Crying wolf on drug safety

Twenty-one years after the first reports of congenital malformations due to thalidomide\(^1\) virtually every Western government has assumed some degree of responsibility for the safety of prescribed medicines. The international pharmaceutical industry has accepted control and regulation to an extent that must be unique in concerns independent of state subsidy. Yet reports of unexpected, sometimes serious adverse reactions continue to appear. Investigative journalists, flying the battle honours of the campaign on behalf of the thalidomide children,\(^2\) continue to expose real and imagined drug hazards and to assert the culpability of the pharmaceutical manufacturers. How effective are the drug-safety regulations? And how effective as an early-warning system are published reports of adverse reactions to drugs?

The replies given to those questions will vary in a predictable way with the background of the individual providing the answers. Within the pharmaceutical industry the government regulations are seen as a burdensome bureaucracy that has achieved relatively little. Certainly the development of new drugs has gradually become more complex, more time-consuming, and more expensive—partly as a result of the regulations, but partly, too, as a result of refinements in commercial practice and pressures from consumer movements. Twenty years ago 50 new products were marketed each year in Britain; now that number is around 20. Similar trends are to be seen in other countries.

A detailed analysis\(^3\) of the work of the Committee on Safety of Medicines for 1971 to 1981 has shown that most of the new drugs licensed in that time have been in a handful of therapeutic categories. Of the 204 new entities, 21 were non-steroidal anti-inflammatory agents, 13 were corticosteroids, 10 were beta-blockers, and 13 were antidepressants or tranquilisers; drugs for hypertension and diabetes and antibiotics also figured prominently. The manufacturers have been concentrating on the chronic conditions which are common in Western society. “Innovation is therefore directed towards commercial returns rather than therapeutic need,” says Griffin and Diggle\(^2\)—a policy that must be seen as the price paid by society for its insistence on stringent safety and licensing requirements. Recently the Committee on Safety of Medicines has been trying to reduce administrative delays and simplify testing procedures, and with the promise of new techniques such as genetic engineering the pace of drug development may well speed up again; but so long as the innovation, testing, and marketing of drugs are subject to statutory controls the process will remain expensive, and the range of new products will reflect economic realities.

The vast edifice of licensing controls in Western countries has given their publics some protection. That is shown by the dubious commercial policies of some international companies in Africa and Asia, where drugs are still sold that have been taken off the market on safety grounds in Britain and the United States. Premarketing tests are, however, less well validated. Thalidomide was almost certainly unique as a teratogen. The prazolotol syndrome, the periodic scares about the safety of oral contraceptives, the doubts about artificial sweeteners, the story of reserpine and breast cancer, and more recently alarmist reports about Debendox and cimetidine have shown that no system can provide a guarantee of drug safety—and that no matter how careful their checks the agencies will still be heavily criticised whenever something goes wrong.

One of the legitimate causes for public complaint has been that doctors are slow to recognise adverse reactions when they occur. The Committee on Safety of Medicines has repeatedly asked for greater co-operation with its yellow-card scheme, but it estimates that only a small fraction of all adverse reactions are reported to it. The traditional early warning system—and the one that has proved effective so often in the past—is publication of case-reports in medical journals. Yet some pharmaceutical companies complain that these anecdotal reports, sometimes based on no more than coincidental events in a single patient, may give a product a bad name with no justification. Certainly the data are often imperfect—as is shown by two papers in this issue of the BMJ. Venulet and his colleagues (p 252) have looked at 5737 articles from 80 countries published between 1972 and 1979. Only half these articles included enough information for a calculation of the incidence of a particular adverse reaction, and many of the reports said nothing about basic details such as the dose and duration of treatment. Too often, indeed, the case against the drug was based on too little evidence. The other study, by G R Venning (p 249) looked at a series of 52 early reports of suspected adverse reactions and at which of these proved valid in the light of later clinical experience. The conclusion is that a chance association is not enough. It should be supported by at least some additional criteria: data from rechallenge; a pharmacological basis for the reaction; the reaction being immediate or localised to the site of administration; the reaction having been reported previously by another route of administration; or the occurrence of rare events in several patients.

Certainly journals should continue to provide an early warning system to alert clinicians to associations that may or
may not prove to be cause and effect. The fetal abnormalities caused by thalidomide and the oculomucocutaneous syndrome caused by practolol were brought to doctors' attention by letters to the *Lancet* and the *BMJ* respectively, and in each case the association was quickly confirmed by further reports.

In contrast, associations may prove false alarms which cast an unwarranted blight on a useful drug. One such was the report associating skeletal malformations with Debendox, which has not been confirmed by later large-scale studies but played a part in the loss of public and medical confidence in the use of the drug by pregnant women.

The *BMJ*'s current policy aims at steering a path between the extremes of crying wolf too often and insisting on near-certain evidence. In general, we are likely to accept a report of a drug side effect if it describes more than one case and if the evidence points clearly to a single drug. Something more than simple coincidence in time is usually required—rechallenge (with the patient's informed consent) or immunological investigations may tip the balance of probabilities. Two other vital sources of information should be checked by authors before submitting a report: Has the manufacturer been told of any similar episodes? And have any reports been made to the Committee on Safety of Medicines?


### Episiotomy

Childbirth in Britain has never been safer than it is today, though we are not yet among the European leaders in the league table of lowest maternal and perinatal death rates. Understandably, pregnant women, their husbands, and doctors are all paying more attention to subtler aspects of care, especially those concerned with making the experience of pregnancy and childbirth more comfortable and pleasurable. With increasing insistence individual women, and sometimes well-organised groups, are asking whether some procedure is manifestly to the advantage of mother and baby or amounts to unnecessary interference by doctors. Among the targets have been the steadily rising incidence of induction of labour (the subject of considerable debate a few years ago1–3), forceps delivery, and caesarean section; and the whole matter of intervention in obstetric practice was recently the subject of special study at a scientific meeting organised by the Royal College of Obstetricians and Gynaecologists.4

The spotlight of public concern has now moved on to episiotomy. The National Childbirth Trust has recently published a collection of essays on the physical and emotional aspects of episiotomy with contributions from obstetricians and midwives, concluding with Sheila Kitzinger's assessment of its effects on postnatal sexual adjustment. On page 243 *Reading et al* report their account of patients' attitudes towards the pain and discomfort that may occur after episiotomy. All these studies show how many questions remain unanswered.

Here is a surgical procedure widely used by doctors and midwives, yet we have few objective data to support claims that perineal incision performed correctly at the appropriate moment eases delivery, protects the head of a small baby from trauma, is more easily repaired than a ragged tear and will heal more quickly and effectively, is less liable to infection than a bruised and torn perineum, and reduces the risk of later complications such as dyspareunia and prolapse. *Reading et al* were largely concerned with the discomfort associated with episiotomy, and the findings are disturbing: many women had severe pain at the time and afterwards, and nine out of 10 who subsequently experienced dyspareunia attributed this directly to the episiotomy scar.

In some aspects, the study of *Reading et al* confirms work that the *BMJ* discussed in 1973, and the questions remain the same. Unfortunately we still do not know whether the pain associated with episiotomy is greater or less than that associated with a perineum that has been allowed to become bruised and torn. On first principles most—though not all—obstetricians would argue that a clean surgical incision in the perineum, correctly timed and repaired, is more likely than a ragged, bruised tear to heal by first intention and cause less trouble at the time and later. But it would be helpful to have firm evidence to support or refute this belief. And as women themselves become better informed and more articulate they are sure to have strong views on this important subject. It would, however, be a pity if clinical practice were changed on insufficient evidence because of a patient-led protest. The answers should come from clinical research.

J K RUSSELL

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### Children’s accidents

1980 was designated Year of the Child and 1981 International Year of Disabled People, and all too often the two concepts overlap. Increasingly, accidents have become a main cause of mortality and morbidity in children of all ages. Reduction in mortality from infectious disease and improvements in chemotherapy and surgery have reduced infant and childhood mortality from other causes, with a consequent increase in the proportion attributable to accidents.

Concern about children’s accidents has been given a focus with the formation of the Child Accident Prevention Committee, which is supported by Government and voluntary funding. In conjunction with the BBC, the Health Education...