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Idiosyncratic drug reactions: a mechanistic evaluation of risk factors

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Introduction

Adverse drug reactions are a major complication of modern drug therapy; they are a considerable cause of patient morbidity and account for a significant number of patient deaths. Furthermore, many serious adverse reactions occur in patients with diseases which in themselves are not necessarily life-threatening, such as depression and epilepsy, but do require long-term drug treatment. It is therefore essential that a better understanding of such reactions is obtained in order to assess more accurately the risk-benefit ratio for the treatment of a patient with a particular drug. Adverse drug reactions may be classified as follows:

Type A: These reactions are predictable in terms of the primary and secondary pharmacology of the drug and are usually dose-dependent. Examples of this type of reaction include hypoglycaemia with oral hypoglycaemics and hypotension with anti-hypertensives. Such reactions should be anticipated, and can often be eliminated by dose reduction.

Type B (idiosyncratic): Unpredictable from a knowledge of the basic pharmacology of the drug and do not show any simple dose-response relationship, i.e. there is a lack of correlation between the dose and risk of toxicity. These reactions occur in only a small percentage of the population, hence the term idiosyncratic, but are often serious and account for many drug-induced deaths.

Type C: Reactions associated with long-term drug therapy, examples of which include benzodiazepine dependence and analgesic nephropathy. These reactions are well-described and can be anticipated.

Type D: Delayed effects such as carcinogenicity and teratogenicity. It is thought that such toxicities are precluded by the extensive programme of preclinical mutagenicity and carcinogenicity studies that a new chemical entity must undergo before a product licence is granted.

In this review we will discuss type B reactions or idiosyncratic reactions, a term used to describe adverse reactions which occur in a small number of patients. These reactions are often serious and are a major cause of iatrogenic disease, and yet the mechanisms involved are, in general, poorly understood. Such reactions are not detected by preclinical toxicology testing in animals and indeed cannot be reproduced in animal models. Investigation of the mechanisms involved is therefore nearly always dependent on retrospective clinical analysis. The clinical characteristics of such reactions are often suggestive of drug allergy or drug hypersensitivity, and thus the term idiosyncratic is often thought to imply an immunological aetiology. However, direct evidence for an immunological mechanism may be lacking, and there is no reason to presume that all such reactions have an immunological mechanism. Thus we suggest that the term idiosyncratic drug reaction should be used as an operational term and should not be taken to imply any specific mechanism.

Idiosyncratic reactions are of major concern both in medical practice and for present and future drug development. At present it is not possible to evaluate new drugs for their potential to cause idiosyncratic reactions, and such adverse reactions are only detected at a relatively late stage in drug development. This is wasteful in terms of commercial investment and human effort and could also be considered an unacceptable risk for patients participating in clinical studies. The discovery of a serious adverse drug reaction in a small number of patients can lead to the abandonment of a potentially useful drug, without any knowledge of cause of the reaction. Indeed, in some instances the drug might not have been the direct cause of the toxicity since many patients participating in clinical trials are taking several drugs, and thus the toxicity may have arisen from an 'idiosyncratic drug interaction' in which the new drug was not the prime offender.

Evaluation of the risk-benefit ratio for a drug associated with an idiosyncratic toxicity is complex. If the reaction is truly idiosyncratic, i.e. limited to a certain sub-group of the population with a unique susceptibility, then withdrawal of the drug provides protection of this sub-group of the population at the expense of denying the majority of the population access to what might otherwise prove to be an efficacious and safe form of drug treatment.

It is therefore important to study and elucidate the chemical, biochemical and immunological mechanisms

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of idiosyncratic adverse drug reactions in order to explain the chemical and cellular basis of the toxicity. Perhaps the most important goal of such studies should be to define the individual factor(s) responsible for the idiosyncratic nature of the adverse reaction. Such information could then be used prospectively to avoid drug toxicities in several ways. First, identification of patients who have a genetically determined susceptibility to certain classes (chemical or biochemical) of drugs, and development of a simple method for genotyping such individuals. This may reveal chemical or biochemical links between unrelated drugs not previously suspected. Secondly, cells derived from patients phenotyped for drug sensitivity could be used in the preclinical evaluation of a new drug, or a new analogue of a drug, that has been withdrawn because of an idiosyncratic reaction. Thirdly, a knowledge of the chemical mechanism of drug toxicity could lead to the design of an analogue which retains the efficacy of the parent drug but cannot produce the (idiosyncratic) toxicity.

Major clinical manifestations

The clinical pattern of idiosyncratic reactions can be remarkably variable even with respect to the same drug. Many of these reactions, although rare, are life-threatening and have resulted in the withdrawal of potentially useful drugs (Table 1).

The most common targets for idiosyncratic drug reactions are the skin, the formed elements of blood and the liver, while the kidney and the nervous system may also be affected. In some instances idiosyncratic reactions show a remarkable degree of organ, even cellular, selectivity. In other instances, cell types that are apparently unrelated, in terms of their physiological function, may be affected simultaneously. In addition, the primary drug-induced lesion may be accompanied by general manifestations such as lymphadenopathy, fever, arthralgia and eosinophilia suggestive of a hypersensitivity reaction.

Hepatotoxicity

More than 600 drugs have been reported to cause hepatic injury (Stricker & Spoelstra, 1985). The pattern of liver injury is variable and includes hepatitis, steatosis, granuloma, cirrhosis and neoplasia (Kaplowitz, 1986; Sherlock, 1986; Timbrell, 1983). Idiosyncratic hepatotoxicity may be due to direct toxicity of a chemically reactive metabolite, so-called 'metabolic' idiosyncrasy (Zimmerman, 1978), or secondary to an immune reaction (Pessayre & Larrey, 1988; Pohl, 1990; Zimmerman, 1978). Some of the drugs reported to cause hepatic injury are listed in Table 2. The clinical presentation of drug-induced hepatotoxicity is also variable, ranging from asymptomatic elevation of liver enzymes to hepatic failure. Withdrawal of the offending drugs leads to clinical and histological resolution in the majority of cases, although with some drugs such as iproniazid (Rosenblum *et al.*, 1960), withdrawal has no effect, the hepatic injury progressing, suggesting drug-induced autoimmunity.

Overt hepatic dysfunction due to drugs is uncommon, with drugs accounting for about 2% of all cases of jaundice (Bjornboe *et al.*, 1967; Koff *et al.*, 1970), although asymptomatic liver enzyme elevation is more common, being as high as 20% for some drugs such as isoniazid (Zimmerman, 1978). For the most severe form of liver injury, i.e. hepatic failure, idiosyncratic drug reactions account for approximately 20% of cases (Zimmerman, 1978), being exceeded only by paracetamol overdosage and viral hepatitis.

Table 1 Product withdrawals due to idiosyncratic drug reactions

Drug	*Adverse reaction*
Alcofenac	Hypersensitivity reactions
Althesin	Anaphylaxis
Benoxaprofen	Hepatotoxicity, nephrotoxicity
Fenclofenac	Toxic epidermal necrolysis
Glafenine	Anaphylaxis
Ibufenac	Hepatotoxicity
Nomifensine	Haemolytic anaemia
Practolol	Oculo-mucocutaneous syndrome
Temafloxacin	Hepatotoxicity, haemolysis
Tienilic acid	Hepatotoxicity
Zimeldine	Guillain-Barre syndrome
Zomepirac	Anaphylaxis

Blood dyscrasias

Drug-induced haematological toxicity can affect either platelets, red cells, white cells or all the cellular elements of the bone marrow leading to thrombocytopaenia, haemolytic anaemia, agranulocytosis or aplastic anaemia, respectively. The most serious of these reactions, because of its high mortality, is aplastic anaemia. Although this is a rare reaction, it has been estimated that between 30% to 60% of all cases of this haematological abnormality are related to drug treatment (Vincent, 1986). The likely target cell in aplastic anaemia is the haemopoietic pluripotential stem cell (Pisciotta, 1990; Vincent, 1986), the damage occurring either due to direct toxicity of the drug, or a metabolite, or secondary to an immune mechanism which may involve either the humoral and/or cellular fractions of the immune system (Treleaven & Barrett, 1990). Selective involvement of the granulocytes, i.e. agranulocytosis, was found by Bottinger and colleagues (1979), to be the most likely cause of death among drug-induced blood dyscrasias. The overall incidence of agranulocytosis in this Swedish study was estimated to be about 2.6 per million inhabitants (Bottinger *et al.*, 1979). However, the incidence is higher for individual drugs such as clozapine (1 in 100; Fischer *et al.*, 1991), captopril (1 in 250; Claas, 1987) and phenothiazines (1 in 1300; Pisciotta, 1973). Table 3 lists some of the drugs which have been reported to cause either aplastic anaemia and/or agranulocytosis.

Clinically, agranulocytosis may be detected on a routine blood count or the patient may present with fever and sore throat. The presentation of a patient with aplastic anaemia may be dependent on which cell line is most severely affected, and thus, fever, sore throat (agranulocytosis), tiredness (anaemia) or bruising and gastrointestinal haemorrhage (thrombocytopaenia) may all be presenting symptoms.

Table 2 Drugs reported to cause idiosyncratic hepatotoxicity

Drugs	*Postulated toxic metabolite*	*Postulated mechanism*	*Comments*	*References*
Anaesthetics				
Halothane	Acyl halide	Neoantigen	Predisposition may lie with immune hyper-responsiveness	Satoh *et al.* (1989); Pohl (1990)
Antidepressants				
Monoamine oxidase inhibitors				
Iproniazid	Isopropyl radical	Immune-mediated	1% incidence. Associated with anti-M_6 autoantibody	Rosenblum *et al.* (1960); Homberg *et al.* (1982); Nelson *et al.* (1978)
Tricyclic antidepressants				
Amineptine	Epoxide	Immune-mediated	Genetic predisposition	Larrey *et al.* (1989)
Imipramine	Epoxide	Immune-mediated		Kappus & Remmer (1975)
Lofepramine	Epoxide	Immune-mediated		Pirmohamed *et al.* (1992)
Mianserin	Iminium ion	Unknown	May be associated with agranulocytosis	Lambert *et al.* (1989)
Anticonvulsants				
Phenytoin, Carbamazepine	Epoxide	Immune-mediated	Possible deficiency of microsomal epoxide hydrolase	Shear *et al.* (1988); Pirmohamed *et al.* (1991)
Sodium valproate	Diene	Enzyme inhibition (see text)	Commonest in infants	Kassahun *et al.* (1991)
Anti-psychotics				
Chlorpromazine	Unknown	Multiple mechanisms involving an interaction of direct toxicity and immune response	Subclinical cholestasis in the majority but overt jaundice in 1% due to unknown predisposing factor	Timbrell (1983); Kaplowitz (1986)
Cardiovascular agents				
Amiodarone	Unknown	Inhibition of intralysosomal phospholipases?	Minority develop severe form—predisposing factor unknown Hypersensitivity manifestations	Babany *et al.* (1986); Kubo & Hostetler (1987)
Calcium antagonists	Unknown	Immune-mediated		Nash & Feer (1983); Abramson & Littlejohn (1985)
Dihydralazine	Unknown	Anti-P450 1A2 IgG	Non-organ specific autoantibodies often present	Bourdi *et al.* (1990)
Labetalol	Unknown	Direct toxicity		Clark *et al.* (1990)
Methyl dopa	Unknown	Immune-mediated	Direct Coombs' test may be positive (3%). More common in females	Rodman *et al.* (1976); Zimmerman (1990)
Tienilic acid	Unknown	Anti-P450 (IIC family) IgG	1 in 800 incidence	Beaune *et al.* (1987); Pons *et al.* (1991)
Infectious diseases				
Amodiaquine	Quinoneimine	Immune-mediated	May be associated with leucopaenia	Clarke *et al.* (1991)
Dapsone	Hydroxylamine	Immune-mediated?	May be part of the sulphone sydnrome	Johnson *et al.* (1986); Coleman *et al.* (1989)

Table 2 Drugs reported to cause idiosyncratic hepatotoxicity (*cont.*)

Drugs	*Postulated toxic metabolite*	*Postulated mechanism*	*Comments*	*References*
Erythromycin	Nitroso derivatives	Immune-mediated	Can occur with estolate, ethyl succinate and proprionate derivatives	Larrey *et al.* (1983a,b)
Isoniazid	Monoacetyl hydrazine	Protein alkylation	Not associated with acetylator status	Timbrell *et al.* (1977)
Sulphonamides	Hydroxylamine	Immune-mediated	Unknown genetic predisposing factor. Higher incidence in AIDs patients	Dujovne *et al.* (1967); Gordin *et al.* (1984); Reider *et al.* (1989)
Rheumatic drugs				
Allopurinol	Unknown	Immune-mediated		Pessayre & Larrey (1988)
NSAID	Unknown	Immune or toxic dependent on compound	Commonest with benoxaprofen and phenylbutazone, least common with fenamates	Pessayre & Larrey (1988); Miller & Prichard (1990); Zimmerman (1990)

Drug-induced thrombocytopaenia and haemolytic anaemia may be immune-mediated. In addition, haemolysis may occur because of an underlying metabolic abnormality, for example, glucose-6-phosphate dehydrogenase deficiency (Beutler, 1991). Readers are referred to extensive reviews for further information on causative drugs (Ammus & Yunis, 1989; Habibi, 1987; Mueller-Eckhardt, 1987).

Cutaneous reactions

Almost every drug currently in clinical practice has been reported to cause cutaneous toxicity. In the majority of cases, the skin reactions are mild and only require withdrawal of drug for resolution. The pathogenesis of such reactions is unknown although with certain drugs, for example, phenytoin, dose-dependency has been demonstrated (Chadwick *et al.*, 1984). With mild cutaneous reactions, patients may have no systemic symptoms suggestive of hypersensitivity although, on occasions, it may be possible to demonstrate specifically sensitised T-lymphocytes in affected patients using patch testing and lymphocyte transformation tests (Bell & Pichler, 1989; Houwerzijl *et al.*, 1977; Zakrzewska & Ivanyi, 1988) suggesting involvement of the immune system. The more severe reactions, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, which may represent different ends of the same disease spectrum (Raviglione *et al.*, 1990), are frequently due to drugs (Chan *et al.*, 1990; Raviglione *et al.*, 1990); the most recent surveys implicating three drug groups, antibacterials (sulphonamides, penicillins), NSAIDs and anticonvulsants, as having the highest incidence (Table 4). Chan and colleagues (1990) have calculated the incidence among out-patients of drug-induced erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis to be 7.0, 1.8 and 9.0 per 10^6 person-years, respectively. These reactions are thought to be immune-mediated, the evidence for this being the association with HLA antigens (Table 6; Roujeau *et al.*, 1987), the occurrence of toxic epidermal necrolysis in acute graft-*versus*-host disease (Saurat, 1981), demonstration of anti-epidermal antibodies (Hensen *et al.*, 1981; Stein *et al.*, 1972) and positive lymphocyte transformation tests (Ruiz-Maldonaldo, 1985). In addition, histologically, epidermal infiltration by CD8-positive T-cells has been demonstrated (Miyauchi *et al.*, 1991).

The precise incidence of idiosyncratic adverse reactions is difficult to define. Reporting rates are subject to numerous factors (Rawlins, 1988). It is also difficult to establish whether adverse events (biochemical or immunological) occur in only a minority of individuals prescribed the drug or whether sub-clinical toxicity is occurring in the majority of individuals but is only expressed as frank toxicity in a small number of those patients. For example, antibodies can be detected in a substantial number of patients taking either procainamide (Blomgren *et al.*, 1972; Woosley *et al.*, 1978) or methyldopa (Worlledge, 1969), but only a small number of these patients will develop systemic lupus erythematosus or haemolytic anaemia, respectively.

Possible mechanisms

In any discussion of the mechanisms involved in idiosyncratic reactions, one must seek to define the chemical basis of the toxicity, the reason for organ-directed or cell-directed toxicity, and why only certain individuals are exceptionally susceptible to the toxicity. A list of theoretically possible mechanisms is presented in Table 5. For each mechanism one must also consider whether the drug or a metabolite is the ultimate toxin.

Idiosyncratic reactions which involve a grossly exaggerated pharmacological response could result from

Table 3 Drugs implicated in causing agranulocytosis and/or aplastic anaemia

Drugs	*Postulated toxic metabolite*	*Postulated mechanism*	*Comments*	*References*
Antibacterials				
Chloramphenicol	Hydroxylamine or nitroso	Multiple metabolic steps including bacterial transformation	Incidence of 1 in 10000–40000	Yunis (1989); Ascheri *et al.* (1985)
Sulphonamides	Hydroxylamine	?Immune-mediated	Unknown predisposing factor(s)	Shear & Spielberg (1985); Reider *et al.* (1989)
Anticonvulsants				
Phenytoin Carbamazepine	Arene oxide	Immune-mediated	Deficiency of microsomal epoxide hydrolase	Gerson *et al.* (1983); Shear *et al.* (1988); Pirmohamed *et al.* (1991)
Antimalarials				
Amodiaquine	Quinoneimine	Immune-mediated	May be associated with hepatotoxicity	Neftel *et al.* (1986); Clarke *et al.* (1991)
Dapsone	Hydroxylamine	Unknown	Associated with bone marrow maturation arrest	Uetrecht *et al.* (1988); Coleman *et al.* (1989)
Antipsychotics				
Chlorpromazine	Unknown	Direct toxicity	Proliferative marrow defect in sensitive individuals	Pisciotta (1990)
Clozapine	Free radical	Unknown	Incidence 1–2%	Fischer *et al.* (1991)
Mianserin	Iminium ion	Direct toxicity	Incidence 1 in 1000–2000	Lambert *et al.* (1989); Coulter & Edwards (1990)
Antirheumatic agents				
Aminopyrine		Peripheral antibody		Moeschlin & Wagner (1952)
D-Penicillamine		Immune-mediated	-SH group may be of importance	Kay (1979); Uetrecht (1990)
Gold		Unknown		Kay (1976); Yan & Davis (1990)
Levamisole	Unknown	Immune-mediated	Associated with HLA B27 > 2% incidence	Thompson *et al.* (1980); Diez (1990)
Phenylbutazone	Hydroperoxide	Multiple metabolic steps	1 in 30000 incidence	Chaplin (1986); Vincent (1986)
Antithyroid drugs				
Propylthiouracil Carbimazole	Sulphonic acid	Immune-mediated	Antineutrophil antibody detected	Guffy *et al.* (1984); Waldhauser & Uetrecht (1991)
Cardiovascular agents				
Captopril		Immune-mediated	Particularly with high doses -SH group implicated	Edwards *et al.* (1981)
Procainamide	Hydroxylamine	Unknown	Can be activated by neutrophils More common with SR preparation	Uetrecht (1990)
Oral hypoglycaemics				
Chlorpropamide	Unknown	Immune-mediated	Can lead to pure white cell or red cell aplasia	Pisciotta (1990)

Table 4 Drugs implicated in causing erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Study	*Ruiz-Maldonaldo* (1985)	*Guillaume* et al. (1987)	*Stern & Chan* (1989)	*Chan* et al. (1990)	*Roujeau* et al. (1990)	*Schopf* et al. (1991)	*Strom* et al. (1991)
Drugs implicated	*Anticonvulsants*	*Sulphonamides*	*Allopurinol*	*Anticonvulsants*	*NSAID*	*Antibiotic*	*Antibiotic*
	Phenytoin	Cotrimoxazole		Phenobarbitone	Isoxicam	Sulphonamides	Penicillin
	Carbamazepine		*NSAID*		Oxyphenbutazone	Penicillins	Sulphonamides
		Anticonvulsants		*Antibiotics*	Fenbufen	Tetracycline	
	NSAID	Carbamazepine	*Phenytoin*	Nitrofurantoin			*NSAID*
	Pyrazolones	Phenytoin		Cotrimoxazole	*Antibiotics*	*NSAID*	Phenylbutazone
			Sulphonamides	Ampicillin	Sulphadiazine	Benoxaprofen	
	Antibiotics	*NSAID*		Amoxycillin	Cotrimoxazole	Oxyphenbutazone	*Anticonvulsants*
	Sulphonamides	Oxicams				Isoxicam	Phenobarbitone
	Penicillin	Phenylbutazone			*Anticonvulsants*		Carbamazepine
					Phenytoin	*Allopurinol*	Phenytoin
	Sulphonylurea	*Allopurinol*					
						Anticonvulsants	
		Chlormezanone				Phenytoin	
						Carbamazepine	

Table 5 Possible mechanisms of idiosyncratic drug toxicity

1. Abnormal receptor sensitivity
2. Abnormal biological system that is only apparent in the presence of drug (metabolite)
3. Abnormality in drug metabolism
4. Immunological
5. Multifactorial

abnormal drug metabolism (see below) or from an abnormal pharmacodynamic response. The latter mechanism might ensue where an individual has exceptionally sensitive pharmacological receptors. Intuitively, one would predict that such a mechanism is unlikely for two reasons. Firstly, individual receptor subtypes show a high degree of structural and functional conservation across species and therefore presumably within species. This reflects the fact that such receptors interact in a highly specific manner with particular endogenous ligands and other regulatory proteins or enzymes (Taylor & Insel, 1990). Secondly, given the normal physiological role of receptors and ion channels, one would anticipate that abnormal physiological activity would accompany idiosyncratic pharmacological response.

The second possibility is that an otherwise undetectable biochemical deficiency becomes apparent in the presence of a drug or drug metabolite. There are two well-established examples of this type of reaction, both of which involve oxidative stress in the red blood cell. Administration of certain antimalarial drugs, such as primaquine, causes haemolysis in about 10% of negroes, because of a deficiency in the enzyme glucose-6-phosphate dehydrogenase (Beutler, 1972, 1978). A less common reaction, is the methaemoglobinaemia produced by nitrites in individuals with a genetically determined deficiency of methaemoglobin reductase (Scott, 1960). In addition, it has been suggested that some forms of drug-induced aplastic anaemia may be related to a deficiency in DNA repair mechanisms, and indeed, it has been postulated that heterozygotes for the Fanconi gene (approximately 1 in 300) may have increased stem cell sensitivity to certain drugs leading to marrow aplasia (Treleaven & Barrett, 1990).

The third possibility is a genetically determined abnormality in drug metabolism. This has been considered an attractive possibility because a) there is a wide inter-individual variation in ability to perform certain biotransformations and b) there can be marked differences in rate and routes of metabolism between man and species used in the preclinical evaluation of drugs. Failure to metabolise drugs, and its toxicological consequences is well illustrated by reference to succinylcholine, which undergoes extensive and rapid hydrolysis in most individuals, but not in homozygotes with an atypical cholinesterase enzyme who experience prolonged apnoea (Lockridge, 1990). Another example is the neuropathy (Shah *et al.*, 1982) and hepatotoxicity (Morgan *et al.*, 1984) caused by excessive accumulation of perhexiline in patients deficient in CYP 2D6. Alternatively, an imbalance between the relative rates of drug detoxication and drug bioactivation may lead to drug toxicity and an

explanation for individual sensitivity and species sensitivity to a particular adverse drug reaction. In this respect, chemically reactive metabolites are of particular importance because they can cause cell toxicity directly and indirectly by an immunological mechanism (Park, 1986).

Many idiosyncratic reactions only occur after chronic treatment, but may recur immediately on rechallenge and have clinical features indicative of a hypersensitivity reaction (Pohl *et al.*, 1988). Involvement of the immune system offers a plausible explanation for the serious nature of idiosyncratic drug reactions since the cytolytic and inflammatory components can be activated by a small amount of signal (drug hapten) located in the target tissue (Park *et al.*, 1987). The ability to mount an immune response on antigen exposure is controlled by the MHC genes, which are the most polymorphic genes known in higher vertebrates (Weatherall, 1991). Such a high level of polymorphism could theoretically result in individuals who are more efficient at recognising certain epitopes than others with the result that only these individuals are more likely to mount a vigorous immune response to drug-related antigens. Thus, the natural selection which maintains a large variety of MHC proteins in the population may, inadvertently, produce a subpopulation of individuals who are more likely to develop drug hypersensitivity. However, a drug reaction can only be considered a true hypersensitivity reaction if it has been proved that specific drug-induced antibody or specifically committed immune cells are involved in the pathogenesis of the drug toxicity.

Assessment of risk factors

Chemistry of the drug

An adverse reaction must be a function of the biology of the individual and the chemistry of the drug. The lower the incidence of the reaction, that is the more idiosyncratic the reaction, then one must suppose the greater the influence of individual (biological) considerations than chemical factors. Nevertheless, even in idiosyncratic reactions the toxicity must be caused by the presence of certain functional groups within the drug molecule or a metabolite. Knowledge of the chemical mechanism may provide a means of designing a safer drug, provided the functional group is not essential for activity, and also the possibility to identify susceptible individuals by the development of non-invasive techniques.

The hypersensitivity reactions associated with penicillins and cephalosporins is attributed to the presence of the strained beta-lactam ring which is directly reactive, in a chemical sense, to nucleophilic groups on proteins (Page, 1984). This chemical reactivity is an integral part of the antimicrobial activity of the drugs but will also produce drug antigen in all individuals, only some of whom will have the ability to mount an immune response (Lafaye & Lapresie, 1988).

Sulphydryl groups in drugs are thought to be a risk factor since they can interact directly with cysteine and cystine groups in proteins. The significant incidence of agranulocytosis associated with captopril was, initially attributed to the presence of the sulphydryl group (Hoorntje *et al.*, 1979, 1980). However, this side-effect, which was apparently dose-dependent (Edwards *et al.*, 1981), was also noted with other ACE-inhibitors which do not contain a free sulphydryl group (Elis *et al.*, 1991), albeit at a lower incidence.

The presence of an aromatic amino group is usually avoided in drug design because oxidative metabolites, such as hydroxylamine and nitroso derivatives can be chemically unstable and extremely toxic, and indeed certain aromatic amines are amongst the most potent carcinogens known. Nevertheless certain drugs still in clinical use such as sulphonamides, sulphones and procainamide do contain a free amino group and have been associated with adverse drug reactions (Coleman *et al.*, 1989; Reider *et al.*, 1989; Uetrecht, 1990; Uetrecht *et al.*, 1988) which are variable, both in terms of incidence and clinical outcome. Yet in each case the initial event in drug toxicity is *N*-hydroxylation which occurs in all individuals taking the drug.

Thiamphenicol, a chloramphenicol analogue with similar antibacterial activity, in which the *p*-nitro group is replaced by a methylsulphonyl group has been widely used in Europe as a chloramphenicol substitute (Yunis, 1989). Although both drugs produce a dose-related erythroid lesion, the more severe aplastic anaemia has only been reported with chloramphenicol but not in more than 12 million people treated with thiamphenicol, which suggests that the nitro group in chloramphenicol is causally related to the aplastic anaemia (Man-Yan *et al.*, 1975).

Variation in receptor function

Malignant hyperthermia, a metabolic disorder of skeletal muscle which is inherited as an autosomal dominant trait (MacLennan *et al.*, 1990), can be triggered in susceptible individuals by anaesthetic agents such as halothane and succinylcholine (Iaizzo *et al.*, 1988). It is one of the major causes of death due to anaesthesia (Heffron, 1988) with a reported incidence of between 1 in 10,000–50,000 anaesthetic procedures (Britt & Kalow, 1970). It has been postulated that malignant hyperthermia results from disruption in the control of intracellular free calcium (Iaizzo *et al.*, 1988; Lopez *et al.*, 1985), the primary defect being in the calcium-induced calcium release channel of skeletal muscle (ryanodine receptor) (Mickelson *et al.*, 1988). Susceptible individuals can be identified by the *in vitro* muscle contracture test according to the European Malignant Hyperpyrexia Group protocol (European Malignant Hyperpyrexia Group, 1984) or by using flanking DNA markers for genetic linkage analysis (in large pedigrees) (Healy *et al.*, 1991).

Variation in drug metabolism

Genetic polymorphisms in various types of drug biotransformations have been described including those in drug oxidation, hydrolysis, acetylation and glutathione conjugation. The pharmacological and toxicological implications for the phenotype with a reduced ability to clear the drug and/or metabolite have been reviewed (Idle, 1991). For many idiosyncratic drug reactions, it is

thought that a metabolite, and in particular a chemically reactive metabolite, rather than the parent drug which is responsible for toxicity. Individual susceptibility to toxicity will depend on the balance between the relative rates of drug bioactivation and detoxication of both parent drug and metabolite. *In vitro* studies have shown that many drugs have the potential to undergo bioactivation, particularly in the presence of the P450 enzymes present in most human livers (Kitteringham *et al.*, 1988). Parallel *in vivo* studies have shown that such bioactivation is normally precluded or severely restricted by competing oxidation and conjugation reactions and that where bioactivation does occur cellular defence mechanisms such as glutathione (transferase) and epoxide hydrolase prevent cell damage. However, in certain individuals the normal balance between this complex pattern of biotransformations may be disturbed either by genetic factors (Ayesh & Smith, 1989) or by host factors such as age, diet, enzyme induction and enzyme inhibition (Park & Kitteringham, 1989), all of which may allow a toxic metabolite to escape detoxication.

Because of its anatomical location, the liver may be considered to be particularly vulnerable to the toxic effects of drugs and their metabolites. It is the major site of drug oxidation but balanced against this is the high capacity of cellular detoxication systems and the large reserve of glutathione (Deleve & Kaplowitz, 1990). Nevertheless, the severity of drug-induced injury is such that drugs are a major cause of hepatic injury (Timbrell, 1983; Zimmerman, 1978). In Table 2 are listed a number of drugs which are associated with idiosyncratic hepatotoxic reactions. For most drugs listed there is evidence for bioactivation *in vitro* by hepatic enzymes resulting in the formation of chemically reactive metabolites which produce hepatotoxicity either directly by alkylation of critical cellular macromolecules or by initiating an immune reaction.

Long term administration of the antitubercular drug isoniazid leads to hepatic dysfunction of variable severity with 10–20% of patients having mild, subclinical signs of toxicity which often subside despite continued therapy (Mitchell *et al.*, 1976), while some 0.1% to 1% of patients develop severe hepatic injury. Although isoniazid hepatotoxicity occasionally has features which suggest hypersensitivity, the majority of cases of isoniazid-induced liver damage do not conform to an immunological mechanism. It is thought that the ultimate toxic metabolite is an alkylating agent formed from sequential acetylation and oxidation biotransformations. Acetylisoniazid and acetylhydrazine (formed by hydrolysis of the former) are extremely hepatotoxic in animals in which the hepatic microsomal enzymes are induced by phenobarbitone (Bahri *et al.*, 1981). Acetylhydrazine is a metabolite in all human individuals (Timbrell *et al.*, 1977) and yet only a few develop hepatotoxicity. The drug and its metabolites undergo multiple acetylation reactions, which probably explains the lack of a simple relationship between acetylator phenotype and isoniazid toxicity (Weber *et al.*, 1983).

Inter-individual variation in cellular detoxification of chemically reactive meabolites produced from drugs also seems to be an important factor in determining predisposition to idiosyncratic toxicity. In this respect, peripheral blood lymphocytes provide a useful, easily accessible source of human cells to assess variability in detoxification of reactive species (Spielberg, 1984). Lymphocytes from patients with and without idiosyncratic adverse drug reactions can be incubated with the suspect drug and a drug metabolising system (i.e. microsomes and NADPH) to assess inter-individual variability in *in vitro* chemical sensitivity (Spielberg, 1980, 1984). Indeed, using this *in vitro* system, it has been shown that lymphocytes from patients hypersensitive to phenytoin (Shear *et al.*, 1988; Spielberg *et al.*, 1981), phenobarbitone (Shear *et al.*, 1988), carbamazepine (Pirmohamed *et al.*, 1991; Shear *et al.*, 1988), sorbinil (Spielberg *et al.*, 1991) and amineptine (Larrey *et al.*, 1989) all exhibit higher *in vitro* sensitivity when co-incubated with the respective drug, than appropriate controls, suggestive of a defect in cellular detoxification. With carbamazepine, *in vitro* studies using a panel of human livers has shown that the majority of human livers can bioactivate it to a cytotoxic metabolite, reinforcing the hypothesis that a defect of detoxication rather than activation may be to blame (Pirmohamed *et al.*, 1991). It has been postulated that all these drugs may form chemically reactive epoxide metabolites, and hence a deficiency of the toxicologically important enzyme (Guenthner, 1990), microsomal epoxide hydrolase, may be the predisposing factor, although no enzyme deficiency has yet been demonstrated in man. The ability of many drugs to be able to form reactive epoxide metabolites also raises the possibility of cross-sensitivity between functionally related and unrelated compounds. With the aromatic anticonvulsants, a higher incidence of *in vitro* chemical cross-sensitivity was demonstrated (Shear *et al.*, 1988), although this was not seen in another study (Pirmohamed *et al.*, 1991) where the lack of clinical cross-sensitivity between carbamazepine and phenytoin corresponded to the lack of *in vitro* chemical cross-sensitivity. This raises the possibility that heterogeneity of the gene defect (for epoxide hydrolase) may determine the occurrence of clinical cross-sensitivity between seemingly unrelated drugs. This *in vitro* system can also be used to assess sensitivity to drugs such as sulphonamides which are not known to form epoxides. Indeed, Reider and colleagues (1989) have shown that sulphonamide hypersensitive patients have higher *in vitro* cytotoxicity with the hydroxylamine metabolites than patients without adverse drug reactions, although the nature of the cellular detoxification defect remains obscure. It has been shown that there is a predominance of the slow acetylator phenotype in patients who have had sulphonamide hypersensitivity (Reider *et al.*, 1991), although this is not the defect which is being observed in the *in vitro* lymphocyte assay since these cells are only known to possess the monomorphic form (NAT-1) of acetyl transferase (Cribb *et al.*, 1991).

Lymphocytes also serve as a useful marker for one form of glutathione transferase (GST), GST μ, which is expressed polymorphically in both liver and lymphocytes (Seidegard *et al.*, 1988); 50% of individuals do not express this enzyme and appear to be at greater risk of cigarette smoke-induced lung cancer than the corresponding positive phenotype (Seidegard *et al.*, 1990). Exposure of lymphocytes from 256 individuals to the model genotoxin *trans*-stilbene epoxide showed a trimodal pattern of susceptibility to chemical-induced

sister chromatid exchanges, which was interpreted as reflecting a dual polymorphism in detoxication involving glutathione transferase μ (Wiencke *et al.*, 1990) and, possibly, epoxide hydrolase. The GST μ negative phenotype has so far not been shown to be of importance in predisposing to sulphonamide (Riley *et al.*, 1991) and carbamazepine (Pirmohamed, unpublished data) hypersensitivity, or to the best of our knowledge to any other form of idiosyncratic drug toxicity.

Age

It is well known that adverse drug reactions occur more frequently in the elderly than in other age groups (Williamson & Chopin, 1980). There are several possible reasons for this: first, the elderly take more drugs and are therefore more likely to be subjected to polypharmacy; secondly, age-related decline in renal function and hepatic metabolism may lead to toxicity through excess drug accumulation as was noted with the anti-inflammatory drug benoxaprofen (Hamdy *et al.*, 1982), and thirdly, it is possible that there are age-related declines in drug detoxication processes and in cellular and DNA repair mechanisms.

The very young are also more susceptible to certain drug toxicities. For example, valproic acid causes an idiosyncratic reaction primarily in children under the age of 2 years who are often on polytherapy and who may have other diseases (Dreifuss *et al.*, 1987, 1989). To date approximately 100 patients have died from valproate-induced liver damage. Histologically, the hepatic injury is characterised by microvesicular steatosis and necrosis (Scheffner *et al.*, 1988), but without any evidence for involvement of the immune system (histologically and clinically). It has been postulated that valproic acid undergoes bioactivation to 4-ene and 2,4-diene metabolites which inhibit fatty acid metabolism by alkylation of 3-ketoacyl-CoA thiolase (Kassahun *et al.*, 1991; Rettenmeier *et al.*, 1985). The major route of metabolism for the parent compound is glucuronidation, while the chemically reactive unsaturated metabolites undergo conjugation with glutathione. These metabolic processes will be influenced by various factors such as age and the effects of concurrently administered enzyme-inducing drugs such as carbamazepine and phenytoin all of which may perturb the normal metabolic profile of the drug, and thus predispose certain individuals to drug toxicity. The importance of glutathione conjugation in the detoxication of valproic acid (metabolites) was demonstrated by the successful treatment of four patients with hepatotoxicity by administration of *N*-acetylcysteine (Kassahun *et al.*, 1991). It was therefore suggested that a combination of enhanced production of toxic metabolites and a deficiency in ability to maintain normal (mitochondrial) glutathione levels could well form the basis for the idiosyncratic nature of the toxicity. A further possible predisposing factor, which is partially relevant to the young is the well-defined functional immaturity of the glucuronyl transferase system.

This functional deficiency of glucuronyl transferase in the young does not necessarily lead to increased risk of toxicity. In the case of paracetamol a reduced capacity of the young to form paracetamol glucuronide is more than compensated by an enhanced rate of production of paracetamol sulphate, and the young are considered to have a reduced risk of paracetamol hepatotoxicity (Lieh-Lai *et al.*, 1984).

Immunological considerations

Adverse drug reactions that involve a specific drug-induced immune response are referred to as drug hypersensitivity reactions. The classification by Coombes & Gell (1986) of the pathological processes involved in hypersensitivity reactions can be applied to drugs and provides a useful mechanistic framework (Figure 1).

It is a well established immunological fact that low molecular weight compounds (< 1000 Da) cannot function as immunogens *per se*, but can initiate an immune response when covalently bound to a macromolecular carrier (Park *et al.*, 1987). Thus a drug, or a drug metabolite, once covalently bound to a protein can elicit the production of specific antibodies or T-cells which recognise either the drug hapten or specific epitopes on the carrier molecule. Hence the non-specific components of the immune response may be 'misdirected' against the host's own cells or tissues and thus produce a hypersensitivity reaction. Our understanding of drug hypersensitivity at the chemical and immunochemical level is reasonably well understood and will not be considered further here (Park *et al.*, 1987; Pohl, *et al.*, 1988). Drugs such as penicillins, cephalosporins and thiol-containing drugs can react directly with proteins, whereas as drugs such as halothane, sulphonamides, amodiaquine and carbamazepine must undergo metabolic activation prior to protein conjugation (Park & Kitteringham, 1990). Thus, in order to elucidate risk factors of an immunological nature, we will focus mainly on those drugs with direct protein reactivity, in order to avoid added complications of variability in drug metabolism.

Immunological risk factors

Key events in the hypersensitivity process which may show interindividual variation are outlined in Figure 2.

The initial event in the overall process is protein conjugation. Experiments in animals have revealed two relevant points: first, that very low levels of circulating antigen are associated with an immune response, and secondly, that antigens located on lymphocyte membranes are more potent immunological stimuli than drug albumin conjugates (Park *et al.*, 1987; Soeberg *et al.*, 1978). Experiments in man have so far been restricted to the measurement of drug antigens on plasma proteins. Lafaye & Lapresie (1988) measured the amount of penicillin bound to circulating albumin in patients taking high doses of penicillin (40–50 $\times$ 10^6 iu per day) and found little interindividual variation in circulating penicilloyl groups, most of which was bound to albumin. The half-life of penicilloylated albumin varied from 7 to 23 h, but did not show any relationship with antibody response.

Penicillamine also forms albumin conjugates which have a much longer half-life 1.65 $\pm$ 0.29 days compared with an elimination half-life of 59 $\pm$ 6 min for penicillamine itself (Joyce *et al.*, 1991). Thus during chronic

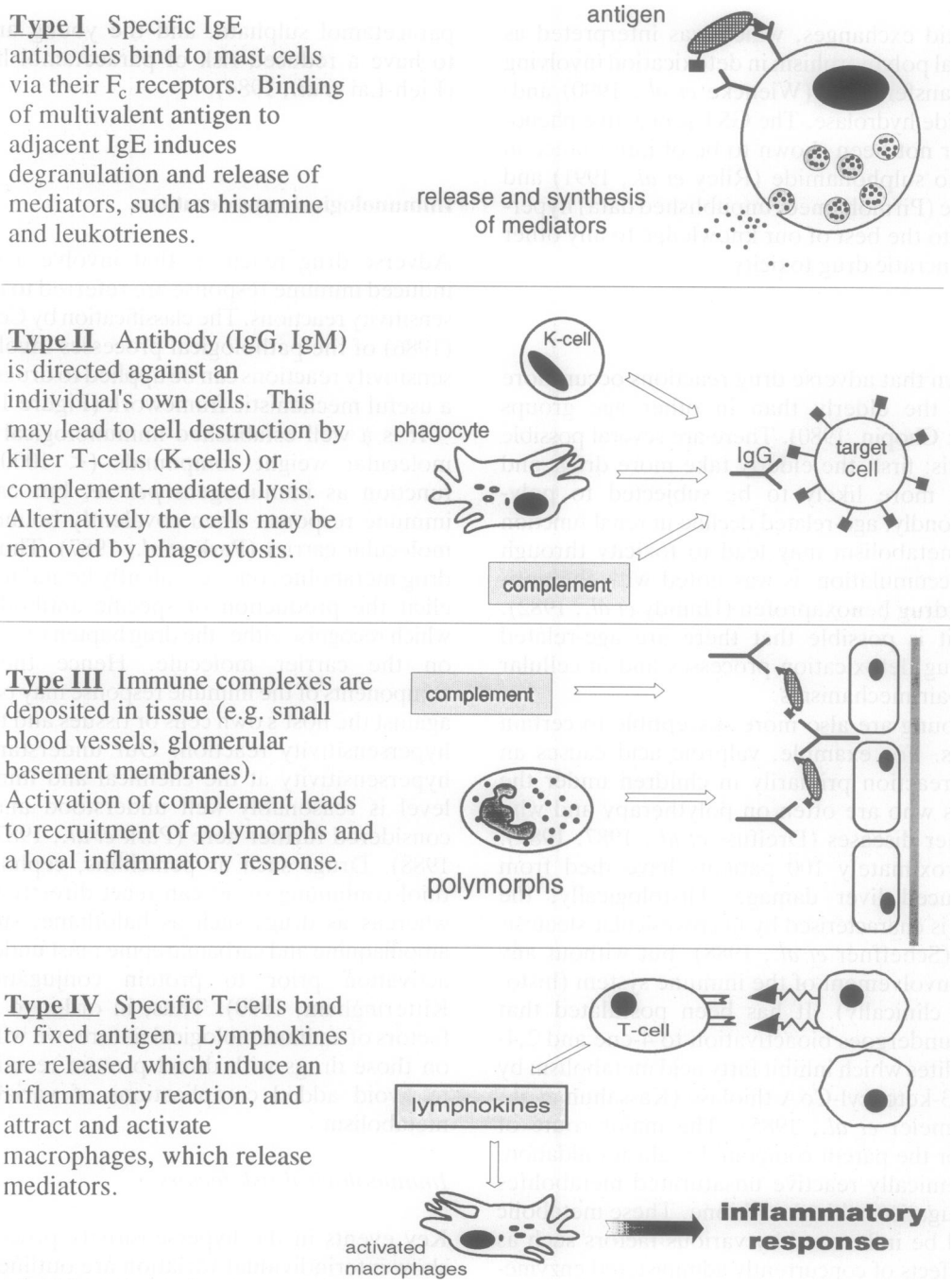

Figure 1 Mechanisms of drug hypersensitivity.

administration of a drug it may take several days to achieve steady-state levels of drug-protein conjugates. It would therefore be of interest to determine such levels in patients with and without adverse drug reactions.

When considering interindividual variation in immune responsiveness to a drug the two factors which need to be considered are the magnitude (titre) of the immune response and the type of immune response, i.e. IgE, IgG or cell-mediated. Studies of penicillins and cephalosporins indicate that in line with other anaphylactic reactions, drug-induced IgE antibody responses are under genetic control. Several studies have shown that there is a genetic restriction of immune responsiveness to the penicilloyl antigen (Adkinson & Wheeler, 1983). A prospective study showed that 62% of patients on a sizeable dose of penicillin antibiotics for at least 10 days had no detectable serological response to the major penicillin antigenic determinant (Adkinson & Wheeler, 1983). Such non-responders are thought to be at reduced risk of not only IgE-mediated allergy, but also of other types of hypersensitivity reaction to the drug.

Given the clear evidence, from both clinical and animal studies, that immune responsiveness is largely under genetic control, and that there are no obvious chemical characteristics (other than covalent binding to macromolecules) which dictate the intrinsic immunogenicity of a hapten, efforts have been made investigate the genetic basis of immune responsiveness in patients with ADRs.

HLA-haplotype and idiosyncratic reactions

One approach to identify the factors associated with immune responsiveness has been to look for empirical

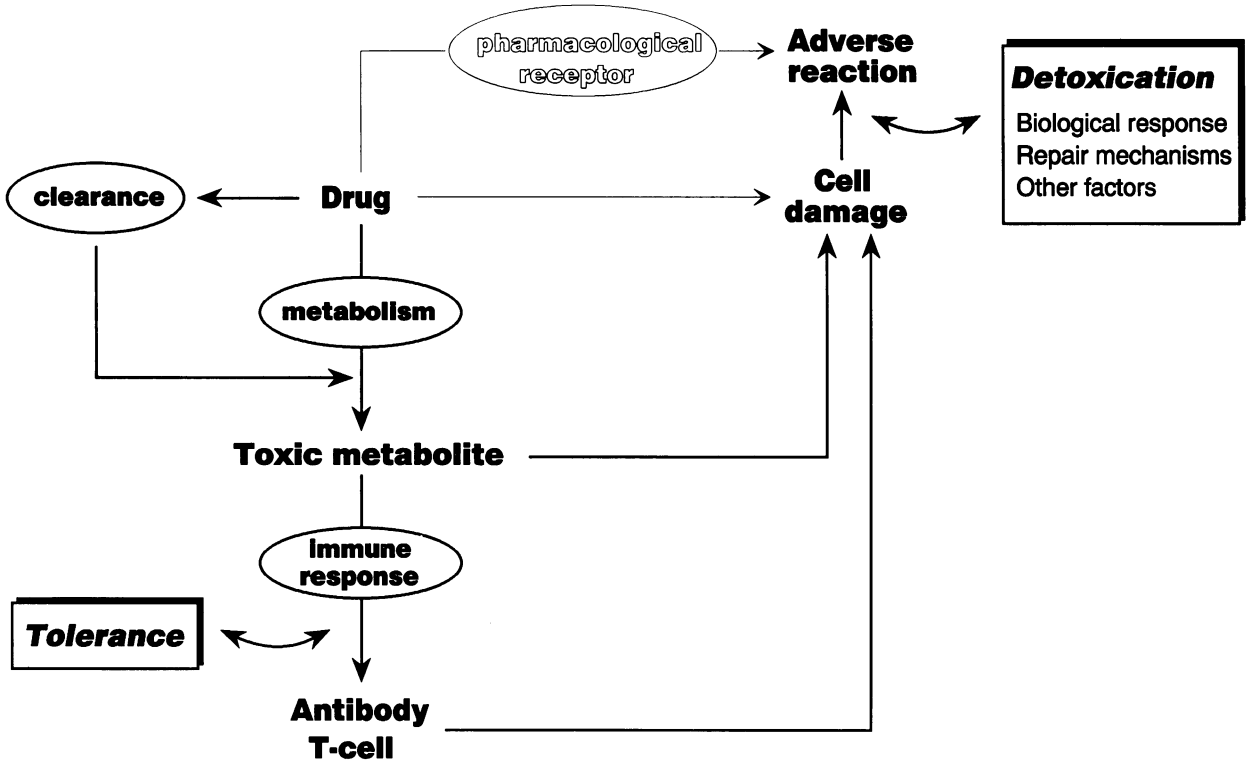

Figure 2 Proposed scheme for the role of toxic metabolites in idiosyncratic drug reactions.

relationships between idiosyncratic reactions and antigens associated with the major histocompatibility complex (MHC) expressed on accessible cells. Two major types of MHC-encoded molecules, class I (HLA-A, -B and -C) and class II (HLA-DP, -DQ, and -DR) can be distinguished by their function (Weatherall, 1991). Thus, the membrane bound-proteins encoded by the MHC serve as antigen presenting markers which are used by the immune system to distinguish self from non-self (Class I) and immune system cells from other cells (Class II). The discovery of Class II MHC proteins came about with the observation that a small number of so-called immune response genes (Ir) govern how an individual responds to all simple antigens. The variation of immunological responses with Class II MHC (Ir) genes suggests that certain Class II MHC protein polymorphisms are less efficient than others at recognising a given epitope. Indeed, epidemiological studies have shown that certain polymorphisms of MHC genes are associated with increased susceptibilities to certain autoimmune diseases such as insulin-dependent diabetes mellitus (Baisch *et al.*, 1990) and coeliac disease (Bugawan *et al.*, 1989).

HLA phenotyping has been investigated in patients with various idiosyncratic drug reactions. In several instances (Table 6), positive associations have been identified. However, although these HLA associations can be used to estimate the relative risk of developing the adverse reaction, they do not absolutely predict individual susceptibility. For example, Batchelor *et al.* (1980) investigated 26 patients with systemic lupus erythematosus induced by hydralazine, 25 of whom were slow acetylators. Although the frequency of HLA-DR4 (73%) was significantly higher in the hydralazine SLE group than in a group of patients treated with hydralazine without developing SLE or in a group of patients with idiopathic SLE, 25% of the control groups were also HLA-DR4 positive. In addition, some studies may give rise to false-positive association between an idiosyncratic drug reaction and a particular HLA subtype because such an association at the 5% level of statistical significance would be expected to occur for every 20 alleles typed. Conversely, true positive associations may be missed because of the difficulty in collecting a large cohort of patients with an idiosyncratic reaction to a drug, resulting in the use of small numbers of patients in such studies.

Other risk factors

Although induction of a drug-induced immune response is the primary event in drug hypersensitivity, it must be remembered that induction of an antibody response alone is not a pathological process. Indeed many patients with anti-drug antibodies or drug-induced autoantibodies remain asymptomatic, and therefore, it is highly likely that there are individual risk factors associated with the translation of an immune response into tissue damage.

Adkinson & Wheeler (1983) have been able to define five factors which they considered to be important with respect to penicillin allergy. First, the ability to respond serologically, as discussed; secondly, the half-life of IgE antibodies which ranged from 10 days to > 1000 days; thirdly, age since penicillin-induced anaphylactic reactions are apparently less frequent in children than adults; fourthly, the route of administration is important because allergic reactions are less frequent after oral than parenteral administration; and finally, an ill-defined factor which relates to the ability to release chemical mediators from mast cells, a process which is regulated by a myriad of physiological and pathological factors.

Table 6 HLA associations with drug toxicity

Drug	*Toxic manifestation*	*HLA association*	*Comments*	*References*
Clozapine	Agranulocytosis	B38, DR4, DQw3	Ashkenazi Jewish population	Lieberman *et al.* (1990)
Gold	1. 'Gold toxicity'	DR3, DRw6	Greek population	Pachoula-Papasteriades *et al.* (1986)
		B8, DR3		Scherak *et al.* (1984)
	2. Proteinuria	B8, DR3		Scherak *et al.* (1984); Pachoula-Papasteriades *et al.* (1986)
		DR3	Caucasians	Wooley *et al.* (1980)
			DR4 protective	Bensen *et al.* (1984)
				Gran *et al.* (1983)
		DQA2, DQB2		Singal *et al.* (1990)
	3. Dermatological toxicity	B7		Scherak *et al.* (1984)
		DR3	DR4 protective	Bensen *et al.* (1984)
		B35		Ferraccioli *et al.* (1986)
		DRw6		Pachoula-Papasteriades *et al.* (1986)
	4. Thrombocytopaenia	DR3	DR4 protective	Bensen *et al.* (1984)
		DQA2, DQB2		Singal *et al.* (1990)
	5. Pneumonitis	B40, Dw1		Hakala *et al.* (1986)
Hydralazine	SLE	DR4		Batchelor *et al.* (1980)
Levamisole	Agranulocytosis	B27		Diez (1990)
Oxicam	Toxic epidermal necrolysis	A2, B12		Roujeau *et al.* (1987)
Penicillamine	1. Penicillamine toxicity	DR3, B8		Scherak *et al.* (1984)
		DR3, DRw6		Pachoula-Papasteriades *et al.* (1986)
		DR3	Impaired sulphoxidation also a risk factor	Emery *et al.* (1984)
	2. Proteinuria	DR3, B8	DR2 protective	Stockman *et al.* (1986)
		B8		Dequeker *et al.* (1984); Scherak *et al.* (1984); Pachoula-Papasteriades *et al.* (1986)
	3. Thrombocytopaenia	A1, DR4, C4BQ0		Stockman *et al.* (1986)
	4. Pemphigus	B15		Zone *et al.* (1982)
	5. Myasthenia gravis	DR1		Delamere *et al.* (1983)
Tiopronin (Penicillamine-like compound)	Nephritis Dermatitis	B35, Cw4		Ferraccioli *et al.* (1986)
Sulphonamides	Toxic epidermal necrolysis	A29, B12, DR7		Roujeau *et al.* (1987)

The amount and site of drug antigen formation is probably the most important factor in determining when sensitisation is translated into tissue damage in type II, III and IV hypersensitivity. Most immunological processes depend on epitope density (i.e. is multivalent) rather than the total amount of epitopes recognisable by the antibody. Because of technical difficulties involved there have been no formal studies on the individual variation in the extent of antigen formation.

However, in studies of halothane hepatitis, in which the drug is thought to form neoantigens from an acylhalide metabolite formed by P450, it is thought that all experimental animals and patients exposed to the drug do generate the antigen (Kenna *et al.*, 1988). The incidence of hepatotoxicity (commonly referred to as halothane hepatitis) is between 1 in 3,500 and 1 in 35,000 (Moses & Mosteller, 1968; National Halothane Study, 1966). Thus it is thought that the difference in susceptible patients is more likely to be in immune response to the antigen rather than in neoantigen generation (Kenna *et al.*, 1988).

Immunological consequences of inter-individual variation in drug metabolism

Covalent modification of a protein by a haptenic group, leads not only to antibody response to the neoantigen, but also to epitopes on the native protein. Antibodies directed against particular P450 isozymes have been detected in patients with hepatic reactions to tienilic acid (Beaune *et al.*, 1987; Pons *et al.*, 1991) and dihydralazine (Bourdi *et al.*, 1990). These studies not only provide a clue to the pathogenesis of drug-induced liver diseases but also raise the possibility that inter-individual variation

in the expression of certain P450 isozymes may be one risk factor, especially for enzymes such as P4501A2 which is known to vary at least 40-fold in people and is inducible by cigarette smoking and dietary factors (Gonzalez, 1989).

The induction of antinuclear antibodies and systemic lupus erythematosus (SLE) by drugs such as procainamide, hydralazine and possibly, isoniazid, seems to be influenced by the polymorphic phase II metabolic pathway, *N*-acetylation. Woosley and colleagues (1978) have shown that although both fast and slow acetylators develop SLE with procainamide, the rate of development of antinuclear antibodies and the lupus syndrome was significantly higher in slow acetylators than in fast acetylators. With hydralazine, lupus occurs almost exclusively in slow acetylators (Batchelor *et al.*, 1980; Perry *et al.*, 1970; Russell *et al.*, 1987; Timbrell *et al.*, 1984). Isoniazid-induced lupus, which is less common than with either procainamide or hydralazine, has been shown by some (Godeau *et al.*, 1973), but not all (Evans *et al.*, 1972) studies to be associated with the slow acetylator phenotype. With all three drugs, acetylation may be acting in competition with the oxidative pathway, and thus, slow acetylators will have a greater proportion of the parent drug undergoing oxidative biotransformation to chemically reactive metabolites (Hein & Weber, 1989) which could form protein- and nucleic acid-adducts resulting in SLE. With procainamide, the protective effect of *N*-acetylation has been further confirmed by antiarrhythmic therapy with *N*-acetylprocainamide which does not induce SLE (Lahita *et al.*, 1979; Roden *et al.*, 1980).

General conclusions

From the general scheme shown in Figure 2 which illustrates the possible mechanisms involved in idiosyncratic reactions it can be seen that all reactions involve several sequential steps each of which may provide sources of inter-individual variation. Each factor in itself

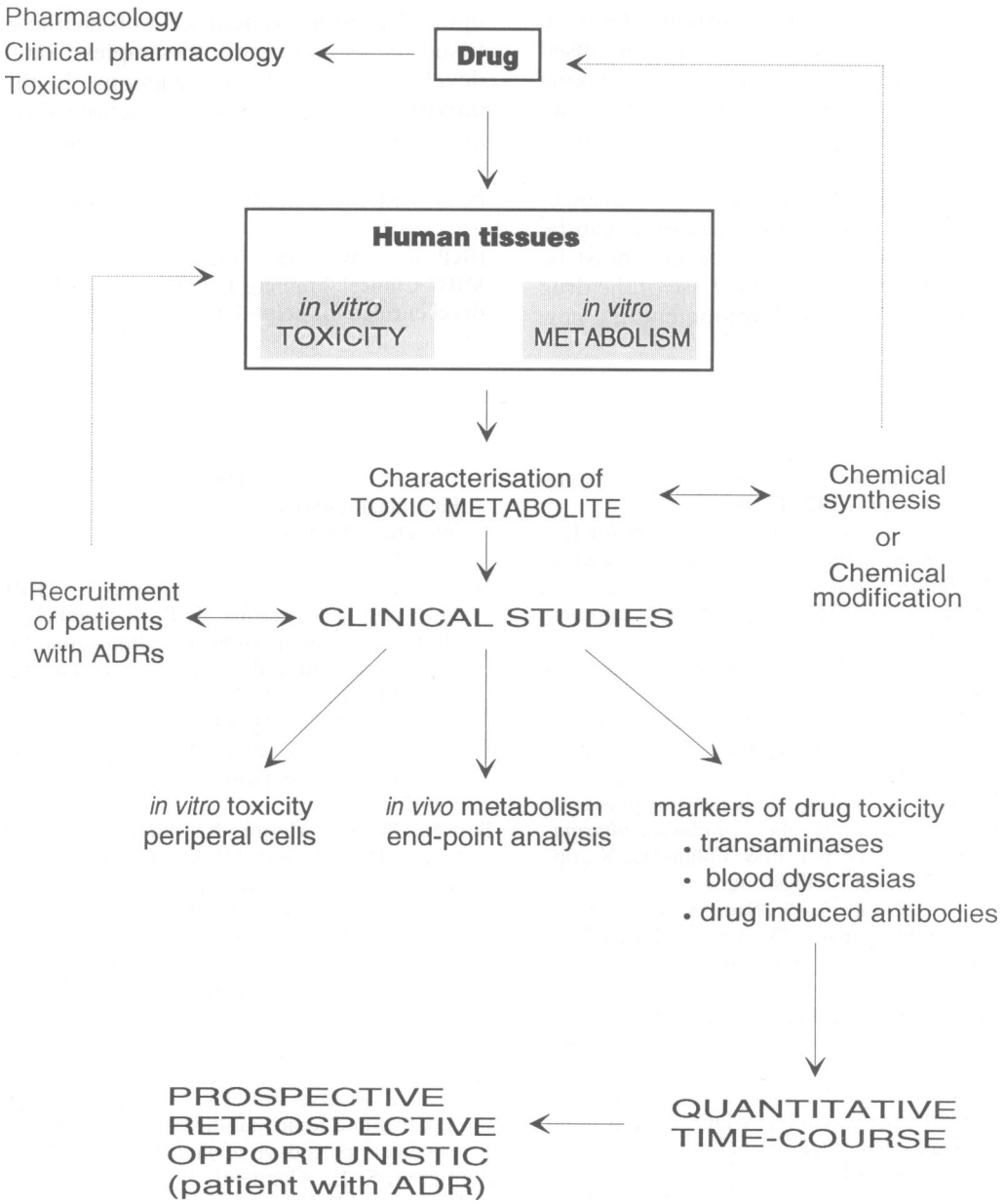

Figure 3 Proposed scheme for the evaluation of toxic metabolites in idiosyncratic reactions during drug development.

may not be sufficient to produce toxicity, but a combination of factors acting collectively in a certain individual may lead to serious toxicity. Thus it may not always be possible to define the risk factor responsible for a particular adverse drug reaction. On the other hand identification of important risk factors, such as deficiency in epoxide hydrolase, by careful chemical, immunochemical and genetic analysis of individual patients with very serious adverse reactions, may give a deeper understanding of the risk posed to such individuals from exposure to other drugs and chemicals in general. Furthermore, having defined a biochemical lesion, it should be possible to develop *in vitro* systems and animal models with which to explore the pathological consequences of exposure to various chemical entities.

It can also be seen from Figure 2 why preclinical safety evaluation in experimental animals does not identify drugs which ultimately cause idiosyncratic reactions in man. First, animal studies are carried out in only a few species of inbred animals and thus do not reflect the marked genetic heterogeneity in factors such as metabolism and immune responsiveness seen in man. Secondly, target organs for toxicity are usually identified at high daily mass doses, which cause a generalised chemical stress, and thus produce toxicity by breaking the weakest link in the detoxication chain, rather than by the more subtle and complex mechanisms thought to be in operation in idiosyncratic reactions in man.

Finally, one must consider whether recent advances in our understanding of idiosyncratic reactions can be used to predict such reactions. The question must be addressed at two levels; (a) the practical use of the drug in the clinical setting and (b) the development of a new drug. Because of the complex nature of idiosyncratic reactions, it seems unlikely that for the majority of drugs, where there is a multifactorial predisposition to idiosyncratic toxicity, a simple, reliable test that could be used routinely to screen patients for risk of toxicity from any drug could be developed for use in clinical practice. Alternatively, where a single important risk factor is responsible for determining individual susceptibility, prediction of risk by *in vitro* testing may be possible. The obvious example of this is the determination of G6PD status prior to primaquine administration. With respect to drug development the picture is more promising. Methods using human cells and tissues which have given a valuable insight into the mechanisms involved in idiosyncratic reactions provide a practical link between laboratory and clinical investigations of drug toxicity in man. A scheme outlining how such methodology could be used to provide an understanding of any adverse events observed during early clinical use of a new chemical entity, and how such information may be fed back into the drug discovery programme is outlined in Figure 3. The development of such a scheme will be dependent upon the establishment of well-characterised human tissue banks and access to samples from patients who develop serious adverse reactions. In this sense, it is important that idiosyncratic reactions should be viewed in the broader context of patient welfare, rather than a reaction to a particular drug which, by itself, would not be considered a major clinical problem.

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