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We may return unduly long letters to the author for shortening so that we can offer readers as wide a selection as possible. We receive so many letters each week that we have to omit some of them. Letters should be typed with double spacing between lines and must be signed personally by all their authors, who should include their degrees. Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue.

Correspondents should present their references in the Vancouver style (see examples in these columns). In particular, the names and initials of all authors must be given unless there are more than six, when only the first three should be given, followed by et al; and the first and last page numbers of articles and chapters should be included.

Postmarketing surveillance of adverse reactions to drugs

SIR,—Professor Michael D Rawlins reviews a number of postmarketing studies, among them prescription event monitoring run by the Drug Surveillance Research Unit at Southampton University in collaboration with the Prescription Pricing Authority (24 March, p 879). Only two of our eight studies are mentioned, which hardly does justice to the magnificent response by general practitioners in England, about three quarters of whom have actively participated (table).

Prescription event monitoring is the second national scheme to have been established since the thalidomide disaster. The green forms used are complementary to the yellow cards. Only a small proportion of the events that are recorded are adverse reactions, but the green

forms allow their incidence to be measured and provide invaluable information about beneficial as well as harmful effects of treatment. The average monthly input of green forms is about the same as the annual input of yellow cards, and about 700 doctors have participated in follow up studies.

Prescription event monitoring has been developed to the stage where we expect to study routinely most new drugs introduced into general practice as soon as their sales are sufficient to produce cohorts of at least 10 000 patients. Delays in detecting rare side effects of new drugs relate as much to their slow market penetration as to difficulties with current monitoring methods.

We are faced with a dilemma familiar to the Committee on Safety of Medicines. All too often stories about problems in drug safety reach patients through the media before their doctors have had an opportunity to study the evidence. Six successive drug withdrawals from general practice (benoxaprofen, zomepirac, zimeldine, indomethacin (as Osmosin), indoprofen, and phenylbutazone) have received wide publicity before the committee could communicate with the profession. Many doctors have reported on the harm this does. For example, the sudden withdrawal of zomepirac was particularly distressing for 400 patients in our series who had metastatic cancer. We regard general practitioners as

coworkers and will ensure that they are the first to hear of our preliminary results through *PEM NEWS* rather than through the media. We also hope to publish more detailed reports, but we do not wish to delay communication to prescribers until the lengthy process of validation and analysis has been completed.

Prescribers need more details of the case investigations that must have preceded certain licensing decisions. This was particularly important with benoxaprofen. Professor Rawlins refers to our survey of 24 000 patients, which covered about 5% of all patients who had been treated with the drug. We have encountered three cases of "Opren jaundice" reported to the Committee on Safety of Medicines on yellow cards and to the unit on green forms. Two of these died from carcinoma of the pancreas, and one of the latter was in the process of litigation against the manufacturers. The results from both national studies were similar. Both signalled jaundice as a problem, but both have suggested that hepatorenal toxicity was very rare—certainly occurring in less than one in 10 000 patients and probably considerably less. The results of these two studies are quite out of line with the experience of Taggart, who reported that all six of the only six patients he had treated with benoxaprofen had died.¹

As Professor Rawlins points out, control populations of comparable age, sex, and

Number and percentage of green forms returned between February 1982 and February 1984.

Drug	Green forms returned
Opren (benoxaprofen)	17 079 (57)
Lederfen (fenbufen)	6 989 (56)
Three antibiotics	9 246 (76)
Zantac (ranitidine)	10 866 (60)
Zomax (zomepirac)	11 074 (60)
Cetiprin (emepromium bromide)	15 920 (65)
Osmosin (indomethacin)	13 132 (60)
Feldene (piroxicam)	14 305 (69)
All	98 611 (63)

diagnosis who are not undergoing active treatment cannot be found. The only comparisons that are possible are between groups of patients treated with different drugs. We have already assembled reports on 77 000 patients treated with five different non-steroidal anti-inflammatory drugs. Although the pattern of serious events varies, there is no evidence so far to suggest that the overall death rate attributable to any one of them differs from the others.

I agree entirely that the yellow card system and the publication of anecdotal reports are the only practical means of detecting adverse drug reactions which have a frequency of less than one in several thousand. Yellow cards are available from the moment a new drug is marketed, while prescription event monitoring can be applied only to those which have achieved substantial sales. Since only small numbers of serious suspected adverse reactions are usually reported, it is easy for the Committee on Safety of Medicines's field workers to follow them up rapidly before any recommendations are made to the Licensing Authority. It is more difficult to follow up the very much larger numbers of events which are identified by prescription event monitoring, only a small proportion of which turn out to be suspected adverse reactions.

None of the problems raised by Professor Rawlins is new, and none is overwhelming. Much more important is the lack of a consensus on what risks are medically and socially acceptable.² Only when this has been decided can we make sensible decisions about the numbers of patients required to measure these risks and whether or not the existing methods of postmarketing surveillance are adequate.

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¹ Taggart HM, Alderdice JM. Fatal cholestatic jaundice in elderly patients taking benoxaprofen. *Br Med J* 1982;284:1372.

² Inman WHW. Risk in medical intervention—balancing therapeutic risks and benefits. In: Cooper MG, ed. *Risk: Man-made hazards to man*. Oxford: Oxford University Press (in press).

SIR,—Professor Michael D Rawlins sets out clearly and fairly the options for postmarketing surveillance of adverse reactions to drugs (24 March, p 879), but a few additional points need to be made.

Firstly, pharmaceutical company schemes of prospective postmarketing surveillance have been not only expensive and disappointing in the yield of information but also criticised on occasions for being a disguised form of promotion. The Association of the British Pharmaceutical Industry has taken such criticisms seriously and has produced guidelines for its code of practice committee and for its member companies (copies available on request) to try to avoid unethical conduct. Inevitably, however, these measures will limit severely studies of this kind whether carried out by a company or by an independent unit.

Secondly, the yellow card data bank held by the medicines division of the Department of Health and Social Security has come to play a crucial role in the decision making process over rare adverse drug reactions, and its role in relation to other systems must be examined. The pharmaceutical industry has always upheld the system, but some of these reports are deficient. Follow up should be common and thorough for the following purposes: verification of a temporal association between an event and use of a drug; validation

that the doctor thinks that there was a causal relation between the event and the drug; and long term follow up of the patient to confirm this causal relation.

The industry has a large and growing staff specialising in the monitoring of adverse drug reactions, but their contact with doctors reporting through yellow cards is precluded—unlike with the *BMJ* unreviewed reports, which are required to be submitted to both manufacturers and the DHSS. Counts of yellow cards, much quoted in parliament and elsewhere, should distinguish between those that have been fully validated from those that have not.

Thirdly, the subject has been made more difficult by external interest which has focused on absolute numbers of serious reactions rather than on the true measure of risk, which is the incidence per number of treated patients. This has led to demands for action on medicines with serious reactions of the order of 1 in 10 000 patients—about the same incidence as penicillin anaphylaxis. The argument has been that if hundreds of thousands of patients are treated with such a drug it will result in some tens of serious reactions and these are unacceptable. We cannot measure reaction rates of this order by present methods with any confidence for purposes of comparative risk benefit assessment, certainly not with the speed demanded by public clamour. Yellow card data should be made available publicly together with at least the approximate number of scripts on, or patients exposed to, the drug in the same period. This highlights the need for a complementary back up system to investigate further any suspicions raised by yellow card or other reports.

The difficult decisions that have to be faced by pharmaceutical companies, the licensing authority, and the Committee on the Safety of Medicines require access by all parties to all available information—the most important of which will remain validated yellow card data. We are discussing together how the resources of the pharmaceutical industry could be made available for stimulating the number of yellow card reports as well as for improving the quality and treatment of the information.

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Disgruntlement with the CSM

SIR,—Clinical freedom is a privilege dependent on clinical responsibility. It is not a right as claimed by Dr Richard K Allday and Dr R C Coladangelo (24 March, p 935). It has been known that phenylbutazone can cause bone marrow aplasia for 20 years, yet it continues to be prescribed for trivial conditions.

Between 1976 and 1979 phenacetin was available only on prescription—about a quarter of a million prescriptions were given. Was this responsible prescribing? Tetracycline continues to be prescribed for children (19 November, p 1515)—and will continue to be prescribed as long as it is available as a syrup. How can this be defended? No doubt if thalidomide and practolol were available they would be prescribed in the name of the same sacred cow—clinical freedom.

The wonder is not that the Committee on Safety of Medicines has taken steps to curtail the prescribing of phenylbutazone but that it has taken so long to do it. Perhaps it could now consider barbiturates and hypnotics.

Finally, Dr Allday claims "startling results" for the effect of phenylbutazone on metastases in neoplastic disease but "for good reasons"

has refrained from publishing the evidence. I am sure the whole medical world will share my intrigue as to what these reasons could be as well as the evidence. There may yet be a place for using phenylbutazone other than in ankylosing spondylitis.

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Hypertension in general practice

SIR,—Your leading article by Dr John Coope on hypertension in general practice paints an extremely gloomy picture, even stating, "Some claim that management of patients with hypertension is beyond the scope of general practice" (24 March, p 880).

The evidence provided is scanty. Much reference is made to the paper by Ritchie and Currie.¹ They looked at only 1000 records from only seven practices, and almost half the records were of patients under the age of 40—hardly surprising that the recording rate is low. Moreover, although published in 1983 all the data were for the years 1968-77, well before the major interest developed in general practice for records and preventive care. The papers that accompany the leading article (24 March, p 903 and 906) are more relevant, but one showed quite reasonable care—almost half of patients had had a recording within the past 10 years, and 84% of those with pressures greater than 160/95 mm Hg were followed up. There are, of course, deficiencies—such as 35% of patients on the pill with no recorded blood pressure, but so many general practitioners still do not record normal results.

Dr Coope makes no reference to the paper by Fleming and me which reported two surveys of 29 practices in the Oxford region in 1980 and 1982. We showed that the rate of recording blood pressure in men aged 40 to 70 was improving rapidly, the improvement being statistically significant ($p < 0.001$) despite there being only two years between the surveys. In 2000 records the average rate for a recording in the past 10 years was 69%. The recording rate is rising fastest among those in their 40s.

All this is not to say that we should not be doing better: of course we should. But the evidence that general practitioners can improve, are improving, and, indeed, are improving fast should not be forgotten. General practice is ideally structured for preventive care, and there is no evidence that centrally based services can carry out such care better than well organised general practice.

Fleming and I are currently reviewing the same 29 practices to try to identify characteristics of practices successful in preventive care. We hope that this will help to point the way forward.

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¹ Ritchie LD, Currie AM. Blood pressure recording by general practitioners in north-east Scotland. *Br Med J* 1983;286:107-9.

² Fleming DM, Lawrence MSTA. Impact of audit on preventive measures. *Br Med J* 1983;287:1852-4.

SIR,—I was disappointed that Dr John Coope made no mention of the important role of the general practitioner in the population approach to preventing hypertension (24 March, p 880). Much evidence exists on the high prevalence of hypertension, and the rise of blood pressure with age in "civilised" countries, due to en-