

We believe that in presenting our experience in Wessex we are adding to the sum of hard data for contemporary clinicians and administrators alike, thereby giving useful evidence for future development in our speciality.

We would like to express our sincere thanks to the junior medical staff, nurses, technicians, laboratory staff, and many others who have contributed so much to our work and who have made this report possible. We would also particularly like to thank Mrs Anne Longhurst for the painstaking retrieval of the information regarding this large number of patients and Mrs Julie Mintram for her secretarial help.

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Clinical Topics

Identification of adverse reactions to new drugs. II (continued): How were 18 important adverse reactions discovered and with what delays?

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In the first half of part II (published last week, p 289) I described how the first 13 out of 18 important adverse reactions to new drugs had been discovered and in each case tried to identify features affecting the initial reports and subsequent verification of causality. I now continue with the remaining five adverse reactions identified and conclude part II by assessing the "avoidable delays" in recognising the major adverse reactions.

Results (continued)

The table published in the first half of part II lists the 18 important adverse reactions selected for review of the discovery process.

(14) PSEUDOMEMBRANOUS COLITIS DUE TO TETRACYCLINES—DRUGS MARKED 1949; NO REGULATORY WARNING IN UK

Alerting—Pseudomembranous colitis was reported by Reiner *et al*¹ three years after tetracyclines had been introduced.

Verification—Klotz *et al*² reported another series of cases in which one patient showed a clear relation of symptoms to repeated re-challenge. Taken in conjunction with characteristic biopsy appearances of a relatively unusual nature causality was established beyond reasonable doubt, but the reaction was extremely rare.

Comment—The incidence is of the order of 1 in a million prescriptions. A cohort approach would have been of no value.

(15) PSEUDOMEMBRANOUS COLITIS DUE TO LINCOMYCIN—DRUG MARKED 1964; UK REGULATORY WARNINGS 1976 AND 1979

Alerting—After four years a clinical trial by Price *et al*³ showed that diarrhoea occurred in 35 out of 71 patients receiving lincomycin, which was significantly more than the 8% and 13% of patients taking phenoxymethylpenicillin and phenethicillin. Against the previous background of colitis with tetracyclines the report of three cases by Benner and Tellman⁴ six years after marketing provided prima facie evidence.

Verification—Three years later Scott *et al*⁵ reported that of seven consecutive cases of pseudomembranous colitis seen in a six month period six patients had received lincomycin, and the antibiotic history of the seventh was obscure. Review of necropsy records at the two hospitals where the authors worked yielded only one additional case over a two year period, also in a patient who had been given lincomycin.

Comment—The long delay before alerting cannot be explained. The incidence is not known; it is not possible to say what sample size would have been needed for a recorded-release cohort study.

(16) PSEUDOMEMBRANOUS COLITIS DUE TO CLINDAMYCIN—DRUG MARKED 1968; UK REGULATORY WARNINGS 1976 AND 1979

Alerting—Clindamycin was developed as an "improvement" on lincomycin and has a similar range of antibacterial activity. In a randomised comparative study with lincomycin in 12 volunteers⁶ diarrhoea occurred after 10 out of 24 single doses of 500 mg clindamycin, compared with eight out of 24 after 500 mg lincomycin. In the first clinical trial, however,⁷ it was thought that diarrhoea was less frequent at a dose of 300 mg six-hourly but no comparative study was performed. The first three cases were reported five years after marketing.⁸

Verification—Confirmatory reports the same year^{9 10} with x ray and biopsy findings made a causal relation almost certain. After an overall delay of 15 years an analysis of adverse reactions notified to the Committee on the Safety of Medicines¹¹ showed a great excess of

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cases related to lincomycin and clindamycin in comparison with other broad-spectrum antibiotics.

Comment—We now know that drug induced pseudomembranous colitis is associated with growth of *Clostridium difficile* in the gastro-intestinal tract, presumably consequent on suppression of other flora by broad-spectrum antibiotics; vancomycin is effective against *C. difficile*. As with lincomycin we do not know the incidence or the size of cohort study that would have been needed to identify this problem.

(17) APLASTIC ANAEMIA DUE TO PHENYLBUTAZONE—DRUG MARKETING 1951; UK REGULATORY WARNING 1965 ABOUT VARIOUS TOXIC EFFECTS INCLUDING BONE MARROW TOXICITY WITHOUT SPECIFIC MENTION OF APLASTIC ANAEMIA

Alerting—The problem was predicted from structural similarity to amidopyrine and other pyrazolones of known toxicity to bone marrow.¹² Agranulocytosis was reported early¹³ followed by aplastic anaemia in a patient who had been given gold.¹⁴ Aplastic anaemia not attributable to other treatment was first reported six years after marketing.¹⁵

Verification—Thirteen years after marketing there were still only seven published reports,¹⁶ but after a further three years the manufacturers reviewed 45 cases known to them¹⁷ (P D Fowler, personal communication, 9 July 1979). In 1965 the Committee on the Safety of Drugs issued a warning on various toxic effects of phenylbutazone and related drugs, including reference to bone marrow damage and blood dyscrasia, without specific mention of aplastic anaemia. In view of the earlier recognition of agranulocytosis with phenylbutazone this does not appear to have been an adequate warning concerning aplastic anaemia, which now appears to be the major cause of death from phenylbutazone induced marrow toxicity. Twenty six years after marketing the Committee on the Safety of Medicines¹⁸ published the experience of death certifications and fatal adverse reactions reported in the yellow card system. There had been 188 deaths from aplastic anaemia or agranulocytosis with an estimated incidence of 1 in 50 000 patients, the risk being higher for older patients in contrast with a younger age pattern for idiopathic aplastic anaemia.

Comment—It is clear that the magnitude of the problem was underestimated for a long time owing to underreporting¹⁹ and that a notification or central registry system for bone marrow toxicity would be useful, as once run by the American Medical Association. The incidence is even lower than that of aplastic anaemia with chloramphenicol, and a cohort approach to postmarketing surveillance would not have been useful.

(18) TARDIVE DYSKINESIA DUE TO PHENOTHIAZINES—DRUGS MARKETING 1953; UK REGULATORY WARNING 1979

Alerting—Extrapyramidal side effects of phenothiazines were noted in the original clinical trials. The specific problem was reported by Hall *et al*²⁰ within three years of marketing. They noted persistence of dyskinesia for 60 days after stopping treatment in six out of 36 patients who had received chlorpromazine for two months or more.

Verification—Ey *et al*²¹ reported persistence for six months after stopping chlorpromazine. In view of the rarity of this neurological syndrome in untreated patients no further confirmation was required. Reports were reviewed 12 years later²² but even at that time the validity of the syndrome was being denied.²³

Comment—Side effects such as this, dependent on major pharmacological actions of new drugs, do not present any particular problem for early recognition.

Comment

For each of the 18 adverse reactions identified in part I of this series²⁴ dates were noted for first alerting, for verification, and for regulatory warning in Britain when this occurred. There were few delays to alerting and rather more to verification, but the longest time intervals were those between verification and regulatory action.

Some comment is needed on the definitions used for alerting and verification, as the dates and the delays identified are dependent on the definitions used. Alerting may be defined without ambiguity as the first published suggestion of a link

between drug and suspected adverse reaction. Assessing the stage at which an adverse reaction may be regarded as satisfactorily verified can, however, be made only in a personal and subjective manner. With some adverse reactions there may be little or no room for disagreement, but with others there may be little prospect for agreement. For the purpose of reviewing mechanisms and overall delays a single definition of verification has been selected for simplicity. Karch and Lasagna²⁵ classified adverse reactions to drugs as doubtful, conditional, possible, probable, and definite but their definitions were designed to help in assessing causality for individual patients with a suspected reaction rather than for identifying a causal relation in the general sense. The level of certainty chosen for verification here corresponds most closely to their "definite" category. It may inevitably sometimes fall short of complete scientific proof. Where Karch and Lasagna emphasise rechallenge as critical for the individual patient other criteria such as dose response and epidemiological data are also important in the present context.

Delays in recognition

An attempt was made to assess the "avoidable delays" in recognising 17 of the 18 adverse reactions. (This was not considered appropriate for tetracycline pseudomembranous colitis. This reaction was included for purposes of analysis of the discovery process considered relevant to the subsequent problems with lincomycin and clindamycin, but the adverse reaction to tetracyclines was not identified as an important problem in its own right.) In evaluating delays to alerting, certain questions were asked. Firstly, would event recording in clinical trials^{26 27} have resulted in alerting before marketing?—if so, the entire time lag from marketing to alerting could have been avoided. This led to the evaluations of the delays to alerting for dermatitis and keratoconjunctivitis with practolol, as pointed out by Skegg and Doll.²⁸ Secondly, does the time interval to alerting seem inappropriate in the context of the frequency of the reaction—that is, would event recording in phase IV clinical trials after marketing, or in a programme of controlled release or postmarketing surveillance, have resulted in alerting at an earlier stage? It was not possible to identify with confidence any example of an adverse reaction with frequency of the order of 1 in 1000 such that a cohort study with a sample size of 10 000 might have led to earlier alerting.

In evaluating avoidability of delays from alerting to verification the question asked is, How soon would the critical verification study have been completed if it had been initiated promptly after alerting? Where verification did not result from a particular critical study the question is how soon it might have been expected as a result of methods of reporting available to regulatory agencies today. The estimates of "avoidable delay" were made by allowing from one to two years for verification studies. In evaluating delays from verification to regulatory action it was assumed that any delay measurable in years was avoidable and that the medical profession should always be notified promptly of the verification of an important adverse reaction when relevant to medical practice in that country. (Delays in regulatory action on clioquinol (subacute myeloptoptic neuropathy) in Britain were excluded as this reaction, widely reported in Japan, was not encountered here.)

Table I shows the length of delays assessed as avoidable. Griffin and D'Arcy²⁹ reviewed the delays from verification to regulatory action for several adverse reactions and arrived at similar conclusions for a number of those reviewed here and have also published data on actions by some other regulatory agencies outside Britain. I know of no previous attempt to assess the earlier delays from marketing to alerting and to verification. For these important adverse reactions the magnitude of the earlier delays was small compared with the delays from verification to regulatory action, but for some adverse reactions there were substantial delays which must have resulted in avoidable deaths and disabilities. For 18 reactions there were avoidable delays to alerting in respect of three, the average delay being three years. There were avoidable delays to verification after alerting in respect of seven adverse reactions, the average delay being four years nine months. Seventeen of the 18 adverse reactions affected British medical practice and, of these, there were delays between verification and regulatory action in 14—namely, all except the three reactions which constituted the practolol oculomucocutaneous syndrome, where the Committee on the Safety of Medicines acted promptly. The average delay for these reactions was 12½ years. This could be regarded

TABLE 1—Delays in recognising major adverse reactions to new drugs (delays in alerting, delays in verification, delays in first regulatory action after verification)

Adverse reaction	Drug	Dates				Years of avoidable delay*			
		Marketed	Alerted (A)	Verified (V)	Regulatory Action (RA)	A	V	RA	Total
Dermatitis	Practolol	1970	1972	1974	1975†	2	2	—	4
Keratoconjunctivitis			1974	1975		4	—	—	4
Sclerosing peritonitis	Oral contraceptives	1958	1974	1975	1969	—	—	—	—
Pulmonary embolism			1961	1967		—	5	2	7
Myocardial infarction	Phenacetin	1887	1963	1970	1974‡	—	5	11+	16+
Nephropathy			1953	1959		—	5	15	20
Lactic acidosis	Phenformin	1969	1959	1959	1980	—	—	21	21
Deaths from asthma	Sympathomimetic aerosols	1961	1965	1968	1967	—	—	2	2
Subacute myelo-optic neuropathy (Japan)*	Clioquinol	1935	1971	—	(1970)*	—	—	—	—
Vaginal cancer (daughters)	Stilboestrol (maternal)	1948	1970	1971	—	—	—	?	?*
Aplastic anaemia	Chloramphenicol	1949	1950	1952	1967	—	—	15	15
Liver necrosis	Halothane	1956	1963	1969	—	—	5	12+	8+
Retroperitoneal fibrosis	Methysergide	1960	1964	1966	—	3	—	14+	17+
Pseudomembranous colitis	Tetracyclines	1949	1952	1953	—	—	—	23	23
	Lincomycin	1964	1970	1973	1976§	—	2	3	5
	Clindamycin	1968	1973	1973	1976§	—	—	3	3
Aplastic anaemia	Phenylbutazone	1951	1957	1967	—	—	9	14+	23+
Tardive dyskinesia	Phenothiazines	1953	1956	1956	1979	—	—	23	23
Total						9	33	164	206

*See text. ‡Further regulatory actions 1977 and 1980. ||General warning 1965.
*Withdrawn 1976. §Further regulatory warning 1979.

TABLE II—Time lags and best estimates of incidence of adverse reactions with unaccounted delays to alerting

Adverse reaction	Drug	Time lag in years	Best estimate of incidence (order of magnitude)	Reference
Pulmonary embolism	Oral contraceptives	3	10 ⁻⁴	Vessey and Doll ³⁰
Myocardial infarction	Oral contraceptives	5	10 ⁻⁴	Mann <i>et al</i> ³¹
Deaths from asthma	Sympathomimetic aerosols	4	10 ⁻³ to 10 ⁻⁴	Inman and Adelstein ³²
Jaundice	Halothane	7	10 ⁻⁴	National Halothane Study ³³
Colitis	Lincomycin	6	10 ⁻³ to 10 ⁻⁴	*
Colitis	Clindamycin	5	10 ⁻⁴	*
Aplastic anaemia	Phenylbutazone	6	10 ⁻⁵	Fowler†

*Estimates based on incidence of voluntary reporting.
†P D Fowler. Marrow toxicity of the pyrazoles. Personal communication, 9 July 1979.

as understating the magnitude of the problem, as the Committee on the Safety of Medicines has never made any communication to the medical profession in respect of some of these reactions.

Comment

The delays at different stages in the process are not comparable. Those between verification and regulatory action should be avoidable entirely, and those between alerting and verification should be minimal if specific studies for verification (usually case-control studies) could be initiated promptly. Interpreting the delays before alerting is not so simple. In six cases the observed intervals could be satisfactorily accounted for: practolol peritonitis, vaginal cancer after maternal stilboestrol, and tardive dyskinesia after phenothiazines are delayed reactions; phenacetin nephropathy is dependent on chronic abuse, and this habit may not have arisen until many years after the marketing of phenacetin; the three year time lag to alerting for colitis due to tetracycline is not unreasonable in view of the exceptionally low incidence of this reaction (perhaps 10⁻⁶ to 10⁻⁷), and in any case this was identified as important only in the context of the more frequent occurrence of colitis after lincomycin and clindamycin; the relation of clioquinol to subacute myelo-optic neuropathy has not been satisfactorily established, and the question of delay to alerting hardly arises. Avoidable delays were identified for only three adverse reactions (table I); with two others there was no delay (phenformin lactic acidosis and chloramphenicol aplastic anaemia). Hence there were seven important reactions with unaccounted delays meriting more detailed analysis.

Table II gives the time lags and best estimates of incidence³⁰⁻³³ (P D Fowler, personal communication, 9 July 1979) of these seven reactions. Their incidence was of the order of 10⁻⁴. Clearly

a sample size of the order of 10 000 as envisaged in many proposals for recorded-release schemes would have been inadequate for earlier first alerting to any of these major problems; 100 000 would usually have been necessary. Phenylbutazone aplastic anaemia had an even lower incidence. I have shown elsewhere³⁴ that haematological effects are the biggest single class of suspected adverse reactions that are not subsequently verified; possibly because a particularly low incidence is not unusual with these reactions, which may present a special problem for identification. For these reactions a registry approach may represent the only feasible possibility for earlier detection, as carried out for a time by the American Medical Association after chloramphenicol aplastic anaemia.

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Part III of this series will be published next week.

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An elderly man has had a myocardial infarct and subsequent attacks of left ventricular failure. He has difficulty sleeping and takes flurazepam and triazolam every night. Is it wise to continue these drugs long term and if not what alternatives are advised?

Triazolam is a relatively short acting benzodiazepine. As with other effective hypnotics, this may cause dependency and in large doses may lead to day time somnolence, but there is no reason why it should not be used long term in cases of clinical need. Flurazepam, on the other hand, is a relatively long acting hypnotic that tends to accumulate in the elderly and should be avoided. It is, in any case, rarely good practice to use concurrently two agents that are pharmacologically similar in order to achieve adequate therapeutic effect. The question raises another important issue, with the implication that some or all of the patient's difficulty with sleep may be due to left ventricular failure. This can practically always be controlled by diuretics, cardiac glycosides, and vasodilators; clearing of residual pulmonary congestion will then itself improve duration and quality of sleep. An opiate may be appropriate as a hypnotic for a few days but only while failure is being controlled. Other preferred hypnotics for elderly frail patients are triclofos and chlormethiazole.—D A CHAMBERLAIN, consultant cardiologist, Brighton.

The DHSS guidelines suggest that pertussis injection should be avoided only when there is history of epilepsy in first-degree relatives. I have a patient whose mother's 19-year-old brother is epileptic and has been taking drugs from the age of 2 years. The health visitor advises against pertussis injection for the baby. I thought epilepsy was important only if history is positive in parents or siblings. Which is correct?

The simple answer is that the DHSS guidelines state first-degree relatives and the child's uncle is not a first-degree relative. Nevertheless, they are only guidelines; the recommendation is not to give the vaccine if there is reason to believe that the child has inherited an increased risk of epilepsy. Thus if, say, two more of the child's second-degree relatives had idiopathic epilepsy then, on the basis of the recommendation, one might hesitate. On the other hand, if the uncle had fits after meningitis as an infant that has no bearing on the decision whatsoever. The recommendation, however, is a judgment based on clinical experience. There is no published evidence that those with a tendency to fit are any more at risk of developing brain damage after whooping cough vaccination. One could argue on

general grounds that such infants are more likely to fit with the illness itself; and in the present unhappy situation the chances of them contracting the illness are high. On the information given in the question, my view would be that the vaccine should be offered.—DAVID HULL, professor of child health, Nottingham.

When I hear of people having strokes the right side of the body is usually affected. What are the comparative figures for right and left sided hemiplegia?

The occurrence of left and right sided hemiplegia is roughly equal. Marquardsen¹ in his large series had 120 with a left sided hemiplegia and 127 with a right. Of 135 patients who survived two weeks in the recent Manchester study,² 69 had a right hemiplegia and 66 a left. The published figures thus do show a slight predominance of right sided hemiplegia but this does not reach statistical significance, and it would be necessary to look at much larger numbers of patients derived from community, as opposed to hospital, populations.—RICHARD LANGTON HEWER, consultant neurologist, Bristol.

¹ Marquardsen J. *The natural history of acute cerebrovascular disease—a retrospective study of 769 patients*. Copenhagen: Munksgaard, 1969.

² Andrews K, Brocklehurst JC, Richards B, Laycock PJ. Stroke: does side matter? *Rheumatol Rehabil* 1982;21:175-8.

After drawing blood for various tests one occasionally sees a foamy, almost fat like layer forming in the blood bottle within 30 seconds or so of the completed venepuncture. Is this normal or should one investigate patients for abnormal lipid metabolism?

A creamy layer may form at the top of a blood sample standing in a container after perhaps as short a time as 15 to 30 minutes, and the underlying serum or plasma may be turbid. This layer consists of chylomicrons, which are particularly rich in triglyceride. If the layer is prominent and forms quickly it suggests underlying hyperlipidaemia, and this is particularly serious in the fasting state, when chylomicrons should not be present. This type of hyperlipidaemia is often associated with alcohol abuse or poorly controlled diabetes mellitus. When suspicion of hyperlipidaemia is raised determination of the fasting cholesterol and triglyceride concentrations should be arranged.—K G TAYLOR, consultant physician, Birmingham.