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Personalities

Leopold Meyler (1903–1973): A pioneer in the study of adverse effects of drugs *

In 1951, more than a decade before the first rumblings of the *thalidomide* catastrophe, a remarkable book appeared in The Netherlands under the authorship of Leopold Meyler, that a year later appeared in English translation as "*Side Effect of Drugs*". At that moment the book was unique in the world — and that is still the case. The concept underlying it was that physician and pharmacist alike should be provided with an overview of all that was known regarding the possible adverse effects of medicines. The need to make existing information widely available remains, even today, a major challenge in the world of pharmacovigilance [1].

Following Meyler's book, others appeared in various languages, several adopting different approaches to the topic. One after another, most of them have vanished; Davis' *Textbook of Adverse Reactions* is a creditable exception, providing an approach to the topic which complements that of the *Meyler* series. In the meanwhile, Meyler's volume, greatly expanded and updated, is still with us and has long been acknowledged as the standard work on the unwanted effects of medicines. The name of the original

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author has become incorporated into the title: and 'Meyler's Side Effects of Drugs' is commonly known to the user simply as "Meyler".

A little over forty years ago, medical interest in drugs – and particularly new drugs – was limited almost entirely to their proven or possible therapeutic benefits. In retrospect, it is fair to say that it was the paper published by McBride in the Lancet of December 16th 1961 which triggered a broadening of that view [2]. His paper, alongside simultaneous observations from Germany, provided the principal clues leading to the realization that there was a link between the use of the hypnotic *thalidomide* and the fact that a great many children were coming into the world with congenital defects [3].

It had of course been realized for a long time that medicines could exert adverse effects. As early as 1779, Prof. Wouter van Doeveren of the University of Leiden, The Netherlands, delivered a public oration entitled *Remedio morbi*, with as subtitle: "Drug diseases, or diseases persons often obtain as a result of medicines they received as a treatment". His conclusion, recorded more than two centuries ago was: "Do not give a drug too readily, with the risk that you may add a second disease to the first, or accelerate the patient's' decease"[4].

Nevertheless, and as late as the mid twentieth century, physicians continued to be primarily concerned with the positive rather than the negative aspects of medicinal treatment, a unilateral interest promoted ever more with the arrival of new drugs which opened therapeutic perspectives hitherto out of reach, such as the effective treatment of tuberculosis. Interest in the side effects which might accompany the use of these new agents remained sporadic [5].

Only with the thalidomide disaster were the medical profession and the public throughout the world alerted acutely to the need both to examine the safety of new medicines critically prior to their admission to the market, and to study systematically their emergent adverse effects once they had come into use. The UK "yellow card" system for the reporting of suspect adverse effects came into being in 1964, and in 1968 W.H.O. set up a pilot project for international collaboration in the monitoring of adverse drug reactions. The latter was to become what is now the W.H.O. Drug Monitoring Programme, that in October 2002 held its 25th Annual Meeting in Amsterdam.

Who was Leopold Meyler, and what inspired him to create this book at the beginning of the fifties?

Meyler was born just a century ago in Rotterdam, where his father was an oil merchant of Jewish extraction. The young Meyler studied medicine at the University of Leiden and went on to specialize in internal medicine. After his qualification he joined the Medical Clinic of the University of Groningen and set up in practice. The ensuing war and the Nazi occupation of The Netherlands were a difficult period for the family. Meyler himself had to go into hiding but his wife, whose mother was not Jewish, was periodically able to visit him. At the time of the liberation, however, Meyler was found to be suffering from pulmonary tuberculosis which he had already acquired before the occupation but which may well have been aggravated by the conditions under which he had been obliged to live. He was admitted to a sanatorium and prescribed a prolonged period of rest. However, enforced rest and inactivity were not in the nature of an active and committed physician such as Meyler. It was then that the specialist treating him suggested a productive task which he could undertake from his bed: let him undertake a literature study of the side effects of drugs.

There was a particular reason for the choice of topic, for Meyler himself had already encountered the problem of adverse effects. To quote the first Dutch edition of his book in 1951: "The notion of bringing together the disagreeable effects which can be associated with the use of medicines was inspired by personal experience, in part of a very serious nature". In his book he describes in detail the experiences of patients such as himself treated with para-aminosalicylic acid (PAS), including the occurrence of fever in individuals with an allergic constitution. It is known that Meyler himself was allergic and suffered

from asthma [6]. In a later *Supplement* to his book he described the serious psychic effects which can be exerted by isonicotinic acid hydrazide (INH).

In order to examine the literature from his hospital bed, Meyler enlisted the help of the library of the University of Groningen. Every week a suitcase full of journals and books was delivered to him, which he was obliged to return within a few days. The arrangement was continued after his return home. And so it was that the first version of his book appeared in 1951 in Dutch, followed by the English version a year later.

Not surprisingly, the unusual approach manifested in the book elicited criticism in some quarters, and his motives were questioned. There were those who imagined that he was in principle opposed to the use of medicines, and some alternative healers even viewed him as an ally in questioning the orthodox practice of medicine. Others criticised the manner in which he had classified drugs. Meyler, however, continued assiduously to gather his evidence and relevant case reports. Supplements were published to bring the original volume up to date, and his introductory editorials provided an answer to his critics, stressing that he sought only to promote the appropriate and safe use of drugs. Behind the scenes, his books were founded in an encyclopaedic venture into the acquisition of hitherto scattered knowledge, carried through in a period where there were no computers or photocopying machines. Instead, he relied on his hand-written notes and a voluminous card system.

Meyler was a remarkable individual, characterized by firm opinions, a critical approach to information and an independence of spirit. He was also a man with a broad interest and an open mind. Above all, he remained a highly competent practising physician with a deep devotion to the interests of his patients. His independence was such that he would not attend meetings sponsored by the drug industry; if invited as a speaker he would insist on paying his own expenses.

His work was formally recognized with his appointment in 1969 as the first professor of Clinical Pharmacology at the University of Groningen. His inaugural oration was entitled “Why clinical pharmacology?” and in it he provides an overview of the tasks which the clinical pharmacologist is called upon to fulfil [7]. Not surprisingly, his paper devotes attention to adverse reactions: “The study of side effects is of the greatest importance. Increasingly the need is felt to understand more exactly how side effects come about, and to devise wherever possible means by which these unwanted complications can be avoided”. The definition of a field of medical science which was new to The Netherlands was a task to which Meyler was well suited. He published in many journals and became a sought-after speaker at meetings both at home and abroad. The Boerhaave courses at the University of Leiden, for which he was in part responsible, led to the publication of a series of complementary volumes under the title *Drug Induced Diseases*, each dealing with a particular aspect of drug toxicology. Re-reading his publications today, one is struck by his extraordinary knowledge and erudition but also by the fact that so many of his views remain entirely valid in our time.

Meyler died suddenly during a vacation in France in 1973, possibly as a consequence of an overdose of adrenaline which he had taken because of his pulmonary disorder. As Lammers wrote in an *In Memoriam* in Holland’s *Nederlands Tijdschrift voor Geneeskunde*: “One can truly say that he was among the very first to have realized how frequently drugs can be the cause of otherwise unexplained disorders. In our time, that realization has become so commonplace and so self-evident that one can hardly imagine how, in the recent past, the subject was barely the subject of enquiry” [8].

Leopold Meyler’s *opus magnum*, *Side Effects of Drugs*, evolved from the first edition onwards, as a multi-author volume with a distinguished team of contributors. Up to the seventh edition in 1972, Meyler himself was Editor-in-Chief, latterly supported by Prof. Andrew Herxheimer in London. From 1973 to 2000 the volume was edited by Graham Dukes and the series will from 2004 onwards be continued

by Jeff Aronson in Oxford, its co-editor for the last decade. Many tens of authors from all parts of the world have made their contributions to "Meyler", which continues to provide practising physicians and pharmacists with a critical review of new data from the scientific literature relating to adverse drug reactions. Yet there are today few who realize that the name "Meyler" on the cover is that of a doctor lying in a sanatorium, looking for something useful to occupy his mind. Meyler laid the foundations for a systematic approach to the problems of side effects. In his own time his was at first a voice crying in the wilderness. Had that voice been heeded earlier, the extent of the thalidomide disaster might well have been much more limited. Even today, with a worldwide system in place for the detection and study of adverse drug reactions, an Editorial in *The Lancet* has rightly raised the question as to how that process can be further refined and extended [9]. As Meyler himself wrote in the forward to his first volume: "Let us be entirely clear that it is not our purpose to discourage the use of any of the drugs in our therapeutic arsenal. The reverse is the case. One will be in a position to use a medicine better if one is aware not only of its benefits, but also of its risks".

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