

The drug-reaction drama

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Responsibility for Drug-Induced Injury. By M.N.G. Dukes and D. Swartz. Elsevier: 1988. Pp. 431. Dfl. 350, \$184.25.

RARELY does a new book have no competitor; Dukes and Swartz have written such a book. The authors' backgrounds are complementary, combining science (including political science) and the law. Although the literature on drug-related injury is abundant, as is that on the litigious implications thereof, Dukes and Swartz concentrate here on the *responsibility* for drug-induced injury. The volume should enjoy brisk sales, at least among lawyers and employees of pharmaceutical companies.

As the opening paragraph of the introduction (after a somewhat pompous first sentence) points out, it is important to determine when and how a drug injury is preventable, and in this assessment we need "to find out what went wrong". Unfortunately, that is often much more easily said than done. The 'Elixir Sulfanilamide' story is the exception; the deaths it caused were easy to explain and could all have been prevented, had the toxic solvent only been tested in animals for safety. Consider, in contrast, the Japanese 'S.M.O.N.' story, a devastating epidemic of neurological disease, blamed on cloquinol, a drug sold widely all over the world without manifesting toxicity like that seen in Japan. Even in retrospect, cloquinol seems likely to have been at best a 'co-villain', perhaps facilitating damage to the central nervous system by some neurotropic virus. And what of thalidomide, with which 'seal babies' could be reproduced in animals only with great difficulty after the fact, with many species, breeds and strains of rabbits, mice, rats, hamsters, dogs and primates failing to show the dreaded anomalies?

Dukes and Swartz say that "several thousand asthmatic patients may have been killed by high dose isoprenaline aerosols". But these high-dose preparations have disappeared, and 'epidemics' of asthma deaths have occurred periodically since then in different countries — only now they are generally attributed to undertreatment (for example with corticosteroids), not drug toxicity. Even with drugs taken off the market (benoxaprofen and Indosmos, for instance), the numbers cited for deaths attributable to them are soft indeed; sick, elderly patients who die while on a drug are not necessarily victims

of the medication.

In an important introductory paragraph (p.6), the authors point out that in some countries (the United States being a prime example), there has been a tendency to seek compensation for injury from "the wealthiest or best-insured party (often the pharmaceutical industry) even when this has entailed redefining such considerations as foreseeability or retrospectively postulating the existence of a duty not



previously recognized". Bendectin (Debendox) was the only prescription drug ever approved in the United States for treating the nausea and vomiting of pregnancy. Lawsuits alleging that it was a teratogen forced its withdrawal from the marketplace worldwide, even though there have been repeated verdicts of 'innocent' from expert panels and courts. One can safely wager that no sponsor will ever again try to market a drug for this indication in the United States (even though an early Australian critic of the drug has admitted faking his data). Fears of litigation have in effect driven most large US companies out of vaccine research and development, despite the clear need for new vaccines both for civilian and military populations.

Dukes has criticized 'me-too' drugs that "were merely slight variants on existing molecules . . . which provided no new benefit but merely introduced new risk". But it must be a rare pharmaceutical company that purposely markets inferior variants in today's very competitive market. Furthermore, half of the World Health Organization's *List of Essential*

Drugs is made up of compounds that were not the first drugs in their therapeutic categories; many of these could be dubbed 'minor chemical modifications' of the breakthrough products. Would we really want to be restricted today to the earliest penicillins or the first sulphonamides?

The book accurately describes the complex basic problems in establishing causality, but does not adequately communicate the fact that certainty about the cause of a drug reaction (or even that one has occurred) is uncommon. Experts shown the data about a suspected reaction quite typically disagree vigorously — not least because multiple medications are often being taken by patients, and it is often impossible to rule out spontaneous comorbidity unrelated to drugs, or the possibility that the patient is manifesting another aspect of his basic illness. One cannot usually state categorically that an ingested drug could *not* have caused a given adverse effect, but it is only rarely possible to state that a given drug was unquestionably the cause. Algorithms to identify causality (an area which my colleagues and I pioneered) are useful primarily as check lists, not as ways to eliminate uncertainty.

This book is not easy reading, and there are variations in the size of type that are difficult to interpret (is small for less-important material?). But potentially 'responsible' parties will ignore it at their peril. The authors address the obligations of a long list of players in the drug-reaction drama: physicians, dentists, medical students, manufacturers, drug retailers, dispensing pharmacists, nurses, patients, governments and official agencies. (One wishes that the legal profession were sometimes more 'responsible'; trivial and capricious suits are by no means uncommon — at least in the United States.)

Dukes and Swartz dedicate their opus to the World Health Organization. One can question, however, their assertion that "materials emanating from the WHO are probably the most authoritative of all documents on drug issues, representing a broad consensus". In my own experience with WHO committees, I have been struck by the compromises made necessary by the fact that the representatives from different countries must hammer out a document with which they can live on their return home. Consensus based on politics is not necessarily the ultimate in scientific authority. □

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