Iatrogenic Diseases

SECOND EDITION

UPDATE 1983

P. F. D'Arcy and J. P. Griffin

Iatrogenic diseases

Second edition

UPDATE 1983

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Preface

The objective of *Iatrogenic diseases Update 1983* is the same as that of the previously published *Update 1981* and *Update 1982*, namely to summarize new information on drug-induced diseases which has appeared in the literature and to correct and amplify in the light of new knowledge adverse reactions referred to in our earlier publications. It is therefore essential that *Update 1983* should be referred to in conjunction with *Iatrogenic diseases,* 2nd edition and *Updates 1981* and *1982*. To aid the reader a cumulative index to these earlier volumes is a feature of the *Update* concept.

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1 Medicines and the media

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This is an update of the chapter entitled 'Monitoring' in *Iatrogenic diseases*, 2nd edition pages 1–18 and of the chapter entitled 'Monitoring medicines and the media' in *Iatrogenic diseases, Update 1981* pages 1–9 and of the chapter entitled 'Medicines and the media' in *Iatrogenic diseases, Update 1982* pages 1–5 to which the reader is also referred

Benoxaprofen and the pursuit of absolute safety

The biggest news feature on adverse drug reactions (ADRs) during 1982 was the suspension of the product licence for *Opren* (benoxaprofen), a non-steroidal, anti-inflammatory agent. The suspension of the product licence for benoxaprofen, initially for 90 days, by the United Kingdom Licensing Authority acting on the advice of the Committee on Safety of Medicines (CSM) took place on 3 August 1982. This was done on the basis of a wide spectrum of adverse drug reactions. Professor A. Goldberg, Chairman of the Committee on Safety of Medicines, writing to the medical and pharmaceutical professions on 3 August 1982 stated:

> The Committee on Safety of Medicines has received over 3500 reports of adverse reactions associated with this drug; included among these reports are 61 fatal cases, predominantly in the elderly. Having regard to these reports there is concern about the serious toxic effects of the drug on various organ systems, particularly the gastro-intestinal tract, the liver and bone marrow, in addition to the known effects on skin, eyes and nails.

When this announcement was made, benoxaprofen was already being marketed in 10 countries, including the United States, South Africa, West Germany, Switzerland, France, Denmark, and Spain. However, the Australian and New Zealand regulatory authorities had not approved the drug for marketing. Benoxaprofen was made available to UK general practitioners in autumn 1980 and was hailed by the manufacturers (Eli Lilly and their UK subsidiary, Dista Products) as a new anti-arthritic with disease-modifying properties, a claim based on animal studies. The drug was put on to the market with massive publicity on the radio and in newspapers encouraging patients to believe it was a major advance in the treatment of arthritis and to ask their doctors specifically for *Opren*. It has been variously estimated that between 500 000 and 750 000 patients had received the drug in the United Kingdom before its withdrawal.

Gastrointestinal ulceration and haemorrhage, photosensitivity, and onycholysis were reported during the clinical trials of benoxaprofen (Mikulaschek, 1980). The first reports of deaths associated with benoxaprofen came in April and May 1982 with accounts (Goudie *et al.*, 1982; Taggart and Alderdice, 1982) from Glasgow and Belfast of eight elderly women taking the drug who had died after developing cholestatic jaundice. Subsequently, several letters describing further cases were published in the correspondence columns of the *British Medical Journal* during June and July 1982 (Prescott *et al.*, 1982; Fisher and McArthur, 1982; Firth *et al.*, 1982; Duthie *et al.*, 1982).

In May 1982, at about the time these reports began to appear in the UK medical literature, the drug was launched in the United States as *Oraflex*. In June 1982, the Health Research Group, a US consumer organization, petitioned the US Department of Health and Human Services seeking an immediate ban on benoxaprofen because of the UK reports of liver damage. The FDA ordered a review of the benoxaprofen toxicity data but did not consider that drastic action was warranted. Meanwhile, in June 1982, Dista Products issued a 'Dear Doctor' letter indicating that the UK data sheet had been revised to include the warning that in patients over the age of 65 the daily dose should be halved. On 2 August 1982, the Danish regulatory authorities limited the prescribing of benoxaprofen mainly to hospitals. However, following further review of the available data, the British authorities decided to suspend the promotion and supply of benoxaprofen on 3 August 1982, only three months after the first report of liver damage associated with benoxaprofen appeared in the literature. Ironically, an article by Mikulaschek (1982) concluded that 'Studies with benoxaprofen in rheumatoid arthritis and osteoarthritis, conducted in more than 2000 patients, continue to demonstrate its safety and effectiveness'.

The reaction of the medical profession to the suspension of the licence for this non-steroidal, anti-inflammatory drug varied from criticism for premature, precipitate, and unjustified withdrawal of the drug to criticism for undue delay in reacting to the reports of adverse reactions received. These extremes of view were reflected in the media. The CSM also came under attack because of a delay between the reporting of *Opren's* with-

drawal in the news media and the doctors receiving the official notification. Professor Goldberg in his 3 August 1982 letter to doctors anticipated this occurrence and stated that this action was regrettable but necessary on grounds of safety. By mid-August 1982 the manufacturer of benoxaprofen had decided on a world-wide withdrawal of the drug from the market.

Subsequently, media and political scrutiny were brought to bear on the systems used currently within the UK for post-marketing surveillance of newly launched drugs. Proposals for new schemes of varying ambitiousness and cost abounded. The statement of a European Workshop held in 1977 on 'Monitoring of drugs' which follows points out that absolute safety is unattainable and its pursuit may do more harm than good.

Medicines can never be entirely safe. Despite extensive testing and monitoring of medicines, unforeseen and unpredictable adverse reactions will continue to occur. The public needs to be aware that treatment with medicines always carries some risk. It is the duty of all concerned to maximise benefit and minimise risk. In the opinion of this group of European scientists it is now advisable to revise our methods of assessment of medicines. We must recognize that existing methods are unsatisfactory. We recommend more rational but less extensive laboratory studies without unnecessary multiplication of detailed clinical trials before registration. Instead we recommend much closer and more extensive surveillance of medicines after they are available for general prescription. Only by the careful study of medicines in everyday use can the greatest benefits be obtained from their administration, the untoward rare potential disaster recognised at the earliest possible moment, and the ill effects minimised. Absolute safety is unattainable and its pursuit, regardless of other considerations, is achieving more harm than good.

Another example of the effect of the benoxaprofen withdrawal was the development of a humourous but cynical approach to industrial pharmaceutical development and drug toxicity in the media, which is typified by the article by Miles Kington in the *Times* (London) of 6 October 1982.

A new miracle drug will be coming on the market next spring, called *Sufferin. It is claimed by its makers to be different from all drugs so far announced as new miracle drugs. Normally, even if a drug cures the condition it is treating, it also has unpleasant side-effects. *Sufferin is different. It only has side-effects and cures nothing . . .

'Yes, I'm very excited about the prospects of *Sufferin,' says chief chemist Louis Exocet. 'It's the very first time we have marketed a drug with an asterisk in front of the name. Previously, you know, we have had terrible trouble thinking up names which had not been registered by someone else. Now, by putting this little star in front, the name is bound to be different. This asterisk is truly the miracle ingredient!'

What about the drug itself? Is there really a market for a drug that cures nothing and only does you harm?

'That shows how little you know about the drug world,' says Exocet.

'People are already used to the idea. Millions of patients every day go to their doctor and say, "Doctor, that stuff you gave me, it hasn't cleared up my condition. But it's given me a funny rash." Well, the doctor is baffled. But with *Sufferin he can never be baffled, for that is the whole intention!

'Also, it will be very good for the people who are malingerers and have nothing wrong really. The doctor has nothing to cure, and gives them *Sufferin, which cures nothing. But it also gives them some real symptoms, which subconsciously they were wanting all along.

'Above all, it is designed for the majority of ailments, which will go away anyway, whether people see a doctor or not. The doctor cannot cure those ailments, but he must give the patient some treatment, because that is the way the patient is comforted. So he gives him *Sufferin. *Sufferin gives him those side-effects. The doctor can cure the side-effects by telling him to stop taking *Sufferin.'

What exactly are the side-effects?

'Slight dizziness. A small rash. Blood-shot eyes. Nothing serious. There is also, though perhaps I should not mention it, a slight urge to take more *Sufferin.'

An addictive drug? Isn't that illegal?

'No more than alcohol.'

Finally, if it is possible to make a drug that has no cure, only side-effects, does this mean that one day there can be a drug which has a cure and no side-effects?

'My friend,' says Louis Exocet, 'you really know nothing about the drug world, do you?'

The benoxaprofen experience and the media reaction to it has reflected adversely on the public confidence in the pharmaceutical industry, the medical profession, and the drug regulatory authorities in the USA, the UK, West Germany, Denmark, and other countries who permitted the drug on to their national markets, but ought to reflect even more seriously on the media who hail trivial new drugs as major advances and raise popular expectation of great advances but are the first to bay for blood when the expectations they themselves have created are shown to be a bubble.

Communicating information on adverse reactions

A great deal of public debate has centred on the detection of adverse drug reactions of low frequency. However, the major problem lies in making the prescribing doctor more aware of the adverse drug reactions that are already known. The term 'information lag' was coined to express the time difference between the identification and confirmation of an adverse drug reaction and the action taken by national drug regulatory authorities to inform their medical and pharmaceutical professions of the problem. Griffin and D'Arcy (1981) in their survey

considered that in many cases the information lag in the UK, Ireland, the USA, West Germany, Sweden, and the Netherlands was unacceptably long.

The information lag – is it improving?

We examined written forms of communication (*Current Problems, Adverse Reactions series,* Chairman's letters) available to the CSM for alerting the UK medical profession to possible ADRs issued after Griffin and D'Arcy's review. Each specific ADR was the subject of a literature search which set out to determine:

1. The first substantial mention of a given adverse reaction in the literature;
2. The date by which the reaction in question could be said to be well established in the literature.

An adverse reaction 'well established in the literature' was defined as one which had been described in three or more papers in the world medical literature, in a review article or editorial devoted to the problem in a major journal, or mentioned in a standard textbook devoted to reviewing ADRs.

Since Griffin and D'Arcy's review there have been four issues of *Current Problems* (three in 1981 and one in 1982) referring to 27 specific adverse reactions associated with 20 different drugs. In *Current Problems,* no. 7 (December 1981) there was one follow-up comment on a warning given in the June 1973 issue of the *Adverse Reactions Series* informing doctors that liver damage due to erythromycin may also occur equally with all the various esters of the antibiotic and with the base itself. A Chairman's letter was issued on 3 August 1982 informing doctors and pharmacists of the suspension of the product licence for benoxaprofen for a period of three months. Table 1.1 shows the dates of the warning and literature references for each of the subjects mentioned in these two forms of communication. There have been no further issues of the *Adverse Reactions Series.*

Of the 27 specific ADRs dealt with in the four issues of *Current Problems* (1981–2), three were issued prior to the first literature reference, three were issued one year after the first report, and 14 were issued prior to or simultaneously with the reaction being reviewed in a standard work. Indeed, piroxicam-induced precipitation of congestive cardiac failure, amiodarone-induced hepatitis, and mianserin-induced arthropathy have not been described in the literature. In addition, the induction of subcutaneous nodules by fluspirilene (*Current Problems,* No. 7, 1981) has not been mentioned so far in any of the standard textbooks on adverse drug reactions.

The number of years that elapsed between the time the reaction was well established in the literature and the time the warning was issued (the 'information lag') varied between 0 and 5 years. However, for 17 of the 27 specific events there was no 'information lag'.

The longest examples of 'information lag' in this latter series of *Current Problems* relate to the problems of the associations between coumarin anticoagulants and chondrodysplasia punctata, sodium cromoglycate and bronchospasm, aminocaproic acid and myopathy, and quinidine and granulomatous hepatitis. One explanation for the delay in bringing the association of chondrodysplasia punctata as a congenital abnormality with maternal use of coumarin anticoagulants to the attention of doctors is that, although this problem was considered by the CSM during late-1978/early-1979, there was a considerable gap between the publication of *Current Problems,* no. 4 (April 1979) and no. 5 (February 1981). Compounding this delay was the difficulty in establishing a cause-and-effect relationship when dealing with congenital malformations. This adverse reaction was described in a review article in 1977 (Shaul and Hall, 1977) and, according to the criteria mentioned previously, was considered to be well established in the literature. However, in 1981 Sullivan and McElhatton considered that this adverse reaction was still far from convincingly proven, although the evidence is suggestive of an association.

Certain topics discussed in *Current Problems* could not be described as well established in the literature but there has been much discussion on these subjects in medical publications (including the standard works on ADRs). These include the associations between triazolam and severe psychotic effects (No. 5, February 1981), cimetidine and stomach cancer (No. 6, July 1981), and *Debendox* and congenital abnormalities (no. 6, July 1981). This indicates an additional role for *Current Problems* in transmitting information in perspective about matters which have received attention from the lay press.

Another example of a differing use of *Current Problems* is the problem of the association of piroxicam and gastrointestinal bleeding and perforation (no. 8, October 1982). All non-steroidal, anti-inflammatory agents are known to be associated with increased gastrointestinal symptoms and blood loss but initial trials indicated a low incidence of ulcers and blood loss with piroxicam (Dessain *et al.,* 1979). Peptic ulceration and gastrointestinal bleeding (in a small number of cases) are indicated as side-effects of piroxicam in the manufacturer's data sheet (Association of the British Pharmaceutical Industry, 1981) but the CSM received a considerable number of yellow-card reports of gastrointestinal bleeding attributed to piroxicam since it was marketed in 1980 indicating that the incidence of serious bleeding with piroxicam had been underestimated, a conclusion borne out by recent publi-

Table 1.1 Details of warnings on specific adverse reactions to drugs issued by the British Committee on Safety of Medicines (CSM) (1981–82), with dates of literature references

Drug/adverse reaction	CSM warning issued via *Current Problems Series* (CPS) or Chairman's Letter	Literature reference		
		First mention	Well-established	Reviewed in standard work on adverse reactions to drugs*
Coumarin anticoagulants				
Chondrodysplasia punctata	February 1981 (CPS no. 5)	1975	1977	1972–7 (SED 7) (SEDA-1)
Topical treatments for otitis externa				
Chlorhexidine deafness	February 1981 (CPS no. 5)	1971	1977	1977–9 (SEDA-1) (ID 2)
Aminoglycoside deafness	February 1981 (CPS no. 5)	1970	1979	1972–80 (SED 7) (SEDA-3, 4) (ID 2)
Polymyxin deafness	February 1981 (CPS no. 5)	1977	1979	1979–80 (SEDA-3, 4)
Triazolam				
Severe psychotic effects	February 1981 (CPS no. 5)	1979	?	1980 (SED 9) (SEDA-4)
Sodium valproate				
Marrow hypoplasia	July 1981 (CPS no. 6)	1980	?	1982 (SEDA-6) (IDU 1982)
Leucopenia	July 1981 (CPS no. 6)	1979	?	1982 (SEDA-6)
Liver damage	July 1981 (CPS no. 6)	1979	1979	1979 (SEDA-3)
Hyperammonaemia	July 1981 (CPS no. 6)	1980	1981	1981 (SEDA-5)
Pancreatitis	July 1981 (CPS no. 6)	1979	1981	1980–1 (SED 9) (SEDA-4) (IDU 1981)
Cimetidine				
Stomach cancer	July 1981 (CPS no. 6)	1979	?	1980 (SED 9) (SEDA-4)
Beta-adrenoceptor antagonists				
Retroperitoneal fibrosis	July 1981 (CPS no. 6)	1978	1981	1980–1 (SEDA-4, 5) (IDU 1981)
Timolol eye drops				
Bronchospasm	July 1981 (CPS no. 6)	1979	1980	1980–1 (SEDA-4, 5) (IDU 1981)
Adverse cardiac reactions	July 1981 (CPS no. 6)	1979	1980	1980–1 (SEDA-4, 5) (IDU 1981)
Sodium cromoglycate				
Bronchospasm	July 1981 (CPS no. 6)	1975	1978	1977–8 (SEDA-1, 2)
Debendox				
Congenital abnormalities	July 1981 (CPS no. 6)	1969	?	1979 (SEDA-3) (ID 2)
Mebhydrolin				
White-cell depression	December 1981 (CPS no. 7)	1972	?	1972 (SED 7) †
Erythromycin				
Jaundice	December 1981 (CPS no. 7)	Follow-up of June 1973 (*Adverse Reaction Series*) warning by CSM		
Fluspirilene				
Subcutaneous nodules	December 1981 (CPS no. 7)	1979	?	Not reviewed
Cimetidine				
Arthropathy	December 1981 (CPS no. 7)	1980	?	1982 (SEDA-6)
Mianserin				
Blood dyscrasia	December 1981 (CPS no. 7)	1979	1982	1981 (SEDA-5) (IDU 1981)

Table 1.1—*continued*

Drug/adverse reaction	CSM warning issued via *Current Problems Series* (CPS) or Chairman's Letter	Literature reference: First mention	Literature reference: Well-established	Reviewed in standard work on adverse reactions to drugs*
Benoxaprofen				
Gastrointestinal tract toxicity	August 1982 (Chairman's letter)	1980	1982	1982 (SEDA-6)
Liver toxicity	August 1982 (Chairman's letter)	1982	1982	Not reviewed
Bone marrow toxicity	August 1982 (Chairman's letter)	1980	1982	1982 (SEDA-6) (IDU 1982)
Skin disorders	August 1982 (Chairman's letter)	1980	1981	1981–2 (SEDA-5, 6) (IDU 1982)
Nail disorders	August 1982 (Chairman's letter)	1980	1981	1981–2 (SEDA-5, 6)
Eye disorders	August 1982 (Chairman's letter)	1981	?	1982 (SEDA-6) (IDU 1982)
Piroxicam				
Gastrointestinal bleeding and perforation	October 1982 (CPS no. 8)	1979	1982	1981 (SEDA-5)
Precipitation of congestive cardiac failure	October 1982 (CPS no. 8)	—	—	—
Amiodarone				
Pulmonary alveolitis	October 1982 (CPS no. 8)	1980	1982	1982 (SEDA-6) (IDU 1982)
Hepatitis	October 1982 (CPS no. 8)	—	—	—
Mianserin				
Arthropathy	October 1982 (CPS no. 8)	—	—	—
Aminocaproic acid				
Myopathy	October 1982 (CPS no. 8)	1969	1978	1975–8 (SED 8) (SEDA-2)
Quinidine				
Granulomatous hepatitis	October 1982 (CPS no. 8)	1974	1977	1977 (SEDA-1)

*SED = Dukes, M.N.G. (Ed.) *Meyler's side effects of drugs:* no. 7 (1972), no. 8 (1975), no. 9 (1980). Excerpta Medica, Amsterdam. SEDA = Dukes, M.N.G. (Ed.) *Side effects of drugs annual:* no. 1 (1977), no. 2 (1978), no. 3 (1979), no. 4 (1980), no. 5 (1981), no. 6 (1982). Excerpta Medica, Amsterdam. ID = D'Arcy, P.F. and Griffin, J.P. (Eds.) (1979) *Iatrogenic diseases,* 2nd edn. Oxford University Press, Oxford. IDU = D'Arcy, P.F. and Griffin, J.P. (Eds.) *Iatrogenic diseases, Update 1981* and *Iatrogenic diseases, Update 1982.* Oxford University Press, Oxford.

†Reference to unpublished cases.

cations (Emery and Grahame, 1982; Ward and Weir, 1982).

The question still remains as to whether the last four issues of *Current Problems* have provided information more quickly and readily than previously. To recap, in the last two years, 27 specific adverse reactions associated with 20 different drugs have been described in *Current Problems,* whereas in the previous 17 years only 34 ADRs associated with 29 different drugs were mentioned in both *Current Problems* and the *Adverse Reactions series.* Certainly, it can be stated that the CSM is communicating much more frequently with the UK medical profession.

The 'information lag' for the 18 issues of the *Adverse Reactions series* (1964–1980) was found to be between 0 and 8 years for 14 ADRs and for the four issues of *Current Problems* (1975–9) the lag was 0–3 years for 20 ADRs (Griffin and D'Arcy, 1981). For the 1981–2 series of *Current Problems* the 'lag interval' varied between 0 and 5 years. However, in the 1981–2 series for 17 of the 27 specific events (63 per cent) the 'lag interval' was 0 years whereas the corresponding figure for the 1975–9 series was 7 of 20 specific events (35 per cent). There have been a few examples of 'information lag' with the most recent issues of *Current Problems,* e.g. chlorhexidine deafness, but, generally, it would appear that information has been given to doctors by the CSM much more quickly over the last two years.

The Chairman's letter relating to the serious side-effects of benoxaprofen was discussed in detail earlier in the chapter.

Venning (1982) recently suggested that any regulatory agency using anecdotal reports of suspected ADRs as a basis for an early warning system should develop criteria

for assessing the validity of such reports. The criteria he suggested were

1. Data from rechallenge;
2. A pharmacological basis for the reaction;
3. Immediate acute reactions;
4. Local reactions at the site of administration;
5. The reaction having been reported previously by another route of administration;
6. The repeated occurrence of rare events.

Could any of these criteria have been applied to the first literature reports of adverse events described in the 1981–2 series of *Current Problems*? Would this exercise have meant that the warning would have been issued earlier than it actually was? For example, reports of the association of the use of timolol eye drops with adverse cardiac reactions and bronchospasm first appeared in the literature in March and August 1979, respectively (Britman, 1979; Jones and Ekberg, 1979). Since these are known adverse reactions to the systemic use of β-blockers, these first references may be considered to indicate causality. Therefore, these ADRs could have been brought to the attention of doctors late-1979/early-1980 when, in fact, they were communicated to the profession in July 1981 (*Current Problems*, no. 6). It should be mentioned here that there was not a 1980 issue of *Current Problems*.

Recently, a brief survey by Velez and Patrick (1982) indicated that American authors of medical articles may be less well aware of the world literature than their British counterparts. Of the 30 first literature reports cited in Table 1.1, 15 (50 per cent) were published in UK journals, 7 (23 per cent) in US journals, and 8 (27 per cent) in non-US, non-UK journals. In addition, Testi (1982) analysed the country of origin of work published in two leading weekly general medical journals, one from the United Kingdom (*The Lancet*) and the other from the United States (the *New England Journal of Medicine*). The international coverage of the British journal was found to be greater than that of the American journal. Of the 30 first reports of adverse drug reactions cited in Table 1.1, 10 (33 per cent) originated from the UK, 9 (30 per cent) from the US, and 11 (37 per cent) from countries outside the UK and US. Of the 15 first reports published in UK journals, 9 of the authors came from the UK, 2 from the US, and 4 from outside the UK and US. The corresponding figures for the seven reports published in US journals are 1, 4, and 2. In conclusion anecdotal reports of ADRs can be used as an integral part of a national early warning system but an international awareness of the world literature is essential.

Do warnings affect the reporting of adverse drug reactions?

In July 1977 the British Drug Regulatory Authority warned, via *Adverse Reactions Series* leaflet no. 15, of the association of perhexiline maleate with peripheral neuropathy, abnormalities of liver function, hypoglycaemia, and considerable weight loss. Table 1.2 shows that reports of all adverse reactions, and reports of neurotoxicity (peripheral neuropathy and paraesthesia) and hepatotoxicity (abnormal liver function tests, jaundice, hepatic cirrhosis, and hepatocellular damage), sent in on yellow cards to the CSM were stimulated by the issuing of this warning. This occurred when the market for perhexiline maleate was in the growth phase. Although the prescribing figures for the drug were the same in 1977 and 1978 the number of yellow cards received declined considerably in 1978 and continued to do so even when the number of prescriptions issued reached a peak in 1979.

Table 1.2 Numbers of reports of adverse reactions to perhexiline maleate received by the UK Committee on Safety of Medicines (1976–81)

		Number of reports received			
Year of report	Number of prescriptions	Total adverse reaction reports	Neurotoxicity † reports	Hepatotoxicity ‡ reports	Neurotoxicity** plus hepatotoxicity reports
1976	16 000	51	12	2	2
1977*	77 200	261	58	21	7
1978	77 200	111	32	11	5
1979	90 900	46	9	8	3
1980	77 400	27	11	4	3
1981	72 400	14	3	3	2

**Adverse Reactions Series* leaflet no. 15 published in July 1977.
†Neurotoxicity reports include peripheral neuropathy and paraesthesia.
‡Hepatotoxicity reports include abnormal liver function tests, jaundice, hepatic cirrhosis, and hepatocellular damage.
**Reports received where both adverse reactions occurred together.

Weber (1980, unpublished observations) investigated the large increase in reports of pseudomembranous colitis due to clindamycin following the publication of a warning in April 1979 (*Adverse Reactions Series,* no. 17). There was a highly significant difference in the number of reports received in 1979 (24 reports) compared to 1978 (11 reports). However, when the reports were examined with regard to date of occurrence of the adverse reaction, the totals for 1979 and 1978 were 18 and 17, respectively. Only three cases reported retrospectively in 1979 were evidently prompted by *Adverse Reactions Series* leaflet, no. 17. However, there was a considerable downward trend in the prescribing of clindamycin before the warning was issued. The number of prescriptions issued in 1979 was 50 per cent of those issued in 1976. The issue of a warning may not necessarily produce a large increase in retrospective or contemporary reports but each situation must be examined individually before further action is taken.

It must be stressed that if even restrained communication of drug-related hazards to the medical profession can result in bias in yellow-card reports made to the CSM, the effect of the popular media on reporting is even greater. It therefore behoves the media to behave responsibly in their coverage both of adverse reactions to drugs and the discovery of 'wonder cures'. This is however something that has been sadly lacking in many sections of the media in recent years. One is left with the impression that the media are using the same techniques to sell a story that they occasionally criticize the pharmaceutical industry for using unscrupulously in order to promote their products. It is well to remember, whether reading a newspaper or watching television, that a 'news story' is a product promoted to the public and every effort is made to enhance its impact – even sometimes at the expense of accuracy.

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2 Epidemiological aspects of iatrogenic disease

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This is an update of the chapter with the above title in *Iatrogenic diseases*, 2nd edition pages 19–44, *Iatrogenic diseases, Update 1981* pages 10–19, and *Update 1982* pages 6–20 to which the reader is also referred

Drug regulations and drug innovation

There have been a number of publications during 1981–2 which have surveyed and investigated the effect of drug regulations on drug innovation. This has almost been an examination of conscience by the official bodies. Since it is the purpose of these bodies to reduce adverse reactions to drugs by preventing the marketing or clinical testing of drugs that present undue hazard, it may be appropriate in this *Update* to review some of those publications and the role of the official bodies in promoting drug safety and efficacy.

In Britain, it is certainly an opportune time to review drug regulations since it was just over a decade ago in 1971 that the Committee on Safety of Drugs ('The Dunlop Committee'), a body collaborating with the pharmaceutical industry on a purely voluntary basis, was replaced by the statutory Committee on Safety of Medicines (CSM) which acts as a formal advisory body to the Licensing Authority.

In a detailed account Griffin and Diggle (1981) have reviewed and explained the nature of the drug legislation which was introduced under the provisions of the Medicines Act 1968; they have also presented a factual account of the products licensed in Britain during the decade 1971–81, which gives a valuable background to the innovative drug scene in the United Kingdom.

Currently some 20 new chemical entities reach the market each year and this is considerably less than the 50 or so new drugs that were introduced each year during the early-1960s. It might well be assumed therefore that the fall in the number of new drugs reaching the market is a consequence of these licensing requirements. Such an assumption would, however, be premature since there is good evidence that, on a world-wide basis, drug innovation fell from 90–100 new drugs per year in the early-1960s to 40–50 per year in the late-1970s. Thus, in Britain, the diminution in the number of new drugs probably preceded the introduction of licensing requirements in Britain and was not a direct consequence of it. The reasons for this fall must be complex, more complex indeed than a simple correlation with 'stringent licensing requirements' although the growing cost to the pharmaceutical industry of the latter must in some way affect the finance required for innovative research and development (Goldberg, 1981).

Interestingly, the bulk of new chemical entities licensed in Britain during the last 10 years have been limited to a relatively small number of therapeutic groups, for example, non-steroidal, anti-inflammatory agents, corticosteroids, cardiovascular agents (including beta-blockers), psychotherapeutic agents, anti-neoplastic drugs, endocrine and metabolic agents, drugs used in asthma, bronchitis, and rhinitis, antibiotics and anti-bacterials, and H_1 and H_2 antihistaminics.

The nature of this list led Griffin and Diggle (1981) to comment that such innovation was largely directed towards conditions that are common, largely chronic, and which occur principally in the affluent Western society. The latter view is also reflected in an article by Lasagna (1982) which poses the question: 'Will all new drugs become orphans?'. His concern is that if sales prove insufficient to justify research and development costs then the outlook for drugs to treat the endemic diseases of the Third World is very bleak indeed. Lasagna believes that the only way to cut research and development costs is to speed up the process of drug development; not surprisingly he suggests that the American FDA and the pharmaceutical industry in collaboration cut the 'drug lag' and speed up approval.

That this advice, in a different context, has also been given and heeded in Britain is evidenced by the description by Griffin and Long (1981) of the new procedures affecting the conduct of clinical trials in the United Kingdom. A review of this paper which appeared in *Inpharma* (1981) led with the heading: 'Regulatory changes in the UK may hasten brain-to bottle time'. This is quite an apt description since the objective of the new regulations which came into force in March 1981 was to bring about earlier clinical studies on new drugs. A follow-up paper by Griffin and Stewart (1982), after six months of the new procedures, showed that this optimism

was justified. The number of new chemical entities being brought to clinical trial during that period was greater than in any six-month period during the preceding two years. An additional paper by Diggle and Griffin (1982) has compared UK and USA licensing times in granting marketing authorization for medicines.

In the USA, the director of the Division of Drugs of the American Medical Association (Ballin, 1982) has also surveyed the regulation and development of new drugs. His paper described the work and regulatory function of the Food and Drugs Administration (FDA) and compares the rate of new drug innovation over the years; interestingly, it also gives some data on new innovations during 1981. During that year the FDA approved 27 new drugs for marketing. This list includes a hepatitis B vaccine; albuterol (salbutamol); new antibiotics: bacampicillin, cyclacillin, mezlocillin, piperacillin, cefotaxime sodium, and moxalactam; an antifungal, ketoconazole; a topical ophthalmic drug, trifluridine; an antiherpes agent, acyclovir; alprostadil (prostaglandin E_1); a general anaesthetic, isoflurane; the anticonvulsant, carbamazepine; and the calcium antagonist, nifedipine. A number of drugs on this list will already be familiar to clinicians in Britain since they have already been marketed there for some time. This illustrates the continuing problem of the 'drug lag' – the longer time for securing FDA marketing approval and the consequent delay of marketing new drugs in the United States compared with foreign countries.

Early warning of adverse drug reactions

Within the international pharmaceutical industry, the governmental drug safety/efficacy regulations may well be seen as a burdensome bureaucracy that has achieved relatively little except to make the development of new drugs more complex, more time-consuming, and more expensive. Within the vast edifices of drug licensing controls in Western countries, it may well be suggested that at least their work over the last two decades has given some protection to the medicated public. The investigative lay journalist might well suggest that the press and the media have a clear role, even a duty to the public, to continue to expose real drug hazards and to assert the culpability of the pharmaceutical manufacturers in evoking them. Their critics, and there are many, may well in turn declaim that the media all too frequently advance into battle in a continuing campaign that is ill informed, headline-orientated, and more concerned with imagined drug hazards than with actual proven eventualities. The editors of medical journals would probably suggest that they are in the front line of the early warning system and that they have a clear responsibility to alert clinicians to associations between drugs and reactions that may or may not subsequently prove to be cause and effect; they would probably admit that on occasions an inherent fault of this function is to publicize associations between drugs and hazards which subsequently may prove to be false alarms which may cast an irreversible and, in the light of hindsight, an unwarranted blight on a potentially useful drug.

The question: 'Do we have an early warning system for adverse drug reactions?' was posed indirectly in an editorial in the *British Medical Journal* (1982) entitled 'Crying wolf on drug safety'. This editorial makes salutory reading and in the same issue of the journal it is reinforced by papers from Venning (1982) and Venulet *et al.* (1982) which attempt to answer that and other related questions.

The problem of 'false alarms'

Venning (1982), a senior medical officer in the Medicines Division, Department of Health and Social Security, London, assessed retrospectively the validity of anecdotal reports of suspected adverse drug reactions, and considered the problems raised by false alarms.

Some 18 years after their publications in the *British Medical Journal, The Lancet,* the *Journal of the American Medical Association,* and the *New England Journal of Medicine,* Venning reviewed adverse drug reactions first reported in 1963 to assess their initial validity and subsequent verification. Of 52 first reports, five were deliberate investigations into potential or predictable reactions, and in each case causality was reasonably established. These five 'first alert' reports were

1. The action of morphine on diverticulosis of the colon;
2. The effect of rectal betamethasone on pituitary-adrenal function;
3. The histological effect of spironolactone on the adrenals;
4. The action of oral contraceptives on thyroid function values;
5. The occurrence of paralytic poliomyelitis after the use of Sabin vaccine.

The other 47 reports reviewed were essentially anecdotal; of these 14 related to categories of adverse reaction where false-positive reports were unlikely: immediate reactions, local reactions, and known reactions caused by a different mode of administration or by a brand of drug previously thought or claimed to be safe. The problem of false alarms arose in the remaining types of reactions, for example, general reactions that did not occur immediately after administration or arose for the first time with a new drug substance. Of the 33 reports of

such suspected adverse reactions, validity was satisfactorily established on the basis of rechallenge, predictability from known pharmacology, or the unique nature of the reaction. Of the remaining 19 reports, further verification has still not been satisfactorily established in 12; seven of these possible 'false alarms' were haematological reactions.

Thus, although 35 of the 47 anecdotal reports were clearly correct, of the 19 reports that were not reasonably validated at the time of the report, only seven were subsequently verified. On the basis of these assessments, Venning has suggested that agencies monitoring ADRs should adopt criteria for assessing the validity of first reports of drug reactions. He advocated that such criteria should include: reactions on rechallenge; a pharmacological basis for the adverse reaction; immediate acute reactions; reactions with a new route of administration of a drug known to provoke such reactions by another route; and the repeated occurrence of very rare events. Thus any drug regulatory agency using anecdotal reports of suspected reactions as a foundation for an early warning system, would clearly have the responsibility of developing adequately effective criteria for assessing the validity of such reports.

How good are adverse drug reaction articles?

Venulet and his colleagues from Ciba-Geigy Ltd, Basle, Switzerland, addressed themselves to answering the question: 'How good are articles on adverse drug reactions?'. They studied 5737 articles from 80 countries published between 1972 and 1979 (Venulet *et al.*, 1982). Only 61 per cent of these articles included information on the numbers of patients treated and the number with adverse reactions – information that is essential for any assessment of the actual incidence of the ADR. In only 55 per cent of the publications that they reviewed did they find sufficient data to calculate the incidence of the reported reaction.

A general plea was made to the authors and their editors (and this bears repetition in this text) to ensure that articles on ADRs should present the following information: drug regimens; number of patients treated; number of patients developing adverse reactions; and the precise (as far as is known) nature and incidence of the reaction. They suggested that 'perhaps unwillingly the journals have the role of guardian of quality', but they hastened to add that the authors should not make this task too difficult. In this respect Jones (1982) has discussed criteria for journal reports of suspected ADRs and Zellmer (1982) has given advice to authors and reviewers of case reports on such reactions. Both these articles give clear guidance to the intending reporters of ADRs.

An early warning system and subsequent epidemiological surveys

To return to the question: 'Do we have an early warning system?'. The consensus answer of international viewpoints would seem to be a qualified 'yes', but this rather begs the question of how effective the system(s) is.

An early warning system common to all countries is the publication of case reports in medical journals, and the articles by Venning (1982) and Venulet *et al.* (1982) have done much to show how the system could be improved and safeguarded. The literature is of course extensive and it is obviously necessary from time to time to collect such reports together into epidemiological surveys which tend to balance out the intrinsic anecdotal and uncontrolled bias of some of the individual reports. An attempt was made in the corresponding chapters to this text in *Update 1981* and *Update 1982* (D'Arcy, 1981, 1982) to review the international ADR scene by discussing a number of general epidemiological papers which collectively gave an overview of current problems and their incidence. A similar approach is followed here in order to update this international view of adverse drug reactions. Such an account cannot claim to be comprehensive; at best it can only be illustrative of the type and extent to which different countries experience adverse effects of therapy.

General epidemiology of adverse drug reactions

Britain

In 1982 the epidemiological scene of ADRs in Britain was dominated by the withdrawal of benoxaprofen (*Opren*), a relatively new non-steroidal, anti-inflammatory drug, from clinical use due to its serious toxic effects on various organ systems. This withdrawal did not come as a complete surprise since clinical reports published in 1981 and early-1982 strongly suggested that the use of the drug was causally associated with phototoxic cutaneous reactions and gastric side-effects, thrombocytopenia, toxic optic neuropathy, hypertrichosis, and accelerated nail growth (Morgan and Behn, 1981; Taylor *et al.*, 1981; Dodd *et al.*, 1981; Fenton *et al.*, 1982; Halsey and Cardoe, 1982; Hindson *et al.*, 1982; Larking *et al.*, 1982; Ledermann *et al.*, 1982; Marsden and Dahl, 1982; Wilkins *et al.*, 1982). The growing evidence that this anti-rheumatic drug seemed particularly prone to provoking a canalicular cholestatic type of drug-induced jaundice in the elderly patient, sometimes with a fatal result (Firth *et al.*, 1982; Fisher and McArthur, 1982; Goudie *et al.*, 1982; Prescott *et al.*, 1982; Taggart and Alderdice, 1982) was also of particular concern.