Monitoring adverse drug reactions*

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PERHAPS the most important part of this survey of the Royal College's contribution to the monitoring of adverse reactions will be reference to other activities as alternatives to direct monitoring.

Ideally, all adverse reactions, as they are observed by clinicians, should be routinely and systematically reported to some central agency. In theory this happens now, but there are grave doubts about the completeness of these returns to the Adverse Reactions Sub-committee of the Committee on Safety of Drugs and to its successor.

Wade (1973) has suggested that clinicians have a block about reporting adverse reactions because " they find it emotionally disturbing to learn that a drug which they prescribe to help patients may harm them." What has the College been doing about this? There have been: formal therapeutic trials, direct monitoring of adverse reactions, colour tagging, prospective and retrospective studies, clinical audits of adverse reactions, and research on prescribing patterns and morbidity.

Formal therapeutic trials

For reasons both ethical and medicopolitical the College has so far deliberately eschewed conventional drug trials. Instead, it has a policy for ' helping ' trials which are believed to have some academic or other purpose beyond the narrower and usually commercial issue. The exceptions to this were the study of the effects of: sulphonamides on the natural history of measles (Watson, 1955) and amantadine on the natural history of influenza (Galbraith *et al.*, 1973).

There was also a trial of anti-emetics, which remains unpublished because the College had no control over publication.

Direct monitoring

The Birmingham Research Unit of the Royal College of General Practitioners, through the system of weekly returns (College of General Practitioners, 1963; World Health Organisation, 1969; Royal College of General Practitioners, 1968–1969) attempts to monitor adverse reactions directly. The Research Unit receives weekly returns from 60 general practitioners caring for a total practice population of about 160,000. They submit a weekly abstract, from their standard disease indexes (College of General Practitioners, 1963) of the number of patients consulting them for the first time with a variety of infections, communicable and respiratory complaints. In addition, since 1966, they have reported any adverse drug reactions encountered. Each report includes the name of the drug concerned, the dose, the route of administration, the type of adverse reaction, and the reason for which the drug was given.

An analysis of these returns is presented in tables 1 and 2 and they are surprising in many ways—particularly the low total rate. For example, the rate in the recording practices of the Royal College of General Practitioners of 34 per 100,000 patients at risk is still four times greater than the equivalent national figure for reports to the Committee on Safety of Drugs which in 1968 (received 3,446 reports per 45,000,000 people or eight reports per 100,000 at risk.

*A paper presented at a conference on *Monitoring of Adverse Reactions in General Practice*, organised by the Committee on Safety of Drugs and the Royal College of General Practitioners on 18 September 1973 at 14 Princes Gate, Hyde Park, London.

Journal of the Royal College of General Practitioners, 1975, **25**, 337—343

TABLE 1

DRUG REACTIONS (1966–1970)
ROYAL COLLEGE OF GENERAL PRACTITIONERS RESEARCH UNIT—WEEKLY RETURNS

	Number of cases	*Rate per 100,000 patients at risk*
Ampicillin (Penbritin)	93	7·9
Penicillin	52	4·4
Other tranquillisers and hypnotics	30	2·5
Nitrofurantoin	26	2·2
Other antibiotics	26	2·2
Tetracyclines	21	1·8
Analgesics	21	1·8
Anti-depressants	17	1·4
Oral contraceptives	5	0·4
Methyldopa	3	0·3
Other drugs	103	8·7
TOTAL	397	33·5

TABLE 2

ADVERSE EFFECTS (1966–1970)
ROYAL COLLEGE OF GENERAL PRACTITIONERS RESEARCH UNIT—WEEKLY RETURNS

	Number of cases	*Rate per 100,000 patients at risk*
Other rash (11 with pyrexia)	287	24·2
Urticaria	31	2·6
Diarrhoea and vomiting	20	1·7
Oedema	15	1·3
Neurological signs	10	0·8
Jaundice, blood dyscrasia, marrow defects	4	0·3
Acute reactions with generalised symptoms and/or collapse	3	0·3
Joint swelling	—	—
Melaena/haematuria	—	—
Other adverse effects	36	3·0
TOTAL	406	34·2

Despite these low rates, a few drugs account for practically all the reported reactions. Furthermore, relatively trivial skin lesions, which, however, are obvious to the patient account for most of the reactions. There are almost no adverse reactions of any severity or significance and very few unexpected or novel.

From carefully conducted prospective studies, it is known that approximately one per cent of the population will have an ampicillin rash each year. The rates recorded in the College study are 7·9 per 100,000 population at risk each year. This is less than one per 100 of the estimated total incidence of ampicillin rashes, but still three times greater than the equivalent rates based on reports to the Adverse Reactions' Sub-committee.

We can draw some tentative inferences from this analysis. Either the practitioners are not seeing the ' run-of-the-mill ' adverse reactions, which is unlikely, or they are reporting them selectively. The reason for non-reporting may simply be their general

biological and clinical insignificance and triviality. The block which Wade suggested may be operating and speaking personally as one of the reporting practitioners, both sets of reasons are true for me. If Wade is right, does it matter? I think it does in one respect only. The good clinician is always on the lookout and sensitive to the *unexpected.* If this tendency is selectively suppressed for adverse reactions, then the need for a systematic type of recording for this is all the more necessary.

Colour tagging

The College has devised a colour coding system (College of General Practitioners, 1964) for tagging records and adverse reactions is one of the groups included. However, ' all that glistens is not gold.' For example, many patients labelled ' penicillin sensitivity ' at worst had on one occasion, a nondescript, insignificant skin rash associated with the administration of penicillin, a correlation which may not even have been cause and effect. Ampicillin rashes are even more common and almost always have no significance.

Prospective and retrospective studies

Indexing systems

The simple identification of some *unexpected* event such as an adverse reaction is still only the first, though the most important phase in monitoring. Once a possible cause-and-effect relationship is suspected between a drug and some adverse reaction, this suspicion has to be established on a more certain basis. For rare events this demands either a conventional prospective survey, which may well take a long time, or a retrospective survey based on some indexing system which can be guaranteed to contain a total or at least a representative cohort of whatever event is being studied.

Since we are studying adverse reactions, such indexing systems should relate to drug prescriptions. However, few, if any, such indexing systems are available in general practice. Luckily, disease indexing systems will often suffice, for the suspected drug can usually be identified indirectly using the clinical notes of the patients with the disease or diseases for which it is usually given.

Also, any serious adverse effects or reaction, even when not originally recognised as such, will be recorded under an appropriate disease heading. This occurred, for example, for the venous thrombo-embolic effects of oral contraceptives (College of General Practitioners, 1967). This approach can be used for any adverse effect which can be included consistently within an equivalent category of the *International Classification of Disease.* Further possible examples are melaena, cataract, agranulocytosis, and liver damage.

The indexing systems, maintained consistently by about 100 general practitioners contain now approximately two million patient-years of records of total reported morbidity, that is some 2.4–3 million episodes of illness.

Retrospective oral contraceptive study

The original retrospective oral contraceptive study (College of General Practitioners, 1967) conducted by the Birmingham Research Unit of the College, is an example of the retrospective type of study. In this study, for the first time, for what it was worth, a relationship between the use of oral contraceptives and venous thrombo-embolism was established at a statistically significant level. Other surveys carried out retrospectively from disease indexes included a study linking the use of isoprenaline inhalers in asthma with a raised mortality rate.

Prospective oral contraceptive study

The current oral contraception study (Royal College of General Practitioners, 1974) is a classic example of the prospective type of survey.

Outcome of pregnancy

The outcome of pregnancy study, carried out by the Research Unit in England and the Scottish Research Committee in Scotland, is another example of prospective work. The results which follow are from the English study, which included records from 140 practitioners caring for 10,000 pregnancies, in 1964–65. The study was stimulated by the thalidomide disaster and was set up to see whether any of the other drugs commonly given to women or illnesses suffered by them in the early weeks of pregnancy (from six weeks before the last menstrual period to 22 weeks after the last menstrual period) were related to abnormal outcomes of the pregnancy.

The drug prescriptions given to and morbidity reported by the women who ultimately were delivered of a normal full-term baby were taken as the expected baseline rates with which the equivalent figures for the mothers with abnormal outcomes were compared. From the initial analyses, table 3, it appeared that a statistically significant excess of prescriptions had been issued to and morbidity was reported by the women who had malformed and/or stillborn outcomes.

TABLE 3
PRESCRIBING RATES IN RELATION TO OUTCOME OF PREGNANCY

Type of outcome	*Number of mothers*	*Number of prescriptions per mother*	*Percentage excess over normal*
Normal babies	8,217	2·29	—
Malformations	385	2·55	*11·4*
Rhesus abnormalities	37	2·62	*14·4*
Stillbirths	100	2·85	*24·4*

TABLE 4
PRESCRIBING RATES IN RELATION TO PREVIOUS ABNORMAL OUTCOME OF PREGNANCY

	Normal sample	*Significant malform-ations*	*Doubtful malform-ation*	*Rhesus abnorm-alities*	*Still-birth*
Total number of mothers	500	245	140	37	100
Previous abnormal outcome	104 (*21%*)	61 (*25%*)	30 (*21%*)	17 (*46%*)	26 (*26%*)
Others	396	184	110	20	74
Number of prescriptions/mother	2·29	2·34	2·90	2·62	2·85
Previous abnormal outcome	2·63	2·41	3·57	2·53	4·26
Others	2·20	2·32	2·72	2·70	1·35

Normal sample

1 in 16 sample from 8,217 normal pregnancies

However, a subsequent, more rigorous and detailed analysis of the results has shown that the correlations do not reflect a direct causal relationship. Instead (table 4), the excesses of prescriptions and reported morbidity in women with abnormal outcomes, probably reflect an enhanced degree of anxiety in the expectant mother. Most of this excess is seen to be related consistently, whatever the present outcome, to the experience

of an abnormal outcome in a *previous* pregnancy. The exceptions are those with a rhesus abnormality where the presence of the abnormality may be known early enough in pregnancy to produce the anxiety and, those with a biologically trivial, insignificant or doubtful malformation as the outcome.

In this latter group, the anxiety is presumably more basic and results not only in an increased reporting of illness and therefore also of prescriptions issued, but also of reported trivial abnormalities in the baby.

In all cases, the anxiety is presumed to be reflected in an enchanced rate of reporting recognised illness to the practitioner. It has been known for some time (Horder and Horder, 1959) that approximately only one recognised aberration from health in every four is brought to a doctor. Rates of reporting illness have a close correlation with the subsequent rates of prescribing of drugs.

I have an uneasy feeling that a similar type of analysis might well demolish many other apparent correlations between drug use and adverse effects.

These ' outcome ' results have also been useful in refuting the suspicion of a possible significant teratogenic effect of tricyclic drugs. This technique of refutation may well be the main use for these results in the future and has other interesting implications.

The general public seems to prefer news of action, death, destruction, and disaster to tranquillity, peace and normality, at least so long as it affects someone else. The Press simply reflects this predilection. The reporting by McBride (1972) of congenital malformation in a series of three mothers who had taken tricyclic drugs during the early weeks of pregnancy was reported by the World's Press and within days had become a major issue. The evidence of refutation from the College studies (Royal College of General Practitioners, 1970; Kuenssberg and Knox, 1973), with those reported by Sim (1972) a psychiatrist, stopped this story dead. There was no further comment of any kind, even in the professional journals.

This non-response was also due partly to a technical problem associated with any process of refutation. The tactics and strategy of scientific problem solving are geared to the null hypothesis and conventional tests of significance for observed *differences*. The smallest difference between the effects of two different factors, however insignificant biologically and clinically, can become statistically significant if enough observations are recorded. Also, there is no equivalent set of rituals and dogmas for degrees of similarity.

There are also the problems of randomisation and in the outcome of pregnancy study, the effectiveness of the randomisation ritual was taken for granted. Only a meticulous, vigorous and detailed re-analysis of every possible source of variability among those factors lumped under the " *randomisation* " ritual finally uncovered an unexpected source of marked variability. This confounding variable was sufficient to explain all the observed differences (highly significant at that) spuriously attributed to the drugs and morbidity.

Clinical auditing and adverse reactions

Because of all the problems and difficulties associated with the more direct approach, the Research Unit, in co-operation with the Department of Engineering Production at Birmingham University, has been engaged on another approach. Not only do we need to inculcate in ourselves a greater awareness of the possibility of adverse reactions of drugs, but more important still, we need, if Wade is right, to alter our basic attitudes, value systems, and clinical performance. I suggest that the mechanism for achieving this is clinical auditing.

Clinical auditing differs from conventional medical auditing in that the data used are not measured against any absolute (but ultimately arbitrary) scales of quality.

Instead these data are used solely for the development of value judgments hammered out dynamically in the context of peer-group discussions. The essential basis for effective clinical auditing is a true peer group, or a group of professionals who have had sufficient time to interact together.

The essence of this group is constituted by the ability of the peer group members to accept comfortably the implicit and even explicit comments and criticisms of their peers without feeling threatened. At the same time, each individual should have built up a respect for each of his peers, a degree of respect which will ensure that he will curb his natural drive to point out indiscriminately idiosyncrasies, if not errors, in the performance of his peers. Only under these circumstances will the individual group members feel able to expose the details of their personal clinical performance to their peers. Without these basic conditions, no form of auditing stands any chance of implementation and fulfilment.

The natural origin of all clinical auditing procedures is the ' case conference '. This is ostensibly a mechanism for ensuring that a specially difficult clinical problem receives the maximum of attention from a peer-group and that the total knowledge available within the group is brought to the solution of the problem.

However, there is a secondary and often hidden but equally important *raison d'être* for the case conference. It is in effect clinical auditing and learning by a peer-group. At a case conference involving a small group of doctors who are meeting regularly, each uses the situation to discover deficiencies in his own knowledge, to purge his mind of intellectual lumber, and generally continuously up-date his capacity as an effective clinician. He can achieve this only where the group is a true peer-group as defined above.

Clinical auditing is, in essence, the combination of a peer-group supplied with a consistent in-put of objective and scientific data, appropriate to the solution of the problem which concerns the group. However, if these external data are presented to the group or any individual in the group with any explicit pre-determined judgment of ' right ' or ' wrong,' they will tend to be rejected. This will be particularly so if there is any explicit or even implicit condemnation of any of the group's present norms.

TABLE 5

PRELIMINARY RESULTS FROM AUDIT OF PRESCRIBING PATTERNS OF SIX GENERAL PRACTITIONERS

	Number of prescriptions/1,000 population/a year							
	1970 England & Wales	*The six general practitioners*						*All doctors*
		A	B	C	D	E	F	
Barbiturate hypnotics	291	70	153	251	163	140	125	151
Non-barbiturate hypnotics	158	13	77	113	94	68	119	77
Tranquillisers	382	297	527	468	417	234	726	426
Antidepressants	142	478	189	278	189	161	380	308
TOTAL	973	858	946	1110	863	603	1350	962

The first of these standardised auditing programmes developed by the Birmingham Research Unit concerns personal prescribing patterns and in particular the use of psychotropic drugs. The auditing takes the form of a seminar discussion, where each practitioner defends his own personal and idiosyncratic habits, if he can. No one likes being the

odd man out in a true peer group. Table 5 shows the preliminary results from a group of practitioners who have used this audit.

In the development of a systematic programme of clinical auditing procedures, the Research Unit of the College can fulfil two important functions. It can design the systematic standardised programmes in the first place, so that any group of doctors using them can be assured that they can be implemented economically and reliably in the practice with minimal involvement of the practitioner's own time. The Research Unit can receive the results of the audits from individual practice groups and consolidate them as a general baseline of information.

The potential for this sytem of auditing is greatly extended if we include auditing by comparative performance and do not concentrate on auditing against some arbitrary scale of excellence set up by others outside the group.

This does not preclude the development of suitable medical auditing procedures by others for the use of such groups. In fact, if we are to extract the maximum advantage from this situation, the central development of auditing procedures, constantly improved and extended by feed-back comment and criticism from the peer group users, is an essential. The aim should be the gradual development of a library of accessible and appropriate auditing procedures, constantly up-dated as the medical care system itself evolves.

The results from the auditing carried out in each small group can be consolidated into an ever extending audit ' baseline ' which each group will therefore have for primary reference.

Prescribing patterns and morbidity

Finally, there is a place for a systematic study of the relationship of clinical problems (including morbidity) with the drugs prescribed by the practitioner. A study of this kind (Rowe, 1973) has been reported by our sister college in Australia. The opportunity exists now for a similar study in Great Britain.

REFERENCES

College of General Practitioners (1967). *Journal of the College of General Practitioners*, **13**, 267–279.
College of General Practitioners: Records and Statistics Unit (1963). *Journal of the College of General Practitioners*, **6**, 217–219.
College of General Practitioners: Research Committee of Council (1963). *Journal of the College of General Practitioners*, **6**, 195–224.
College of General Practitioners: Research Committee of Council (1964). *Journal of the College of General Practitioners*, **8**, 94–95.
Galbraith, A. W., Schild, G. C., Potter, C. W. & Watson, G. I. (1973). *Journal of the Royal College of General Practitioners*, **23**, 34–37.
Horder, J. & Horder, E. (1954). *Practitioner*, **173**, 177–187.
Kuenssberg, E. V. & Knox, J. D. E. (1973). *Lancet*, **1**, 198.
McBride, W. (1972). *The Times*, 4 March.
Rowe, I. L. (1973). *Medical Journal of Australia*, **1**, 589–593, 642–644.
Royal College of General Practitioners (1970). *British Medical Journal*, **4**, 178–179.
Royal College of General Practitioners (1974). *Oral Contraceptives and Health*. London: Pitman Medical Press.
Royal College of General Practitioners: The Records and Research Advisory Service (1968–1969). *Summary of Weekly Returns*.
Royal College of General Practitioners: Research Committee of Council (1968). *British Medical Journal*, **2**, 244.
Sim, M. (1972). *British Medical Journal*, **2**, 45.
Wade, O. L. (1973). *Journal of the Royal College of General Practitioners*, **23**, *Suppl.* No. 2, 62–66.
Watson, G, I. (1955). *British Medical Journal*, **1**, 5–10.
World Health Organisation (1969). *Weekly Epidemiological Record*, No. 44.