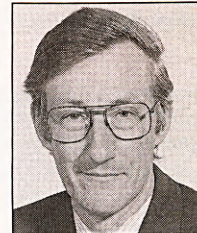# Pharmacovigilance: paradise lost, regained or postponed?

The William Withering Lecture 1994

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Prologue

William Withering (1741–1799) was a man of many accomplishments. He was both an expert botanist and a geologist, but he is best remembered by physicians as the father of clinical pharmacology. His *Account of the foxglove and some of its medical uses*, published in 1785, is a remarkable work [1]. Its contents would do justice to an Expert Report, accompanying a product licence application, to the drug regulatory authority of any member state of the European Union. He describes, in detail, how to collect and prepare the leaves of the purple foxglove (*Digitalis purpurea*) to obtain a product of reasonable consistency, and he outlines the effects of digitalis in an experimental animal (turkeys). But the *Account* is largely devoted to his observations of the effects of digitalis in patients. He investigated its dose-response characteristics; he showed that it could both slow the heart rate and induce a diuresis; he identified almost all its adverse effects; and he demonstrated how its toxicity could be minimised by careful dose-titration.

The main cardiac glycoside in the leaves of *Digitalis purpurea* is digitoxin. Digitoxin was the universal cardiac glycoside until the 1930s when it began to be replaced by digoxin, prepared from the leaves of the European foxglove (*Digitalis lanata*). Digoxin is still extracted from the European foxglove grown as crops, and reaped mechanically using specially adapted combine harvesters.

The introduction of digoxin, in 1934, coincided with the start of a 25 year period of unparalleled pharmaceutical innovation. The extraordinary range of effective new drugs, introduced between 1935 and 1960, has recently been described by Dollery as the pharmacological revolution [2]. They included the first effective antimicrobials, antipsychotics and anti-depressants as well as the appearance of the earliest effective anticancer drugs, the first oral antidiabetic and antihypertensive agents, and the start of the modern vaccination programme. By 1959 as many as 60 new active substances were being introduced to the market each year [3]. Coupled with the emergence of

the randomised controlled trial as the basic tool of experimental therapeutics [4], medicine appeared to have entered a pharmacological paradise.

The thalidomide disaster brought this pharmacological paradise to an abrupt halt. Introduced as an 'atoxic' hypnotic in 1956, thalidomide was marketed in Britain with specific claims for safety in both the elderly and children. Initial reports, in 1961, suggesting that thalidomide might be teratogenic [5,6] were quickly confirmed but not before several thousand babies, exposed to the drug *in utero,* had been afflicted by the characteristic embryopathy. The thalidomide disaster had profound effects on drug development, the pharmaceutical industry, and professional and public attitudes to drug safety. It resulted in the institution of legal controls on pharmaceutical manufacturers throughout the Western world, and it spawned the development of what is now known as 'pharmacovigilance'.

Pharmacovigilance: the problem

Pharmacovigilance is the process of identifying, and then responding to, safety issues about marketed drugs [7]. It is thus concerned not merely with surveying the safety of drugs used in clinical practice but also with developing strategies to minimise risk and optimise benefit.

The absolute necessity for pharmacovigilance of a new drug is evident from the data in Table 1. At the time a new active substance is introduced into clinical practice, experience of its effects in humans is inevitably limited [8]. Although the range is wide, the median number of patients in the overall safety database is about 1,500, and in the case of drugs to be given for long periods, rarely more than around 100 patients will have received the product for more than a year. Consequently, whilst there can be confidence in the efficacy (for their licensed indications) of new drugs at the time of their introduction, conclusions about their safety must remain provisional. Only during wider clinical experience is it possible to identify less common adverse reactions, those occurring during use in heterogeneous patient populations, or those developing during long-term exposure.

It might be argued that the need for effective pharmacovigilance would be lessened by including larger numbers of patients in prelicensing trials. On statisti-

Table 1. Numbers of healthy volunteers and patients exposed to new active substances at the time of marketing (1987–1989).

	Median (range)
Healthy volunteers	67 (41–742)
Efficacy studies	1,120 (43–4,906)
Safety database	1,528 (43–15,962)

After Rawlins and Jeffreys [8].

cal grounds, however, a ten-fold increase in the size of the pre-marketing safety database would be necessary to have any significant effect on identifying further hazards. If such requirements were to be introduced (and no national drug regulatory authority has done so) two consequences would follow. First, the costs of development of a new drug (currently estimated at $200 million) would become prohibitive. Second, patients generally would be denied the benefits of major new products whilst such studies were being undertaken. Pharmacovigilance thus attempts to address the inevitably provisional assessment of safety at the time a drug first enters routine clinical use.

Pharmacovigilance: the objectives

Pharmacovigilance has four main objectives. First, it is concerned with identifying previously unrecognised drug safety hazards, whether they be of short or long latency. In addition, pharmacovigilance seeks to quantify the frequencies of these hazards either as relative or (preferably) absolute risks.

Second, pharmacovigilance attempts to elucidate those factors predisposing to toxicity which, if avoided, might substantially improve a drug's therapeutic ratio. For example, initiating treatment with lower doses, avoiding use in certain age groups, or restricting the duration of therapy, are all means by which toxicity may be minimised. Where such risk reduction strategies are inappropriate, or fail, it may be necessary for drugs to be totally withdrawn from use. Table 2 shows those compounds licensed in the UK after 1972 (when modern drug regulation started) which have subsequently been withdrawn for safety reasons. They represent, approximately, 3% of all new active substances licensed during the period, and are a salutary reminder of the provisional view of safety that is inevitable when a new drug is first marketed.

Third, where it is appropriate, pharmacovigilance also attempts to obtain evidence of safety so that a new drug's uses may be widened. Thus, with increasing confidence in its safety, a drug's indications may be broadened, its dosage range extended, or its duration of use lengthened. Indeed, under some circumstances it may be suitable for supply, without prescription, as an 'over-the-counter' product.

Table 2. Safety withdrawals: new active substances licensed between 1972 and 1993.

Year licensed	Year withdrawn	Product	Reaction
1972	1984	Alkesin	Anaphylaxis
1974	1975	Polidexide	Impurities
1977	1986	Nomifensine	Haemolysis
1977	1991	Triazolam	Psychiatric disorders
1978	1984	Feprazone	Multi-organ toxicity
1978	1984	Fenclofenac	Lyell's syndrome
1980	1982	Benoxaprofen	Multi-organ toxicity
1981	1983	Zomepirac	Anaphylaxis
1982	1982	Indoprofen	Gastrointestinal toxicity
1982	1983	Zimeldine	Neuropathy
1985	1986	Suprofen	Nephrotoxicity
1986	1992	Metipranolol	Uveitis
1986	1991	Terodiline	Arrhythmias
1991	1992	Temafloxacin	Multi-organ toxicity
1991	1993	Centoxin	Increased mortality
1991	1994	Remoxipride	Aplastic anaemia
1992	1993	Flosequinan	Increased mortality

Finally, pharmacovigilance is essential for the refutation of 'false positive' adverse drug reaction signals. The 'scare story', often started innocently enough but amplified by the media, may not merely embarrass pharmaceutical manufacturers and drug regulatory authorities but can also have serious detrimental effects on public health. For example, in the early 1970s, annual whooping cough vaccination rates were consistently around 60–70% (Fig 1). In 1974, however, stories began to appear in the medical literature of a possible association between pertussis vaccination and permanent neurological damage. The story was quickly adopted by the lay media and, as a consequence, vaccination rates fell. The numbers of cases of whooping cough then rose. Only during the 1980s, as accumulating evidence confirmed that pertussis vaccination was not causally associated with irreversible brain damage, did vaccination rates rise again and the incidence of whooping cough fall. The failure to undertake effective pharmacovigilance of whooping cough vaccines in the 1960s was directly responsible for a public health disaster in the 1970s and early 1980s.
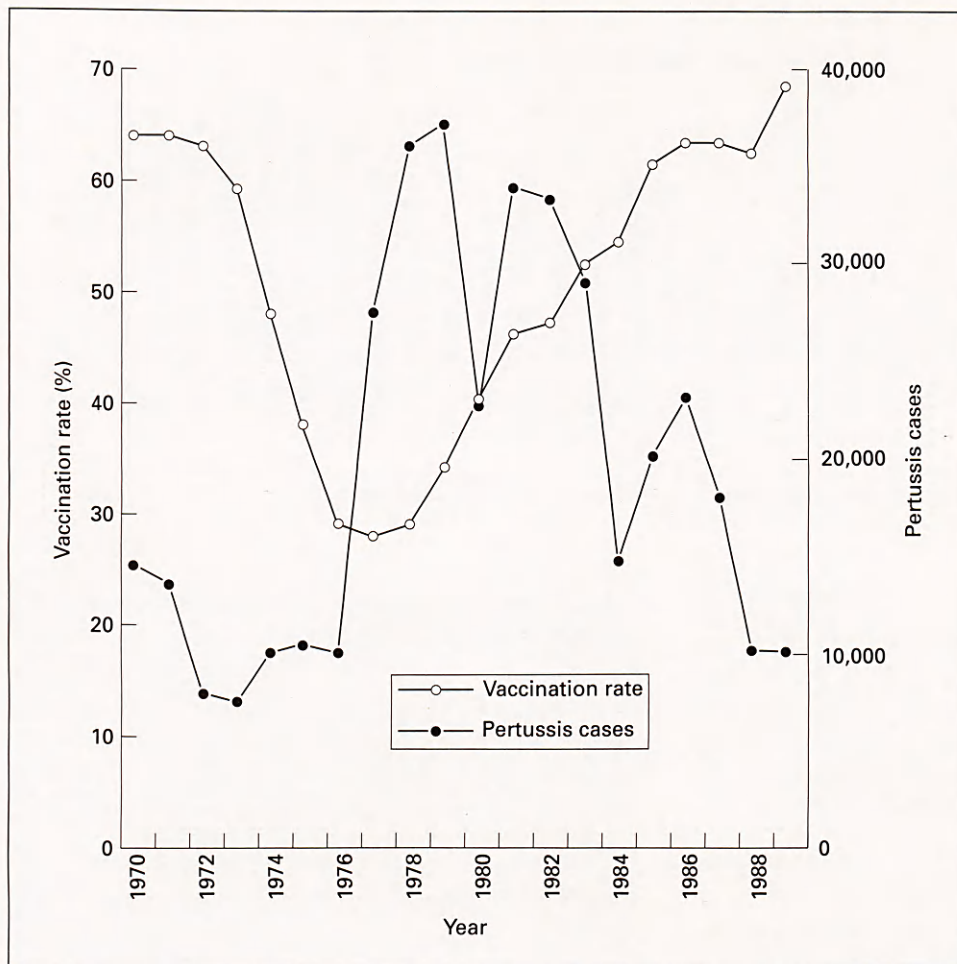
Fig 1. Annual rates of whooping cough vaccination and of numbers of cases of pertussis (1970 to 1990). Open and closed symbols represent vaccination rates and pertussins cases respectively.

Pharmacovigilance: the methodology

Spontaneous reporting schemes

The Committee on Safety of Medicines' (CSM) spontaneous reporting scheme for adverse drug reactions (the 'yellow card' scheme) has underpinned pharmacovigilance in Britain for 30 years. The technique was originally introduced by *The Lancet* towards the end of the last century in an attempt to determine whether ether or chloroform was the safer anaesthetic [9]. The Lancet Commission invited doctors, both in Britain and the colonies, to report all anaesthetic deaths to it and the findings were published in a series of articles in 1893. The Commission concluded that the problem lay more with the doctors administering these agents than with either anaesthetic individually.

Under the CSM's 'yellow card' scheme doctors, dentists and Her Majesty's Coroners are invited (under terms of strict confidentiality) to provide the Committee with details of all suspected reactions to new drugs, and serious reactions to established ones. Over the years reporting has increased from 2,000 to 3,000 per annum at the inception of the scheme to current rates of around 20,000 per annum. Annual reports expressed in relation to the number of NHS prescriptions (Fig 2) have also risen strikingly during the same period, negating any suggestion that the rise in the total numbers is attributable to the increasing use of drugs. The number of reports received by the CSM is the highest of any member state of the European Union, and UK reporting rates in relation to prescription volume are matched only by Ireland and Denmark.

The proper interpretation of 'yellow card' reports, however, requires a close understanding of the characteristics of the database [10]. First, reporting rates for individual drugs tend to be highest shortly after marketing. Comparisons between drugs therefore have to be made using comparable periods of time after their introduction into clinical use. Second, estimates of the completeness of reporting suggest that it is rare for more than 10% of serious reactions to be reported; and that reporting is rarely better than 2–4% for non-serious reactions. At least part of the problem is the relatively poor reporting by hospital doctors who contribute only a third of reports despite the fact that serious reactions are most likely to present in hospital.
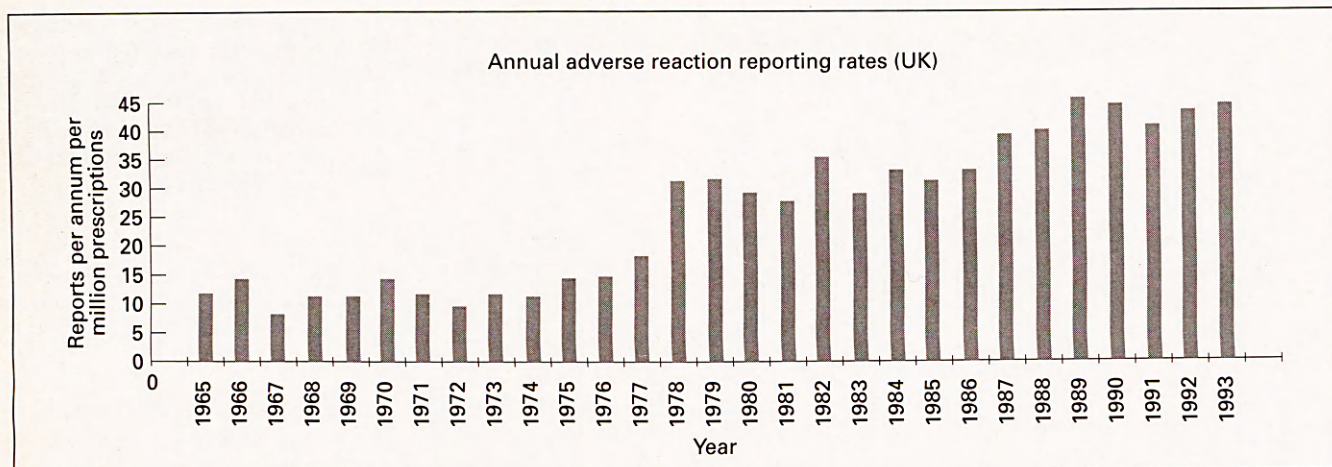
Fig 2. Annual rates of reporting suspected adverse drug reactions (reports per million prescriptions).

Moreover, a recent survey has shown that hospital staff are less clear about the purposes of the 'yellow card' scheme than their counterparts in general practice [11]. Third, because of under-reporting, the 'yellow card' scheme is susceptible to significant bias, particularly when there has been adverse professional or lay media attention to particular safety issues. Such bias can apply to both 'true positive' and 'false positive' adverse drug reaction signals.

Notwithstanding the scheme's inherent limitations, it has been invaluable [12] in four particular ways:

1. The scheme has provided numerous 'early warnings' of drug hazards. Some of those published over the past two to three years are shown in Table 3. Of most recent concern have been the reports of fibrotic lesions in the ileocaecal region of children with cystic fibrosis treated with high potency pancreatin products. The original cluster of five cases described by Smyth *et al* [13] has now been joined by similar reports from elsewhere in the UK, Ireland, Denmark and the USA. Once again the British 'yellow card' scheme has alerted the world, and not just the UK, to a particular drug hazard.

2. The 'yellow card' scheme can also provide information about factors that predispose to adverse reactions. Examples include the influence of dose (thromboembolism with oral contraceptives, hypotension with angiotensin-converting enzyme inhibitors) and age (fatal blood dyscrasias with co-trimoxazole and mianserin, acute dystonias with metoclopramide).

3. Comparisons of adverse reaction 'profiles', between products within the same therapeutic or pharmacological class, are regularly used in assessing the significance of reports of possible iatrogenic problems. Such comparisons may help in distinguishing reactions inherent in the pharmacology of a drug (ie type A reactions) from those that are specific to one member. Thus, the

Table 3. Early warnings of adverse reactions from the UK spontaneous reporting scheme.

Year	Product	Reaction
1991	Omeprazole	Diarrhoea
1991	Flecainide	Fibrosing alveolitis
1991	Clozapine	Convulsions
1991	Terodiline	Ventricular arrhythmias
1992	Terbinafine	Hepatoxicity
1992	Propofol	Metabolic acidosis (children)
1993	Paroxetine	Withdrawal reaction Acute dystonias
1993	Clozapine	Myocarditis
1993	Botulinum toxin	Dysphagia
1993	Remoxipride	Aplastic anaemia
1994	High potency pancreatins	Ileocaecal strictures

reports of hepatitis and Guillain-Barré syndrome that resulted in the withdrawal of the first selective serotonin reuptake inhibitor (SSRI), zimeldine, have not recurred with the newer members of the class (fluvoxamine, fluoxetine, paroxetine and sertraline). On the other hand, reports of withdrawal reactions [14] with one of the newer SSRIs (paroxetine) suggest that this may be specific: the particular problem had not received any prior attention in either the lay or professional press; reporting differences with other SSRIs are substantial, with individual reports indicating that symptoms rapidly regress when the drug is reintroduced; and it may be relevant that the half-life of paroxetine is shorter than that of other SSRIs.

Comparisons of adverse reaction profiles, however, need to be undertaken with great care. Reporting may be influenced by subtle differences in the licensed indications, or promotion, of a particular product. Reporting may also be biased by adverse publicity. For example, the CSM has received an excess of reports of suicidal ideation and suicidal behaviour with one of the new SSRIs (fluoxetine). This, I strongly suspect, is due to widespread media interest in both the UK and USA. Certainly, careful scrutiny of the clinical trial database has failed to substantiate that suicidal behaviour is more common with fluoxetine than with other antidepressants [15]. The evidence suggests that this is an example of the 'false positive' signal discussed earlier.

4. Finally, the 'yellow card' scheme allows for continued safety monitoring of a product throughout its life-span as a therapeutic agent. Although it is unusual for the method to delineate entirely novel reactions to well-established agents, it may detect adverse reactions occurring as a result of changes in manufacture or formulation.

The UK's 'yellow card' scheme has thus served us well and will, I am sure, continue to do so. Its success is entirely due to the efforts of the British medical and dental professions. I might, therefore, be forgiven for feeling occasional twinges of irritation when its immense contributions are trivialised or its database abused! There is no doubt, however, that our spontaneous reporting scheme is inherently unable to meet all our requirements for pharmacovigilance. It is insensitive at picking up reactions that mimic commoner conditions; it cannot distinguish between events causally related to a drug, and those which are complications of the disease being treated; it is poor at detecting long latency reactions; and, at best, it only provides a minimum estimate of the incidence of a particular reaction. Effective pharmacovigilance often requires us to use other methods of assessing drug safety.

Monitoring vital health statistics

It has occasionally been possible to infer (or refute) a causal relationship between secular changes in the rates of certain diseases and the use of particular classes of drugs. The correspondence between the increase in asthma mortality rates in the 1960s and the use of the earliest inhaled non-selective beta-agonist (isoprenaline) is an example that is often quoted [16]. The approach, however, is fraught with difficulties. Changes in disease classification, in coding rules, or in diagnostic methods may confound apparent changes in mortality rates, and correlations with changes in drug use can be fortuitous. The method may, on occasions, provide collateral evidence of value for pharmacovigilance purposes. Thus, there have been suggestions (particularly from New Zealand) that the use of modern beta-agonists has, in the last decade or so,

been associated with an increased mortality from asthma [17,18]. Figure 3 shows the UK mortality rates from asthma between 1980 and 1990, together with the annual number of prescriptions dispensed by general practitioners over the same time [19]. It is clear that although the consumption of beta-agonists has increased three-fold, asthma mortality rates have remained essentially unaltered. Since we know, from other sources, that the incidence of asthma has not declined over this period (indeed it has almost certainly increased) this lack of correspondence largely negates the hypothesis that beta-agonists, as used in the UK, are a major public health hazard.

Case-control studies

The case-control method is, in principle, simple. It involves comparing drug exposure amongst cases of a particular condition, thought possibly to have an iatrogenic basis in some patients, with exposure amongst controls [20]. From this, it is possible to calculate an odds ratio which is an estimate of the relative risk. Case-control studies have been used, successfully, to study many associations between drug exposure and potential iatrogenic diseases including thromboembolism (with oral contraceptives), endometrial cancer (with hormone replacement therapy), and upper gastrointestinal haemorrhage (with non-steroidal anti-inflammatory drugs).

A case-control study, however, is an observational, rather than an experimental investigation. It shows whether there is an *association* between a particular condition, and exposure to a drug. Such an association may exist because of bias, or confounding, and the technique must therefore be used with exquisite attention to detail in design, and the greatest care in interpretation. In deciding whether any association is *causal* four criteria should, ideally, be satisfied. The association should be biologically plausible; it should be reasonably strong; it should be consistent between studies; and there should be a dose-reponse (or duration-response) relationship.

In the case of the examples discussed earlier, these criteria have all been met and a causal relationship is well established. Biological plausibility, however, may sometimes be difficult to impute with type B reactions, and dose-response relationships impossible to determine where single fixed doses are administered. Significant interstudy differences may indicate the presence of bias or confounding as a result of failures in study design. In the absence of biological plausibility, consistency between studies of appropriate design and power becomes of major importance in establishing a causal association.

The case-control study is a powerful method for pharmacovigilance purposes. It can be performed retrospectively, thus avoiding further exposure of large numbers of patients. It can be undertaken rapidly, and may provide information of major public health
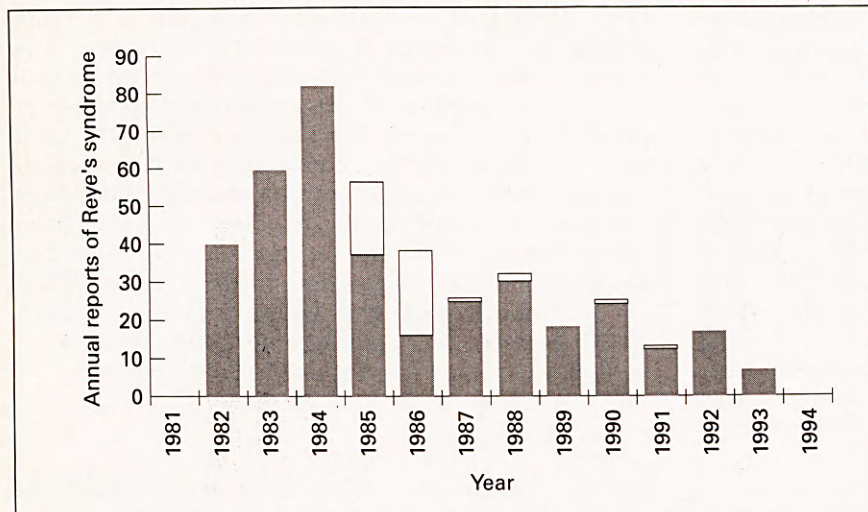
Fig 3. Annual rates of asthma deaths and numbers of prescriptions for beta-agonists. Reproduced by kind permission [19].

importance with relatively small numbers of subjects. The rapid recognition of an association between exposure to L-tryptophan and the development of the eosinophilia-myalgia syndrome [21] is a clear example.

The technique does, however, have disadvantages. In general, it is necessary to have a prior hypothesis to test. Moreover, whilst the method provides an estimate of the relative risk, it does not measure absolute risk. Furthermore, the statistical power of a case-control study is maximal when exposure rates to the drug of interest are around 10–40% amongst controls. Few drugs ever achieve this degree of usage amongst the general population, and where exposure amongst controls falls to less than one in a thousand, very large numbers are needed if quantitative estimates of risk are to be made. For this reason, increasing interest is being taken in a variant of the case-control method known as the case-cohort study [22].

In the case-cohort approach, drug exposure amongst cases of interest are assembled in the usual way. However, instead of comparing drug exposure rates with individual controls, exposure amongst an appropriate population is used instead. Table 4 shows the result of a case-cohort study of corticosteroid use amongst children with disseminated varicella [23].

Table 4. Case-cohort study of disseminated childhood varicella in non-immunosuppressed patients.

	Cases (n = 19)	Controls (n = 10,000)
Exposed	5	20
Non-exposed	14	9,980

Odds ratio = 178 (95% CI 59 to 541)

After Dowell and Bresee [23]

Cases included children with disseminated varicella admitted over a ten-year period to a Canadian tertiary referral centre. Children with underlying immunosuppressive disorders (eg leukaemias, lymphomas) have been excluded in this analysis. Controls were derived from a search of the computerised records of a group health cooperative and matched to produce an age and sex distribution comparable to the cases. The very high odds ratio, when considered in conjunction with the biological plausibility of the association, make a causal relationship likely.

Case registers

Case registers have not, hitherto, been widely used for pharmacovigilance purposes but have considerable potential. Two varieties are possible—the disease-based registry and the drug-based registry.

One of the earliest disease-based registries, instituted for drug safety surveillance, was that initiated in the early 1950s by the American Medical Association for the monitoring of blood dyscrasias. It was the forerunner of the US spontaneous reporting scheme. Experience in the UK is perhaps best exemplified by the British Paediatric Surveillance Unit's survey of Reye's syndrome, which started in 1981. Although the survey did not attempt, during its first three years, to obtain information about antecedent aspirin exposure, data from the fourth and fifth years provided evidence of an association with aspirin use in a third to a half of cases. Taken together with the results of four North American case-control studies, this prompted the CSM to advise, in 1986, against the use of aspirin as an antipyretic or analgesic in young children. Subsequently (Fig 4) the number of cases of Reye's syndrome and antecedent use of aspirin has fallen substantially [24].

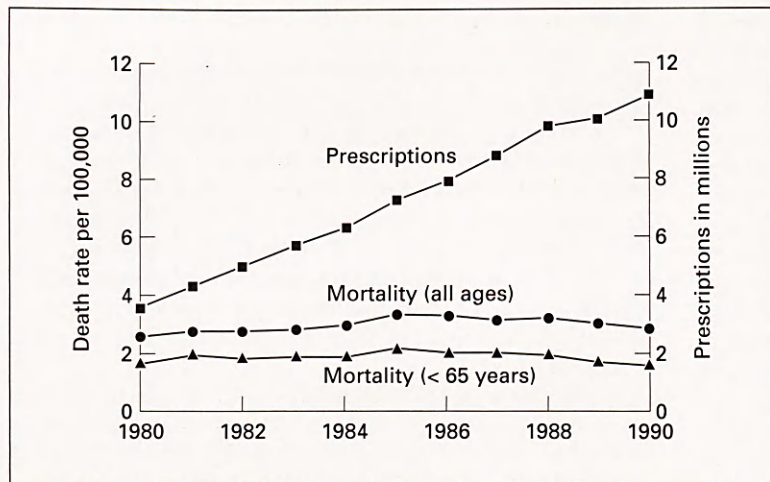An example of the drug-based registry is exemplified by clozapine. Clozapine is a novel antipsychotic

Fig 4. Annual reports of Reye's syndrome to the British Paediatric Surveillance Unit [24]. The open bars represent the number of cases with an antecedent history of aspirin exposure.

agent with a spectrum of pharmacological and therapeutic activity that differs markedly from other conventional neuroleptics. It produces few extrapyramidal reactions, and improves both the positive and negative features of schizophrenia. It did, however, cause agranulocytosis in premarketing studies with an incidence of about 1 in 200 treated patients. Furthermore, there was some evidence to suggest that this incidence might show pronounced inter-racial variation. When clozapine was introduced in the UK, a special monitoring programme was instituted which ensured that all recipients were registered and monitored for blood dyscrasias. Subsequent UK experience has confirmed the original estimate of the incidence of agranulocytosis with 0.36% cases amongst 4,402 treated patients.

The case-registry is an approach to pharmacovigilance that has considerable potential. Provided there is unbiased ascertainment, the disease-based registry offers a particularly useful way for monitoring rare diseases that frequently have an iatrogenic aetiology such as aplastic anaemia, fulminant hepatic failure and acute renal failure. The drug-based registry is one that is applicable to products known to be associated with special problems (eg clozapine) but is likely to be of particular value for the safety monitoring of biotechnology products, including the recipients of gene therapy.

Cohort studies

Cohort studies for the purpose of pharmacovigilance may be either experimental or observational in design.

Experimental cohort studies, with random allocation of two (or more) treatments and unbiased ascertainment of outcomes, are a special form of the controlled clinical trial. Indeed post-approval trials, designed primarily for the further assessment of clinical efficacy, may make important contributions to overall safety monitoring if they incorporate appropri-

ate design features. Experimental cohort studies designed primarily for the purpose of safety monitoring are unusual, but the Serevent National Surveillance Study is a recent example [25]. In this, 25,000 asthmatic patients were randomised, in general practice, to treatment for four months with either regular salmeterol or salbutamol. Mortality and hospitalisation rates (for asthma-related conditions) at four months were not significantly different between the two groups. This study was important for two reasons: it demonstrated that such large-scale investigations could be successfully carried out in general practice; and it provided some reassurance about the safety of salmeterol at a time when there was considerable concern at the theoretical possibility of its downregulating bronchial beta-receptors.

Observational cohort studies have been used much more commonly than experimental studies for pharmacovigilance. Indeed, the approach dates back at least 100 years to the work of John Snow who studied the safety of both ether [26] and chloroform [27] shortly after their introduction. The method involves the identification of recipients of a particular product under normal conditions of use and then ascertaining their fate. Recipients can be identified through their prescribing doctor via the dispensing pharmacist or from the prescription itself. Patient outcomes, either generally (in the form of adverse events) or specifically (by seeking information about particular diseases), can be ascertained by enquiry of their regular doctor, from patients themselves, or from regional or national registers. Studies may be short- or long-term.

The observational cohort study is, potentially, extremely valuable in pharmacovigilance. It can identify new hazards and estimate their absolute incidence; it can identify predisposing risk factors; and it can refute 'false positive' signals. The technique, however, requires three central design features if it is to generate useful information [28]. First, on statistical grounds, cohorts generally need to be an order of

magnitude larger than those used in prelicensing studies unless the question to be answered involves only a circumscribed patient population (eg children or the elderly). Second, studies must be sufficiently robust to enumerate reliably all serious adverse events that occur following the start of treatment. Third, studies must incorporate an appropriate control or comparator group against which to compare adverse event rates, unless the event in question can be assumed to have a zero background incidence.

These are harsh requirements and I fully recognise that they are not easily or economically accomplished. Such studies can be most readily undertaken using computerised databases. Automated databases, originally developed for administrative purposes, have proved to be of considerable value in North America for pharmacovigilance. With the increasing use of computerised records in primary health care in Britain, there should also be real possibilities for us on this side of the Atlantic [29]. Indeed the VAMP databases and Media Plus have already proved to be effective tools for pharmacovigilance, and the Tayside database (MEMO) also has potential. Moreover, automated databases are not merely useful for cohort studies; they can also be invaluable in undertaking case-control or case-cohort studies.

Pharmacovigilance: the future

Effective pharmacovigilance is essential if the best interests of the public health are to be met. Failure to build on both the lessons and achievements of the past will damage the pharmaceutical industry and prejudice the well-being of present and future generations of patients. We must therefore develop a strategic approach to pharmacovigilance based on three premises.

First, when new drugs enter clinical use, we should unashamedly be prepared to anticipate their potential problems. Such suspicions may be based on the known class actions of previous similar products, on the pharmacological and toxicological properties revealed during preclinical studies, or on the experiences of patients treated during pre-marketing trials.

Second, we must ensure that when a new product reaches the market, we have a coherent and explicit pharmacovigilance proposal based on these potential problems. Such a plan might, in some cases, rely simply on spontaneous reports in the first instance. But the pharmacovigilance plan must be flexible and capable of modification in the light of events.

Third, we need to invest in methodological research in pharmacovigilance. The pharmaceutical industry and drug regulatory authorities should be encouraged to be experimental and innovative; and those working in academia and the health services should be active participants. A pluralistic approach to pharmacovigilance, rather than a rigid adherence to dogma or to a particular methodology, will benefit us all.

Epilogue

One hundred years before Withering published *An account of the foxglove* John Milton wrote *Paradise lost* [30]. It is, without doubt, the finest epic poem in the English language and it recounts the story of Adam and Eve in the Garden of Eden. But *Paradise lost* is, predominantly, a poem about the loss of innocence and about knowledge and choice. Shortly before his death Milton published *Paradise regained* which tells of Christ's triumph over Satan in the wilderness. It is a tale of the supremacy of good over evil and of right over wrong.

Pharmacovigilance, in the dying years of the twentieth century, is neither a story of paradise lost, nor one of paradise regained. It is, rather, a tale of continuing endeavour and incremental advances by physicians and scientists in the pharmaceutical industry, regulatory authorities, health services and academia. But for the moment it is a paradise postponed.

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Edited by Anthony Hopkins

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