of the cell cytosol, mitochondria, or of the blood plasma, and reductions and hydrolyses (but not oxidations) catalysed by enzymes of the microflora present in the gastrointestinal tract (see Table 1). The major types of conjugation reactions are glucuronylations, sulphations, methylations, acetylations, and peptide conjugations with glutathione and various amino acids (see Table 2).

The major sites of metabolism by mammalian enzymes are the liver and gastrointestinal tract, with lesser activity present in the lungs, kidneys and the skin. The xenobiotic-metabolizing enzymes of the intestine are similar to those of the liver,

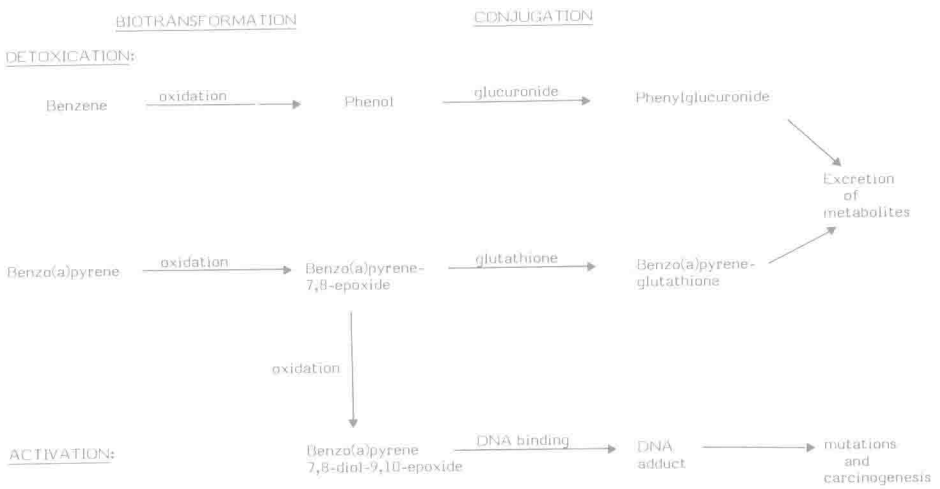


Figure 2. The roles of metabolism in the detoxication and activation of carcinogens and toxic chemicals.

except that in general they give rise to lower rates of metabolism (Chhabra, 1979). The extrahepatic metabolism of xenobiotics has recently been reviewed (Vainio and Hietanen, 1980).

(a) Biotransformation

The phase I reactions of oxidations, reduction and hydrolysis are catalysed by enzymes of the endoplasmic reticulum (microsomes) and of the cell cytosol. The microsomal mixed-function oxidases of the endoplasmic reticulum of liver and other tissues catalyse numerous oxidations of xenobiotics, including aromatic and aliphatic hydroxylation, epoxidation, *N*-oxidation, *S*-oxidation, dealkylation and deamination (see Table 1).

These mixed-function oxidations are mostly catalysed by an enzyme system consisting of the terminal oxygen transferase, cytochrome *P*-450, coupled to cytochrome *P*-450 reductase (a flavoprotein containing both FAD and FMN) and linked to a source of electrons from NADPH (see Fig. 3) (Hodgson, 1979).

Recent studies of this membrane-bound cytochrome *P*-450 system have enabled the enzyme to be solubilized, separated and purified, and have thus revealed that cytochrome *P*-450 and cytochrome *P*-450 reductase both exist in multiple forms, and that lipid, especially phosphatidylcholine, is essential for enzymic activity (Guengerich, 1979). These multiple cytochromes *P*-450 are regarded as isoenzymes, or enzyme variants with overlapping substrate specificities, and have been shown to have identical or very similar active sites (Dus, 1982). Further structural and kinetic studies have shown that, in contrast, the active site of cytochrome(s) *P*-448 is different to that of cytochrome *P*-450 (Dus, 1982; Phillipson et al., 1982). The different tissue distribution (*P*-448 predominates in extrahepatic, placental, foetal, neonatal and neoplastic tissues; *P*-450 predominates in the gut and liver) and the

TABLE I

MAMMALIAN BIOTRANSFORMATION REACTIONS OF XENOBIOTICS

Microsomal Mixed Function Oxidations

Aliphatic oxidation: $R\text{-}CH_3 \longrightarrow R\text{-}CH_2OH$

Aromatic oxidation:

Epoxidation: $R\text{-}CH{=}CH_2 \longrightarrow R\text{-}CH(O)CH_2$

Oxidative deamination: $R\text{-}CH(NH_2)(CH_3) \longrightarrow [R\text{-}C(NH_2)(OH)(CH_3)] \longrightarrow R\text{-}C(=O)\text{-}CH_3 + NH_3$

N-Dealkylation: $R\text{-}N(CH_3)(CH_3) \longrightarrow [R\text{-}N(CH_2OH)(CH_3)] \longrightarrow R\text{-}NH(CH_3) + HCHO$

O-Dealkylation: $R\text{-}O\text{-}CH_3 \longrightarrow R\text{-}OH + HCHO$

S-Dealkylation: $R\text{-}S\text{-}CH_3 \longrightarrow R\text{-}SH + HCHO$

N-Oxidation: $R_3{\geqslant}N \longrightarrow R_3{\geqslant}N{\leftarrow}O$

N-Hydroxylation

Sulphoxidation: $R_2S \longrightarrow R_2S{\leftarrow}O \longrightarrow R_2S{=}O$

Desulphuration: $R_2C{=}S \longrightarrow R_2C{=}O$

Dehalogenation: $R\text{-}CH_2Cl \longrightarrow R\text{-}CH_2OH$

Non-microsomal Oxidations

Monoamine and diamine oxidation: $R\text{-}CH_2NH_2 \xrightarrow{O_2} R\text{-}CH{=}NH \xrightarrow{H_2O} R\text{-}CHO + NH_3$

Alcohol dehydrogenation: $R\text{-}CH_2OH \longrightarrow R\text{-}CHO$

Aldehyde dehydrogenation: $R\text{-}CHO \longrightarrow R\text{-}COOH$

Microsomal Reductions

Nitro reduction: $R\text{-}NO_2 \longrightarrow R\text{-}NO \longrightarrow R\text{-}NHOH \longrightarrow R\text{-}NH_2$

Azo reduction: $RN{=}NR^1 \longrightarrow RNH\text{-}NHR^1 \longrightarrow R\text{-}NH_2 + R^1\text{-}NH_2$

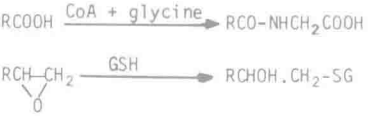
Reductive dehalogenation: $R\text{-}CCl_3 \longrightarrow R\text{-}CHCl_2$

TABLE 1 (continued)

Non-microsomal Reductions	
Aldehyde reduction:	
Hydrolyses	
Ester hydrolysis:	
Amide hydrolysis:	
Epoxide hydration:	

TABLE 2

MAMMALIAN CONJUGATION REACTIONS OF XENOBIOTICS

UDPGA-mediated Glucuronylations	
Ether glucuronide:	
Ester glucuronide:	
N-Glucuronide:	
S-Glucuronide:	
PAPS-mediated Sulphate Ester Formation	
Alkyl or aryl sulphate:	
Sulphamate:	
S-Adenosylmethione-mediated Methylations	
O-Methylation:	
N-Methylation:	
S-Methylation:	
Acetylations	
Peptide Conjugations	

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