Adverse drug reactions: back to the future

Munir Pirmohamed & B. Kevin Park

Department of Pharmacology and Therapeutics, The University of Liverpool, Ashton Street, Liverpool L69 3GE, UK

Primum non nocere

(‘first of all be sure you do no harm’)

Hippocrates (460–370 BC)

Introduction

The above is a long-held principle in medicine. Unfortunately, this principle has never been achieved. Historically, there are many ways in which patients have come to harm through the practice of medicine, and this unfortunately continues in the present day. Adverse drug reactions have to be considered as one of the major causes of iatrogenic disease [1] and are as old as Medicine itself [2]. Adverse drug reactions can present clinically in many different ways, and indeed have taken over from syphilis and TB as the mimic of disease [3]. Although many adverse drug reactions are mild, there are many others that are severe, and occasionally life-threatening. Many adverse reactions are preventable [4], and ideally should not occur, but it is also true to say that there are as many other adverse reactions that cannot be prevented largely because we do not understand why and how they occur. Drugs continue to be withdrawn from the market because of unacceptable safety profiles [5]; over the last 25 years, approximately 10% of new drugs that were approved in the USA either had to be withdrawn or were labelled with a ‘Black Box’ warning [6]. This is of major concern to many pharmaceutical companies given that there are relatively few new products in the pipelines.

Can we improve on this as we enter a new century? We feel that the answer to this has to be affirmative. In this review, we provide some examples where there have already been advances, but point out where more work needs to be done to translate these advances into clinical practice (where appropriate), in order to reduce the burden of adverse drug reactions.

Epidemiology of adverse drug reactions

A meta-analysis by Lazarou and colleagues of studies performed in the US suggested that adverse drug reac-

tions (ADRs) were the fourth commonest cause of death in 1994, causing more than 100 000 deaths per year [7]. Although the methodology used in this study has been criticised [8], it nevertheless underlines that ADRs can kill patients. A more recent systematic review has shown that 7% of all admissions are due to ADRs, with the overall impact in the UK being 4 out of 100 hospital-bed days [9]. This equates to between 4–6 400-bed hospitals having their entire capacity being subsumed in ADR-related admissions at an annual cost to the NHS of approximately £400 million. This study also suggested that the ADR incidence may have decreased since 1985; however, this has to be interpreted with caution, particularly in the UK, where there have only been nine studies involving 26 000 patients. In comparison, in the US, there have been 29 studies involving 240 000 patients. A recent pilot study in Liverpool showed that 7.5% of admissions were due to ADRs [10]; this has been followed by a more extensive study of over 18 000 patients, which is due to report in 2003, and will provide more up-to-date data of the burden of ADRs on the NHS in the UK.

Detection of adverse drug reactions

At the time of licensing, only 1500 patients will have been exposed to the drug [5]. This provides limited statistical power to detect adverse drug reactions. The more common type A ADRs (reactions that are an augmentation of the normal pharmacological actions of the drug) may already have been identified by the time of licensing. By contrast, type B ADRs (bizarre reactions that cannot be predicted from the known pharmacology of the drug), which are relatively uncommon, will only be detected after licensing through postmarketing surveillance [1]. Since the thalidomide tragedy, the cornerstone of postmarketing surveillance in the UK and other countries has been spontaneous reporting schemes such as the yellow card scheme [11]. This scheme has identified numerous ADRs, which has resulted in regulatory action (Table 1). However, the scheme has its deficiencies, most prominent of which is the degree of under-reporting [11]. This can result in a lengthy delay between licensing and detection of the adverse reaction, and any regulatory action. For example, almost 7 million patients had been exposed to fenfluramine before

Correspondence: Professor M. Pirmohamed, Department of Pharmacology, The University of Liverpool, Ashton Street, Liverpool L69 3GE, UK. Tel.: 44 15179 45549; Fax: 44 15179 45540; E-mail: munirp@liv.ac.uk

Received 17 December 2002, accepted 27 January 2003.

Table 1 Identification of adverse drug reactions through the yellow card scheme.

<i>Year</i>	<i>Drug</i>	<i>ADR</i>	<i>Action</i>
1992	Metipranolol	Uveitis	Withdrawal
1993	Remoxipride	Aplastic anaemia	Withdrawal
1993	Pancreatins	Colonic stricture	Advice
1994	Rifabutin	Uveitis	Warnings and dose reduction
1995	Tacrolimus	Cardiomyopathy	Warnings, dose reduction
1996	Alendronate	Oesophageal reactions	Warnings
1997	Methotrexate (low dose)	Blood dyscrasias	Advice
1998	Vigabatrin	Visual field defects	Warnings
1999	Clozapine	Gastrointestinal obstruction	Advice
2000	Amethocaine gel	Local skin reactions	Warning and advice
2001	Bupropion	Various adverse effects	Altered dosing, warnings and advice
2002	Pergolide	Fibrotic reactions	Warnings

its potential to cause valvular heart disease led to regulatory action [12].

Thus, there should be continuous evaluation of any spontaneous reporting schemes so that changes can be introduced when needed to ensure that signals of possible ADRs are detected as soon as possible after licensing. In the UK, various initiatives have been introduced to the yellow card system since its inception in 1964 including the following:

- 1 The setting up of regional monitoring centres, akin to the system used in France, to support and encourage local reporters.
- 2 Allowing pharmacists and more recently nurses to report ADRs after pilot schemes in Newcastle [13] and Liverpool [14], respectively, showed that reports received from this group of health-care professionals were equivalent to those received from doctors. The increase in pool of reporters may allow an increase in numbers of serious ADRs that are reported, without a worsening of the signal-noise ratio.
- 3 The development of an electronic yellow card (<https://http://www.mca.gov.uk/ourwork/monitorsafequalmed/yellowcard/submityc/ycreporter.htm>) to allow potential reporters greater choice in reporting methods.

An issue that has not yet been tackled in the UK is the reporting of ADRs by patients. This is currently allowed in the US via the MEDWATCH scheme run by the FDA [15]; however, whether this has led to detection of new ADRs not reported by health-care professionals seems unlikely. Whether direct reporting by consumers will improve the process of pharmacovigilance needs further objective evaluation.

Detection of signals generated via spontaneous reporting schemes can be regarded as a hypothesis-generating tool. These hypotheses have to be tested using epidemi-

ological approaches. To this end, the availability of computerized databases in the UK such as GPRD [16] and MEMO [17] can be regarded as a major advance that has highlighted numerous drug safety issues, with the consequent protection of public health. The further development of these databases so that all sectors of healthcare, and the interface between them, are covered is essential in the future to maintain the initial successes of the currently available systems. It is also possible that, with the wider availability and uptake of computerized prescribing systems, it can be envisaged that many ADRs will be prevented through prospective identification of prescribing errors, and it will be possible to better monitor iatrogenic disease by linkage of prescription and clinical data. The technology to develop such computerized systems is already available, but advances have been slow because of lack of resources.

Clinical manifestations of adverse drug reactions

ADRs can present in many different ways, affect any bodily system and mimic any naturally occurring disease process. The many different manifestations of ADRs have been systematically covered elsewhere [18]. This variability in manifestations means that clinicians always have to consider that the drug may be the cause of the patients' symptoms. With the completion of the human genome project and the anticipated increase in drug targets, it is likely that new challenges will be faced as new drugs are introduced, which will have to be detected through clinical evaluation of patients. A typical example is protease inhibitors, used in the treatment of human immunodeficiency virus (HIV), which in combination with nucleoside reverse transcriptase inhibitors, have been reported to cause lipodystrophy, a fat redistribution syndrome characterized by fat atrophy, fat hypertrophy and metabolic derangements [19]. The pathogenesis of this syn-

drome is complex and poorly understood, and involves an interaction between the drugs, disease and genetic constitution [20]. Similarly, biotechnology compounds, which are likely to increase in number over the next decade, may also cause adverse reactions that would not have been predicted from the known biology of the system that they are interacting with. This is perhaps best exemplified by antagonism of tumour necrosis factor (TNF)- α , which has been reported to cause various adverse reactions including blood dyscrasias and systemic lupus erythematosus [21, 22].

Examples of adverse drug reactions

Below are specific examples of some ADRs, which are discussed in greater detail to highlight either their importance and/or recent findings that have provided insights into their mechanisms.

Non-steroidal anti-inflammatory drugs and peptic ulceration

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs, particularly in the elderly. About 40% of patients over the age of 65 years receive at least one NSAID for more than 75% of any year [23, 24]. NSAIDs cause a wide range of adverse effects, the most important of which in public health terms, is their ability to induce peptic ulceration [24]. Between 15 and 35% of all peptic ulcer complications are due to NSAIDs. In the US, there are 41 000 hospitalizations and 3300 deaths per year among the elderly that are attributable to NSAIDs [24]. In the UK, the corresponding figures are 12 000 hospital admissions and 2000 deaths per year [25]. Overall, NSAIDs kill 1 in 1200 people who take them for 2 months or more [26]. Epidemiological studies have been extremely important in elucidating risk factors, which include older age, previous history of intolerance and a past history of ulceration or gastro-intestinal haemorrhage [24]. Furthermore, the risk of peptic ulceration varies among the different NSAIDs that are available: ibuprofen has the lowest risk while the risk with azapropazone is 9.2-fold greater than with ibuprofen, with the most commonly used NSAIDs such as diclofenac and naproxen having an intermediate risk [27]. The ulcerogenic ability of a NSAID correlates well with its ability to inhibit prostaglandin synthesis, and this is exacerbated by gastric acid. Neutrophils may also be involved in the injury to the mucosa through production of oxygen-free radicals, proteases, cytokines and leukotrienes [28].

Various manoeuvres have been used to reduce NSAID-mediated injury to the gastric mucosa. Co-prescription of proton pump inhibitors or misoprostol reduces the risk of gastric ulceration with NSAIDs, and

this is better than the use of H₂-receptor antagonists [28]. The identification of two isoforms of cyclo-oxygenase (COX-1 and COX-2) [29], of which COX-2 is pro-inflammatory, has led to the development of highly selective COX-2 inhibitors such as rofecoxib and celecoxib. These newer compounds are associated with a lower risk of peptic ulceration than nonselective inhibitors [30, 31], but this therapeutic advantage is offset by the use of low-dose aspirin for cardiovascular prophylaxis, and channeling of high-risk patients (i.e. those with a past history of ulceration) to the use of COX-2 inhibitors. Furthermore, COX-2 inhibitors may have their own particular safety problems including an increased risk of cardiovascular thrombotic events because of the lack of antiplatelet effects [30], potential to cause hypersensitivity [32] and renal adverse effects (equivalent to those caused by non-selective inhibitors) [33]. The recent identification of a COX-3 isoform may allow the development of novel analgesic drugs [34], but it is unlikely to obviate the need for compounds with both analgesic and anti-inflammatory effects. Given the continued high use of NSAIDs, and their potential to cause such serious adverse events, it is essential that novel methods are sought to improve their safety.

Warfarin and bleeding

Warfarin is one of the oldest and most widely used drugs in the therapeutic armamentarium. Its use has increased since trials showed that it decreases the risk of strokes in patients with nonvalvular atrial fibrillation [35]. The number of patients attending anticoagulant clinics has doubled in the last 5 years, and the trend is set to continue [36]. The major risk of warfarin treatment is haemorrhage with an incidence of 10–17 per 100 patient-years [37]. The risk of bleeding increases with the intensity of anticoagulation in a log-linear fashion, and recently, it has been shown that the INR is positively correlated with the risk of mortality [38]. ADR surveys often show warfarin as one of the drugs most commonly implicated in causing hospital admission [39].

Many patients are highly sensitive to warfarin and require very low doses to achieve and maintain anticoagulation. This is partly due to an inability to metabolize the more active enantiomer S-warfarin by the polymorphically expressed P450 isoform CYP2C9 [39]. Patients with variant CYP2C9 alleles (which possess between 5 and 12% of the activity of wild-type alleles) require low warfarin doses, are more difficult to stabilize, and are at higher risk of bleeding [40]. The role of CYP2C9 allelic variants in determining warfarin dosage has now been shown in several studies, with the mean daily dosage of patients with the CYP2C9*3/*3 genotype being 1.6 mg, compared with 5.5 mg for the wild type genotype

(CYP2C9*1/*1) [41]. It is possible that pre-prescription genotyping by allowing more accurate prediction of dose requirements will reduce the risk of over-anticoagulation and possibly bleeding, but whether this would be clinically effective and cost-effective requires further study [42].

Drug hypersensitivity reactions

Hypersensitivity reactions to drugs are typical examples of type B reactions: (i) they cannot be predicted; (ii) they do not show an obvious relationship to dose; and (iii) affect a minority of patients, suggesting that host-dependent factors are important and (iv) cannot be reproduced in animal models [43]. The assumption that the immune system is involved in the pathogenesis of these reactions even now is usually based on clinical manifestations such as the latency period on initial exposure and the rapid recurrence on re-exposure. One of the first examples where the involvement of the immune system in the pathogenesis of an ADR was based on a combination of both clinical and laboratory data is that of methylidopa-induced haemolytic anaemia. Breckenridge and coworkers were able to show on the basis of careful clinical observation, linked to mechanistic investigations, that 20% of patients on methylidopa had a positive Coombs test, and the rate of disappearance after stopping methylidopa varied between different patients [44–46]. Subsequent studies have suggested that the ability of methylidopa to lead to immune-mediated reactions is due to a disturbance of immunoregulation [47].

The necessity to combine both clinical and basic science in the investigation of complex problems in clinical pharmacology (as advocated by Breckenridge [48, 49]) is highlighted by this example, but also by the increasing realization that adverse drug reactions, and in particular idiosyncratic ADRs, have a complex multifactorial pathogenesis. This can be further illustrated by recent studies from our group in Liverpool (Figure 1).

Carbamazepine, one of the most widely used anticonvulsants, is associated with a hypersensitivity syndrome characterized by skin rash, fever, eosinophilia, lymphadenopathy and extra-cutaneous manifestations [50]. Mild skin rashes have been observed in about 10% of patients, while the more severe hypersensitivity syndrome is less common occurring in 1 in 1000 patients. Several sequential steps are thought to be important in the pathogenesis of carbamazepine hypersensitivity:

- 1 Carbamazepine is extensively metabolized with over 20 stable metabolites. It also undergoes bioactivation to toxic metabolites including arene oxide and quinone metabolites [51]. This is catalysed by the P450 isoforms CYP2C9 and CYP3A4/5. Carbam-

Figure 1 A schematic of the complex pathogenesis of carbamazepine hypersensitivity.

azepine also induces its own metabolism, and may thus increase the formation of its own toxic metabolites [52].

- 2 The formation of the toxic metabolites was surmised through demonstration of covalent binding and formation of glutathione conjugates [53, 54]. Glutathione and its associated enzymes (glutathione transferases, peroxidases, reductase and synthetase) therefore seem important in the bio-inactivation of the toxic metabolites. Other enzymes involved in bio-inactivation include microsomal epoxide hydrolase, quinone reductase and catechol O-methyl transferase.
- 3 If there is an imbalance between bio-activation (process 1) and bio-inactivation (process 2), the toxic metabolite will bind to cellular and serum proteins to form haptens [43]. The imbalance between bio-activation and bio-inactivation may arise because of constitutive differences in enzyme activity, or as a result of differential induction of phase I and phase II enzymes. Many of the enzymes involved in carbamazepine metabolism are polymorphically expressed, but to date, analysis of genes coding for enzymes responsible for drug bio-activation including

CYP2C9 and CYP3A5, and drug bio-inactivation including microsomal epoxide hydrolase, glutathione transferases, catechol-O-methyl transferase and quinone reductase have failed to reveal an association with CBZ hypersensitivity [55–57].

- 4 For an immune response to be manifested, the patient's immune system must be able to recognize and respond to the antigen formed from carbamazepine. This may be determined by certain HLA antigens (MHC restriction) [58]. In only a proportion of the patients, the immune response will be translated into tissue injury, which phenotypically is manifested as a hypersensitivity reaction [1]. Analysis of the promoter region polymorphisms in the TNF- α gene that may be functionally active has shown that serious, but interestingly not nonserious, hypersensitivity reactions to CBZ showed an association with the -308 (TNF2 allele), but not the -238, polymorphism [59]. The association with severe reactions was stronger with the MHC haplotype TNF2-DR3-DQ2 than with the TNF2 allele by itself [59]. This suggests that the immune response genes act as more important determinants of susceptibility to carbamazepine hypersensitivity than drug metabolizing enzyme genes.
- 5 According to the hapten hypothesis, the ultimate antigen responsible for the immune response will be derived from the toxic metabolites of carbamazepine [43]. However, recent evidence suggests that T cells can also respond to the parent drug binding noncovalently to the MHC [60]. However, this is based on *in vitro* studies, and the nature of the antigen leading to the immune response *in vivo* needs further study.
- 6 Carbamazepine- and metabolite-specific drug T cells have been identified in patients with a history of hypersensitivity. These cells were Th1 cells secreting high levels of interferon- γ , had specific V β T cell receptor phenotypes, showed DR restriction and expressed the skin homing receptor and perforin, the latter being responsible for death of keratinocytes [61, 62].

The predominant effect of immune response genes may also apply to hypersensitivity reactions with other drugs. This is exemplified by recent studies with abacavir, a nucleoside reverse transcriptase inhibitor used in HIV disease, which causes hypersensitivity in 4% of patients. A strong association of abacavir hypersensitivity with a MHC haplotype comprising HLA B57*01 was reported in an Australian population [63], confirmed in a US population [64] and more recently by ourselves in a UK population (unpublished data). Given the strength of the association of abacavir hypersensitivity with HLA B57, it has been suggested that this could be used to individu-

alize prospectively abacavir treatment by excluding the use of the drug in patients who are positive for HLA B57. However, the clinical utility of such an approach needs to be tested.

Conclusions

Adverse drug reactions continue to be a major public health problem. Research is essential in order to identify, understand and predict, and ultimately reduce the burden of adverse drug reactions. The availability of new technologies such as genomics and proteomics, the completion of the human genome project and the increasing understanding of the human immune system, provide us with unparalleled opportunities to achieve these aims. Indeed, advances are being reported every week in areas that are relevant to drug safety. These need to be harnessed by clinicians, scientists and the pharmaceutical and biotechnology industries (to name a few), not in isolation, but in collaboration, to tackle the problem of adverse drug reactions. Encouragingly, there is also increasing realization by governments of the public health importance of adverse drug reactions, but this needs to be translated into increased research funding.

The authors would like to congratulate Professor Breckenridge on this milestone in his career, and thank him for his guidance, encouragement and friendship throughout their careers. We are both grateful to Alasdair Breckenridge for our introduction into Pharmacology, and the awareness he gave us of the importance of science in medicine, and of tackling complex clinical problems using a multidisciplinary approach. Alasdair has also played a major role in the development of the science outlined in this article. The guiding role of the work has always been the seamless application of basic science to clinical medicine, and thereby the clinical application of sound analytical techniques to clear clinical observation. Such a philosophy, coupled with collective responsibility, has enabled the Department of Pharmacology in Liverpool to tackle major public health issues, from molecule to man. During the course of the work, new principles in clinical pharmacology have been defined and the fundamental challenges that have arisen in basic Pharmacology have been pursued. The new concepts have direct application and interaction with clinical medicine and drug regulation. In this regard, Alasdair Breckenridge nurtured new research and also provided guidance for implementation of the new science in the safer use of medicines in man.

References

- 1 Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. *Br Med J* 1998; **316**: 1295–1298.
- 2 Routledge P. 150 years of pharmacovigilance. *Lancet* 1998; **351**: 1200–1201.
- 3 Pirmohamed M, Kitteringham NR, Park BK. The role of active metabolites in drug toxicity. *Drug Saf* 1994; **11**: 114–144.

- 4 Hallas J, Harvald B, Gram LF, *et al.* Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med* 1990; **228**: 83–90.
- 5 Jefferys DB, Leakey D, Lewis JA, Payne S, Rawlins MD. New active substances authorized in the United Kingdom between 1972 and 1994. *Br J Clin Pharmacol* 1998; **45**: 151–156.
- 6 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002; **287**: 2215–2220.
- 7 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients – A meta-analysis of prospective studies. *JAMA* 1998; **279**: 1200–1205.
- 8 Kvasz M, Allen IE, Gordon MJ, *et al.* Adverse drug reactions in hospitalized patients: a critique of a meta-analysis. *Medgenmed* 2000; **6**: E3.
- 9 Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients. A systematic review of the prospective and retrospective studies. *Bandolier Extra* 2002; 1–16.
- 10 Green CF, Mottram DR, Rowe PH, Pirmohamed M. Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study. *J Clin Pharm Ther* 2000; **25**: 355–361.
- 11 Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? *J Roy Coll Phys London* 1995; **29**: 41–49.
- 12 Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines: do recent market removals mean there is a problem? *JAMA* 1999; **281**: 1728–1734.
- 13 Lee A, Bateman DN, Edwards C, Smith JM, Rawlins MD. Reporting of adverse drug reactions by hospital pharmacists: pilot scheme. *Br Med J* 1997; **315**: 519.
- 14 Morrison-Griffiths S, Pirmohamed M, Walley T. Reporting of adverse drug reactions: practice in the UK. *Nursing Times* 1998; **94**: 52–54.
- 15 Love L, Couig MP. The MedWatch Program. *J Toxicol Clin Toxicol* 1999; **37**: 803–807.
- 16 Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997; **350**: 1097–1099.
- 17 Evans JM, McNaughton D, Donnan PT, MacDonald TM. Pharmacoepidemiological research at the Medicines Monitoring Unit, Scotland: data protection and confidentiality. *Pharmacoepidemiol Drug Saf* 2001; **10**: 669–673.
- 18 Davies DM, Ferner RE, de Glanville H. *Davies's Textbook of Adverse Drug Reactions*, 5th edn. London: Chapman & Hall Medical, 1998.
- 19 John M, Nolan D, Mallal S. Antiretroviral therapy and the lipodystrophy syndrome. *Antivir Ther* 2001; **6**: 9–20.
- 20 Maher B, Alfirevic A, Vilar FJ, Wilkins EG, Park BK, Pirmohamed M. TNF-alpha promoter region gene polymorphisms in HIV-positive patients with lipodystrophy. *AIDS* 2002; **16**: 2013–2018.
- 21 Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002; **359**: 579–580.
- 22 Day R. Adverse reactions to TNF-alpha inhibitors in rheumatoid arthritis. *Lancet* 2002; **359**: 540–541.
- 23 Smalley WE, Ray WA, Daugherty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *Am J Epidemiol* 1995; **141**: 539–545.
- 24 Griffin MR. Epidemiology of nonsteroidal anti-inflammatory drug-associated gastrointestinal injury. *Am J Med* 1998; **104** (3A): 23S–29S; discussion 41S–42S.
- 25 Blower AL, Brooks A, Fenn GC, *et al.* Emergency admissions for upper gastrointestinal disease and their relation to NSAID use. *Aliment Pharmacol Ther* 1997; **11**: 283–291.
- 26 Tramer MR, Moore RA, Reynolds DJ, McQuay HJ. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. *Pain* 2000; **85** (1–2): 169–182.
- 27 Garcia Rodriguez LA. Variability in risk of gastrointestinal complications with different nonsteroidal anti-inflammatory drugs. *Am J Med* 1998; **104** (3A): 30S–34S; discussion 41S–42S.
- 28 Chan FK, Leung WK. Peptic-ulcer disease. *Lancet* 2002; **360**: 933–941.
- 29 Yeomans ND, Cook GA, Giraud AS. Selective COX-2 inhibitors: Are they safe for the stomach? *Gastroenterology* 1998; **115**: 227–229.
- 30 Bombardier C, Laine L, Reicin A, *et al.* Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000; **343**: 1520–1528.
- 31 Silverstein FE, Faich G, Goldstein JL, *et al.* Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-Term Arthritis Safety Study. *JAMA* 2000; **284**: 1247–1255.
- 32 Wiholm BE. Identification of sulfonamide-like adverse drug reactions to celecoxib in the World Health Organization database. *Curr Med Res Opin* 2001; **17**: 210–216.
- 33 Ahmad SR, Kortepeter C, Brinker A, Chen M, Beitz J. Renal failure associated with the use of celecoxib and rofecoxib. *Drug Saf* 2002; **25**: 537–544.
- 34 Chandrasekharan NV, Dai H, Roos KL, *et al.* COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc Natl Acad Sci USA* 2002; **99**: 13926–13931.
- 35 Lip GY, Hart RG, Conway DS. Antithrombotic therapy for atrial fibrillation. *Br Med J* 2002; **325**: 1022–1025.
- 36 Evans JM, Henderson LE, Goudie B, MacDonald TM, Davey PG. Demand for warfarin anticoagulation monitoring in Tayside. *Scotland Health Bull (Edinburgh)* 1997; **55**: 88–93.
- 37 Fihn SD, Callahan CM, Martin DC, McDonnell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. *Ann Intern Med* 1996; **124**: 970–979.
- 38 Oden A, Fahlen M. Oral anticoagulation and risk of death: a medical record linkage study. *Br Med J* 2002; **325**: 1073–1075.
- 39 Rettie AE, Wienkers LC, Gonzalez FJ, Trager WF, Korzekwa KR. Impaired (S)-warfarin metabolism catalysed by the R144C allelic variant of CYP2C9. *Pharmacogenetics* 1994; **4**: 39–42.
- 40 Aithal GP, Day CP, Kesteven PJJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet* 1999; **353**: 717–719.
- 41 Pirmohamed M, Park BK. Pharmacogenetics of adverse drug reactions. In *Horizons in Medicine 14*. ed. Neuberger J. London: Royal College of Physicians, 2003; in press.

- 42 Pirmohamed M, Park BK. Genetic susceptibility to adverse drug reactions. *Trends Pharmacol Sci* 2001; **22**: 298–305.
- 43 Park BK, Pirmohamed M, Kitteringham NR. The role of drug disposition in drug hypersensitivity: a chemical, molecular and clinical perspective. *Chem Res Toxicol* 1998; **11**: 969–988.
- 44 Carstairs KC, Breckenridge A, Dollery CT, Worlledge SM. Incidence of a positive direct Coombs test in patients on alpha-methyldopa. *Lancet* 1966; **2**: 133–135.
- 45 Breckenridge A, Dollery CT, Worlledge SM, Holborow EJ, Johnson GD. Positive direct Coombs tests and antinuclear factor in patients treated with methyldopa. *Lancet* 1967; **ii**: 1265–1267.
- 46 Carstairs K, Worlledge S, Dollery CT, Breckenridge A. Methyldopa and haemolytic anaemia. *Lancet* 1966; **i**: 201.
- 47 Murphy WG, Kelton JG. Methyldopa-induced autoantibodies against red blood cells. *Blood Rev* 1988; **2**: 36–42.
- 48 Breckenridge A. A clinical pharmacologist's view of drug toxicity. *Br J Clin Pharmacol* 1996; **42**: 53–58.
- 49 Breckenridge A. Science medicine and clinical pharmacology. The Lilly Lecture 1994. *Br J Clin Pharmacol* 1995; **40**: 1–9.
- 50 Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 1995; **155**: 2285–2290.
- 51 Pearce RE, Vakkalagadda GR, Leeder JS. Pathways of carbamazepine bioactivation *in vitro* I. Characterization of human cytochromes P450 responsible for the formation of 2- and 3-hydroxylated metabolites. *Drug Metab Dispos* 2002; **30**: 1170–1179.
- 52 Pirmohamed M, Alott A, Green VJ, Kitteringham NR, Chadwick D, Park BK. Lymphocyte microsomal epoxide hydrolase in patients on carbamazepine therapy. *Br J Clin Pharmacol* 1994; **37**: 577–581.
- 53 Madden S, Maggs JL, Park BK. Bioactivation of carbamazepine in the rat *in vivo* – evidence for the formation of reactive arene oxide(s). *Drug Metab Dispos* 1996; **24**: 469–479.
- 54 Lillibridge JH, Amore BM, Slattery JT, *et al.* Protein-reactive metabolites of carbamazepine in mouse liver microsomes. *Drug Metab Dispos* 1996; **24**: 509–514.
- 55 Gaedigk A, Spielberg SP, Grant DM. Characterization of the microsomal epoxide hydrolase gene in patients with anticonvulsant adverse drug reactions. *Pharmacogenetics* 1994; **4**: 142–153.
- 56 Green VJ, Pirmohamed M, Kitteringham NR, *et al.* Genetic analysis of microsomal epoxide hydrolase in patients with carbamazepine hypersensitivity. *Biochem Pharmacol* 1995; **50**: 1353–1359.
- 57 Leeder JS. Mechanisms of idiosyncratic hypersensitivity reactions to antiepileptic drugs. *Epilepsia* 1998; **39**(Suppl 7): S8–S16.
- 58 Park BK, Pirmohamed M, Kitteringham NR. Idiosyncratic drug reactions: a mechanistic evaluation of risk factors. *Br J Clin Pharmacol* 1992; **34**: 377–395.
- 59 Pirmohamed M, Lin K, Chadwick D, Park BK. TNFalpha promoter region gene polymorphisms in carbamazepine-hypersensitive patients. *Neurology* 2001; **56**: 890–896.
- 60 Pichler WJ, Yawalkar N. Allergic reactions to drugs: involvement of T cells. *Thorax* 2000; **55**(Suppl 2): S61–S65.
- 61 Naisbitt DJ, Depta J, Wong G, *et al.* Anticonvulsant hypersensitivity syndrome: methodology to investigate the role of metabolism and processing of carbamazepine to T-cells. *Br J Clin Pharmacol* 2002; **53**: 443P–443P.
- 62 Naisbitt DJ, Britschgi M, Wong G, *et al.* Anticonvulsant hypersensitivity syndrome: characterization of the phenotype and cytokine profile of carbamazepine-specific T-cell clones. *Br J Clin Pharmacol* 2002; **53**: 418P–419P.
- 63 Mallal S, Nolan D, Witt C, *et al.* Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. *Lancet* 2002; **359**: 727–732.
- 64 Hetherington S, Hughes AR, Mosteller M, *et al.* Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet* 2002; **359**: 1121–1122.