ELSEVIER

MEYLER'S Side Effects of Drugs

The International Encyclopedia of Adverse Drug Reactions and Interactions

Fifteenth Edition

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In this list the main contributors to the Encyclopedia are identified according to the original chapter material to which they made the most contribution. Most have contributed the relevant chapters in one or more editions of the *Side Effects of Drugs Annuals* 23-27 and/or the 14th edition of *Meyler's Side Effects of Drugs*. A few have contributed individual monographs to this edition.

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Foreword

My doctor is
A good doctor
He made me no
Iller than I was

Willem Hussem (The Netherlands) 1900–1974
Translation: Peter Raven

"*Primum non nocere*"—in the first place, do no harm—is often cited as one of the foundation stones of sound medical care, yet its origin is uncertain. Hippocrates? There are some who will tell you so;[1] but the phrase is not a part of the Hippocratic Oath, and the Father of Medicine wrote in any case in his native Greek.[2] It could be that the Latin phrase is from the Roman physician Galenius, while others attribute it to Scribonius Largus, physician to one of the later Caesars,[3] and there is a lot of reason to believe that it actually originated in 19th century England.[4] Hippocrates himself, in the first volume of his *Epidemics*, put it at all events better in context: "When dealing with diseases have two precepts in mind: to procure benefit and not to harm."[5] One must not become overly obsessed by the safety issue, but it is a necessary element in good medical care.

The ability to do good with the help of medicines has developed immensely within the last century, but with it has come the need to keep a watchful eye on the possibility of inflicting harm on the way. The challenge is to recognize at the earliest possible stage the adverse effects that a valuable drug may induce, and to find ways of containing them, so that risk never becomes disproportionate to benefit. The process of drug development will sometimes result in methods of treatment that are more specific to their purpose than were their predecessors and hence less likely to produce unwanted complications; yet the more novel a therapeutic advance the greater the possibility of its eliciting adverse effects of a type so unfamiliar that they are not specifically looked for and long remained unrecognized when they do occur. The entire process of keeping medicines safe today involves all those concerned with them, whether as researchers, manufacturers, regulators, prescribers, dispensers, or users, and it demands an effective and honest flow of information and thought between them.

For several decennia, concerned by its own errors in the past, the science of therapeutics put unbounded faith in the ability of well-planned clinical trials to arrive at the truth about the properties of medicines. Insofar as efficacy was concerned that was and remains a sound move, closing the door to charlatanism as well as to well-meant amateurism. Therapeutic trials with a new medicine were also able to delineate those adverse effects that occurred in a fair proportion of users. If serious, they would bar the drug from entry to the market altogether, while if transient and reasonably tolerable they would form the basis for warnings and precautions as well as the occasional contraindication. The problem lay with those adverse drug reactions that occurred rather less commonly or not at all in populations recruited for therapeutic trials, yet which could soon arise in the much broader spectrum of patients exposed to the drug once it was marketed across the world. The influence of race or climate might explain some of them; others might reflect interactions with foods, alcohol, or other drugs; yet others could only be explained, if at all, in terms of the particular susceptibility of certain individuals. Scattered across the globe, these effects might readily be overlooked, regarded as coincidental, or at worst dismissed contemptuously as "merely anecdotal".

The seriousness of the adverse effects issue became very apparent even as the reputation of controlled trials deservedly grew, and it touched on both newer and older drugs. The thalidomide calamity, involving several thousand cases of drug-induced phocomelia, was fortunately recognized by Widukind Lenz and others in the light of individual case reports within two years of the introduction of the product. On the other hand, generations elapsed between the patenting of aspirin in 1899 and the realization in 1965 that it might induce Reye's syndrome when used to treat fever in children. Such events, and many less spectacular, showed that, however vital well-controlled studies had become, there was good reason to remain alert for signals emerging from individual cases. Unanticipated events occurring during drug treatment might indeed reflect mere coincidence, but again they might not; and for many of the patients who suffered in consequence there was nothing in the least anecdotal about them.

Fortunately, the 1950s and 1960s of the 20th century saw the first positive reactions to the adverse reaction issue. Effective drug regulation emerged in one country after another. In 1952, Prof. Leo Meyler of The Netherlands produced his first "Side Effect of Drugs" to pull together data from the world literature. A number of national adverse reaction monitoring bureaux were established to gather data from the field and examine carefully reports of suspected side effects of medicines, creating the basis for the World Health Organization to establish its global reporting system. The pharmaceutical industry has increasingly realized its duty to collect and pass on the information that comes into its possession through its wide contacts with the health professions. Later years have seen the emergence, notably in Sweden and in Britain, of systems through which patients themselves can report possible adverse effects to the medicines they have taken. All these processes fit together in what the French language so appropriately terms "pharmacovigilance", with vigilance as the watchword for all concerned.

In this continuing development, the medical literature provides a resource with vast potential. The world is believed to have some 20 000 medical journals, of which a nuclear group of a thousand or so can be relied upon to publish reports and analyses of adverse effects—not only in the framework of formal investigations but also in letters, editorials, and reports of meetings large and small. Much of that information comprises not so much firm facts as emergent knowledge, based directly on experience in the field and calling urgently for attention. The book that Leo Meyler created has, in the course of fifteen editions and with the support of an ever-larger team of professionals, provided the means by which that attention can be mobilized. It has become the world's principal tool in bringing together, encyclopedically but critically, the evidence on the basis of which adverse drug effects and interactions can be recognized, discussed, and accommodated into medical practice. Together with its massive database and its complementary *Side Effects of Drugs Annuals*, it has evolved into a vital instrument in ensuring that drugs are used wisely and well and with due caution, in the light of all that is known about them. There is nothing else like it, nor need there be; across the world, *Meyler* has become a pillar of responsible medical care.

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Notes

1. Lichtenhaeler C. Histoire de la Médicine, Fayard, Paris, 1978:117.
2. Smith CM. Origin and uses of *Primum non nocere*. J Clin Pharmacol 2005;45:371–7.
3. Albrecht H. Primum nil nocere. Die Zeit, 6 April, 2005.
4. Notably in a book by Inman T. *Foundation for a New Theory and Practice of Medicine*. London, 1860.
5. I am indebted to Jeffrey Aronson for his own translation of the Greek original from Hippocrates *Epidemics*, Book I, Section XI, which seems to convey the meaning of the original [ἀσκεῖν περὶ τὰ νοσημάτα δῦο, ὠφελειν ἢ μὴ βλάπτειν] rather better than the published translations of his work.