

Book reviews

U. Schüklenk, *Access to Experimental Drugs in Terminal Illness*, Pharmaceutical Products Press (Haworth Press), New York, NY and London, 1998. ISBN 0-7890-0563-8. Hard copy \$49.95; paperback (in bulk) \$29.95.

It is no criticism at all of this remarkable and ambitious book to point that out that, by the time it appeared in print (1998), an important part of the battle that it set out to fight had already been won. A substantial part of the author's argument is that the United States FDA was wrong to deprive AIDS sufferers, during the initial years of the epidemic, of access to experimental drugs on the ground that their efficacy and safety had not yet been established. In the USA, where difficult issues like this tend to be handled in a very black-and-white manner and where solutions are commonly attained by political pressure and lobbying rather than calm study or consensus, the conservative majority in Congress from 1990 onwards obliged the FDA to relax its attitude. Many concluded as a result that the cowboys had won a noble battle against the villains. But the story was in fact a great deal more subtle, both in America and in the rest of the world where the confrontation was much less acute. There were rights and wrongs on both sides; both were faced with conundrums and the dilemmas which largely remain unresolved. That is why the story deserves this careful analysis and documentation, for the sort of conflict which arose around AIDS in fact exists for many other serious illnesses for which there is as yet no proven treatment, whether with drugs, surgery or otherwise.

In the initial and most difficult section of his book, Udo Schüklenk turns to the writings of ethicists and philosophers over a long period to examine the permissibility of society adopting a paternalistic approach to its members in matters such as this. Immanuel Kant (1724–1804) laid a philosophical basis for the autonomy of the individual in society. The famous *Essay on Liberty* by John Stuart Mill (1806–1873), like the writings of Aristotle and Schopenhauer, sets the scene for a weak form of paternalism, in which society can act to protect its members from their own errors and weaknesses, though in Mill's view such interference with the individual will only be permissible if thereby harm to others is prevented. The present-day Australian philosopher Robert Young is more prone to find arguments for restricting individual autonomy.

It is very doubtful whether those who brought modern drug regulation into being had considered the views of the philosophers very much. They acted, as the author realizes, largely because with the large-scale commercialization of drug supply things were tending to go wrong. Classic dramas such as those relating to thalidomide and elixir of sulfonilamide showed that without a sufficient form of control patients could find themselves exposed to drugs the efficacy/safety balance of which was far from proven. The community found itself obliged to create impartial agencies to ensure that such matters (as well as quality and the flow of drug information) were properly assessed in the interests of the patient. All this Schüklenk appreciates, though it is a pity that he does not devote attention to the ongoing facet of this development; much research on drug regulation shows how frequently the introduction of new drugs still has to be delayed or prevented if reasonable assurances against risk and charlatanism are to be provided.

What happened in the American confrontation with regard to AIDS is that the federal Food and Drug Administration found itself very much unconvinced of the merits and safety either of the anti-viral drugs which might arrest (or even cure) the disease itself, or of some drugs with potential value in the secondary infections which so often dominate the course of the illness and precipitate death: for a period,

pentamidine had to be brought into the USA quietly from Mexico and elsewhere; at one point this book attributes 17,000 deaths to the FDA's prolonged refusal to approve pentamidine.

The result of such a situation was inevitably an outcry, demanding that adult patients who were in fact facing a virtually certain decline to death should have the freedom to use experimental drugs. The demand was made in the full realization that neither the safety nor the efficacy of such drugs were established, and that they might readily do more harm than good. The result of the conflict was essentially capitulation by the authorities, with much greater access to experimental drugs being granted to the American prescriber patient. The situation came to resemble more closely that in European countries where there have long been provisions for the importation and prescribing of unapproved drugs on "special licence" for patients who need them.

As noted already however, the US story (and the same principles apply elsewhere) is beset with dilemmas which remain unresolved. In examining them, the author of this volume is generally dispassionate, though occasionally he seems a little too inclined to search for bogey-men and rascals.

One basic problem arose when the relatively precipitate release of AZT was followed by a period of persistent and even increasing doubt as to its merits and safety. A particular dilemma was posed by the classic 1987 study by Fischl, Richman and others which essentially was the basis on which AZT was approved in the US, and which seeded its approval elsewhere. There was no other reasonable study available on the basis of which an FDA under pressure could have approved AZT, but the deficiencies of the investigation were apparent. As Sonnabend pointed out at the time: "The differences in mortality appear dramatic. However, since the efficacy of AZT was measured against death in the group receiving placebo, it is important to know what the causes and circumstances of these deaths were and that survival in the group receiving AZT can be reasonably attributed to an effect of the drug, that could not have been achieved by any less toxic means." That in turn raised the question how the results would have been if a further comparator group had been treated mainly for opportunistic infections; to keep the study "pure" this had not been done, yet it would have been realistic. The AZT approval also raised questions as regards the drug's apparently serious side effects which became increasingly obvious as it came into more general use.

Schüklenk has a problem in general with the ethics of clinical trials, discussing at length the fate of those patients with any serious disease who are exposed to placebo therapy in order to provide a control group. He appears to believe that with early release of an experimental drug experience in the field can do much to profile its efficacy and safety without controlled studies. The difficulty in extracting clear data from such experience is however well known. It might have been better for this volume to look more closely at existing alternatives to the double-blind clinical controlled trial. As early as 1960, for example, the methodology of sequential testing had been well developed by Bradford Smith and others, rendering it possible to identify the better of two treatments at the earliest possible stage. Schüklenk also has a problem with some clinical investigators, arguing that in some cases they are much more concerned with their research than with the welfare of patients; while the introduction of ethical committees has done much to avoid any such problem, he is probably right with respect to some of the clan. He points, for example, to the fact that at the time of writing placebo-controlled trials of trimethoprim/sulfa were still being carried out on the Ivory Coast on AIDS patients with secondary infections, in whom the drug's value was already well established.

The question of liability for injury and of the course of litigation is dealt with more briefly; some of it relates to the lateness of FDA approval, some conversely to the fact that the FDA approved an unproven drug at all. Especially in view of the current move to bring civil cases against European regulators for rash decisions, the course of US litigation deserves a more thorough study.

While the closing lines of the book present precisely the main conclusion towards which the author has been working throughout his text, this book is not merely an attempt to confirm a preconceived idea. Read carefully, it is an extremely instructive analysis of the manner in which society has in a classic instance struggled with the issue of paternalism in health care, and will undoubtedly struggle again.

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

L.J.G. Veehof, *Polypharmacy in the Elderly*, Drukkerij Regenborg, Groningen, The Netherlands, 1999. ISBN 90 72156 757. MD Thesis, University of Groningen.

During the last twenty years, it has become widely known that old people are often heavily and continually medicated, and that in principle they sometimes receive more medicines than they need take, even having regard to their age and state of health. No-one any longer doubts that it happens, and that this is a situation which society, from Iceland to East Africa, needs to correct. Quite apart from the toxicity resulting from multiple medication of elderly people who may have impaired mechanisms for drug metabolism and excretion, there is the aspect of social functioning. Some individuals dismissed as senile are shown in fact to have been tranquillised into a state of stupor.

This thesis is largely a further documentation of the over-medication problem, here as it was found to exist in part of The Netherlands, with useful findings on possible adverse health consequences for the people concerned. There are good reviews of the literature, and much original investigation to complement them. About 35% of people studied were found to be using two or more drugs throughout the six-month period which was examined, and in at least 5% there was "major polypharmacy" (involving use of five or more drugs over this long period). If one took into account shorter-term use, the figures were much higher, and for technical reasons there may have been some under-estimation of the use of some types of drugs, including self-medication. Certainly some studies from other countries show higher figures, but Holland is a country where people are generally critical about drug use. Cardiovascular drugs (including diuretics and anticoagulants) and psychotropic drugs were most prominent. Particularly in cardiac failure, asthma and diabetes there seems to be a risk that a patient will end up taking a series of medicines in parallel over a long period, and that not all these drugs will be needed. The number of drugs used tends to go up as the patient gets older; especially where it goes up rapidly one has to suspect that too much is being given. Surprisingly, side effects and interactions caused by multiple medication do not seem to be a major problem. According to Veehof's own work, even giving non-steroidal anti-inflammatory drugs to patients already using diuretics does not seem to have fulfilled the prediction of some people that the effect of the latter would be undermined.

It is good that people go on studying this "polypharmacy" phenomenon and reporting on it, so that we do not lose sight of the problem. However, with the situation already well documented in many countries, what we have to look for in any new publication are clues as to why this situation arises and what can be done about it. This was not the main point of this series of Dutch studies, and with the relatively modest figures found in Holland there are obviously a fair proportion of the patients who indeed need all these drugs, and in whom they have been initiated with good reason by one or more specialists.

In tackling whatever problems there are, Dr Veehof sensibly allocates a central role to general practice, which is his own field of special knowledge. Only the GP can curb over-medication resulting from the un-coordinated treatment of a patient by various specialists. All the same, some general practitioners

do seem to contribute to the problem, especially in prescribing psychotropic drugs (calming agents, sleeping remedies) uncritically. It is surprising that, according to work presented here, the indication for giving these drugs at all (and in particular for giving them chronically) very often seems to be poorly defined. Taking that into consideration (as well as the known fact that this particular type of over-medication seems to get more pronounced with admission to a nursing home), the work done here could be a stimulus to taking a closer look at what is going on. If it is true, as people like Breggin have claimed, that chronic use of calming agents often makes senile mental retardation much worse, or even emulates it, we need to tackle this problem much more vigorously. Old people without tranquillisers may be more troublesome to deal with, but they may also be much better at taking care of themselves.

A last remark on the accessibility of data like this. Since the book by Dr Veehof is composed largely of research papers which have been published before, a lot of the content can be tracked down in the journals. Where university theses contain new data for which there is no alternative source, it can be difficult to locate them, even when they appear in the form of printed books. They do not get into *Medline*, and often no publisher and no price is indicated. If successful Ph.D. and MD students who have done health research want to help the community by making their findings available they at least ought to deposit them in a lot of university libraries, including those in developing countries such as our own.

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Stroke care – a matter of chance?¹ A national survey of stroke services

Stroke Care in Britain (1999) Obtainable from The Stroke Association, Stroke House, Whitcross Street, London WC1Y 8JJ, UK.

Stroke is the biggest single cause of death and disability in the United Kingdom. Organized stroke services have been widely evaluated and are an effective means of reducing death, disability and institutional placement following acute stroke. There is a growing awareness of the need to improve the quality of stroke services and to implement organized stroke services more widely.

A Stroke Association survey conducted in 1992/1993 found that such services were not widespread. The charity decided last year that it was time to review the position. It wanted to provide national data on stroke services and to implement organized stroke services (structure, operational policies and practices, research and audit, and planning) to act as a benchmark against which current standards can be audited. Two national surveys were therefore commissioned: one of all consultants in the UK responsible for the care of stroke patients to provide hospital data on services, and one of all health authorities and health boards in the UK providing data on commissioning of stroke services.

But what are “Organized stroke services”? They are generally recognized as being provided by interdisciplinary teams in hospitals and usually work in a geographically-defined stroke unit. Occasionally such teams care for stroke patients throughout a hospital without a defined stroke unit. Features distinguishing such services from general medical services are: coordinated interdisciplinary care, involvement of family and carers in the rehabilitation process, specialization, and education of staff, patients and carers.

¹This review was originally commissioned by “The Health Summary”, London, and is reproduced here in consultation with the Editor.

The response rates were phenomenal: 2945 (87%) of eligible consultants returned questionnaires. Of these, 1716 (58%) cared for stroke patients. A total of 103 (82%) out of 124 health authorities and health boards completed questionnaires.

The main findings of the report can be summarized as follows: the majority of stroke patients are managed by consultants in general medical specialties (54%) and geriatric medicine (27%). Only 44 (3%) consultants looking after stroke patients identified themselves as specialists in stroke medicine. Perhaps worryingly, the number of patients managed by consultant from different specialties varies widely, with geriatricians and stroke medicine specialists responsible on average for 9 and 15 patients on the day of the survey, respectively. The report revealed that over three-quarters of consultants have access to organized stroke services, although approximately half of stroke patients do not get into them. This results in between 4,500 and 5,000 avoidable deaths and institutional placements every year, of which deaths account for just under half.

Despite an overall improvement in access since 1992/1993, the document shows a wide and unacceptable variation around the country in chances of being managed by an organized stroke service. Patients in Northern Ireland, Scotland and Wales are approximately twice as likely to be managed by organized stroke services as patients in England. Patients in the south-west region of England are only half as likely to be managed by organized stroke services as patients in the rest of the UK. The Stroke Association's report also shows that the patients of only a third of consultants are usually managed on a stroke unit or by a stroke team, resulting in only half of stroke patients receiving optimal specialist stroke services.

Access to neuroradiology remains difficult, according to the survey's findings. Provision of CT scanning has improved, but urgent access still appears to be difficult. Only just over a third (37%) of consultants said they were able to get a CT scan for their patients the same day or next day after admission. Urgent CT scanning will be essential should a safe and effective stroke treatment be found. Hospitals will have to work out how to provide a 24-hour neuroradiology service for stroke patients.

A glimmer of hope shows through as consultants are fairly well informed about the benefits and hazards of specific acute and preventive treatments for stroke. Most (74–85%) were uncertain of the effects of low molecular weight heparin and thrombolytic therapies. Ninety percent of stroke patients are admitted within 24 hours of onset, which allows accurate diagnosis and supportive treatments to be used early.

The consultants taking part in the survey considered stroke rehabilitation units to be very valuable (66%) and also considered other services very valuable: acute stroke units (18.4%), family support workers (23.7%), community stroke team (27.6%), transient attack clinics or rapid outpatients departments (39.3%). There was more uncertainty about these latter services, reflecting the limited evidence for these services. However, while the commissioners of health services were also sure of the value of stroke unit, both acute and rehabilitation, they were less convinced of the value of combined acute/rehabilitation units, family support workers, and TIA clinics or rapid outpatients departments.

Levels of audit and research in stroke are surprisingly high with over half of consultants reporting an audit and a third carrying out research in the last five years. These activities have direct benefits for patients who will be more likely to receive standardized care, regular assessment and follow up.

The report also shows that only 3% of those looking after stroke patients are specialists in stroke medicine. These consultants were more likely to be well-informed about local policies, to use standard assessment protocols, to provide patient information, to perform research and audit, and to organize in-service staff training than other consultants. Promotion of specialists in stroke medicine is not a priority for health service commissioners. Many of the consultants who responded are working in an information and policy vacuum. Just under half (42%) of consultants reported that a written stroke strategy existed,

only a fifth had defined minimum standards of care. Opportunities to improve services through written strategies, contracting, minimum care standards and training are being missed. These gaps are a reflection of a lack of leadership in stroke services.

Stroke is certainly viewed as a priority for district service commissioners. However, there is a variable approach to commissioning with both specific stroke services or general acute and rehabilitation services being used. The current organization of services means that stroke services are commissioned in a piecemeal fashion which makes integration difficult.

The survey of district health authorities and health boards in parallel with the consultant survey has allowed The Stroke Association to “triangulate” the findings and to be more certain that the consultants’ opinions are comparable to the district commissioners’ reports. This adds further to the validity of the findings.

In conclusion: variation in access to and use of stroke services is unacceptable and requires urgent action by health service commissioners. Better information and management tools are required for both consultants and health service commissioners. The lack of basic information on numbers of stroke patients and costs of care makes planning services difficult. Stronger medical leadership is required. The development of a new sub-specialty of stroke medicine might improve leadership, organization, service planning, leading to better patient care.

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