

Book reviews

Detecting unwanted drug reactions

M.D.B. Stephens, J.C.C. Talbot and P.A. Routledge, *Detection of New Adverse Drug Reactions*, 4th edn, Macmillan Reference Ltd., London and Basingstoke, 1998. ISBN 1 565159 190 4.

If any group should be considered capable of reviewing the state of the art as regards the detection of drug risks, then it is the body of physicians working within the pharmaceutical industry which handles both the performance of pre-marketing clinical trials and the study and collation of adverse reaction reports emerging after marketing, either from Phase IV studies or from spontaneous reporting system. The present fourth edition of what is still essentially Myles Stephenson's book tackles this vast topic very well, drawing heavily on experience within industry but also on the world literature, and with academic contributions to balance out the picture.

It is clear from the impressive overview of world knowledge presented here that our means of detecting adverse reactions, though far greater than a generation ago, are still deficient. Under-reporting from the field is a major problem. No-one expects (or would be happy with) a reporting system which gathered 100% of information on old or new reactions in every patient; all one would want is a representative cross-section of what is going on. Even this is hardly attained with the sort of figures which Stephens et al. quote (pp. 6–7); Baum's figures from the USA suggest a reporting rate of only 1.5% for moderate or serious reactions, and Lumley's small study in UK arrived at only a 6% reporting rate even when physicians knew that their performance was being recorded. Examining cases where cough had occurred with angiotensin converting enzyme inhibitors, Begaud et al. in France found that only 1 incident in 1300 was reported. It is true that in the case of some spectacularly publicized effects the reporting rate may rise to nearly 100% but this is commonly a matter of locking the stable door after the horse has gone. There are good examples of serious reactions being picked up promptly from field reports, and the authors are able to cite them, but they remain exceptional.

On the means of obtaining reliable adverse reaction information during pre-marketing trials the book is superb, facing squarely up to the problems. It is reasonable to devote especial attention to those effects which might be anticipated, but how can one do this without overshadowing the need for vigilance as regards entirely unexpected effects which were not seen with the drug's congeners or suggested in animal studies? How is one to exclude effects that could be due to the primary disease and not to the drug at all? Chapter 7, by Dr Stephens himself, provides as good an overview of the difficulties and the possible solutions as one will find anywhere in the literature. Not all those preparing New Drug Applications, unhappily, meet his standards.

Chapter 5, contributed from Italy, provides a sensible and understandable approach to dealing with Quality of Life data, whether these reflect the therapeutic benefit of a drug or its unwanted effects. Chistine Bendall in Chapter 14, looks at legal aspects of pharmacovigilance, primarily as regards the duties created in this respect in the countries of the European Community. It would have been helpful to examine more closely here the United States FDA (information on which is scattered throughout the book); one might also well consider, for a future edition, considering what can be learnt from litigation relating to adverse reactions; there have been many cases relating to the duties of the industry and of

health professionals, and although much of the information is buried in settlement agreements a fair number have found their way into the journals.

Of the appendices, one provides a helpful overview of some 75 products withdrawn for safety reasons over the period 1961–1995; with respect, however, one might submit that this is not a complete picture of the safety problem. Many older pre-registration were quietly taken off the market for the same reason during that period, since they were not safe enough to withstand regulatory procedures, and a very large number indeed have succumbed during the latter phases of clinical trials because safety problems arose which had not been predicted. There are also hundreds of drugs which have been the subject of warnings and restrictions during the last generation, whilst remaining on sale for particular purposes.

If one would like to see some additions and changes in the volume, this is not because it is in any sense defective; all one might hope for is that the progress made from the first to the fourth Edition will continue into a fifth. The book is balanced, informative, clearly written, and extraordinarily well documented. For anyone entering into the field of adverse reaction monitoring one could not wish for a better primer. For those already working in the field, much of this book is worth careful study and reflection; so many things relevant to adverse reaction studies could be done better, and time and again the contributors to this excellent volume show the way.

M.N.G. Dukes

Editor, *Int. J. Risk and Safety in Medicine*

Patient-centered medicine

Basic Document for the Quality System of the University Hospital, RITØ, Tromsø, Norway, 1994.

This book is as excellent as it is small. Why should quality assurance procedures in hospitals be hidden away in unreadable manuals? Since 1994, anyone wanting to understand how patient-centred care operates in an academic hospital in the Arctic Circle can find the answer in just 41 tiny pages, and in English at that. For particular departments there is more detail to be found in specialized documents, to which the basic text cross-refers the reader. The entire Quality System has three central objectives: the first being to give the patient a better spectrum of health services, the second to create and disseminate knowledge, and the third to raise and maintain quality in every sector. The codewords – respect, equality, openness and co-determination – put it succinctly – medical democracy at work. Very highly recommended, wherever you work in health care.

The professionalized patient

J.F. Alberts, *The Professionalized Patient*, Centre for Health Care Research, University of Groningen, Northern, The Netherlands.

This academic thesis is based essentially on work, not in The Netherlands, but in the Netherlands dependency of Curacao in the Antilles. Much of the study – on the manner in which health services are used by patients – turns on the development of knowledge within the lay public and the assimilation of professional knowledge and attitudes into popular culture. The “proto-professionalized” patient assumes a more equal footing with health care providers in terms of status, mutual expectations and decision making, which facilitates access to diagnostic and treatment facilities. One explanation of inequities in

health care proves to be the fact that a large part of the population does not attain this standard. One means of tackling that problem could well be an attempt to “deprofessionalize” the provider, essentially taking the doctor down from his pedestal. The author has clear ideas as to how this might be approached – and a small community like Curacao looks like a fascinating arena in which to try it out. The study as a whole also provides a good model for investigating the phenomenon elsewhere.

L. Martensson, *Deprived of Our Humanity: The Case Against Neuroleptic Drugs*, The Voiceless Movement, Geneva, 1998, 224 pp. ISBN 2 88462 039 7, SKr. 110.-

The Swedish-American psychiatrist Lars Martensson has been well known for many years as a tireless campaigner against the reckless use of neuroleptic drugs. The present paperback comprises a series of writings on the subject, some by himself, some by other authors having similar experiences and views. One of those – Loren R. Mosher – was the founder of Soteria House, a nursing home outside San Francisco which became famous for the manner in which, in Dr Mosher’s words, it “demedicalized, dehospitalized, deprofessionalized and deneurolepticized psychosis”. Soteria found little sympathy in American psychiatry and had to abandon the unequal struggle, but clones of it have been established in Sweden and Switzerland.

Lars Martensson’s own writings have drawn in part on his experience with a young Swedish patient known to the reader only as Hebriana, who developed psychotic traits in 1978 and was under his care. At the time, as he puts it, reality was falling apart for her. Artistically gifted, she sought to convey her experiences through drawings, some of which illustrate the book. Instead of treating her with a neuroleptic drug which “would have devastated her inner world, would have destroyed her puzzle and her visions” leaving her mind an empty wasteland, Martensson provided her with an intensive and highly personal mentorship as she went through her experience. “I had to be there with a deep but completely quiet interest in her puzzle and in her predicament, knowing that only she herself could re-create her world. I had to be there, but not aloof and observing, and not intrusive, but fully present with a pure and open mind. . . Her interest had to be mine. No ulterior thoughts.”

The story of Hebriana is too long to be recounted in this review, but thanks to the support and guidance which she received she recovered over a five year period and today functions normally in society, and as a wife and mother. That is not to say that her psychosis of twenty years ago was cured or even suppressed; she lives with it and has accommodated to it. As she herself wrote in 1998: “I still am who I am. What I experienced then is still reality. Those fundamental experiences are still going on. But I have become better at relating to them. Now I don’t need to be destructive when I am afraid. The instrument that is me, ‘Hebriana’, has improved.”

It is easy to criticize Martensson’s view as reflecting only anecdotal experiences, or demonstrating that the psychotic individual requires such an intensive form of personal care that society simply cannot provide it. One should remember, however, that Hebriana herself came from a northern Swedish family notorious for the fact that psychosis has existed in it from one generation to another. One should also bear in mind the similar success stories on record from Soteria, the Swedish centre at Falun and elsewhere. Taking all things together there is today much reason to respect Lars Martensson’s view that neuroleptics are at best a rough-and-ready tool, and at worst a destructive cudgel which destroys the individual mind. Very well, let us admit that society has not yet found the human resources to treat psychotic patients as well and as intensively as they deserve; so long as human care is expensive and drugs are cheap, society may claim that it must persist on its pharmacological road, which it may assert is the best it can afford. But if people like Lars Martensson can at least bring society to admit this much, they will be halfway to convincing the world that it got to rethink its priorities.

CMAJ: *Lifestyle Modifications to Prevent and Control Hypertension*, Canadian Medical Association, Toronto, 1999. Issued as a supplement to Canadian Medical Association Journal, May 9th, 50 pp.

O.H. Klungel *Studies of the pharmacological treatment of hypertension in the general population*, University thesis, State University of Utrecht, The Netherlands, 1999. Price not stated.

Yet again Canada comes with a sensible overview of how medicine can be practised safely and creatively. Although the principles of preventing and correcting hypertension by adjusting lifestyles rather than by prescribing medication are well-established, it is still fatally easy to seize the prescription pad as the tool of first (instead of last) recourse.

The seven readable reviews and recommendations in this slim volume were drawn up by working groups of the Canadian Medical Association with backing from a series of other bodies and foundations in the field of health and preventive medicine. They deal in turn with reduction in body weight, the influence of alcohol consumption, physical exercise, dietary salt, potassium, magnesium and calcium, and the management of stress; an overview paper puts all the possibilities into perspective. Throughout, the full texts are backed up by clear abstracts which summarise the objective of each approach, the available options, the evidence of efficacy, and the benefits and risks.

Sound advice of this type has too often been provided in indigestible form or scattered throughout the literature. What we now need is some monitoring of the effects of such advice when it is provided as clearly as is here the case. Any pharmaceutical company running an advertising campaign for an antihypertensive drug will spend a fair part of its budget on market research to determine its effects on prescribing. If the CMA is as creative as it surely is, it should make an effort to see what doctors do with this advice. How many have read it? how many recall its broad approach? and how many have changed their attitude to hypertension because of it? Armed with the answers to questions like that, even if they are sometimes disappointing, one will be equipped to go on moving medicine in the right direction in the future.

Klungel's book from The Netherlands, in fact an extensive PhD thesis in book form, adopts a complementary approach, examining the quality of drug treatment for hypertension in the population at large. Data were taken on the one hand from 42 population-based studies covering a range of countries, and on the other from a long-term monitoring project on risk factors for cardiovascular disease which has been running in The Netherlands since 1987. Klungel's concern is on the one hand with the fact that much of the hypertensive population never gets treated at all – a failure in health service provision – and on the other hand with the fact that when drugs are used for this purpose they are not always used appropriately. Reading his book immediately after that from the Canadian Medical Association one might wish he had also taken more account of the extent to which non-pharmacological methods are employed.

As regards inadequacy of treatment, his conclusion derived from the Dutch population study is that the proportion of strokes which can be attributed to the inadequate treatment of hypertension is as high as 26% in men and 29% in women. Data on the nature of treatment seem to show that men are less frequently treated with first-choice antihypertensive drugs than are women, though on present evidence it is not possible to determine what consequences, if any, this has.

In both men and women treated pharmacologically for hypertension a substantial proportion *remained* hypertensive – as many as 42% of men and 29% of women. It seems clear that this was often attributable to inadequate prescribing or poor compliance on the part of the patient, but (again in the light of the Canadian recommendations – and various of the national “guidelines” which Klungel cites) one wonders

to what extent failure to reduce such risk factors as obesity and stress played a role in the failure of pharmacological treatment. This was not a question which Klungel set out to answer, but it needs answering, if we are avoid concluding incorrectly that to tackle the hypertension problem we simply need more and better prescribing.

D.S. Tatro, *Drug Interaction Facts 1999*, Facts and Comparisons, St. Louis, 1999, US\$ 58.95.

Authors of books on drug interactions (and for that matter on side effects as well) seem to be in a constant state of struggle as to how much information they can provide without stifling the reader or becoming so voluminous that their writings are simply set aside. The dilemma is inherent in the nature of the material; there is evidence of tens of thousands of drug interactions, yet the number which are both clinically significant and likely to occur with drugs in everyday use is very small. Pocket reference cards exist which provide the average GP with all the knowledge of interactions which he is likely to need from day to day. However, a day will come when he runs into what appears to be a less evident and less common drug interaction and needs to find the information on it quickly. It is here that volumes like that edited by Tatro with a strong supportive team are needed – not intended to be read as textbooks but ideal for rapid and reliable reference.

Tatro's text deals with precisely 1203 drug interactions, one on each page. Since some relate to an entire class of drugs (e.g., benzodiazepines) the number of individual drugs involved is naturally rather higher. The data are laid out systematically in tabular form: the significance, mechanism and consequences of each interaction are sketched and the principal references summarise. There is an excellent index.

Unavoidably, by the very openness of the presentation, the author illustrates the sort of problem which one meets when documenting this field of knowledge. The very first page in the reference section, for example, deals with an interaction between acetaminophen (paracetamol) and anticholinergic drugs, but the most recent reference traced to this is from 1983, it is of minor severity and the cause-effect relationship is in the light of this evidence listed merely as "possible". All the same, the fact that anticholinergic drugs do delay gastric emptying is perfectly well known, and it is reasonable to anticipate that some drugs (such as paracetamol) which are absorbed from the intestine will as a result reach effective blood levels much later. A physician with a fair insight into pharmacology will be able to draw that conclusion and instruct his patient accordingly, even if the specific evidence relating to paracetamol justifies no more than an assessment as "possible". This is not a criticism of Tatro's book, merely a recognition of the difficulty which such an author faces.

The book cannot be faulted as a source of quick reference, which belongs in any medical library. Should it not also be available on diskette?

Judith Green, *Risk and Misfortune: The Social Construction of Accidents*, UCL Press, London, 1997, ISBN 1 85728 560 3 HB and 1 85728 561 1 PB, £14.95.

In the course of the years, there has been some nonsensical and unbalanced writing about risk. Such writing generally has an ulterior motive, setting out to persuade the reader that accidents in a particular field – whether it be aviation, surgery or environmental science – are either a great deal more alarming (or, conversely, much less problematical) than common sense would lead one to believe. Welcome, then to a scientific, sensible and sober treatment of the subject by Judith Green of the London School of Hygiene and Tropical Medicine.

Defining an accident is an initial step which some writers seem to ignore; Ms Green, more thoughtfully, sets out to make it clear that the term needs to be used with some restraint. "Ideal" accidents may be blameless and unpredictable events, but "accidents in practice are potentially surrounded by moral enquiry" and such enquiry can lead to clear explanations in terms of specific failure; in such cases the "accident" is in fact the logical and foreseeable consequence of certain acts or omissions. This is the way in which both law and medicine at their best can approach the phenomenon of accidents and develop the basis for risk management.

Health care relates to accidents in various ways, a major one being the approach to accidents as a preventable disease. In that respect a lot of success has been attained – in England and Wales, for example, fatal accident rates have declined steadily since 1950 when public health authorities first adopted accident reduction as a specific target to be met, with approaches ranging from public education to improved motor vehicle design. The health statisticians and epidemiologists have also had their successes during this period. As the present study points out, so long as "Sudden Infant Death" did not form a category in the International Classification of Diseases (which was the case down to 1971) the deaths in question were scattered over other groups and subgroups of puzzling "accidents"; the condition was thus in public health terms invisible and thus not likely to be seen as a specific entity demanding attention. As soon as they became a disease entity, cot deaths could be approached methodically, with attention for possible predisposing or causal factors, such as respiratory infection, use of drugs or low social class.

Public health also touches on the accident problem where medical injuries and accidents are concerned. It is no criticism of Ms Green that these receive little attention in her study, for she has a vast number of examples from other fields to provide the basis for her analysis. But that is the very reason why this book is so fascinating from the point of view of risk and safety in medical care. Having developed a scientific view of the nature, degree of acceptability and preventability of risk as broad social issues, one can then apply this understanding logically to the fields of medicine and surgery. This should render it easier to defuse the emotional response which commonly arises among professionals involved in instances of supposed medical misadventure, where even raising the possibility that one has been involved in any such thing may be regarded as an insulting accusation of professional incompetence. Just as children will continue to fall off swings and roundabouts, innocently but painfully, so medical men and surgeons will have inevitably experience instances where, viewed in retrospect, they could have treated their patients better and more safely. Of course there will be instances where lack of skill or care is demonstrable and a reprimand is called for, but for every one such instance there will be a hundred others which, examined soberly in retrospect, will be a learning experience.

Some health professionals may be a hesitant to wade through the sociological terminology in this book, but one does not need to follow it all in order to benefit from it. It deserves a place in even a modest medical library, and most certainly in post-graduate training.

R.H.B. Meyboom, *Detecting adverse drug reactions: Pharmacovigilance in The Netherlands*, Benda Drukkers bv, Nijmegen, the Netherlands, 1998, ISBN 90 9012054 8, price not stated.

The Netherlands has for more nearly half a century been one of the pioneering countries in adverse reaction monitoring. The late Prof. Leo Meyler established his famous "Side Effects of Drugs" as early as 1952, collating from the world literature evidence of drug-induced disorders. From 1968 onwards that venture was complemented by one of the first national adverse reaction monitoring systems, which sought to induce health practitioners to submit to a monitoring centre their observations of possible

adverse effects. The present volume of studies is by Ronnie Meyboom who assumed responsibility for the centre in 1973 and to whom much of the credit for its success is due.

Distilling evidence from “spontaneous” adverse reaction reports is an art as well as a science; the first evidence that a drug may be capable of causing a particular type of injury is often flimsy and open to criticism. Yet recognizing in good time those early signals which do comprise evidence rather than reflecting mere coincidence may save much suffering and sometimes many lives. Meyboom shows himself a master both in defining the principles of signal detection and in understanding the various ways in which the art has been developed in Europe. Beyond that he provides a critical assessment of the way in which this work could develop further in the future. Tools varying from new legislation to wider use of electronic communication will clearly play a role, but above all he points out that spontaneous reporting must become an integral part of the entire process of acquiring knowledge in this field. It will always complement controlled clinical trials and epidemiological studies, but it is no longer merely their poor relation. Those who continue to dismiss what they choose to term “mere anecdotal reports” of adverse drug effects will increasingly do so at their peril – or at the peril of their patients.