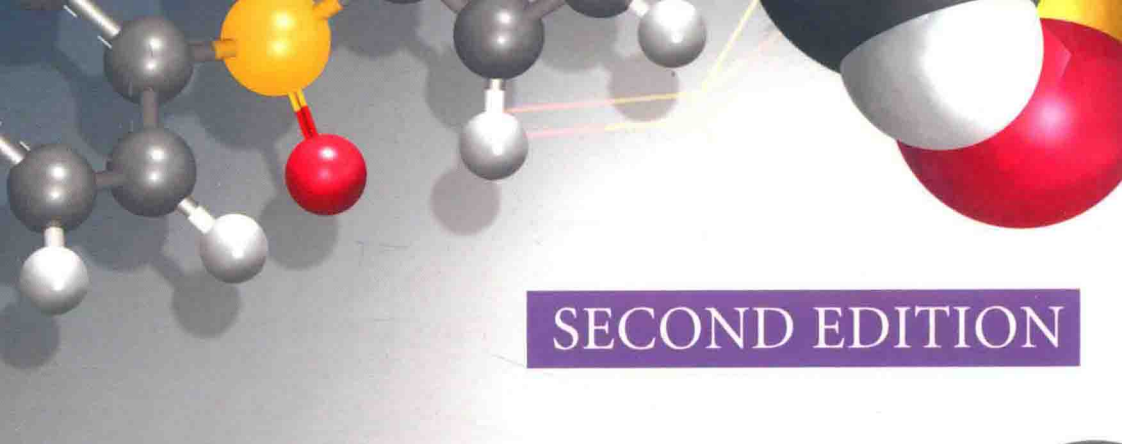
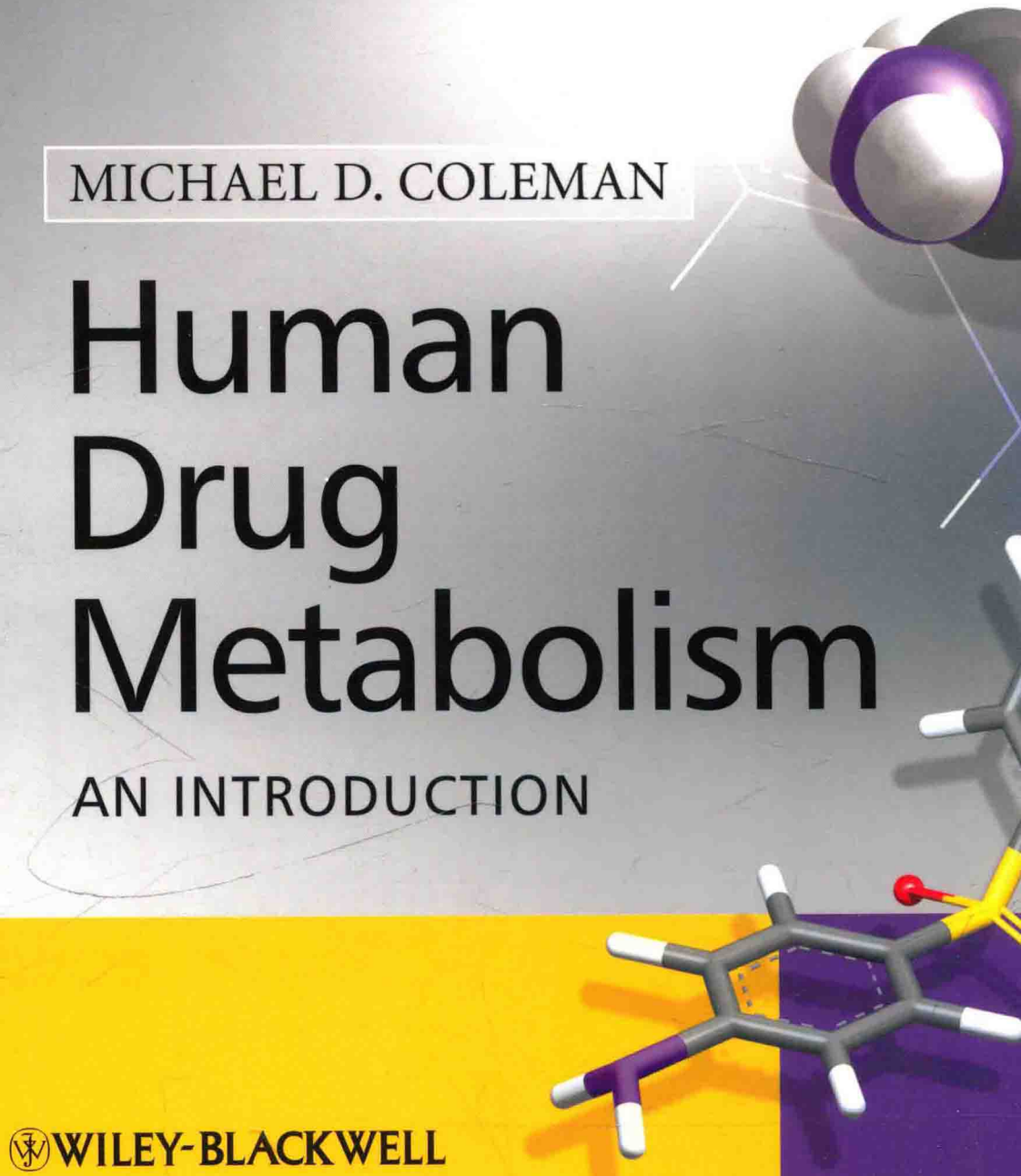


SECOND EDITION

MICHAEL D. COLEMAN

Human Drug Metabolism

AN INTRODUCTION



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Human Drug Metabolism

An Introduction

Second Edition

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First impression – 2010

Human Drug Metabolism

For Mark, Carol and Devon

Preface

In the five years since I wrote the first edition, it is not surprising that advances in the understanding of drug metabolism and toxicity have been rapid and wide-ranging, both experimentally and in patients. *In vitro*, the refinement of many analytical techniques has illuminated how the major drug metabolising enzymes, the cytochrome P450s, accomplish their catalytic activities on a molecular level. This is reflected in the considerable expansion of detail available on how these isoforms manage to combine the apparently contradictory features of selectivity and flexibility. Aside from the role of the CYPs, Chapter 3 now includes more focus on other enzyme systems involved in oxidative drug metabolism, such as the flavin monooxygenases. Since the first edition was written, the interdependence and communication of the various nuclear and cytoplasmic receptor systems that control CYP expression is now better understood and this area has been broadened in Chapter 4. The marked expansion of clinical knowledge of the impact made on co-administered drugs by the selective serotonin reuptake inhibitors has been addressed more fully in Chapter 5. More is also understood about conjugative systems, not only with regard for their ability to accelerate the clearance of drugs, but also their important role in detoxification, which is underlined in the updated Chapter 6.

With respect to the situation *in vivo*, one of the most important issues clinically is the relevance of human polymorphisms in drug metabolism to the 'real world'. Again, the scientific and medical literature has grown considerably in recent years and surprisingly, polymorphisms can be beneficial in several therapeutic areas and in others, the anticipated impacts on drug efficacy and toxicity have not been as severe as expected. Hence, Chapter 7 is now more than twice the length of its predecessor. Regarding Chapter 8, the areas concerning the competing theories on drug hypersensitivity have been expanded and the powerful impact of microarrays in the possible prediction of future hepatotoxins is underlined. Appendix A provides an updated summary of some major methods in drug metabolism pertaining to drug discovery and Appendix B describes advances in our understanding of the metabolism of drugs of abuse, although some are clinically essential. Appendix C remains as an uncompromising guide to those who wish to excel academically and Appendix D is retained and slightly expanded. The further reading section has also been updated and widened in scope with the intention of providing improved insights into the detail of the different areas.

Overall, I have tried to expand the clinical aspects of drug metabolism, whilst retaining some of the scientific detail that informs the clinical drug disposition process. An understanding and appreciation of biotransformation remains crucial in the perpetual struggle

to harness safely the sheer power of modern drug efficacy. Again, I must thank my wife Clare for her tolerance and my mother Jean for her continued encouragement while I have been updating this book, which I hope will be of help to your studies.

M.D. Coleman, DSc.
September 2009

Preface to First Edition

'Throw physic to the dogs; I'll none of it' exclaims the eponymous Macbeth in Act 5, Scene 3, in one of Shakespeare's shortest and most violent plays. This response to the lack of efficacy and severe toxicity of early seventeenth-century therapeutics unfortunately has some resonance today. Despite the spectacular advances made in the last 50 years, many medicines in practice are neither beneficial nor safe. Indeed, increasing numbers of patients are dying as a result of their treatment, rather than their condition. There are many reasons for our inability to eradicate 'iatrogenic' (literally, physician induced) disease; these might include pharmacological interactions or factors relating to the patient's condition. However, the metabolism of drugs by the patients' own systems can have a powerful influence on the success of treatment.

This book is intended to provide a basic grounding in human drug metabolism, although it is useful if the reader has some knowledge of biochemistry, physiology and pharmacology from other sources. In addition, a qualitative understanding of chemistry can illuminate many facets of drug metabolism and toxicity. Although chemistry can be intimidating, I have tried to make the chemical aspects of drug metabolism as user-friendly as possible.

Regarding the layout of the book, Chapter 1 uses the idea of the therapeutic window to outline how both efficacy and toxicity are dependent on drug concentration, which is in turn linked to the rate of drug removal from the system. Biological systems actively eliminate small xenobiotic (foreign) molecules and how quickly this happens is a strong determinate of treatment outcome. Chapter 2 tries to put the metabolism of drugs in the context of other biological processes. Human metabolizing systems must synthesize endogenous molecules, inactivate them when their purpose is served and defend the body from foreign molecules. Drugs fit into the latter category and are treated by biological systems as foreign and unwelcome. Chapter 3 outlines how human metabolizing systems have availed themselves of highly specialized metabolizing enzymes of bacterial and eukaryotic origin, particularly cytochrome P450s. Phase I, the initial, mainly oxidative, phase of metabolism, begins the process of the conversion of lipophilic drugs to easily excreted water-soluble metabolites. The chapter considers the remarkable flexibility and capability of these oxidative enzymes. Chapter 4 reveals the mechanisms whereby the presence of some drugs can induce a massive adaptive increase in the metabolizing capability of cytochrome P450s. The threat to clinical drug efficacy posed by the resulting acceleration of drug removal from the body is outlined in a number of drug classes. By contrast, the inhibition of drug-metabolizing systems described in Chapter 5 is shown to cause life-threatening drug accumulation in a very short space of time. The mechanisms of cytochrome P450 inhibition are explained in the context of the main pharmacological features of enzyme inhibition. Chapter 6 illustrates the processes of conjugation, which can either act as companion

processes for oxidative metabolism, or eliminate drugs in their own right. In conjugative metabolism, large hydrophilic molecules are either attached directly to drugs or oxidized metabolites with the object of increasing their water solubility and molecule weight. This process, in concert with Phase III efflux pump systems, facilitates the removal of the metabolites from cells to the urine and the bile. Chapter 7 discusses other factors that influence drug-metabolizing processes, such as genetic polymorphisms, age, gender, diet, alcohol intake and disease. Chapter 8 explains some of the toxicological consequences of xenobiotic metabolism. The roles of cytochrome P450s in the origins of reversible and irreversible effects on the body are discussed. Irreversible events associated with reactive species formation due to cytochrome P450 metabolism include necrosis, immune-related toxicity and cancer.

At the end of the book, in Appendix A, there is a brief discussion of the role of drug metabolism in the commercial development of new therapeutic agents. The increasing popularity of illicit drugs makes it interesting to include some background on the metabolism of some major drugs of abuse in Appendix B, although it does include clinically useful agents such as opiates. Many readers of this book will be studying for formal examinations of some type, so some accumulated general advice on the preparation for examinations is supplied in Appendix C. Appendix D contains a brief list of cytochrome P450 substrates, inhibitors and inducers, and finally there is a list of suggested reading for those interested in a deeper, more detailed knowledge of the subject.

Whilst no human effort is without error and this book is no exception, it is hoped that it will facilitate understanding of the impact of metabolizing systems on drug therapeutic outcomes. All of us eventually participate in healthcare in some capacity, if not professionally, then as patients. Therefore, it is our duty to constantly update our therapeutic knowledge to liberate the full potential of the many remarkably effective drugs currently available.

I am very grateful to Mr Graham Smith for drawing the detailed figures. I would like to acknowledge the support and encouragement of my wife Clare, as well as my mother Jean, during the writing process and I very much hope you, the reader, find this book useful.

M.D. Coleman, DSc.

Contents

1 Introduction

1.1 Therapeutic window

1.1.1 Introduction

It has been said that if a drug has no side effects, then it is unlikely to work. Drug therapy labours under the fundamental problem that usually every single cell in the body has to be treated just to exert a beneficial effect on a small group of cells, perhaps in one tissue. Although drug-targeting technology is improving rapidly, most of us who take an oral dose are still faced with the problem that the vast majority of our cells are being unnecessarily exposed to an agent that at best will have no effect, but at worst will exert many unwanted effects. Essentially, all drug treatment is really a compromise between positive and negative effects in the patient. The process of drug development weeds out agents that have seriously negative actions and usually releases onto the market drugs that may have a profile of side effects, but these are relatively minor within a set concentration range where the drug's pharmacological action is most effective. This range, or 'therapeutic window' is rather variable, but it will give some indication of the most 'efficient' drug concentration. This effectively means the most beneficial pharmacodynamic effects for the minimum side effects.

The therapeutic window (Figure 1.1) may or may not correspond exactly to active tissue concentrations, but it is a useful guideline as to whether drug levels are within the appropriate range. Sometimes, a drug is given once only and it is necessary for drug levels to be within the therapeutic window for a relatively brief period, perhaps when paracetamol (acetaminophen) is taken as a mild analgesic. However, the majority of drugs require repeated dosing in time periods which range from a few days for a course of antibiotics, to many years for anti-hypertensives and antithyroid drugs. During repeated intermediate and long-term dosing, drug levels may move below or above the therapeutic window due to events such as patient illness, changes in diet or co-administration of other drugs. Below the lowest concentration of the window, it is likely that the drug will fail to work, as the pharmacodynamic effect will be too slight to be beneficial. If the drug concentration climbs above the therapeutic window, an intensification of the drug's intended and unintended (off-target) pharmacodynamic actions will occur. If drug levels continue to rise, irreversible damage may occur which is usually described by the word 'toxicity'. To some extent, every patient has a unique therapeutic window for each drug they take, as there is such huge variation in our pharmacodynamic drug sensitivities. This book is concerned with what systems influence how long a drug stays in our bodies.

Human Drug Metabolism 2E, Michael D. Coleman

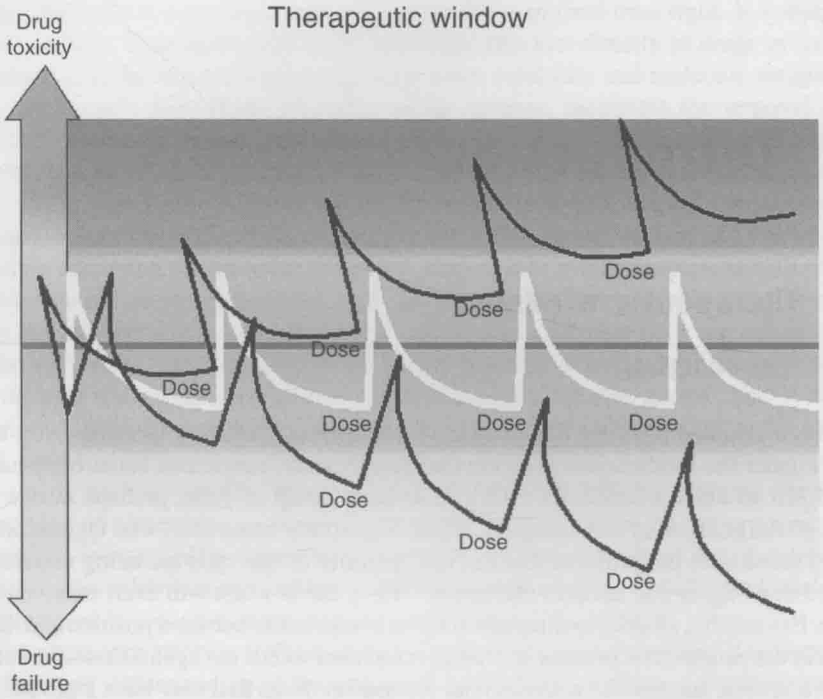

Figure 1.1 The 'therapeutic window', where drug concentrations should be maintained for adequate therapeutic effect, without either accumulation (drug toxicity) or disappearance (drug failure). Such is human variation that our personal therapeutic windows are effectively unique for every drug we take.

Whether drug concentrations stay in the therapeutic window is obviously related to how quickly the agent enters the blood and tissues prior to its removal. When a drug is given intravenously, there is no barrier to entry, so drug input may be easily and quickly adjusted to correspond with the rate of removal within the therapeutic window. This is known as 'steady state', which is the main objective of therapeutics. The majority of drug use is by other routes such as oral or intramuscular rather than intravenous, so there will be a considerable time lag as the drug is absorbed from either the gastro-intestinal tract (GIT) or the muscle, so achieving drug levels within the therapeutic window is a slower, more 'hit and miss' process. The result from repeated oral dosing is a rather crude peak/trough pulsing, or 'sawtooth' effect which you can see in the diagram (Figure 1.1). This should be adequate, provided that the peaks and troughs remain within the confines of the 'therapeutic window'.

1.1.2 Therapeutic index

Drugs vary enormously in their toxicity and the concentrations at which one drug might cause potentially lethal effects might be 10 or 100 times lower than a much less toxic drug. A convenient measure for this is the 'therapeutic index'. This has been defined as

the ratio between the lethal or toxic dose and the effective dose that shows the normal range of pharmacological effect.

In practice, a drug (such as lithium) is listed as having a narrow TI if there is less than a twofold difference between the lethal and effective doses, or a twofold difference in the minimum toxic and minimum effective concentrations. Back in the 1960s, many drugs in common use had narrow TIs, such as barbiturates, that could be toxic at relatively low levels. Over the last 30 years, the drug industry has aimed to replace this type of drug with agents with much higher TIs. This is particularly noticeable in drugs used for depression. The risk of suicide is likely to be high in a condition that takes some time (often weeks) to respond to therapy. Indeed, when tricyclic antidepressants (TCAs) were the main treatment option, these relatively narrow TI drugs could be used by the patient to end their lives. Fortunately, more modern drugs such as the SSRIs (selective serotonin reuptake inhibitors) have much higher TIs, so the risk of the patient using the drugs for a suicide attempt is greatly diminished. However, there are many drugs (including the TCAs to a limited extent), which remain in use that have narrow or relatively narrow TIs (e.g. phenytoin, carbamazepine, valproate, warfarin). Therefore the consequences of accumulation of these drugs are much worse and happen more quickly than drugs with wide TIs.

1.1.3 Changes in dosage

If the dosage exceeds the rate of the drug's removal, then clearly drug levels will accumulate and depart from the therapeutic window towards toxicity. If the drug dosage is too low, levels will fall below the lowest threshold of the window and the drug will fail to work. If a patient is established at the correct dose that does not change, then this is the oral version of 'steady state'. So, theoretically, the drug should remain in its therapeutic window for as long as therapy is necessary unless other factors change this situation.

1.1.4 Changes in rate of removal

The patient may continue to take the drug at the correct dosage, but drug levels may drop out of, or exceed, the therapeutic window. This could be linked with redistribution of the drug between bodily areas such as plasma and a particular organ, or protein binding might fluctuate; however, the major factor in the maintenance of drug levels within the therapeutic window is the rate of removal and/or inactivation of the drug by bodily processes.

1.2 Consequences of drug concentration changes

If there are large changes in the rate of removal of a drug, then this can lead *in extremis* to severe problems in the outcome of the patient's treatment: the first is drug failure, whilst the second is drug toxicity (Figure 1.2). These extremes and indeed all drug effects are directly related to the blood concentrations of the agent in question.

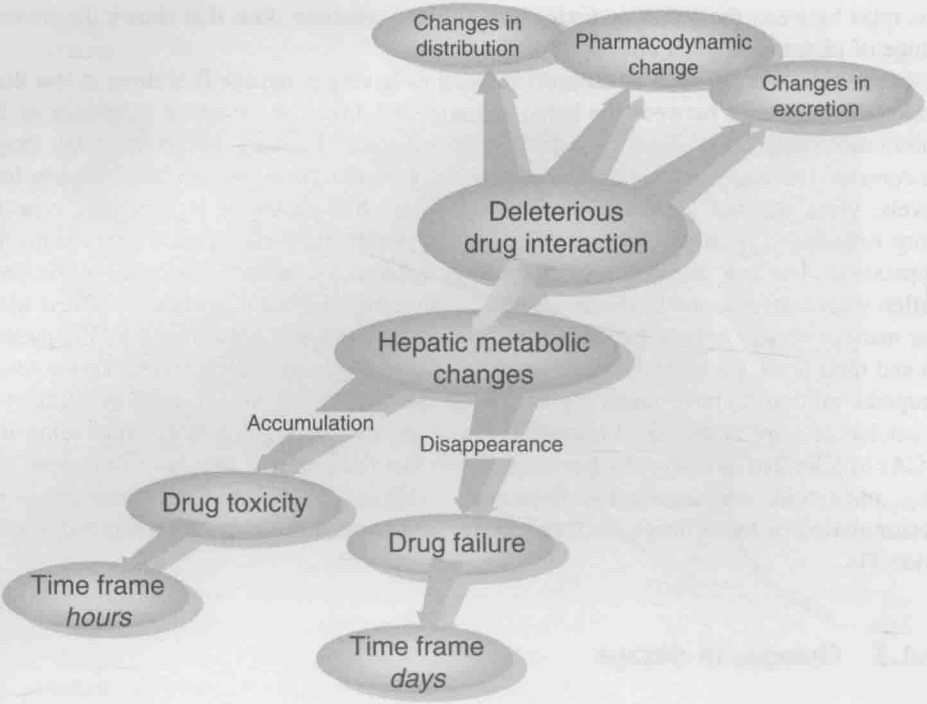

Figure 1.2 Consequences of drug interactions in terms of metabolic changes and their effects on drug failure and toxicity

1.2.1 Drug failure

Although it might take nearly a decade and huge sums of money to develop a drug that is highly effective in the vast majority of patients, the drug can only exert an effect if it reaches its intended target in sufficient concentration. There may be many reasons why sufficient concentrations cannot be reached. Drug absorption may have been poor, or it may have been bound to proteins or removed from the target cells so quickly it cannot work. This situation of drug 'failure' might occur after treatment has first appeared to be successful, where a patient becomes stabilized on a particular drug regimen, which then fails due to the addition of another drug or chemical to the regimen. The second drug or chemical causes the failure by accelerating the removal of the first from the patient's system, so drug levels are then too low to be effective. The clinical consequences of drug failure can be serious for both for the patient and the community. In the treatment of epilepsy, the loss of effective control of the patient's fits could lead to injury to themselves or others. The failure of a contraceptive drug would lead to an unwanted pregnancy and the failure of an antipsychotic drug would mean hospitalization for a patient at the very least. For the community, when the clearance of an antibiotic or antiparasitic drug is accelerated, this causes drug levels to fall below the minimum inhibitory concentration, thus selecting drug-resistant mutants of the infection. Therapeutic drug failure is usually a gradual process, where the time frame may be days before the problem is detected (Figure 1.2).

1.2.2 Drug toxicity

If a drug accumulates for any reason, either by overdose or by a failure of drug removal, then serious adverse reactions will result. A reduction in the rate of removal of the drug from a system (often due to administration of another drug), will lead to drug accumulation. Toxicity can be an intensification of a drug's therapeutic action, or an unrelated damaging effect on a tissue or organ system. If the immunosuppressive cyclosporine is allowed to accumulate, severe renal toxicity can lead to organ failure. Excessive levels of anticonvulsant and antipsychotic drugs cause confusion and drowsiness, whilst the accumulation of the antihistamine terfenadine, can lead to lethal cardiac arrhythmias. In contrast to drug failure, drug toxicity may occur much more rapidly, often within hours rather than days.

1.3 Clearance

1.3.1 Definitions

The consequences for the patient when drug concentrations either fall below the therapeutic window or exceed it can be life threatening. The rate of removal of the drug from the body determines whether it will disappear from, or accumulate in the patient's blood. A concept has been devised to understand and measure rate of removal; this is known as 'Clearance'. This term does not mean that the drug disappears or is 'cleared' instantly. The definition of clearance is an important one that should be retained:

Clearance is the removal of drug by all processes from the biological system.

A more advanced definition could be taken as:

A volume of fluid (plasma, blood or total body fluid) from which a drug is irreversibly removed in unit time.

Clearance is measured in millilitres of blood or plasma per min (or litres per hour) and is often taken to mean the 'clearance' of the drug's pharmacological effectiveness, which resides in its chemical structure. Once the drug has been metabolized, or 'biotransformed', even though only a relatively trivial change may have been effected in the structure, it is no longer as it was and products of metabolism, or metabolites as they are known, often exert less or even no therapeutic effect. Whether or not they retain some therapeutic effect, metabolites are usually removed from the cell faster than the parent drug and they will eventually be excreted in urine and faeces. There are exceptions where metabolites are as effective as the parent drug (some tricyclic antidepressants, such as desipramine and morphine glucuronides), and there are metabolites that are strangely even less soluble in water and harder to excrete than the parent compound (acetylated sulphonamides), but in general, the main measure of clearance is known as total body clearance, or sometimes, systemic clearance:

$$Cl_{\text{total}}$$