the rest of the community—for example, differences in drug metabolising or immune systems or even major differences in dietary habits. Inevitably difficult decisions will have to be made and each individual case will have to be considered on the balance of probabilities.

FINANCIAL CONSIDERATIONS

The study group has given considerable thought to the financial considerations. It suggests that the fund should be set up and financed jointly by bodies with an interest in promoting medical research and organisations which provide professional indemnity for those who conduct research. The fund could be established with moneys provided by the Medical Research Council, the universities, the Department of Health and Social Security, the pharmaceutical industry, the medical protection societies, and private organisations funding research. These contributions would be equivalent to insurance premiums. The major advantage of operating such a scheme through a central fund would be that all who finance and conduct human experiments would contribute and thus the insurance cover could be provided much more economically than if individuals and organisations were left to make independent arrangements with insurance companies. The proportion from each of these bodies should be adjusted in the light of experience of the claims made. The fund should use as its guideline in determining compensation the levels of compensation paid for similar disabilities in the courts. The costs of such a scheme cannot be predicted, although information from Sweden suggests that they are unlikely to be very great.

Copies of the full paper of the Study Group are available from the Information Officer, The Ciba Foundation, 41 Portland Place, London W1.

Reference

[1] Royal Commission on Civil Liability and Compensation for Personal Injury. *Report*. London: HMSO, 1978 (Cmnd 7054).

(*Accepted 17 April 1980*)

Scientifically Speaking

Post-marketing surveillance

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Washington DC—If this weren't a presidential election year in the United States, the recent final report of the Joint Commission on Prescription Drug Use might have got a lot more attention. The commission's three-year existence was the direct result of a suggestion in 1975 by Senator Edward M Kennedy that this country needed a better system for monitoring the use and effects of prescription drugs after they are marketed.

But when the commission met in a Senate office building to deliver its report, Senator Kennedy, busy campaigning against an incumbent president of his own political party, sent a staff assistant to receive the document. His absence could not help but reduce the limelight for a report that pulls together an unusual amount of information on existing and potential methods of "post-marketing surveillance" (PMS) of pharmaceuticals.

There is no organised and integrated system for such surveillance in the US now. There are dozens of programmes that touch on one or another aspect of PMS, or whose data collections would be invaluable for a nationwide system of surveillance, but they operate in relative isolation of purpose from each other. The Food and Drug Administration (FDA), whose duty it is to ensure that prescription drugs marketed here are safe and effective, puts most of its efforts into the pre-marketing phases of drug development.

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Planning a safe system

The Joint Commission ("joint" because of its sponsorship by seven professional organisations and the Pharmaceutical Manufacturers Association, which paid most of the commission's bills) did not have to reach further than the reason for its own existence to arrive at its first major recommendation: a systematic and comprehensive system of PMS should be developed for the US. There are some 54 000 drug products on the market, representing about 1900 active ingredients, and 1024 of those are chemicals that have been newly introduced since 1940, the commission noted. But, even today, the clinical trials that precede drug marketing hardly begin to reflect the circumstances in which the drugs are eventually used.

Clinical trials, which are the last assessment before a drug goes on the market, are conducted in a few patients, usually only 500 to 3000. The patient cohort understandably excludes infants, pregnant women, adolescents, the elderly, and persons with multiple diseases or who are taking several other drugs. Clinical trials are conducted over a relatively brief period—usually no longer than two years, according to the commission. To make real improvements in pre-marketing trials would require greatly increased expenses for a bigger patient population and a longer period of drug administration and observation. But, even if those expenses were assumed, the commission cautions that the trial results still would not account for the infants, pregnant women, and others likely to receive the drug once it is marketed; the results would also fail to disclose long-term effects of the drug, and protracted trials would delay further the introduction of the drug.

Another major recommendation of the Joint Commission, therefore, is that a PMS system should detect adverse reactions

that occur more than once per 1000 uses of a drug, and should develop methods to detect less frequent reactions. As the commission's arithmetic indicates, a 1:1000 proved sensitivity is no mean feat. In a cohort study that enrols one untreated person for each patient receiving a particular drug, 18 000 treated patients and 18 000 controls would be required to disclose a twofold increase in incidence of an untoward effect whose incidence in the untreated population is 1:1000. Cohorts of that size simply are not assembled for the vast majority of clinical trials. Even if they were, some important information would continue to be beyond reach; most cancers, almost all birth defects, and many other conditions occur with a frequency of less than 1:1000.

The problem of large numbers of patients and controls required for a cohort study can be avoided if a case-control study is applicable to the trial. But applicability depends on a drug's adverse effect being a somewhat uncommon disease. The commission report uses the example of an association of oral contraceptive use and myocardial infarction in women under 50. Only about 200 such patients and 200 controls would be required to make that association for a twofold increase in risks, whereas the same determination by cohort studies would require more than a million women in each group. The frequency of myocardial infarction in women under 50 is less than 1:100 000, which lends itself well to a case-control approach when the number of drug exposures is as large as for oral contraceptives. If, however, both the frequency of event and frequency of drug exposure are low, neither cohort nor case-control studies can be used.

Some drug-disease associations that would not have been found by clinical trials of normal feasibility include oestrogens and endometrial cancer, phenformin and lactic acidosis, chloramphenicol and aplastic anaemia, and thalidomide and phocomelia. That last example, the commission comments in a footnote, is doubly hidden to clinical trials because of the prohibition against enrolling pregnant women and an incidence so low that only case-control study is feasible.

Unexpected adverse reactions from new drugs are not the only class of events that the commission wants discovered by PMS. Its report indicates a nearly comparable interest in describing the natural history and measuring instances of drug toxicity that could be more or less expected, such as anaphylaxis after penicillin; in finding out more about the intended efficacy of a drug, such as confirming old indications for its use; and even in establishing unintended efficacy of a drug. In its several mentions of this last category, the commission gives one example—the apparent reduction in myocardial infarction among persons taking aspirin for other reasons—that has recently been called into question. But the commission seems to regard a drug's unintended benefits as a major justification for post-marketing surveillance.

Comparative studies

Aware that a good many PMS activities are under way in other countries, the commission conducted a fact-gathering tour of Europe and also arranged for a study of a variety of PMS-like efforts in other nations. Of interest here are some comparisons between the United Kingdom and the US, particularly in the matter of voluntary reporting by doctors of adverse drug effects. The UK "yellow card" reporting system is not too different from the "drug experience report" put into general use by the FDA in 1972. But, while the UK is said to be getting more than half of its adverse effect reports from general practitioners, the FDA got only 14% of such notices from physicians in 1977, and another 7% from hospitals. Part of the reason for that disparity appears to be an inverse disparity in the reporting done by pharmaceutical manufacturers: 71% in the US and much less than 15% in the UK. Manufacturers in both countries are legally bound to make adverse effect reports, the commission documents say.

Although follow-up of voluntary adverse effect reports is routinely conducted in both countries, the UK method of sending fieldworkers to conduct on-site investigations of selected instances seems to provide more definitive information than the FDA gets from a follow-up that is largely conducted through further correspondence, and occasionally by telephone. The commission finds another appreciable difference between the actions of the two countries in communicating back to practising physicians the information that might help them prescribe more circumspectly. The FDA has only recently undertaken a routine, although very limited, programme of listing "drug reaction alerts" in a column citing published work carried by the *American Journal of Hospital Pharmacy*. The Joint Commission's documents indicate an impression that medical and scientific journals in the UK carry many more articles and letters about adverse effects of drugs than are seen in the US.

Voluntary reporting of adverse effects has its place, the commission concedes, but there are some distinct practical limitations to its usefulness. The individual doctor reporting will not usually detect delayed adverse reactions; denominators are usually missing entirely; even an estimate of incidence is difficult; and there is danger of glutting the system with trivial observations.

The commission, whose 16 members were unanimous in the recommendations of the report, believes that it has found some non-experimental possibilities for PMS among the 30 or so suggestions examined. So-called health maintenance organisations, for example, could help to establish long-term cohorts for drug monitoring. Such prepaid health plans as the Group Health Co-operative of Puget Sound have already published PMS-related studies; an example in the UK is the Oxford Drug Monitoring Study. Pharmacy-based studies, which would identify and enlist co-operating patients, could assemble a large cohort for almost any prescription drug; the difficult part might be to assemble a concurrent control group. Panels of "matched physicians" (one prescribing a new drug, the other prescribing the current drug of choice) drawing their patients from similar populations could be established in various practice specialties as needed for newly marketed drugs.

Move towards a centre

Many more potential methods exist for PMS, including some that are experimental, but require development work before they can be validated. While the FDA is making progress in its PMS efforts and should try harder, the commission says, the prime locus of PMS research and training activities should be a "center for drug surveillance," which it is proposed should be a private, non-profit organisation located in an academic setting. The commission emphasises that such a centre would complement the FDA's work and would be completely separate from the FDA's regulatory function.

A mixture of government and private funding should be readily available to support such a centre, the commission believes. The FDA spends more than $1m a year on its adverse drug effect reporting system; one pharmaceutical manufacturer spends more than $2m a year for reviewing published work; a single study of beta-blocking agents was predicted to cost $25m.

How much less expensive and more effective it would be, the commission indicates, to establish a centre for drug surveillance on a beginning budget of $10m a year. To put that figure in perspective, commission chairman Kenneth L Melmon told the group's final meeting that $10m is about the cost of "two miles of interstate highway." In a society of dwindling gasoline supplies, it's hard to tell if that was a good analogy to use or not.

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