

fails to share information with his patient and to predict what is likely to happen later that night soon learns his lesson when called at 02.00 to deal with the patient he saw earlier in the day. Aspirin for otitis media may be even more important than an antibiotic.

Teaching practices are expected to provide opportunities for trainees to obtain experience in a wide range of activities. These include preventive sessions as well as consultations during surgery hours; they include teaching sessions and simple audit exercises. No less important than any of these activities is experience in emergency care and this must include supervised responsibility for care for full 24-hour periods. Training practices can reasonably be expected to provide opportunities for trainees to obtain this experience.

A number of options are open to the teaching practice for organizing out-of-hours experience for trainees. Even those practices who use deputizing services throughout the night should be able to make provision for this, and the argument that the trainee will then do more work than his trainer can be countered by arranging suitable time off, for example, by a later start the next morning.

There is much to be said for out-of-hours experience to be acquired by working within the practice itself, rather than by working for a deputizing service as some trainees have done. Experience within the practice enables the trainee to provide continuity of care for the

practice population and to compare the behaviour of his own patients by day with their behaviour in the night. He can also appreciate the gratitude and goodwill of those people that he has visited out of hours and can note its beneficial effect on his future consultations with them.

Interpretation of the JCPTGP statement about adequate experience for night and weekend emergency care is difficult, but surely it does not imply no emergency care throughout the night. Such care can provide a trainee with insights into human behaviour, including his own, that can be obtained in no other way. The experience must not be acquired unsupervised and should form the basis of fruitful teaching between the trainee and his trainer.

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## The safety of medicines

'The collection, tabulation and analysis of the adverse effects of medicines on a national and international computerized scale is likely to be of inestimable value to doctors and the community.'

Sir Derrick Dunlop, 1973

**P**UBLIC concern, expressed through the news media and in Parliament, is increasingly evident in respect of the safety of prescribed medicines. This disquiet is justifiably founded when it is based on the evidence of damage to health attributed to certain drugs, but the wide extent of the concern is less justified because, at present, the public has no means of assessing the relative risks of taking medicines and therefore this issue is seen out of a proper perspective.

Patients show their anxiety by their frequent enquiries about the side effects of medicines prescribed for them and particularly in regard to newly marketed products. This expressed disquiet supports the view that steps need to be taken to increase awareness of the safety of medicines and enable attitudes to develop that allow comparison of relative risks and benefits. Patients know that, while there are sophisticated procedures involving laboratory experiments and controlled clinical trials through the various phases in the development of a new

medicine prior to marketing, there is, remarkably, no formal systematic observation of medicines once they are released on general prescription. Yet medicines prescribed in general practice are used in very different situations from those of controlled clinical trials: the patient population is less well-defined, other medicines may be taken concurrently, compliance with recommended dosage cannot be guaranteed and the physical environment is more variable. Even with the most careful pre-marketing studies unforeseen side effects, both beneficial and deleterious, can occur. All medicines have side effects. Most high-risk drugs are prescribed in hospital, where the seriousness of the condition makes a higher level of unwanted side effects acceptable. In general practice however, the position is quite different, for dangerous side effects are very rare and most drugs are prescribed in situations that are not life-threatening and where harmful side effects are unacceptable. For these reasons, and because the range of prescribing in general practice is 10 times greater than in hospital, the testing of drugs in the environment of general practice becomes increasingly more important.

Where the doctor clearly suspects a side effect linked to the medicine prescribed, reporting through the

present 'yellow card' system introduced in 1964 provides one form of alert and about 1,000 adverse reactions are reported each month—mainly from general practitioners. There are, however, serious defects in monitoring systems based on random reporting.<sup>1-3</sup> It is equally important to detect side effects where the association with the drug is not obvious and which may take the form of a naturally occurring event, such as jaundice or a heart attack, occurring more frequently in the drug user than in a control population. To detect these side effects formal studies of large numbers of users are necessary, especially in the first year after marketing.

British general practice is uniquely placed to contribute to studies on drug safety where large numbers of patients require to be observed because the registration system in the United Kingdom defines the population for which each doctor is responsible, controls are easily identified, and through the NHS record card information is available on all aspects of illness whether managed by the general practitioner or through the hospital. For the past 15 years the safety of medicines has been a matter of special interest to the College. The Research Unit in Manchester, under Dr Clifford Kay, has, during this period, conducted an extended study into oral contraceptive drugs—mobilizing 1,400 general practitioners in the observation of 47,000 of their female patients.<sup>4</sup> This research project is generally recognized as being the largest study of its kind and it has produced a great deal of information regarding the effects of oral contraception, both beneficial and harmful. The Birmingham Research Unit, under Drs Crombie and Fleming, in producing the National Morbidity Surveys in general practice, is served by 147 doctors who undertake the continuous recording of all events for which their patients consult them and involves a study population of 300,000.<sup>5</sup> Skegg and Doll<sup>6</sup> confirmed that total morbidity recording in a general practice could enable the relationship between clinical events and drug consumption to be studied, while Inman<sup>7</sup> has collected data about significant events from patients identified by prescriptions retrospectively. The study by Drury and Hull<sup>8</sup> also showed that prospective monitoring for adverse reactions to drugs in general practice was possible for medicines other than oral contraceptives. The potential therefore exists to develop in Britain a more effective system for post-marketing surveillance of medicines used in general practice than has so far been attempted, with the College able to play a central and co-ordinating role.

Large-scale prospective studies are capable of generating hypotheses to link a medicine and a significant adverse reaction occurring at a level of 1:10,000 takers. The verification of the hypothesis then requires testing through the intensive scrutiny of patients' records, involving small numbers but depending on success of validation or refutation on the quality of the data recorded of past events in the patient's history. If

general practitioners are to make a major contribution to the safety of medicines sentinel practices will require to be appointed, using the experience of the National Morbidity Surveys, in which a standard of record keeping and data collection can be guaranteed and carrying a status similar to the present vocational training practices. Record linkage to a central computer will be a logical development, and Professor Paul Grob is already testing this methodology using the Prestel View-data system.

Venning<sup>3</sup> stated that the ideal system for the identification of adverse drug reactions would be a drug linkage system recording data on the incidence of reactions among drug users and also identifying the problems of usage of drugs among patients with diseases and syndromes which might be drug-induced. Such a system is possible and it would meet the plea made by Oliver<sup>9</sup> when commenting on the wide use of drugs: in the hope of preventing vascular disease he called for a comprehensive monitoring system to determine 'when the risk of correcting risks by drugs is greater than the uncorrected risk'. A comprehensive monitoring system would therefore make an immense contribution to research in clinical medicine in addition to the specific issue of drug safety.

The time has come for a major advance in relation to the marketing of medicines in Britain. The concern of the public and of the profession demands such a development. There are signs that the pharmaceutical industry now appreciates the need for systematic observations of medicines after marketing, for this carries potential long-term advantages to the industry even though the short-term cost may be high. The complexity of the task may be formidable, but the professional skills and technological resources exist to allow the advance to be made. Encouragement to the pharmaceutical industry to undertake, voluntarily, post-marketing surveillance should be given by the Government through extension of patents to cover the period of time necessary for effective surveillance of drugs. It will certainly require a political decision by the Government to secure a system that synthesizes the many interests and organizations already involved in this field. The influence of patients through the disquiet they are expressing provides a stimulus, the proper response to which would be 'of inestimable value to doctors and the community'.

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## Promoting prevention

IT is now two-and-a-half years since the College published the first three of its reports from general practice on prevention. It was in February 1981 that 33,000 of these booklets were posted with the *Journal*, marking the opening salvo of a national campaign. *Health and prevention in primary care* (No. 18) was the co-ordinating, or key, document and it was accompanied by *Prevention of arterial disease in general practice* (No. 19) and *Prevention of psychiatric disorders in general practice* (No. 20). Six months later saw the publication of *Family planning—an exercise in preventive medicine* (No. 21) which was followed in July 1982 by the last and the lengthiest of the series, *Healthier children—thinking prevention* (No. 22).

This set of documents was produced to initiate a debate about prevention in health care, and this it has done. The interest generated has been substantial and some of the reports have become regular references in the medical literature. Only in April the Thames Valley Faculty ran a most successful symposium before the RCGP Spring meeting on 'Aspects of prevention' which stretched the minds of all who attended.

Now the final link in the chain has been forged. Another working party, under the chairmanship of Dr Colin Waite, has produced a discussion document<sup>1</sup> which is intended to pull together some of the main threads running through five reports and above all to identify practical steps which can be taken now to implement preventive care.

The document includes a carefully thought-out list of recommendations which, if implemented, would make a substantial impact. The College cannot act alone. It can and does exhort and enthuse but at the end of the day progress must depend on co-operation between many individuals and organizations. This new publication is therefore being sent to many organizations, both medical and non-medical, and is available to the public for discussion.

### Reference

1. *Promoting Prevention, Occasional Paper 22*, is available now from the Publications Sales Department, Royal College of General Practitioners, 14 Princes Gate, Hyde Park, London SW7 1PU, price £3.00. Payment should be made with order.

## Hormonal defects in patients with anorexia nervosa

Previous studies have indicated that many patients with anorexia nervosa have defects in urinary concentration or dilution suggestive of abnormal secretion of the antidiuretic hormone arginine vasopressin. We examined the response of plasma vasopressin to intravenous hypertonic saline in anorexic patients before and after correction of their weight loss. Basal levels of the hormone in the cerebrospinal fluid were measured. In all four subjects studied, before correction of weight loss, the response to hypertonic saline was abnormal: in one, the plasma level of arginine vasopressin increased subnormally relative to the plasma sodium level; in the other three, it fluctuated erratically, with no relation to plasma sodium. These defects persisted in the three patients studied three to four weeks after recovery of body weight. In two patients who were initially studied

when they were underweight, the defects were gone six months after recovery; in five of seven other patients the response was normal at least six months after recovery but not while they were underweight. Abnormalities in the osmoregulation of plasma arginine vasopressin were not accounted for by nonosmotic stimuli and were almost always associated with an absolute increase in the level of arginine vasopressin in the cerebrospinal fluid or a reversal of the normal (<1.0) cerebrospinal fluid/plasma ratio of arginine vasopressin. These results indicate that most if not all patients with anorexia nervosa have abnormal levels of arginine vasopressin in their plasma and cerebrospinal fluid that are corrected very slowly with weight gain. The cause and consequences of these abnormalities remain to be determined.

Source: Gold PW, Kaye W, Robertson GL, *et al.* Abnormalities in plasma and cerebrospinal-fluid arginine vasopressin in patients with anorexia nervosa. *N Engl J Med* 1983; 308: 1117-1123.