EIDOS
A Mechanistic Classification of Adverse Drug Effects

Robin E. Ferner[1,2] and *Jeffrey K. Aronson*[3]

1   West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham, UK
2   Department of Clinical Pharmacology, University of Birmingham, Birmingham, UK
3   Department of Primary Health Care, Headington, Oxford, UK

Abstract
        The mechanisms of adverse drug effects have not been adequately classified. Here, we propose a comprehensive mechanistic classification of adverse drug effects that considers five elements: the Extrinsic chemical species (E) that initiates the effect; the Intrinsic chemical species (I) that it affects; the Distribution (D) of these species in the body; the (physiological or pathological) Outcome (O); and the Sequela (S), which is the adverse effect. This classification, which we have called EIDOS, describes the mechanism by which an adverse effect occurs; it complements the DoTS classification of adverse effects (based on clinical pharmacology), which takes into account Dose responsiveness, Time course, and Susceptibility factors. Together, these two classification systems, mechanistic and clinical, comprehensively delineate all the important aspects of adverse drug reactions; they should contribute to areas such as drug development and regulation, pharmacovigilance, monitoring therapy, and the prevention, diagnosis, and treatment of adverse drug effects.

An elderly woman falls and fractures her femur. There are many ways in which drugs could have contributed to the fall:
- postural hypotension (nifedipine);
- complete heart block (atenolol) or a cardiac arrhythmia (terfenadine), causing syncope;
- ataxia (carbamazepine);
- parkinsonism with a festinant gait (prochlorperazine);
- a peripheral sensory neuropathy (isoniazid);
- proximal muscle weakness (levothyroxine sodium);
- visual impairment (the anticholinergic effects of oxybutynin);
- a slippery bath (emulsifying ointment used to rehydrate dry skin).

In addition, glucocorticoid-induced osteoporosis would increase the risk of a fractured femur after a fall. Each of these adverse effects is produced by a different mechanism.

We define an adverse drug reaction as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product'.[1] Here we use the term 'drug' as shorthand to refer to the whole medicinal product, although the species that produces the adverse effect may not be the drug itself. The terms 'adverse reaction' and 'adverse effect' refer to the same phenomenon, but an adverse effect is seen from the point of view of the drug, while an adverse reaction is seen from the point of view of the patient; the drug causes an effect, while the patient experiences a reaction.

Previous discussion of the general mechanistic aspects of adverse drug effects has been incomplete and has concentrated on susceptibility factors,[2,3] pharmacological/immunological mechanisms, or the actions of metabolites,[4] or has been limited to biological agents.[5] There has been no systematic attempt to classify these mechanisms.

Here we propose a comprehensive mechanistic classification of adverse drug effects. Many adverse drug effects are described as 'avoidable' or 'preventable', including those that arise from prescribing faults, prescription errors, and other types of medication errors.[6] We do not discuss the systems factors or behavioural factors that permit such adverse effects to occur. We consider only the biological mechanisms that give rise to adverse drug effects.

1. Classifying Adverse Drug Effects Mechanistically

We call this mechanistic classification system EIDOS (table I, figures 1–3), which is a mnemonic for its components, and also reflects the Greek word eidos, which means, among other things, formal cause:

E = the Extrinsic chemical species that initiates the effect;
I = the Intrinsic chemical species that it affects;
D = the Distribution in the body of these species;
O = the (physiological or pathological) Outcome;
S = the Sequela (the adverse effect).

This mechanistic classification complements the clinical pharmacological classification that we have previously described – DoTS (figure 3).[7] DoTS classifies on the grounds of (i) Dose responsiveness, detailing the relation between the dose-response curve for benefit and the dose-response curve(s) for harm and thus distinguishing among hypersusceptibility, collateral, and toxic reactions; (ii) Time course, which can be rapid, first-dose, early, intermediate, late, or delayed; and (iii) the presence or absence of factors that alter the Susceptibility to the adverse effect.

EIDOS describes aspects of the mechanism by which the adverse effect arises, while the DoTS classification describes the clinical features of the adverse effect once it has occurred.

1.1 The Extrinsic Species Involved in the Adverse Effect

Adverse drug effects result from the introduction into the body of an extrinsic chemical species (E) in a medicinal product, or a species derived from it (E′), e.g. by metabolism. Different extrinsic species can be involved in adverse effects:

- *The drug molecule itself.* For example, indometacin inhibits renal prostaglandin synthesis and can cause renal impairment as a result.[8]
- *An excipient.* For example, polyoxyl 35 castor oil (Cremophor EL), which is used to make aqueous solutions of lipid-soluble drugs, such as ciclosporin (Sandimmun®), can cause non-IgE-mediated anaphylactic reactions.[9]
- *A contaminant*, such as 1,1′-ethylidenebis (L-tryptophan), a by-product of manufacture present in certain batches, produced eosinophilia-myalgia syndrome in patients treated with L-tryptophan.[10]
- *An adulterant*, such as lead or arsenic in herbal remedies,[11] or over-sulfated chondroitin sulfate deliberately introduced into batches of heparin.[12]
- *A degradation product* (before introduction into the body), such as the degradation products in outdated tetracycline that led to renal tubular damage.[13]
- *A derivative* (E′) of one of the above, particularly a metabolite of the parent compound,[14,15] e.g. the hepatotoxin hydrazine, a metabolite of isoniazid.[16]

Identifying the type of extrinsic species responsible for an adverse effect has practical implications: if it is the parent drug, the drug may have to be avoided or its dosage reduced; an excipient, contaminant, or adulterant can be removed from the formulation; when breakdown products of tetracycline were identified as causing Fanconi's syndrome, the limited shelf life of tetracycline was recognized; the identification of acrolein as a metabolite of cyclophosphamide led to the introduction of mesna to prevent haemorrhagic cystitis.

Table I. The EIDOS mechanistic classification of adverse drug effects

Feature	Varieties	Examples
E. Extrinsic species	The parent compound	Insulin
	An excipient	Polyoxyl 35 castor oil
	A contaminant	1,1′-ethylidenebis (L-tryptophan)
	An adulterant	Lead in herbal medicines
	A degradation product formed before the drug enters the body	Outdated tetracycline
	A derivative of any of these (e.g. a metabolite)	Acrolein (from cyclophosphamide)
I. The intrinsic species and the nature of its interaction with the extrinsic species:		
(a) molecular	Nucleic acids	
	DNA	Melphalan
	RNA	Mitoxantrone
	Enzymes	
	reversible effect	Edrophonium
	irreversible effect	Malathion
	Receptors	
	reversible effect	Prazosin
	irreversible effect	Phenoxybenzamine
	Ion channels/transporters	Calcium channel antagonists; digoxin and Na^+/K^+-ATPase
	Other proteins	
	immunological proteins	Penicilloyl residue hapten
	tissue proteins	N-acetyl-p-benzoquinone-imine (paracetamol [acetaminophen])
(b) extracellular	Water	Glucose 5%
	Hydrogen ions (pH)	Sodium bicarbonate
	Other ions	Sodium ticarcillin
(c) physical or physicochemical	Direct tissue damage	Intrathecal vincristine
	Altered physicochemical nature of the extrinsic species	Sulindac precipitation
D. Distribution	Where in the body the extrinsic and intrinsic species occur (affected by pharmacokinetics)	Antihistamines cause drowsiness only if they affect histamine H_1 receptors in the brain
O. Outcome (physiological or pathological change)	See table II	
S. Sequela	The adverse effect (Dose, Time, Susceptibility [DoTS] classification)[1]	

1.2 The Intrinsic Species and the Form of its Interaction with the Extrinsic Species

There are three types of interaction between an extrinsic chemical species and an intrinsic chemical species (a tissue or fluid in the body) that can result in an adverse effect.

1. *Molecular interactions*: Most interactions between the extrinsic species (E or E′) and the intrinsic species (I) are molecular, i.e. E (or E′) will bind with some affinity to one or more intrinsic molecules of the types listed in section 1.2.1).

2. *Alterations in the extracellular environment*: Some adverse effects result from alterations in the
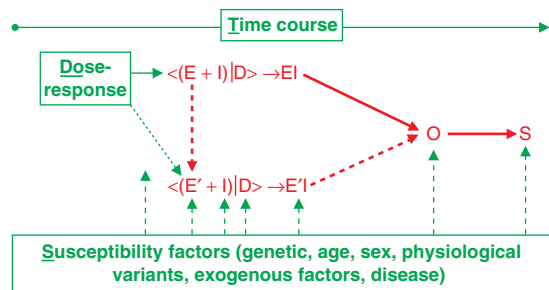
Fig. 1. The relationship between the EIDOS and DoTS classifications. EIDOS classifies the mechanism by which a medicine causes an adverse reaction. E (or E′) is the extrinsic species (or metabolite) that interacts with I, an intrinsic species, provided D, the distribution, brings the two into contact. EI (or E′I) engenders O, an outcome, whose sequela, S, is observed as the adverse effect. Clinically, S is seen at some characteristic time after the administration of a dose (or many doses) of the medicine, as described by the time course, T. The probability that an adverse reaction will occur depends on Do, the relationship between the dose-response curve of the beneficial effect and the dose-response curve of the adverse effect, and on several possible susceptibility factors, S, that can operate anywhere along the causal pathway. The EIDOS and DoTS systems are outlined in figure 3.

composition of the extracellular fluid, e.g. by dilution, alteration of hydrogen ions, or alterations in the concentrations of solutes, such as sodium or potassium ions.

3. *Physical or physicochemical effects*: Adverse effects sometimes result from physical or physicochemical effects, such as direct tissue damage or precipitation of a drug (e.g. within the renal tubules, in the bile, or in the stomach).[17]

1.2.1 Molecular Interactions

The intrinsic molecules that can be involved in interactions with extrinsic molecules include:

- *Nucleic acids*: Covalent adducts between cellular DNA and alkylating agents, such as melphalan,[18] probably explain the increased risk of leukaemia in patients treated with these drugs.
- *Enzymes*: Most drug action involving enzymes is via enzyme inhibition. Some drug interactions involve induction.

(a) *Reversible effects*: The peptidase that metabolizes angiotensin I to angiotensin II, angiotensin-converting enzyme (ACE), also metabolizes bradykinin; ACE inhibitors therefore inhibit the breakdown of bradykinin, whose increased concentration probably ex-

plains the adverse effects of angioedema and cough.[19] Drugs that inhibit or induce enzymes related to drug metabolism are also associated with adverse effects through drug interactions, and these are included as susceptibility factors in the DoTS classification.[1]

(b) *Irreversible effects*: Inhibition of platelet cyclo-oxygenase by aspirin (acetylsalicylic acid),[20] with a consequent tendency to haemorrhage that persists for several days after the end of treatment, is irreversible.

- *Receptors*: Pharmacological receptors (including neurotransmitter, hormone, and cytokine receptors) are the main targets for the actions of drugs. Adverse effects can result from altered receptor action, in the target organ or elsewhere, either by a direct effect of the drug on the receptor (e.g. agonists and antagonists) or by indirect effects (e.g. neurotransmitter releasers or inhibitors of neurotransmitter reuptake or metabolism). For example, fenfluramine increases the release of serotonin, which stimulates the serotonin 5-HT$_{2B}$ receptor, activating
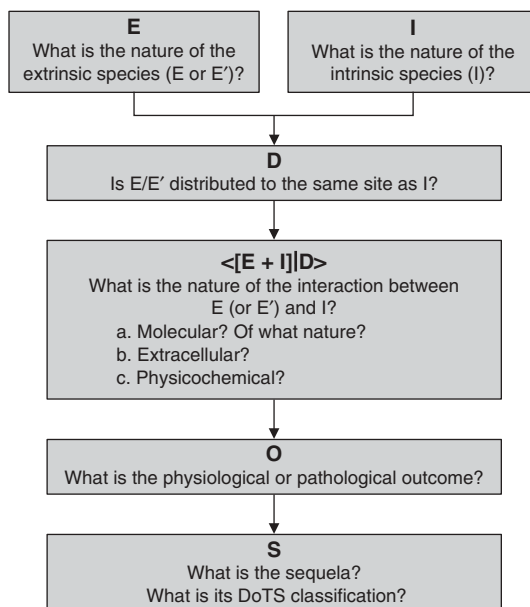

Fig. 2. The questions to be asked at each stage of the EIDOS classification process. **DoTS** = Dose relationship, Time course, Susceptibility.[1]
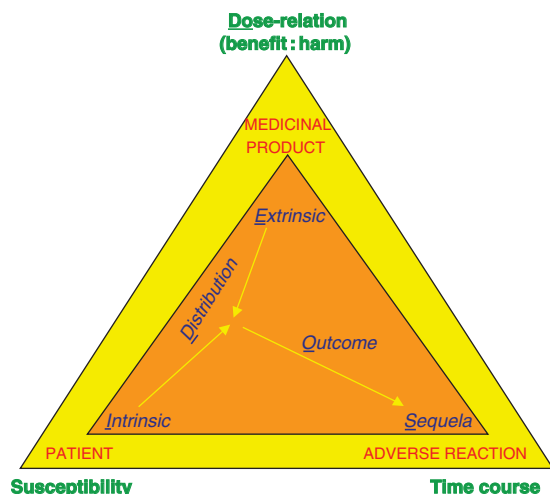
Fig. 3. Two complementary forms of classification of adverse drug reactions. An adverse reaction occurs when a medicinal product is administered to a patient (red upper case text). Adverse reactions can be classified mechanistically (EIDOS; blue italicized text) by noting that the extrinsic (drug) species, when co-distributed with one or more intrinsic (patient) species, has a pharmacological or other effect (the outcome), producing the adverse effect (the sequela). It can be further classified using the DoTS clinical classification (green bolded text), which defines the important aspects of the drug (the relationship between the dose-response curves for benefits and harms, the patient (susceptibility factors), and the reaction (its time course).

kinases that stimulate cell growth in pulmonary valve tissue, causing pulmonary valve lesions.[21] Irreversible receptor inactivation by covalent interaction, e.g. inhibition of α-adrenoceptors by phenoxybenzamine,[22] can lead to collateral adverse effects.

- *Ion channels/transporters*: Inhibition of potassium channels in the distal convoluted tubule of the kidney by triamterene causes hyperkalaemia.[23] Excess inhibition of the $Na^+/K^+/2Cl^-$ co-transporter by loop diuretics in the loop of Henle in the kidney causes hyponatraemia and dehydration.[24]
- *Other proteins*:
  (a) *Immunological proteins*: Immunological effects of all the four types classified by Gell and Coombs[25] can result from interactions between large extrinsic molecules (e.g. peptides and proteins) and intrinsic proteins or cells, from direct effects on components of the immune pathway, or by formation of immuno-

genic adducts, as exemplified by the haptens formed between the penicilloyl moiety of β-lactam antibacterial agents and intrinsic proteins.[26] Such effects include the interaction between penicillins and IgE, causing anaphylaxis in sensitized individuals, or between proteins in horse serum and IgG, leading to serum sickness in those treated with horse-derived snake anti-venoms.[27]

(b) *Tissue proteins*: Direct damage to structural proteins can cause functional derangement, as happens when the metabolite N-acetyl-*p*-benzoquinone-imine (NAPQI) binds covalently to sulfhydryl-containing hepatic and renal proteins after paracetamol (acetaminophen) poisoning.[28]

1.2.2 Alteration of the Extracellular Environment

The extracellular environment can change as a consequence of molecular interactions of the types mentioned above, as happens, for example, when chlorpropamide acts on vasopressin receptors.[29] However, there can be direct or non-specific effects on the components of the extracellular environment. These can affect water, hydrogen ions (pH), and other ions.

- *Water:* Crystalloids, such as 5% glucose, can cause water intoxication directly; absorption of glycine solution during transurethral resection of the prostate gland[30] can have important, albeit transient, effects on cardiovascular and neurological function.
- *pH*: Changes in hydrogen ion concentration can lead to important local or systemic adverse effects. Large-volume infusions of solutions (such as sodium chloride 0.9%) that contain strong anions can cause metabolic acidosis.[31]
- *Other ions*: High concentrations of cations, such as sodium, can result directly from the use of antibacterial drugs made up as salts, such as sodium ticarcillin.[32]

1.2.3 Physical or Physicochemical Interactions

Examples of adverse effects that result from physical or physiochemical effects include renal calculi due to precipitation of triamterene in the renal tract and gallstones due to precipitation of

sulindac in the biliary tract.[15] Corrosives, for example phenol used for nerve ablation, can cause non-specific tissue damage.[33]

1.3 Distribution

The extrinsic (E [or E′]) and intrinsic (I) species will interact only when they are both found in the same place. Thus, the pharmacokinetics of the extrinsic species can affect the occurrence of adverse effects. For example, histamine H_1 receptor antagonists (antihistamines), such as chlorphenamine, that cross the blood-brain barrier can act on CNS histamine receptors and cause drowsiness. Newer antihistamines, such as cetirizine, do not generally cross the blood-brain barrier in significant amounts and do not reach CNS H_1 receptors; they therefore do not cause drowsiness.[34]

1.4 Outcome of the Interaction

Interactions between extrinsic and intrinsic species in the production of an adverse effect can result in physiological or pathological changes. Examples of these are listed in table II, using a pathological classification based on that described in *Robbins & Cotran Pathologic Basis of Disease*.[46] Some adverse effects arise through a combination of mechanisms.

1.5 Sequelae

The sequelae of the pathological changes induced by a drug constitute the final step in this

Table II. Examples of physiological and pathological changes in adverse drug reactions (some categories can be broken down further)

Type of change	Examples
Physiological changes	
Increased actions	Hypertension (monoamine oxidase inhibitors); clotting (tranexamic acid)
Decreased actions	Bradycardia (β-adrenoceptor antagonists); QT interval prolongation (antiarrhythmic drugs)
Cellular adaptations	
Atrophy	Lipoatrophy (subcutaneous insulin); glucocorticoid-induced myopathy
Hypertrophy	Gynaecomastia (spironolactone)
Hyperplasia	Pulmonary fibrosis (busulfan); retroperitoneal fibrosis (methysergide)
Metaplasia	Lacrimal canalicular squamous metaplasia (fluorouracil)[35]
Neoplasia[36]	
benign	Hepatoma (anabolic steroids)[37]
malignant	
hormonal	Vaginal adenocarcinoma (diethylstilbestrol)[38]
genotoxic	Transitional cell carcinoma of bladder (cyclophosphamide)[39]
immune suppression	Lymphoproliferative tumours (ciclosporin)[40]
Altered cell function	IgE-mediated mast cell degranulation (class I immunological reactions)
Cell damage	
Acute reversible damage	
chemical damage	Periodontitis (local application of methylenedioxymetamfetamine [MDMA, 'ecstasy'])[41]
immunological reactions	Class III immunological reactions
Irreversible injury	
cell lysis	Class II immunological reactions
necrosis	Class IV immunological reactions; hepatotoxicity (paracetamol, after apoptosis)
apoptosis	Liver damage (troglitazone)[42]
Intracellular accumulations	
Calcification	Milk-alkali syndrome[43]
Drug deposition[15]	Crystal-storing histiocytosis (clofazimine)[44]
	Skin pigmentation (amiodarone)[45]

Table III. Examples of the classification of adverse effects using the EIDOS and DoTS systems

Classification	Examples		
	a fall due to nifedipine	*a fall due to prochlorperazine*	*osteoporosis due to a glucocorticoid*
EIDOS			
Extrinsic species	The parent drug	The parent drug and metabolites	The parent drug
Intrinsic species	Calcium channel antagonists	Dopamine receptors	Calcium homeostasis; osteoblasts
Distribution	Vascular smooth muscle	Extrapyramidal tracts	Sites of calcium transport; bone
Outcome	Physiological: vasodilatation	Physiological: parkinsonism	Atrophy: osteoporosis
Sequelae	Fall and fracture	Fall and fracture	Fracture
DoTS			
Dose relation	Toxic	Collateral	Collateral
Time course	Time independent	Early persistent	Late
Susceptibility factors	Old age, other drugs	Old age	Postmenopausal women

classification and describe the clinically recognizable adverse drug reaction. There may be more than one sequela of an adverse drug effect; in our introductory case, a drug-related fall led to a fracture.

Sequelae can be classified using the DoTS system, thus completing the combined mechanistic and clinical classification, as the examples in table III show, drawing again on our introductory case.

Adverse drug interactions can also be accommodated in this classification. An adverse effect that arises as a result of an interaction can be classified mechanistically by EIDOS in the same way as any other adverse effect. The fact that it is due to an interaction is dealt with by the susceptibility part of DoTS; the interacting drug constitutes the susceptibility factor. An example is given in table III (see the column relating to nifedipine).

2. Discussion

The DoTS classification is a clinical classification of the observed features of adverse drug reactions. It could be used, for example, in pharmacovigilance planning[47] and in developing regulatory strategies for dealing with new adverse drug reactions after a drug has been given marketing authorization.[48] EIDOS, which considers the mechanisms of adverse drug effects, extends the idea of rational classification to encompass non-clinical information. When relevant data are absent, EIDOS provides a framework for assembling them. It cannot, of course, guide decisions in the absence of such data.

3. Conclusion

We believe that the DoTS and EIDOS classification schemes, which comprehensively delineate all the important aspects of adverse drug reactions, could together contribute to areas such as drug development and regulation, pharmacovigilance, monitoring therapy, and the prevention, diagnosis and treatment of adverse drug reactions.

Acknowledgements

References

1. Aronson JK, Ferner RE. Clarification of terminology in drug safety. Drug Saf 2005; 28 (10): 851-70
2. Rawlins MD, Thomas SHL. Mechanisms of adverse drug reactions. In: Davies DM, Ferner RE, de Glanville H, editors. Davies's textbook of adverse drug reactions. 5th ed. London: Chapman & Hall, 1998: 40-64
3. Pirmohamed M, Park BK. Mechanisms of adverse drug reactions. In: Mann RD, editor. Pharmacovigilance. 2nd ed. Chichester: John Wiley & Sons, 2007: 85-103
4. Williams DP. Toxicophores: investigations in drug safety. Toxicology 2006; 226: 1-11

5. Pichler WJ. Adverse side-effects to biological agents. Allergy 2006; 61: 912-20

6. Aronson JK. Medication errors: what they are, how they happen, and how to avoid them. Q J Med 2009; 102: 513-21

7. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ 2003; 327: 1222-5

8. Cheng HF, Harris RC. Renal effects of non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors. Curr Pharm Des 2005; 11: 1795-804

9. Gelderblom H, Verweij J, Nooter K, et al. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer 2001; 37: 1590-8

10. Simat TJ, Kleeberg KK, Müller B, et al. Synthesis, formation, and occurrence of contaminants in biotechnologically manufactured L-tryptophan. Adv Exp Med Biol 1999; 467: 469-80

11. Bayly GR, Braithwaite RA, Sheehan TMT, et al. Lead poisoning from Asian traditional remedies in the West Midlands: report of a series of five cases. Hum Exp Toxicol 1995; 14: 24-8

12. Blossom DB, Kallen AJ, Patel PR, et al. Outbreak of adverse reactions associated with contaminated heparin. N Engl J Med 2008; 359: 2674-84

13. Gross JM. Fanconi syndrome (adult type) developing secondary to the ingestion of outdated tetracycline. Ann Intern Med 1963; 58: 523-8

14. Pirmohamed M, Kitteringham NR, Park BK. The role of active metabolites in drug toxicity. Drug Saf 1994; 11: 114-44

15. Nelson SD. Molecular mechanisms of adverse drug reactions. Curr Ther Res 2001; 62: 885-99

16. Tafazoli S, Mashregi M, O'Brien PJ. Role of hydrazine in isoniazid-induced hepatotoxicity in a hepatocyte inflammation model. Toxicol Appl Pharmacol 2008; 229: 94-101

17. Aronson JK, Hauben M. Anecdotes that provide definitive evidence. BMJ 2006; 333: 1267-9

18. Tilby MJ, Newell DR, Viner C, et al. Application of a sensitive immunoassay to the study of DNA adducts formed in peripheral blood mononuclear cells of patients undergoing high-dose melphalan therapy. Eur J Cancer 1993; 29A: 681-6

19. Mukae S, Aoki S, Itoh S, et al. Bradykinin B(2) receptor gene polymorphism is associated with angiotensin-converting enzyme inhibitor-related cough. Hypertension 2000; 36: 127-31

20. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclo-oxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001; 345: 1809-17

21. Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT(2B) receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation 2000; 102: 2836-41

22. Minneman KP. Phenoxybenzamine is more potent in inactivating alpha 1- than alpha 2-adrenergic receptor binding sites. Eur J Pharmacol 1983; 94: 171-4

23. Walker BR, Capuzzi DM, Alexander F, et al. Hyperkalemia after triamterene in diabetic patients. Clin Pharmacol Ther 1972; 13: 643-51

24. Spino M, Sellers EM, Kaplan HL, et al. Adverse biochemical and clinical consequences of furosemide administration. CMAJ 1978; 118: 1513-8

25. Coombs RRA, Gell PGH. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell PGH, Coombs RRA, Lachmann PJ, editors. Clinical aspects of immunology. London: Blackwell Scientific Publications, 1975: 761-81

26. Pichler WJ. Immune mechanism of drug hypersensitivity. Immunol Allergy Clin North Am 2004; 24: 373-97, v-vi

27. LoVecchio F, Klemens J, Roundy EBA, et al. Serum sickness following administration of antivenin (Crotalidae) polyvalent in 181 cases of presumed rattlesnake envenomation. Wilderness Environmental Med 2003; 14: 220-1

28. James LP, Mayeux PR, Hinson JA. Acetaminophen-induced hepatotoxicity. Drug Metab Dispos 2003; 31: 1499-506

29. Durr JA, Hensen J, Ehnis T, et al. Chlorpropamide up-regulates antidiuretic hormone receptors and unmasks constitutive receptor signaling. Am J Physiol Renal Physiol 2000; 278: F799-808

30. Collins JW, MacDermott S, Bradbrook RA, et al. The effect of the choice of irrigation fluid on cardiac stress during transurethral resection of the prostate: a comparison between 1.5% glycine and 5% glucose. J Urol 2007; 177: 1369-73

31. Morgan TJ. The meaning of acid-base abnormalities in the intensive care unit. Part III. Effects of fluid administration. Crit Care 2005; 9: 204-11

32. Finch RA. Hypernatremia during lithium and ticarcillin therapy. South Med J 1981; 74: 376-7

33. Bodine-Fowler SC, Allsing S, Botte MJ. Time course of muscle atrophy and recovery following a phenol-induced nerve block. Muscle Nerve 1996; 19: 497-504

34. Kaliner MA, Check WA. Non-sedating antihistamines. Allergy Proc 1988; 9: 649-63

35. Prasad S, Kamath GG, Phillips RP. Lacrimal canalicular stenosis associated with systemic 5-fluorouracil therapy. Acta Ophthalmol Scand 2000; 78: 110-3

36. Farber E. Possible etiologic mechanisms in chemical carcinogenesis. Environ Health Perspect 1987; 75: 64-70

37. Farrell GC, Joshua DE, Uren RF, et al. Androgen-induced hepatoma. Lancet 1975; 1: 430-2

38. Rubin MM. Antenatal exposure to DES: lessons learned … future concerns. Obstet Gynecol Surv 2007; 62: 548-55

39. Knight A, Askling J, Granath F, et al. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis 2004; 63: 1307-11

40. Ryffel B. The carcinogenicity of ciclosporin. Toxicology 1992; 73: 1-22

41. Brazier WJ, Dhariwal DK, Patton DW, et al. Ecstasy related periodontitis and mucosal ulceration: a case report. Br Dent J 2003; 194 (4): 197-9

42. Bae MA, Song BJ. Critical role of c-Jun N-terminal protein kinase in troglitazone-induced apoptosis of human HepG2 hepatoma cells. Mol Pharmacol 2003; 63: 401-8

43. Goldsmith DJ. Milk-alkali syndrome with metastatic calcification. Am J Med 1996; 100: 481-2

44. Sukpanichnant S, Hargrove NS, Kachintorn U, et al. Clofazamine-induced crystal-storing histiocytosis producing chronic abdominal pain in a leprosy patient. Am J Surg Pathol 2000; 24: 129-35

45. Adams PC, Holt DW, Storey GCA, et al. Amiodarone and its desethyl metabolite: tissue distribution and morphologic changes during long-term therapy. Circulation 1985; 72: 1064-75

46. Cotran RS, Kumar V, Collins T. Robbins and Cotran Pathologic Basis of Disease. 7th ed. Amsterdam: Elsevier, 2008: 3-46

47. Callréus T. Use of the dose, time, susceptibility (DoTS) classification scheme for adverse drug reactions in pharmacovigilance planning. Drug Saf 2006; 29: 557-66

48. Aronson JK, Price D, Ferner RE. A strategy for regulatory action when new adverse effects of a licensed product emerge. Drug Saf 2009; 32: 91-8

Correspondence: Professor *Robin E. Ferner*, City Hospital, Dudley Road, Birmingham B18 7QH, UK.
E-mail: r.e.ferner@bham.ac.uk