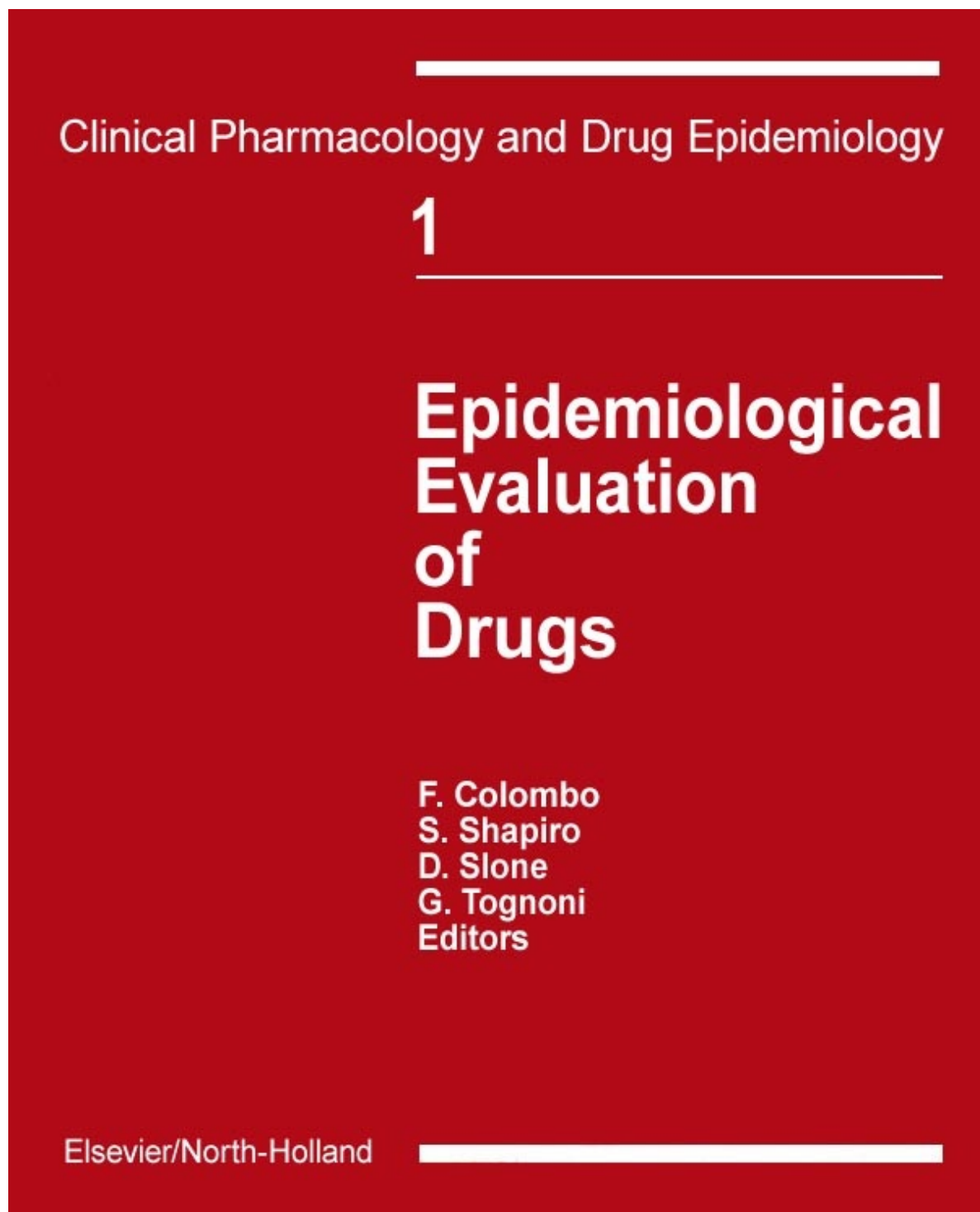


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**Title pages**

# EPIDEMIOLOGICAL EVALUATION OF DRUGS

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Proceedings of the International Symposium on Epidemiological Evaluation of Drugs held in Milan, Italy, 2-4 May, 1977. Organized jointly by the Istituto di Ricerche Farmacologiche Mario Negri and by the Drug Epidemiology Unit, Boston University Medical Center.

## *Editors:*

F. Colombo  
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## PREFACE

The contents of this book represent the proceedings of a Symposium that took place under the joint sponsorship of the Mario Negri Institute of Milan and the Drug Epidemiology Unit of the Boston University Medical Center.

In recent years substantial advances have been achieved by epidemiologists in evaluating drug effects. However, despite these advances, recent experiences with drugs such as practolol (which, after it was believed to be safe, was found to cause serious ocular, peritoneal and other lesions) have indicated that a great deal more needs to be achieved before it will be reasonable to claim that drugs are under adequate surveillance. Thus the Symposium was timely; it was convened both to review what had been accomplished and to consider the future directions in which research might proceed. It was also timely from another point of view in that it immediately preceded a Workshop convened by the European Economic Community to consider issues related to drug monitoring in Europe. Professor H.J. Jesdinsky, who was the organizing Chairman of the Workshop, believed that the Symposium would provide a background which would facilitate the deliberations of the Workshop. In the event, this was the case. At the Symposium there was a stimulating and lively exchange of ideas - ideas that we believe should be shared with others and it is in this belief that the papers and discussions\* are presented in this volume.

The Editors.

### Acknowledgements

We wish to express our particular thanks to those who helped make the Symposium possible:

The Commission for Medical Research and Public Health of the European Economic Community, for sponsorship and support given to the Workshop, whose participants also greatly contributed to the Seminar;

The Department of Health of the Regione Lombardia, for its interest and contribution;

Prof. S. Garattini, Director of the Mario Negri Institute, whose hospitality was greatly appreciated.

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\* Unfortunately, due to technical difficulties, a few of the discussions could not be transcribed, and are not presented in this volume.

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## C O N C L U S I O N S

Richard Doll  
University of Oxford, England

It is only two days ago that dr. Schneiderman warned us in graphic terms, of the danger of saying that anything was generally agreed. But every rule has its exception. I am confident that there will be general agreement that this conference, organized jointly by the Mario Negri Institute for Pharmacological Research and the Boston University Drug Epidemiology Unit has been a resounding success. The data presented have been of a uniformly high scientific standard, the issues discussed have been important and difficult of solution and most unusually the participants have demonstrated a community of purpose and a degree of mutual understanding which, in my experience, is uncommon in a scientific gathering. Nevertheless the problems that we have been trying to tackle are so difficult, and the facilities for tackling them vary so greatly from country to country, that some of us may have drawn quite different conclusions; and I am conscious that those that I am putting forward may be more idiosyncratic than representative.

First, it seems to me, that the greatest problem is not so much the recognition of adverse reactions, as the education of the medical profession to use drugs appropriately. A risk of an adverse reaction, even quite a serious one, may be acceptable if the patient has a reasonable chance of benefitting from the drug; but, even a small risk is unacceptable if the drug is given inappropriately - and we have only too much evidence that potentially dangerous drugs were being given to millions of people when other less dangerous drugs, or no drugs at all, would have been equally efficacious. How this problem can be dealt with is beyond the scope of this meeting, but I believe myself that one of the most promising lines of attack is the creation of a strong department of clinical pharmacology in every medical school.

Secondly, I have been impressed once again by the extraordinary difference in the use of drugs in different countries. This may be just another reflection of the need for better medical education; but I wonder if we are doing enough to find out whether one country is providing less efficient treatment, or whether the differences are just a matter of fashion which is immaterial because all the drugs are equally efficacious - or inefficacious, as the case may be.

Thirdly, there is a need for a great deal more research to determine the conditions that will enable us to extrapolate confidently from the results of animal experiments to the treatment of man. Interest in this field has been reviewed recently by the development of quick in vitro tests for mutagenicity and

there is increasing reason to believe that it may eventually be possible to calibrate the results of such tests so that carcinogenic effects on man can be predicted both qualitatively and quantitatively. This, however, lies many years ahead. Meanwhile we now face the danger that these tests will be used before we have learnt how to interpret them, to prevent valuable drugs like isoniazid even being tested in practice.

Fourthly, no amount of post-marketing surveillance can compare in value with the large-scale controlled trial carried out before the drug is released for general use, which has the inestimable advantage of quantifying benefits as well as risks. That such trials ought to be carried out much more often than they are is clear. It has to be admitted, however, that there are great difficulties in organizing trials that require large numbers of patients to be observed over long periods and it would be quite impracticable to demand, as a matter of routine, trials that could be both big enough and of long enough duration to answer many of the questions that have been raised during the course of the conference .

Some form of post-marketing surveillance is, therefore, essential ; but what should it be ?

First, experience has shown that systems of voluntary reporting can provide only a background which stimulates the interest of the profession, constitute sources of data for special investigation by other methods, and occasionally - but only very occasionally - provide the first indication of an unsuspected hazard.

Much more work needs to be done to discover how to fine them down, so that they do not result in the collection of thousands of reports of well-known or trivial reactions which cannot be examined in detail, but yet encourage the reporting of events that are not already under suspicion as attributable to drug use. Systems of voluntary reporting should be encouraged; but we delude ourselves if we think that they can ever provide a complete solution to the problem of post-marketing surveillance .

Secondly, the systems that have emanated from Boston - the initial system of intensive hospital monitoring and the new system of relatively non-specific case-control enquiry - have made, or promise to make, valuable contributions: but neither meet all our requirements. I am particularly impressed by the argument that the new system will provide a mechanism by which specific case-control studies can be organized quickly ; but whether that will prove to be its most important contribution is for the future to show. Meanwhile its evolution will be watched by many of us with considerable interest .

Thirdly, the case-control study planned to meet specific conditions will remain the principal method of investigating difficult problems, as it has been in the past. There is no need to apologize for it at a meeting of scientists. I do not propose to do so now. The fact that it has been so violently attacked by

individuals who are interested for emotional or other reasons in discounting some of the results of such studies confirms, if confirmation were needed, that it is often the only method available for demonstrating a relationship before the adoption of the crucial test of removing the agent and seeing if the effect disappears. That it has led to false conclusions either by chance or because of incorrect interpretation, is no reason for condemning the method. What experimental method hasn't? The important point is that it has often led to right conclusion which have been validated by successful elimination of the hazard. We must recognize, however, that it has its limitations and can be used successfully only when exposure can be recalled reliably or determined objectively from existing records.

Fourthly, with all these methods we are still left with as many gaps in our defences as bastions. They can be closed, in my opinion, only by a system in which the fact of drug prescription is recorded (I assume compliance), the patient is identified, and the records of treatment are linked with the patient's subsequent medical history. How this can be achieved is likely to vary from country to country, depending on the way that medical services are provided, and it will certainly be easier in some countries than in others. How such a system can be organized has not been the subject of the present conference and it would be inappropriate to elaborate on it. Our conference, however, has pointed clearly to the conclusion that some such system is needed.

I began, Mr. Chairman, by stating a conclusion that I was confident represented the views of everybody who had attended this conference and I went on to say that the rest of the conclusions were my own. I would like to end on the same note with conclusions that are respectively personal and representative of all the participants. The personal conclusion is that if governments are going to involve themselves so directly in determining the conditions under which new drugs are introduced, they should also accept a share of the blame if things go wrong. Power without responsibility is always dangerous and I see no reason why the licensing of drugs should be an exception. Perhaps, if this were so, we might hope to see a general appreciation of the rule that lawyers who sue for compensation should be paid only a statutory fee that is unrelated to the size of the compensation secured.

The representative conclusion refers to the report that the World Health Organization is likely to have less interest in the problems of drug evaluation than it had in the past. This, if true, would be sad indeed as there are few aspects of medicine which have greater need for international collaboration than the assessment of drug effects and the publicizing of reliable information about them. Let us, therefore, join in sending a message to the World Health Organization assuring it of the value of the work which it has done in the past and expressing the hope that it will continue to give much needed leadership in this field in the future.