Programming cycles also allows a successful programme to run with reduced monitoring of follicular development. Assay of steroid hormones is still important, but the information is used retrospectively rather than as a prospective guide.

Outpatient oocyte recovery under the control of ultrasound enables a unit that has no facilities for laparoscopy to offer in vitro fertilisation. Having an IVF programme in an academic department that studies the development of early pregnancy provides the opportunity for clinical research as well as a treatment for fertility problems.

There are other costs to the NHS that do not appear in our budget. Although we follow the Voluntary Licensing Authority guidelines and transfer only a maximum of three embryos to the uterus, just under a third of the current pregnancies are twins, and although we have had no neonatal problems yet, this form of fertility treatment may have clinical consequences for neonatal units.

The most successful units in the world are usually those that devote large resources to in vitro fertilisation. This is not practical for every unit, and couples may find travelling to prestigious units and living away from home stressful and expensive. Adopting new approaches tailored to the needs of small units means that in vitro fertilisation can be successful and need not be a burden on NHS resources.

This project would not have succeeded without the help of Professor Alec Turnbull, Nuffield Professor of Obstetrics and Gynaecology. It could not

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New Drugs

Adverse reactions. I

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"At the beginning of the twentieth century syphilis was the great mimic of systemic disorders. Later, tuberculosis took over this role. Both of these diseases have been tamed by chemotherapy and now 'drugs' head the list of disease simulators."

Committee on Safety of Medicines, 1985¹

Adverse drug reactions are a great concern of the general public, the pharmaceutical industry, the regulatory authorities, and the professions. It is only recently, however, that the concept that the use of drugs carries a variable but finite risk has become widely accepted. The evaluation of this risk and its relation to the benefits of treatment determine not only whether a drug is developed and licensed but also how widely it will be used. An understanding of the ways in which drug safety is assessed is therefore important in understanding the available information and assessing the risk to

individual patients. This paper reviews the current methods of monitoring adverse reactions and how they have contributed to detecting drug toxicity in recent years.

Classifying adverse reactions

Though several classifications of adverse reactions have been proposed, most are too complex for routine use. The suggestion by Rawlins and Thompson that adverse reactions can be divided into only two categories² is therefore welcome and provides a pragmatic basis for understanding drug toxicity.

Adverse reactions may present as an augmented but qualitatively normal response to a drug (type A) or as a bizarre, unexpected response (type B). Type A reactions occur in patients who are unusually susceptible to the pharmacological action of the drug—examples include postural hypotension with antihypertensive agents, gynaecomastia with dopamine antagonists, and diarrhoea with broad spectrum antibiotics. These reactions are fairly common, are increasingly frequent at higher doses, and can be predicted from a knowledge of the drug's actions. A reduction in dose will improve the symptoms, which are not usually severe and seldom cause death.

By contrast, type B reactions are usually severe and proportionately more often fatal. They are not related to the drug's known pharmacological effects and do not improve when the dose is

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reduced—the drug must be withdrawn. These reactions are often immunologically mediated (for example, anaphylactic shock) or may have a genetic basis (for example, malignant hyperpyrexia and possibly halothane hepatitis), and they are very rare. None the less, the detection of type B reactions often results in the withdrawal of a drug from general use, examples including benoxaprofen (hepatorenal syndrome), zomepirac (anaphylaxis), and zimeldine (adverse neurological effects).

Some well established adverse reactions do not fall easily into this classification because of the severity of the reaction (for example, blood dyscrasias caused by cytotoxic drugs are potentially fatal and severe but are common and dose dependent) or because the mechanism of the reaction has been explained by the pharmacology of the drug (for example, thrombosis induced by oral contraceptives). None the less, the type A-type B classification fits well with the way in which adverse reactions are detected during the development and clinical use of a drug.

Evaluation before marketing

ANIMAL STUDIES

Though it is difficult to draw direct parallels between toxicity in animal models and potential risks to man, long term animal studies are used to screen for toxicity, carcinogenicity, and teratogenicity. These studies produce an overall picture of the toxicology of a drug and show which organs are at greatest risk of damage induced by drugs. This is linked with pharmacokinetic data to estimate the risk in man. Mutagenicity studies are completed at an early stage in drug development, but because drugs may also “promote” neoplasms carcinogenicity studies are of long duration (24 months).

Animal studies may occasionally show toxicity at a late stage in a drug's development. For example, proxicromil, under development for the treatment of asthma, was abandoned in 1981 only 10 months before the anticipated marketing date after tests in animals had shown “unexpected findings.” Many older drugs were marketed at a time when these studies were not routinely performed. Subsequent investigation may then show—as in the case of the laxative danthron—that the drug is potentially carcinogenic.

VOLUNTEER STUDIES AND CLINICAL TRIALS

By the time a drug is marketed it will usually have been given to fewer than 3000 people, usually in small studies of fewer than 100-200 subjects each. This limited experience provides an estimate of the most appropriate dose range, balancing greatest efficacy against the lowest incidence of type A adverse reactions. Subgroups who are particularly at risk are occasionally identified. For example, the elderly were found to have higher blood concentrations of the new non-steroidal anti-inflammatory drug nabumetone, and the maximum dose for this group of patients has been set at 1 g daily. In other cases unexpected but common adverse reactions are identified, and a suitable warning can be included in the data sheet. Nausea and vomiting typically occur in a small proportion of subjects in clinical trials, but almost one third of patients given fluvoxamine developed this reaction.

By the time a drug becomes available for widespread use there is usually no indication of the nature of its type B toxicity. These reactions, which may have an incidence of one in 10 000 or less, occur so occasionally during clinical trials that their occurrence may be coincidental and unrelated to drug treatment. It is therefore only after much wider use that very serious adverse reactions to most drugs are detected, and several methods of surveillance after marketing are currently in use.

Surveillance after marketing

There are several methods of monitoring safety when a drug is in general use. Each has its faults and cannot alone fulfil all the

requirements of a monitoring system. These can be summarised as: speed—rapidly detecting new adverse reactions and rapidly responding when appropriate; sensitivity—sufficient to detect rare adverse reactions but not to be overwhelmed by common reactions; and scope—of a size that will enable the risk to be quantified—for example, by estimating incidence.

CASE REPORTS

The publication of reports of isolated adverse reactions in medical journals has proved to be an important means of detecting new and serious type B toxicity. This method of reporting should allow a quick response, as the reaction is published very soon after its detection. As Venning has pointed out, however, such reports have not always been assiduously dealt with by regulatory authorities and may remain unvalidated after several years' further use.³

The sensitivity of case reports is inherently high, as the reporting doctor does not usually have to pick out an important new reaction from among several others. The doctor must, however, recognise that the symptoms are induced by the drug rather than caused by other factors. The publication of case reports is invariably followed by reports of similar cases, both to the Committee on Safety of Medicines and to the publishing journal, as doctors are alerted about the reaction. Though this further emphasises the causal—rather than coincidental—link between drug and symptoms, it confounds the estimation of the incidence of the reaction. Case reports alone provide no information about the population exposed to the drug; at present only correlation with national data on prescribing or sales figures gives an estimate of the risk. It is also difficult to identify from case reports which subgroups of patients are at risk, as even the existence of a few common characteristics in a small sample can bias the data.

Case reports have none the less been the first means by which some of the main type B adverse reactions in recent years have been identified.³ Five years after its introduction in 1970 practolol was firmly associated with dermatitis, keratoconjunctivitis, and sclerosing peritonitis by letters to the *Lancet* and the *British Medical Journal*. The Committee on Safety of Medicines issued a regulatory warning in 1975, and the drug was withdrawn in 1976. The first case that reported part of this syndrome was published in 1972.⁴

Benoxaprofen, a non-steroidal anti-inflammatory drug, was first marketed in 1980. Clinical trials in nearly 1700 patients had not indicated that the drug was exceptionally toxic, though photosensitivity and onycholysis had been reported in 9% of patients.⁵ In 1982 two reports in the *British Medical Journal* highlighted the adverse effects that would eventually result in the drug's withdrawal. Photosensitivity induced by benoxaprofen was found to be due to phototoxicity rather than allergy and to be dose dependent.⁶ The reaction would therefore occur in all patients given sufficient drug and sunshine, and the true incidence would therefore be greater than the 10% estimated by studies performed before marketing. By this time eight cases of fatal cholestatic jaundice in elderly women had been reported.^{7,8} The half life of benoxaprofen was known to be greater in the elderly, and this prompted the Committee on Safety of Medicines initially to vary the product licence to allow a reduced dose in the elderly. Subsequently, however, the large number of case reports, both in the medical press and to the Committee on Safety of Medicines, led to the suspension of the product licence. By this time there were over 3500 reports to the Committee on Safety of Medicines, of which 61 were fatal reactions.

The publication of case reports is therefore an important alerting system for type B adverse reactions, but publications require validation—preferably but not essentially by controlled studies—to discriminate between coincidence and causality.

COHORT STUDIES

The influence of bias can be minimised by monitoring drugs prospectively and comparing the morbidity and mortality of a group

treated with drugs with that of a control group. Such studies must be very large, and they must be continued for many years if they are to detect less common adverse reactions. They are therefore very expensive to conduct, and it may be unrealistic to expect that they can be carried out for all drugs. Prescription event monitoring is a type of cohort study that is considered separately below.

The cohorts of patients in these studies can be randomised or non-randomised. In non-randomised studies a treated group is compared with a non-treated "control" population who do not have the condition for which the target drug is indicated. Two of the best known cohort studies of this type currently under way are the multicentre cimetidine surveillance study and the Royal College of General Practitioners' oral contraceptives study.

The cimetidine study started in 1978 with a grant from the drug's manufacturers, recruiting almost 10 000 patients and 10 000 controls by identifying prescriptions for cimetidine in four centres in the United Kingdom. Its results have largely substantiated the safety of cimetidine in routine use but have done little to resolve the controversy surrounding the drug's association with impotence.^{9,10} This is because the detection of reactions depends on the general practitioner detecting and recording the event in the notes, whereas there is some evidence that men do not readily complain of impotence.¹¹ This study does not seem to have detected any new adverse reactions to cimetidine.

The Royal College of General Practitioners study began in 1968, recruiting 46 000 women and 1400 general practitioners. Again the detection of reactions depends on symptoms being reported to the doctor and might therefore underestimate the incidence of symptoms that might be sensitive (for example, the effects on libido). This study has, however, quantified the risk of many serious type B adverse effects, notably cardiovascular disease¹² and excess mortality.¹³

Cohort studies may also be randomised, when the drug under investigation is also indicated in the control population but they receive a placebo instead. The best known example of this approach is the World Health Organisation's study of the prevention of ischaemic heart disease by clofibrate.¹⁴ This trial identified a 47% excess of deaths during treatment in the group given clofibrate, but this increased mortality disappeared when the drug was withdrawn.¹⁵ The suspicion that treatment with clofibrate directly caused these deaths is therefore strong, though the mechanism remains unclear.

Cohort studies are therefore an excellent—if slow and expensive—method of quantifying and, in some cases, identifying the more common types of drug toxicity. Though they show an association between a drug and symptoms, however, they do not necessarily prove a causal link, and most are too small to detect type B reactions reliably.

PRESCRIPTION EVENT MONITORING

The method of detecting adverse reactions that has been developed by the Drug Surveillance Research Unit in Southampton differs from other systems of surveillance after marketing but is a type of cohort study. Patients who have received specific drugs are identified from prescriptions supplied by the Prescription Pricing Authority. The general practitioner is then asked to report on a form provided any adverse events that have been detected (that is, warranted an entry in the patient's notes) while the drug is being taken. The response rates of general practitioners have been between 50% and 75%.

Two advantages are claimed for prescription event monitoring over other surveillance methods. Firstly, the emphasis on detecting "events" rather than "reactions" obviates the need for judgment by the general practitioner on a causal link between drug and effect. This ought to enhance the detection of new adverse reactions and of diseases that are only rarely associated with drugs and should favour the detection of type B reactions. Secondly, the incidence of events can be calculated, as the number of both prescriptions and events is known accurately. Though this estimates the incidence of all events in the cohort of identified patients, these data must be compared

with those from a matched control group before the incidence of the events that are actually induced by the drug can be reliably determined. Reports of prescription event monitoring suggest that patients are being used as their own controls by comparing the incidence of events during and after treatment with the drug.¹⁶⁻¹⁸ This method, however, means that intercurrent illness or treatment with other drugs confounds interpretation of the data.

The system is claimed to be capable of detecting events that have an incidence of one in 5000, a sensitivity between that of clinical trials and the yellow card system. As most cohorts have contained between 10 000 and 15 000 patients, however, the detection of an excess of two to three cases above the normal incidence of these symptoms is difficult. The duration of monitoring individual drugs by prescription event monitoring may also be too short for some type B reactions. For example, the average duration of treatment with benoxaprofen was 8.5 months in patients who developed the hepatorenal syndrome, whereas treatment in those monitored by prescription event monitoring lasted for seven months.¹⁹

More recently prescription event monitoring has identified a new event associated with enalapril.²⁰ In a population of 12 500 patients monitored over one year 19 patients developed deafness. This is in excess of the five patients who were expected to develop deafness (though a control group was not defined). Further research is now required to validate these reports.

CASE-CONTROL STUDIES

When a type B adverse reaction has been identified its association with a drug is often investigated by a case-control study. In this retrospective method patients who have the identified disease—for example, breast cancer—are matched with a control group who are similar in potentially confounding factors (for example, smoking, parity) but who do not have the disease. The drug histories of the two groups are then compared, and a significant excess of drug takers in the disease group may be evidence for a causal link with the drug.

Case-control studies have been widely used in evaluating the link between oral contraceptives and various cancers. This methodology is ideal under these circumstances because, like other type B reactions, cancer induced by drugs is rare, and huge numbers would have to be recruited to a cohort study to provide meaningful data. Further, cancer induced by drugs takes many years to become apparent, and the expense of a cohort study would be considerable. By contrast, the case-control study is relatively quick to carry out and much cheaper.

The findings of some case-control studies have, however, been controversial and contradictory. Some show an association between oral contraceptives and breast cancer,^{21,22} whereas others consistently do not.^{23,24} Different conclusions have been formed depending on the age of the recruited cases; some methods of identifying controls (for example, by random telephone dialling) have been criticised; and attempts to analyse the risks of different doses of hormones have been unsuccessful. There is less disagreement over the results of some other studies. The association between oral contraceptives and cervical cancer is now accepted, though the level of risk is still unclear, and the apparent protective effects against endometrial and ovarian cancer seem to be undisputed.

The association between aspirin and Reye's syndrome has been explored by no fewer than five case-control studies in the United States, and each has shown a consistent association between the drug and disease. Though there have been criticisms of the design and conduct of these studies, the consensus of their conclusions has provided good evidence for a rare but serious adverse reaction to aspirin that occurs in only a subgroup of the population.²⁵ Though a prospective study in the United Kingdom suggests that the epidemiology of Reye's syndrome in this country differs from that in the United States, these studies formed the basis of the Committee on Safety of Medicines' recommendation to remove paediatric formulations of aspirin.²⁶

Case-control studies therefore provide valuable information on

the incidence of type B adverse reactions and the association between drugs and disease. There are, however, important problems in their interpretation that require careful consideration.

YELLOW CARDS

Spontaneous reporting of adverse reactions to drugs to a central body was introduced in the United Kingdom in 1964 after the establishment of the Dunlop Committee, later the Committee on Safety of Medicines. This scheme is familiar to most doctors and dentists in the United Kingdom, but fewer than 20% have ever completed a yellow card, and it is estimated that even for serious and fatal adverse reactions only about 10% are reported to the Committee on Safety of Medicines. Despite these problems the yellow card system has provided some important data on drug safety and toxicity.

The principle of the system is that doctors will report suspected, not necessarily proved, adverse reactions to the Committee on Safety of Medicines. For older drugs the Committee on Safety of Medicines is particularly interested in severe, usually type B, reactions, but for newly introduced drugs (marked with a ▼ in the *British National Formulary*) doctors are asked to report all suspected adverse reactions. The yellow cards therefore provide a large database of case reports drawn from the entire population of the country, and the system can detect both type A and B reactions.

The yellow card system thus has the potential to record unusual, unexpected, adverse effects not detected in clinical trials and, by correlation with prescribing data, to estimate the incidence of these reactions. Thus in the case of the angiotensin converting enzyme inhibitors captopril and enalapril the yellow card system identified the risk of urticaria and confirmed the occurrence of cough, which had first been documented in case reports.

The system can also be used to examine the epidemiology of adverse reactions. It has to be assumed that the reporting rate does not differ for different subgroups of patients, and additional data on prescribing patterns are also required, usually from a commercial source. The population at risk is usually estimated from the number of prescriptions but this is an inaccurate denominator, as no distinction can be made between "first" and "repeat" prescriptions. Furthermore, reporting rates tend to decline the longer a drug has been on the market, and comparisons among drugs must be made using data drawn from a comparable period, usually the first five years of marketing. This information is none the less valuable in formulating the Committee on Safety of Medicines' recommendations on the regulation of drugs to the licensing authority.

An example of the use of these data to make regulatory decisions in the assessment of the risk of toxicity of non-steroidal anti-inflammatory drugs. The decisions to suspend the product licences of osmosin and benoxaprofen were based partly on the very high number of reports per million prescriptions of both type A and type B reactions for these drugs compared with other drugs in this class. It is also possible to determine which drug in a therapeutic group is the least toxic. For example, ibuprofen seems from the data from yellow cards to be the safest anti-inflammatory drug, and the decision to license it as an over the counter medicine was based largely on these data.

The information from yellow cards can also be used to examine the risks of subsets of the population. By this method the elderly were identified as being particularly at risk of bone marrow toxicity from cotrimoxazole but not from other antibiotics.²⁷ By contrast, the young, and girls in particular, are at greatest risk of acute dystonic reactions to the dopamine receptor antagonists metoclopramide, prochlorperazine, and haloperidol.^{28, 29} Again there is some evidence that some members of this group of drugs might be less toxic than others.

The yellow card system costs about £500 000 a year, and, in terms of the data it generates, it is inexpensive. Its success depends on the

cooperation of doctors and dentists. Recently attempts to improve reporting rates have included the introduction of yellow cards into the *British National Formulary* and FP10 prescribing pads. The yellow cards seem likely to remain the most cost effective method of detecting unusual adverse reactions to drugs.

Other techniques

Other methods of surveillance after marketing that are under investigation in the United Kingdom include record linkage, in which the health records of a defined population (for example, within a health authority district) can be correlated with data on the use of drugs.

National data on morbidity and mortality can also be scrutinised for trends that may be associated with changes in drug use. Changes in mortality from asthma highlighted the risk of inhalers containing adrenaline in the United Kingdom in the 1960s. This technique is not very sensitive compared with other methods but can generate hypotheses for further investigation.

The evaluation of drug safety is complex, and there are many methods by which adverse reactions are detected. Each of these has advantages and failings, and no single system can offer the security that the community now demands.

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