SIDE EFFECTS OF DRUGS ANNUAL I

A worldwide yearly survey of new data and trends

EDITED BY
M.N.G. DUKES

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SIDE EFFECTS OF DRUGS ESSAY *

the moments of truth

'Truth lies within a little and certain compass, but error is immense'
Henry St. John, Viscount Bolingbroke, 1678–1751

'Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing had happened'
Sir Winston Churchill, 1874–1965

There was a time, some three centuries ago, when any book of substance in the English language was supposed to begin with an 'Apology', in which the Editor or the Publisher explained his motives for putting pen to paper. John Bunyan composed eight pages of verse to justify his having written the 'Pilgrim's Progress'. William Harvey's study of 'The Motion of the Heart and Blood' begins with a lengthy preamble recalling that he has presented his findings repeatedly for nine years to the College of Physicians before considering it necessary and proper to commit them to print. The meaning of the word 'apology' may have changed a little since then; but the appearance of a new book – the first of a series – on the Side Effects of Drugs deserves at least to be explained, if not defended.

No one could reasonably maintain that there has, up to the present, been a shortage of printed material on the adverse reactions to drugs; the problem, and the justification for this Annual, is just the reverse. For twenty years, as the number of useful new drugs coming into medicine has gradually declined, so the volume of words devoted to them, and indeed to all medicines, has gone up at an ever-increasing rate. Leo Meyler's first 'Side Effects of Drugs', a valiant effort to tame the rising flood, was a readable little book of 128 pages; the latest edition of the encyclopaedic work which it has become runs to more than 1100 pages of small print. At this rate, one would by the end of the century need a treatise of ten volumes to supply the physician with even a summary view of what is known, or supposed to be known, about adverse drug reactions. But the exponential growth of 'Meyler' is merely symptomatic of the underlying problem. The number of published papers on drugs and their wanted or unwanted effects has become staggering and virtually indigestible. Truth, ever evasive, has now become embedded in a vast haystack of repetitions, assertions, denials, arguments and irrelevancies. Are there any answers to such a problem?

The *Side Effects of Drugs Annual*, in which an international team of physicians has set out to grapple with the flow of new data, provides one answer. By selecting critically from the year's writing all that is truly new and informative (and pointing equally critically to much which is misleading) the

*Future 'Essays' in this series will be by guest authors from the various countries which contribute to the Annual

Annual should prove an up-to-date and reliable guide to developments in current knowledge. Where facts are wanting, the Annual may nevertheless venture to advance an opinion; but, as John Milton remarked long ago, opinions in good men are but knowledge in the making. Medicine is still an art as well as a science, and the one must sometimes supplement the other.

Such is our approach. It would be very thoughtless, however, to offer even a partial solution to the problem as it currently exists without looking very carefully to the state and future of adverse reaction reporting as a whole. For it is necessary, not only to contain the problem for the moment, but also to ensure that it will continue to be manageable in the future. That may entail finding new ways of collecting our facts and forming our views; like the wise old owl who sat in the oak, we may find it advisable to talk rather less and think rather more.

If we ponder on the matter, generalizing a little from the examples which lie within our own experience, we are likely to conclude that true and well-founded knowledge is not expanding at nearly the same rate as so-called information. The word 'data' in its original and most literal sense ('that which has been given') is the only proper description of most of what gets into print, for it does not imply that what has been given is necessarily useful, welcome or true. Unhappily, we have forgotten our Latin, and 'data' is usually equated with 'facts', since facts are deemed to be sacred, what is given is avidly taken, printed and published. But the process does not end there. For what has been published is then with great alacrity abstracted, cited, republished, processed by computers and xeroxed a thousand times until every molehill becomes a mountain and every querulant correspondent in the *Lancet* a much-quoted authority. It is quite proper that important data be exalted in this way, but the process is currently carried to ludicrous lengths. If the young lady for whom I have prescribed a supposedly bland lanoline cream develops a curious rash I may, suspecting a side effect, feel it advisable to consult my colleagues on the matter, and I may even choose to consult them in print; but there is no need for my modest hypothesis to be disseminated, as it is likely to be, from Dunedin to Vladivostok, much less for it to swell the adverse reactions statistics which are so readily used and misused to scatter alarm and despondency across the world.

Let us for a moment go back to first principles. Why is it so difficult to be sure about side effects? The answer is simply that there is no reasonable model for a sick patient except another sick patient, and even this model may be deficient. It follows that most of the information which we need on the problems caused by drugs has to be obtained in actual practice, and this in a situation where an optimal experiment cannot usually be performed without prejudicing the interests of our patients. What the experience delivers is often no more than a surmise or a hypothesis that a particular drug may have caused a particular unwanted effect. Many more such observations may be needed before we can be reasonably certain that this is indeed an adverse reaction of the drug concerned; and many hundreds more such observations may be required if we are ever to learn how frequently the complication arises, under which circumstances it is prone to occur, and how it may be prevented or relieved. We may thus need a waggonload of reports before we can be certain of all our facts. Yet all this is – at least where serious side effects are concerned – information which must be obtained for every drug in regular use, if that drug is to be properly and selectively employed. At the moment a drug is brought on to the market, experience will already be such as to define the broad lines of its tolerance and intolerance; the details will have to be filled in during the months and years which follow.

This statement of the situation could be made, with slight variations, for every new technique introduced into medicine or surgery. Where drugs are concerned, however, there are also some ancillary factors which complicate

the issue. Almost every new drug at the present day is a research product of the pharmaceutical industry; unlike any other medical innovation, therefore, a new drug has a watchful and powerful guardian angel in the form of its parent company. It is an arrangement which, whether one likes it or not, has been tacitly acknowledged in the systems of drug control pertaining in almost every country, East or West. It is an arrangement which has great merit, but which also engenders patent absurdities at some points along the long road which a drug travels.

The earliest point in the career of the drug when one obtains a glimpse as to which its adverse effects might be is, without doubt, the phase of pharmacological and toxicological studies in animals. Very properly, the community requires of the pharmaceutical industry that the work performed at this stage be conscientiously carried out and painstakingly reported when the drug is submitted to Drug Control Authorities with a view to clinical trial or marketing. Very *im*properly, the community then goes on to tolerate a situation whereby these reports, having been used for this purpose, are then commonly deposited in confidential archives where they are inaccessible to the medical world at large. It is still exceptional for chronic toxicity data on a drug to be published in detail. True, if there are clear indications in these reports that the drug might have certain adverse effects, they may find their way into directions folders and data sheets; the greater part of the preparatory data, however, all too often disappears from view. It follows that when the first clinical evidence of a particular and unexpected side effect reaches us there is often no simple and direct means of comparing it with what has been reported in dogs, rabbits and mice. If these data were public property, it might be simpler to identify at an early stage those adverse reaction reports from the clinic which, because they run parallel to animal findings, deserve particular and urgent attention. A first conclusion one might draw, then, is that when a drug comes onto the market in any country, the pre-clinical work which has been carried out with it should be filed in a public place, where it can be consulted if the need arises. It is understandable that a manufacturer may express reticence in the matter, fearing that the data will serve the interests of his competitors or will be unsympathetically interpreted; but it is hard to see how, at this stage in a drug's existence, these elements can really injure his interests, or can outbalance the demands of public health.

The veritable conundrums in this field naturally arise as the drug comes into use on a larger scale. The clinical trials prior to this time should have elicited those side effects which are reasonably frequent; it is usually the practising physician who will help us to determine more clearly how, when and how often these side effects are likely to occur, and who will pick up the less common adverse reactions which the medicine may produce. If we are to avoid producing a great deal of superfluous information at this stage we must direct our attention to these primary questions. Not every physician proves capable of doing so; most Adverse Reactions Monitoring Centres find that they rely on a small and faithful group of observant practitioners who have learnt to look at new (and even older) drugs with healthy but objective scepticism, and who can distinguish a potentially important finding from a trivial detail. Experience from Sweden and Germany tends to suggest that if we attempt to cajole the bulk of the medical profession into reporting adverse reactions, we shall merely end up with additional data on nausea caused by oral contraceptives and drowsiness due to antihistamines.

One is thus looking primarily to the individual practitioner and specialist for pointers to the unexpected, irrespective of whether the element of surprise lies in the nature of the reaction, its severity, or the circumstances of its occurrence; in this setting, the merest shadow of suspicion is sufficient to justify a record of the event. Such a record often need not go into print at all. If it is entrusted to an Adverse Reactions Monitoring Centre, one will very

soon know whether the suspicion is justified or not. Such a Centre – and the network in which such Centres work together – is very well placed to set these observations alongside one another, to look for trends and parallels, and to alert the medical community (without alarming it) when such parallels emerge. It is a way of working which saves time, confusion and injury; it also saves paper.

At the same time one will be looking primarily to larger hospital centres for a further elucidation of known side effects, insofar as this is really needed. For in this situation too, we must look to our priorities. The exact incidence of a side effect is often not a matter of great importance; the knowledge that it is constant, frequent, occasional or exceptional is for most purposes quite enough; exact figures are in any case only likely to be valid for the situation in which they obtained; and they are less likely to be used than misused. The exact quantitative study of an adverse reaction is only vital in two situations: one is where the reaction is so serious or hindersome in nature that it becomes essential to determine which of a particular family of drugs is least likely to induce it, even if the difference is only marginal; the other situation, unfortunately, is that in which the seller of the drug is emphatically claiming for his product a degree of innocuousness which is at least open to question. If the pattern of pharmacotherapy is not to be distorted by purely commercial pressures, such claims will sometimes have to be scientifically challenged.

On specific matters such as these, much could be done to make drug reporting more efficient. But there is also a more general point to be made. If one's first impression of the world's clinical literature is that of its fearsome immensity, one's second is likely to be that of its appallingly poor average quality. The two are obviously interconnected; the drug literature is overburdened by a vast volume of superfluous and even dangerous rubbish. The standard of medical journals ranges from the sublime (of which there are very few) to the disgraceful. No physician, confronted with this literature as a whole from week to week, can be very proud of what his profession is on average producing. It is astonishing, *anno* 1977, to encounter a situation in which many thousands of drug studies yearly consist of little more than vague testimonials to a drug's efficacy and safety ('Résultat clinique formidable ... Verträglichkeit immer vorzüglich'). Many other studies have to be discarded as evidence because of elementary errors in recording ('... other medicaments were administered as required ...'). And alongside this there are the vast numbers of repetitive publications presenting conclusions which, as we say in Holland, are as evident as cows. Much of this purely repetitive work is clearly performed at the instigation of industry, as a means of promotion. Some of it may be attributable to the vanity of scientists, some to the forwardness of publishers. Now and again, one suspects that the investigator has simply not been aware of what he has been doing. Why, in 1976, should an Italian internist of some renown have studied the side effects of a well-known anticholinergic drug, and solemnly have concluded in print that it had anticholinergic side effects? The answer would appear to be that the drug had recently been remarketed in Italy under a new name as an asthma remedy, without any indication whatsoever as to its true nature or identity. This is not the only example of its type; so long as drugs are sold not only under multiple names but also under differing connotations, scientists will be confused, effort wasted, and patients harmed.

This is, then, one of the instances where the guardian angel has been overplaying his role. It is not the only one. The declining flow of new products emanating from research, to which Professor Franz Gross of Heidelberg has pointed, has undoubtedly led to a crisis in the drug industry. This in turn has meant a sharpening of competition; old products have been reburnished, dying drugs revitalized, and the second rate forced into the front rank. In such a situation the objectivity of pharmaceutical promotion is increasingly

open to question, and misleading statements are just as likely to be made about the nature of a drug as about its tolerance or its efficacy. So long as commercial promotion is identifiable as such, one can set it quietly aside and proceed with one's studies; but when promotion interferes with the flow of honest observation and opinion or masquerades as scientific evidence (and there is still many an editor and many a physician who will sell his soul for a mess of pottage) it can only impede and protract the process of analysis.

Let us, however, also recall that whilst a drug with a guardian angel may present problems, a drug without one may be an even greater liability. The fact that a manufacturer considers himself responsible for a drug throughout the world, and indeed is held responsible for it by the community, is sometimes a matter of great convenience; he it is who will be saddled with the responsibility for subsidiary studies when a suspicion of danger arises; in addition he may prove to be a more fruitful source of information on all that is known about the drug than any other which we have. By contrast, the old and no longer patented drugs which circulate more freely and are used on a vast scale are mere waifs and strays. If tomorrow a major problem were to arise with such a drug, who should we call upon to solve it? Such difficulties arose in the seventies with phenacetin; they could develop in the eighties with paracetamol, phenophthalein or L-dopa. There are many more such drugs, a lot of them of value, which have outlived their patents, yet which have never been adequately studied. If they are incriminated, no individual manufacturer will be sufficiently interested to bring his scientific resources to their defence; the result may be an imbalance in which even ill-founded but emotionally appealing accusations will suffice to put paid to them. The responsibility which devolves upon investigators, drug controllers and authors with regard to such drugs is not inconsiderable, for it is much easier to kill a useful drug with a prod of the pen than to create a better one.

All in all, despite the difficulties which confront us, we cannot be dissatisfied with the progress which the study and analysis of adverse reactions is currently making. It is conceivable that a thalidomide drama could occur again, but the indications are that it would in the present situation be handled with a great deal more despatch than was possible in 1961. Reports of major haematological disorders possibly induced by drugs – burimamide, aprindine and clozapine come to mind – have, rightly or wrongly, been the subject of international consultation within weeks, days and even hours; many other, less acute, situations have been met without delay. These are, however, the exceptions which prove the rule that the evaluation of side effects is generally a laborious and slow process which demands as much perseverance as perspicacity. Now and again we gain a glimpse of the truth, as through a glass, darkly. Slowly, haltingly, as time goes by, the real facts about any drug emerge into full view. Sometimes, indeed, the drug is dead and buried (again, rightly or wrongly) before that day comes. Shall we ever know, now that it has been condemned on the basis of a study in bitches, whether megestrol acetate was indeed a dangerous oral contraceptive? Will any one ever be able to tell us why clioquinol caused ten thousand cases of subacute myelo-optico-neuropathy in Japan, and a mere handful elsewhere?

If all the truth were to be told about all the drugs we have, the books would be thinner, for speculation is bulkier than fact, and many a drug survives only because we are not sure how ineffective and how noxious it is. Such a moment will not come in our time. The best that we can do is to struggle with the brief glimpses of reality which are accorded us; to discourage those people who have an interest in anything but honest proof; and to divert our energies away from what is purely repetitive or pedantic. Hopefully, the moments of truth will then come a little earlier, even though the day of judgement be still far removed.

Breukelen,
The Netherlands

M. N. G. DUKES

how to use this book

PERIOD COVERED

The starting point for the 1977 Annual is the Eighth Edition of the international standard reference work *Meyler's Side Effects of Drugs* (1975) which covers the world literature on adverse drug reactions down to approximately January 1975. The present Annual reviews all reports presenting significant new information on adverse reactions since then, up to August 1st, 1976. Some more recent papers have been included where possible. Subsequent Annuals will cover the literature appearing yearly between August 1st of one year and July 31st of the next. *Meyler's Side Effects of Drugs*, as a standard reference work, will be updated approximately every four years.

CLASSIFICATION

Drugs are classified according to their main field of application or the properties for which they are most generally recognized. In borderline cases, however, some supplementary discussion has been included in other chapters relating to secondary fields of application. Fixed combinations of drugs are dealt with according to their most characteristic component.

DRUG NAMES

Drug products are in general dealt with in the text under their most usual non-proprietary names; where these are not available, chemical names have been used; fixed combinations usually have no non-proprietary connotation and here trade names have been used as necessary.

SYSTEM OF REFERENCES

References in the text are coded as follows:

R: In the original paper, the point is *reviewed* in some detail with reference to other literature.

r: The original paper *refers* only briefly to the point, on the basis of evidence adduced by other writers.

C: The original paper presents detailed *original clinical evidence* on this point.

c: The original paper provides *clinical evidence*, but only briefly.

The code has not been applied to animal pharmacological papers. The various Editions of Meyler's Side Effects of Drugs are cited in the text as SED VII, SED VIII etc.

INDEXES

The Index of Drugs provides a complete listing of all references to a particular drug in the Annual. The Index of Side Effects is necessarily selective, since a particular side effect may be caused by very large numbers of different compounds; the latter Index is therefore mainly directed to those side effects which are acute or life-threatening, those which are discussed in special detail in the present Annual, and those which are unexpected. Before assuming that a given drug has not been reported to have a particular side effect, however, the reader should always consult the relevant chapter.

In future Annuals indexing will be cumulative over four-year periods, at the end of which the revised *Meyler's Side Effects of Drugs* appears. To obtain complete information on the side effects of a drug, it will therefore be sufficient to consult the most recent edition of *Meyler's Side Effects of Drugs* and the latest Annual.

The indexes have been compiled by Dr H. Kettner, Middelburg, The Netherlands.

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contents

P. H. Connell

1 central nervous system stimulants and anorectic agents

INTRODUCTION

The main thrust of interest represented in the literature of the past year has been in the field of the assessment of the newer anorectic agents and in particular the use of double-blind techniques to carry out such studies. The present review will devote particular attention to three of these agents: diethylpropion, fenfluramine and mazindol.

The paucity of reports of studies of amphetamines probably reflects the placing of these drugs on much stricter control regimes in many countries and the reluctance of physicians to use them in view of this, the dangers of abuse and doubts as to their efficacy in clinical conditions for which they had previously been used.

The question of changes in the brain produced by amphetamines remains a point of interest (1). Of continued interest, also, is the significance of biochemical abnormalities in schizophrenia and in amphetamine psychosis in which an overstimulation of dopaminergic receptors, probably located in the limbic cortex, is one hypothesis for which there is a considerable body of evidence (2^R).

ANALEPTICS

AMINOPHYLLINE

A report of 4 patients (3^C) who were all over 40 years of age with a long history of bronchial asthma but no previous epilepsy describes the development of serial seizures with focal onset during treatment of status asthmaticus which appeared to be related to administration of aminophylline. This report quotes an earlier report (4^C).

A study of parenteral aminophylline (5^C) notes that there was little information concerning the blood concentrations of theophylline required to induce a bronchodilator response and none to indicate the necessary intravenous dosage of aminophylline to achieve and sustain such a concentration. The study which measured blood concentrations of theophylline in a variety of conditions employed spirometry and body plethysmography. Airway response was correlated with blood concentrations. It was found that the bronchodilator effect of theophylline was directly related to blood concentrations within the range of 2.0–8.0 μg/ml and that to continue with doses that produce higher concentrations invites the risk of dangerous toxicity without any additional bronchodilatory response. The occurrence of nausea or otherwise unexplained tachycardia indicated an excessive blood concentration and the need for immediate reduction of the dose. In practice, in adults, an initial intravenous dose of 375 mg of aminophylline followed by 1.0 μg per day by continuous or intermittent administration would appear to combine safety with efficacy.

A study of the effect of bronchodilators on patients with chronic obstructive pulmonary disease who had atrial and/or ventricular arrhythmias following cessations of therapy for 16–24 hours compared isoproterenol (Iso) aerosol with 250 mg theophylline orally or intravenously (6^C) and stressed that theophylline compounds often worsened arrhythmias and should be used with caution.

A study of a new preparation, Phyllocontin tablets, consisting of aminophylline 225 mg in a continuous release base given once or twice a day to patients with asthma and/or chronic bronchitis with airways obstruction was carried out on 15 adults and 2 children aged 8 years. Clinical signs and symptoms were monitored objectively and peak expiration flow (PEF) was measured at regular weekly intervals during the treatment period of 8 weeks (7^C). All patients at the