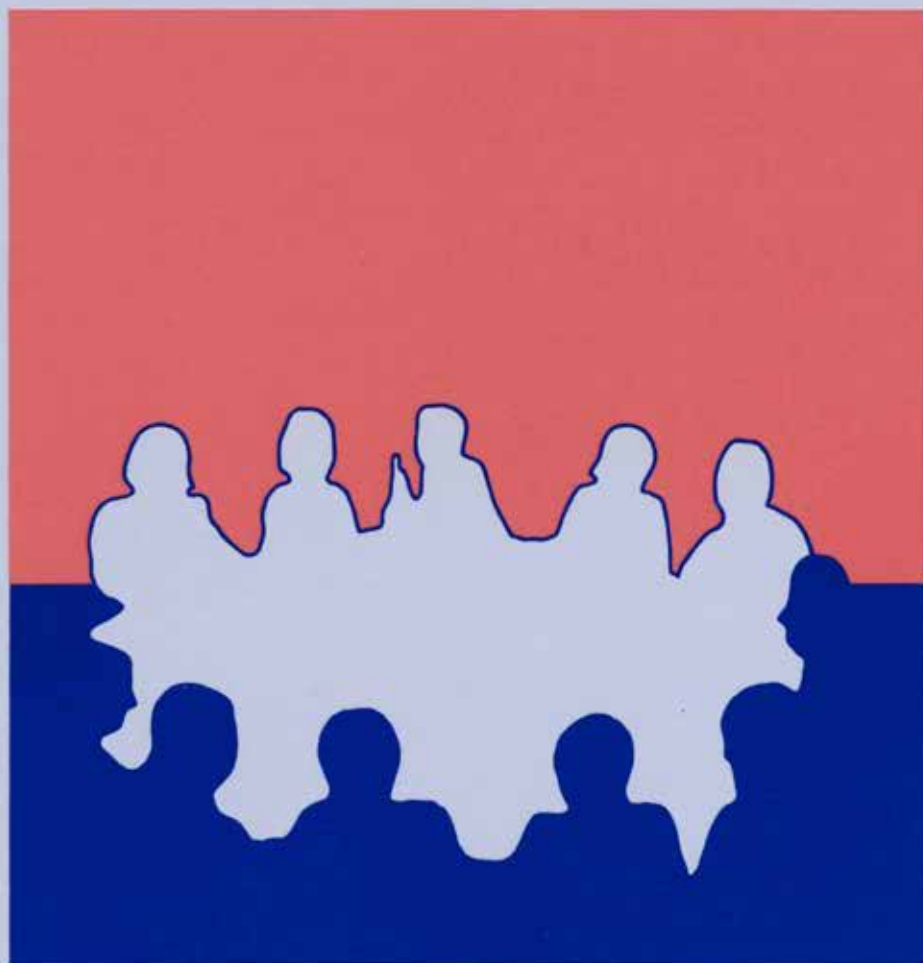


DRUG SURVEILLANCE: INTERNATIONAL COOPERATION PAST, PRESENT AND FUTURE

Proceedings of the XXVIIth CIOMS Conference
Geneva, Switzerland
14-15 September 1993

Edited by Z. Bankowski and J.F. Dunne



DRUG SURVEILLANCE: INTERNATIONAL COOPERATION PAST, PRESENT AND FUTURE

Proceedings of the XXVIIth CIOMS Conference
Geneva, Switzerland
14-15 September 1993

Organized for the 25th Anniversary of
the World Health Organization's Programme for
International Drug Monitoring

Edited by Z. Bankowski and J.F. Dunne



Geneva
1994

CONFERENCE PROGRAMME COMMITTEE

Bankowski, Z. Secretary-General, Council for International Organizations of Medical Sciences (CIOMS), Geneva, Switzerland

Bryant, J.H. Chairman, CIOMS Standing Committee on Health Policy, Ethics and Human Values — An International Dialogue, Moscow, Vermont, U.S.A.; Chairman of Conference.

Dunne, J.F. Director, Division of Drug Management and Policies, World Health Organization, Geneva, Switzerland

Edwards, I.R. Director, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

ten Ham, M. Chief, Drug Safety, World Health Organization, Geneva, Switzerland

Venulet, J. CIOMS Consultant, Former Chief, WHO International Drug Monitoring Programme, Geneva, Switzerland

TABLE OF CONTENTS

ACKNOWLEDGEMENTS	vi
INTRODUCTION	vii
OPENING OF THE CONFERENCE	
F. Vilardell , Outgoing President, CIOMS	1
J. H. Bryant , Incoming President, CIOMS	1
WELCOME ADDRESS	
F. S. Antezana , Assistant Director-General, WHO	1
OPENING REMARKS	
J. H. Bryant	3
KEYNOTE ADDRESS	
Sir William Asscher	5
SESSION I: 25 Years of International Drug Surveillance	
The WHO Drug Monitoring Programme:	
The Formative Years (1968-1975)	
J. Venulet	13
The WHO Drug Monitoring Programme:	
Current Activities	
I. R. Edwards	22
Future Prospects of International Surveillance	
of Drug Reactions	
F. Sjöqvist	28
The Broader Perspective	
M. D. Rawlins	34
What Has Been Achieved?	
Panel Discussion	
J.F. Dunne , Chairman	38
SESSION II: Methodological Approaches:	
Contribution to Drug Surveillance	
Spontaneous Reporting	
R.-J. Royer	61

Case-Control Studies S. Shapiro	67
The Contribution of Controlled Clinical Trials to Drug Safety M.J.S. Langman	73
Adverse Drug Reactions: Causality Assessment J. Venulet	82
SESSION III: Harmonization of Reporting and Terminologies of Adverse Drug Reactions	
Introduction R. D. Mann	91
Towards a Dictionary of Adverse Drug Reactions, or Should Existing Terminologies be Harmonized? C. Bénichou	95
The Three CIOMS Working Groups on Drug Safety W. M. Castle and D. Chen	99
The International Conference on Harmonization: Expediting Reporting of Adverse Drug Reactions A. J. Gordon	109
Standardization of Adverse Experience Terminology R. Herman	115
SESSION IV: Challenges for Drug Surveillance	
Drug Surveillance and Educational Challenges M. Thomas	121
Needs in Developing Countries: Current State of Antimalarial Drug Resistance N. J. White	126
Needs in Developing Countries: Onchocerciasis and Surveillance for Resistance to Ivermectin K. Awadzi	136
Needs in Developing Countries: Surveillance of Resistance to Anti-Tuberculosis Drugs P. Nunn and M. Felten	141
Monitoring the Safety of Biological Products S. S. Ellenberg	148
New Approaches to Pharmacovigilance and Alternative Strategies B.-E. Wiholm	152

SESSION V: Access to Information: Patients and Communities

Introduction	
R. J. Levine	159
Legal Aspects of Access to Information on Drug Reactions	
B. M. Dickens	161
The Paradox of Widely Available and Restricted Information	
J. K. Jones	174
Access to Patient Information	
C. Medawar	176
The Use of Anonymized Patient Data	
N. Taylor	180
Drug Safety Measures and Public Release of Drug-Product Information in Japan	
O. Doi	183
The French Information Programme	
R.-J. Royer	187
CLOSING OF THE CONFERENCE	189
LIST OF PARTICIPANTS	191

ACKNOWLEDGEMENTS

The Council for International Organizations of Medical Sciences (CIOMS) gratefully acknowledges the support of the World Health Organization in the planning and conduct of the Conference. Dr. J. F. Dunne, Director of the Division of Drug Management and Policies, and Dr M. ten Ham, Chief, Drug Safety, of the same Division, made invaluable contributions. CIOMS is much indebted also to the WHO Collaborating Centre for International Drug Monitoring, at Uppsala, Sweden, and its Director, Dr I. R. Edwards, for its valued cooperation.

Dr Jan Venulet's considerable effort in planning and rallying support for the Conference is highly appreciated.

CIOMS acknowledges also, with much appreciation, the financial support of the Ministry of Health and Welfare of the Government of Japan to the Conference and the publication of its proceedings; and the generous donations of the following pharmaceutical companies: Bayer, Wuppertal, Germany; Hoechst, Frankfurt-am-Main, Germany; INTERPHARMA, Basel, Switzerland; Rhône-Poulenc Rorer S.A., Antony, France; Roussel Uclaf, Paris, France; and Sanofi Recherche, Gentilly, France; and of the Sandoz Foundation, New York, U.S.A.

We thank Professor J.H. Bryant for his able chairmanship of the Conference, and the authors of the conference papers, as well as the chairpersons and members of the panels, and the other discussants.

Special thanks go to Dr. J. Gallagher for his help in editing the conference proceedings; and to the administrative and secretarial staff — Mrs. K. Chalaby-Amsler and Mrs. C. Dübendorfer of CIOMS, and Mrs. C. Encrenaz of the WHO Division of Drug Management and Policies — for their help before and during the Conference, and in the preparation for publication of these proceedings.

INTRODUCTION

In the early 1980s, in close collaboration with the World Health Organization (WHO), the Council for International Organizations of Medical Sciences (CIOMS) launched its programme on Drug Development and Use — Medical, Social and Economic Implications. The stimulus for this joint programme was a conference, convened in 1977, on Trends and Prospects in Drug Research and Development. The conference recognized that CIOMS, as an independent organization, was well placed to bring policy-makers of research-based pharmaceutical industries into discussion with their counterparts in government and academia, and to convene groups of experts from these constituencies to make recommendations on specific issues. Since then, in collaboration with WHO, CIOMS has undertaken a variety of projects of direct concern to manufacturers and prescribers of drugs. For some years, the emphasis of CIOMS activities in relation to drugs has been on the monitoring of drug safety and the reporting of adverse drug reactions; this has resulted in a series of publications on the monitoring and assessment of adverse drug effects, international reporting of adverse drug reactions, and standardized procedures for periodic safety-updating of drugs.

In 1988 the WHO Collaborating Centre for Drug Monitoring, at Uppsala, Sweden, held a symposium on “Adverse Drug Reactions — a global perspective on signal generation and analysis”. This technical meeting drew attention to many of the issues in drug-safety monitoring at the 20th anniversary of the WHO International Drug Monitoring Programme. Up to that time the work of the Programme had been mainly to support the work of the national agencies which were Programme members. This CIOMS Conference heralded a much wider perspective for the Programme, particularly because of comments from academics, pharmaceutical manufacturers and consumer advocates.

The subject of the XXVIIth CIOMS Round-Table Conference, the history and future of international cooperation in drug monitoring, is timely because of a resurgence of interest in this scientifically challenging area.

Quality, efficacy and safety are the three criteria which determine the acceptability of drugs for public use. Much attention is given to safety before a drug is registered, but, unlike the evaluation of quality and efficacy, *in vitro* studies and animal and controlled human exposure give only a limited picture of safety in general clinical use.

After the limitations of these safety measures were emphasized by the thalidomide tragedy, WHO set up a programme to coordinate the surveillance efforts of national drug regulatory bodies, including the pooling of case data and the production of collated and summarized outputs — now done at the Collaborating Centre at Uppsala — for the use of national regulatory agencies. Having started with a few

developed countries primarily using data for regulatory support, the programme currently involves over 40 countries in a network of activity. The computer network allows experts easy access to one another and to international case data; cooperative review of international data has resulted in the recognition of new adverse-drug-reaction signals. New initiatives on signal analysis using drug-use data, and the examination of international differences in adverse-drug-reaction reporting, are two of the developments of the last five years. CIOMS has complemented the work of the Programme by bringing together drug regulators and representatives of the pharmaceutical industry to harmonize terminology and definitions, and to explore new areas such as periodic drug-safety data-sheets and safety aspects of drug package inserts.

Now there are new challenges and opportunities in drug safety. New drugs are introduced rapidly into the international markets and new biotechnology produces drugs that influence body processes ever more profoundly. The promise is that more selectivity of action will make them safer, but this has to be proven, particularly when therapy may be lifelong. New techniques in pharmacoepidemiology make it possible to determine more clearly the mechanisms of adverse drug reactions and may yield information important for the better use of drugs.

With these examples alone it is easy to see that the cooperative effort begun 25 years ago is still valid, if drug-safety problems are to be identified and investigated as rapidly as possible, thus giving patients throughout the world the optimal balance of benefit to risk from their treatment, at the most reasonable cost.

Zbigniew Bankowski
Secretary-General, CIOMS

OPENING OF THE CONFERENCE

Professor Francisco Vilardell

Outgoing President, CIOMS

I was President of CIOMS until yesterday afternoon, when I was succeeded by Professor Bryant. However, it gives me much pleasure to greet you and welcome you to the CIOMS meeting, and to greet Dr Antezana, Assistant Director-General of WHO, who is representing the Director-General. Most particularly, I wish to greet Professor Bryant himself, who is chairing this conference, and whose election to the Presidency of CIOMS has pleased me greatly.

Dr John H. Bryant

Incoming President, CIOMS

Thank you very much, Professor Vilardell. Let me join in his welcome to all you. May I introduce Dr Fernando Antezana, who is an Assistant-Director-General of the World Health Organization. He is experienced in the field of drugs and essential drugs, and their general uses around the world. We now invite him to speak on behalf of Dr Nakajima, Director-General of WHO.

Dr Fernando S. Antezana

Assistant Director-General, World Health Organization

It is both a pleasure and a privilege for me to welcome you on behalf of the Director-General of the World Health Organization, Dr Hiroshi Nakajima, to the Twenty-seventh Round Table Conference of the Council for International Organizations of Medical Sciences. WHO and UNESCO were the founding fathers of CIOMS, in 1949. Among its objectives are "to promote international activities in the field of medical sciences whenever the participation of several international associations and national institutions adhering to the Council is deemed necessary; and to serve the scientific interests of the international biomedical community in general".

Over the years the Council has developed as an influential forum for discussion of bioethical topics and I am pleased to have this opportunity to place on record the appreciation of the Director-General and his staff of the support that CIOMS has offered on many occasions to the work and objectives of WHO. All of us here are indebted to Professor Vilardell and the Executive Council of CIOMS and, of course, to the unstinting efforts of Dr Bankowski, its Secretary-General. Over the many years that we have worked with him, he has come to epitomize the spirit of CIOMS. In recent times —

notwithstanding the vicissitudes brought about by global economic depression — he has maintained and progressively broadened the scope of CIOMS collaboration with WHO.

One of his major initiatives was to launch, in the early 1980s, in collaboration with WHO's Division of Drug Policies and Management, an open-ended programme of activities on Drug Development and Use — Medical, Social and Economic Implications. The stimulus for this was a conference, convened in this room in 1977, on Trends and Prospects in Drug Research and Development. Since then, in collaboration with WHO, CIOMS has undertaken various projects of direct concern to manufacturers and prescribers of drugs, which have resulted in a series of publications on the monitoring and assessment of adverse drug effects, international reporting of adverse drug reactions, and standardized procedures for periodic safety-updating of drug products.

The conference that is about to take place offers a valuable opportunity to review what has been achieved within this programme of work. At the same time, of course, it provides an occasion to mark the 25th anniversary of WHO's own Programme on International Drug Monitoring and perhaps to signpost some options for its future development. Not least, it provides the occasion to acknowledge the vital operative role of the WHO Collaborating Centre on International Drug Monitoring, located since 1978 at Uppsala, Sweden, where it has been maintained with the generous support of the Swedish Government.

But the focus of this conference is of course one of the most important and ubiquitous public-health challenges facing governments and health professionals in the developed and developing world: how can the performance of drugs in routine use be best assessed in terms of benefit and risk and of cost-effectiveness? Without the data on which to make the necessary comparative assessments, how can we meaningfully define efficient and effective drug use? Indeed, how can we coherently discuss the rational use of drugs?

The only feasible approach to such a daunting task is surely through broad interdisciplinary collaboration, international cooperation, and timely exchange of information. It is evident from the interest already evoked in this meeting, and from the calibre of the participants, that CIOMS is well placed to bring policy-makers within research-based pharmaceutical companies into discussion with their counterparts in government and academia. We in WHO expect much of this exchange and we wish everyone, and particularly your Chairman, Professor John Bryant, every success over the next two days.

Dr John H. Bryant

Chairman of the Conference

Thank you very much, Dr Antezana, for your comments and those of the Director-General. It is an immense pleasure to be present at this conference, which marks 25 years of WHO's involvement in the surveillance of adverse drug reactions. The excellent preparatory material and the participation of some outstanding people in the field are in keeping with the high importance of the subject. What I find particularly interesting are the nature of the field and the dynamics of its change, and how these fit into the pattern of international development. We have seen the careful beginning and then the accelerating maturation of this field of science. There are the biological events — the adverse drug reactions, and the developing science-based methods for dealing with them. These phenomena in turn are embedded in the complexities of the global society — the growing population density with the inherent crowding and the importance of this for communicable diseases; the indiscriminate use of drugs in many places; and the complexities, the commercialization of products, which marketing and uses bring to the picture; the inherent capacities of infectious organisms to develop resistance to antimicrobials and even their genetic capacities to transfer resistance, which gives them an apparently unlimited potential to escape effective management. Then, we have this network of concerned organizations, scientists, corporations and the public, with a global determination to respond to these challenges. Of course there is not a fixed target that represents any kind of an end-point in this field. Clearly it will be continually evolving, the frontiers endless.

The field has its peculiarities. There are some traps that could be diversions to progress — for example, complacency about the capacity to respond to the need for new products so as to match the evolving needs. There is occasionally bias and naivety in the use of science. There are conflicts of interest — they are inevitable: the involvement of manufacturers in post-marketing surveillance, manufacturers' support of cost-effective studies, the sharing of access to large data-sets. Our background papers describe how each of these contains some inherent conflict of interests. It is particularly interesting that the response to those areas of conflict has been not to avoid them but rather to decide to live with them and contain them. These are other words for growing trust among the partners in this important field.

Then there are the special strengths of epidemiology and the new field of pharmaco-epidemiology, and of the evolving capacity for managing very large data-sets. These two particular areas of science development are crucial to handling the challenges in this field.

So here we see an intriguing interweaving of science and society, where its emergence and maturation are within easy memory of most of us here. Now against this background we can see the importance of the

commitment of WHO, including the Collaborating Centre for International Drug Monitoring, at Uppsala, of CIOMS and the industry, the regulatory authorities, the universities, and those, including public advocates, with a general concern for the impact of this field on the wellbeing of the public.

We are not here only to celebrate these 25 years; we are here to learn and probe, and our purpose is to review the past, to consider the present, to try to understand the future. Our agenda is designed to accomplish this and our speakers are ready to carry us in that direction. With that I would like to proceed with the next item of the agenda and introduce Sir William Asscher who will deliver the keynote address of the Conference.

KEYNOTE ADDRESS

Sir William Asscher

Principal, St. George's Hospital Medical School, University of London, England.

Keynote addresses pose particular hazards. If you don't strike the right key all the notes may be wrong and I am not too sure that I have got the right key for this meeting. One thing I could do which would certainly strike the right note would be to congratulate the international drug monitoring programme on its 25th anniversary. I know you have made a very considerable contribution. Your data bases have frequently been of use to us in the United Kingdom when evaluating drug scares, and we are deeply grateful to you for creating such an excellent data base. May your international drug monitoring programme flourish for many years to come.

I am not usually given to looking backwards, so I thought the best topic I could choose today was to point out some steps by which we might achieve greater drug safety in the future, and that is the theme of this presentation. Before launching into it, I want to pay a compliment to both industry and regulatory bodies. You may, Professor Bryant, know a humorist called Mark Fisher, who said "half the modern drugs could well be thrown out of the window except that the birds might eat them". All of us in this room would agree that we could do with fewer drugs. It would lead to greater drug safety, as doctors would have greater familiarity with the use of a smaller number of remedies. Just as the best way to prevent disease is contraception, so the best way of obtaining greater drug safety is to use fewer drugs. The second part of Mark Fisher's statement suggests that drugs are inherently dangerous. This I take issue with. A Royal Society symposium in England some while ago considered the safety of drugs in relation to everyday diagnostic procedures that you and I might perform in our own wards. Take a liver biopsy, for instance. One might advise this for non life-threatening liver disease just to find out what's going on. The risk of death, even in experienced hands, associated with this procedure is 1 in 5,000 and I think that any chairman of a regulatory body would agree with me that any drug with such a high risk of mortality would only be used if the mortality from the disease it attempts to cure is extremely high. So there is reason to congratulate industry and regulators alike for making our drugs as safe as they are, but there is, of course, no reason for complacency either. Anything can always be improved. The first chairman of the Committee on Safety of Medicines (UK), Sir Derrick Dunlop, said "show me a drug that has no adverse effects and you are showing me a placebo". Even that was not true, for placebos also have adverse effects, but nevertheless it is a fact that adverse effects of drugs can never be eliminated altogether.

Now what then can be done to mitigate adverse effects of medicines? Before addressing this, let me examine the size of the problem. An extremely interesting publication from the Harvard Medical Practice Group, published in 1991, showed that the size of the problem in a highly developed country such as the USA is very considerable. Two physicians studied 30,195 hospital records from non-psychiatric acute hospitals in the State of New York; 3.7% of them showed evidence of disabling injury related to medical intervention. These medical interventions included the actions of physicians, surgeons and anaesthetists, as well as the direct adverse effects of drugs themselves. The single largest cause of these injuries in some 20% of the cases was the adverse effects of drugs. It was not so much the drugs themselves that caused the harm but the way in which they were being used. The conclusion one draws from the Harvard Medical Practice Study is that there are probably more dangerous doctors than dangerous drugs. Indeed, in a recent study Professor Charles George showed that half of all patients who take medicines do not do so in the correct manner. Thus there are difficulties in communication between doctor and patient, which represent an important and preventable source of harm done by drugs. The particular drugs involved in the adverse events noted in the Harvard Medical Practice Study were antibiotics, anti-tumour drugs, anticoagulants and cardiovascular drugs in that order of frequency. Psychiatric drugs do not figure highly, because psychiatric hospitals were excluded from the study. The systems that were involved were the bone marrow and central nervous system, in that ranking order.

One of the first questions we must address in order to minimize adverse effects of treatment is whether one needs treatment with a medicine at all. This may seem a stupid question to ask, but it is a very important one. My own experience of the problem goes back to the early 1960s when I worked with Professor Ed Kass, whom some of you here may remember. As a nephrologist I got extremely interested in his discovery that most patients with urinary tract infection were symptomless. He had in fact discovered a method of detecting symptomless infection by simply counting the number of micro-organisms in a fresh sample of urine. This can most readily be done in population studies by the use of a simple dip-slide. When organisms are present in numbers exceeding 100,000 per ml of urine it is very likely that this is indicative of infection. Such symptomless infections are indeed exceedingly common in populations throughout the world. The prevalence rate is age-related and, as one enters the geriatric age-group, up to 30% of patients in geriatric wards are found to have symptomless infection. Clearly the question that had to be asked was: "Could symptomatic urinary tract infection and kidney damage from urinary tract infection be prevented by treating these symptomless infections?". We and others did a series of prospective controlled studies of treating these covert infections and found that, in adult women who did not

have any obstruction of the urinary tract, treatment of the symptomless infection precipitated rather than prevented symptoms, because the re-infections with organisms different from those which were originally present were more commonly associated with the development of symptoms than the continuing infections in the untreated subjects. It was as if there was a kind of symbiosis between micro-organism and host which was disturbed by short-term treatment with antibacterials. What is more, we followed up all these adults with urinary tract infection to see whether their renal function deteriorated, but here again we drew a blank. The conclusion, therefore, after many years of study was that symptomless infection in the adult in the absence of obstruction was not worth treating with antimicrobial agents. It was only worth while screening and treating symptomless urinary tract infection in women who were pregnant and in children in whom the urinary tract infection was associated with vesico-ureteric reflux. In the former case, symptomatic infection in pregnancy can be prevented if the symptomless infection is treated; in the latter, scarring of the kidneys can be prevented if the urinary tract infection is treated on a long-term basis. Thus our experience of symptomless urinary tract infection in adults shows that before one advises screening for symptomless conditions one must satisfy the criteria of Jungner and Wilson, laid down in 1977. They are: (a) that the condition sought for must be an important public health hazard; (b) that there is a latent phase of the condition that can be detected by a simple, reliable test; (c) that the natural history of the condition is understood, that there is a beneficial response to treatment, and that facilities for follow-up and treatment are available; and lastly, (d) that the cost of screening and treatment is economically balanced against the cost of health care as a whole. Unless these criteria are satisfied there is no point in treating symptomless conditions. Lest you feel that I have chosen a somewhat esoteric example in covert bacteriuria, let me remind you that there are many other examples. What of the need to treat a raised serum-cholesterol with expensive agents that reduce cholesterol and that have their own adverse effects? Many other examples could be given. What's more, no doubt Dr White will be telling us that there are many ways in which public health measures, for instance, can be better than drug therapy, as in the case of diarrhoeal diseases, where rehydration instead of antimicrobial agents is the more important measure; and as in the cases of schistosomiasis and malaria, where public health measures are of greater importance than drugs in reducing morbidity and mortality.

Next I wish to turn to the value of preclinical tests in forecasting adverse reactions rather better than they do at present. Let's first of all look at the correlates between preclinical tests and human toxicity. There are all sorts of permutations and combinations here. The worst is where animal tests do not reveal any toxicity and human use throws up a problem — a so-called false negative. There are many reasons for such false-negative results, not least the fact that animal tests are

performed on small numbers of animals that may have a different metabolism of the drug in question, that the animals are always inbred, and that there may be masking of adverse reactions which occur late in administration of the drug. Two suggestions may be helpful to make preclinical toxicity testing more worthwhile. The first is that in the archives of the pharmaceutical industry there are a very large number of data regarding animal toxicity studies. If only there were greater "glasnost" it would be possible to obtain some very valuable information regarding animal-toxicity testing from the experiences of the industry with substances that never reached the market and may have been dropped during initial volunteer studies. Some of you may have read the excellent book produced by Professors Lawrence, McLean and Weatherall. In this monograph, six companies had disclosed their data on toxicity testing of drugs, some of which never came on the market. Much was learned from that study and I commend the book to you. The second point I wanted to make about preclinical testing concerns harmonization. No less than three international conferences, in Brussels, Orlando and Tokyo, have taken place and some around this table have no doubt participated. Such conferences on harmonization are good news for rapid licensing, but not so for toxicology. The reason why I say this is simply that, if you have too many guidelines and too many directives, people will begin to behave like automatons, and toxicology may become like painting by numbers. What is needed is tailor-made toxicology. There needs to be a much more physiological approach to toxicological studies to make them more relevant to the particular use that the substance is going to have in human medicine.

I would now like to turn to the third way in which I believe we may be able to improve the safety profile of drugs, namely the question of whether clinical trials can be made to reveal ADRs better. My answer to this question could be very brief, simply to say *no*. But, just to elaborate, clinical trials are an extraordinarily artificial exercise, and the control over the medication given to the patients in clinical trials is very much better than that when the drug is let loose on the market after it has been licensed. Secondly, clinical trials are never big enough to show ADRs, but if they do show serious ADR problems it is really quite unlikely that the drug will be licensed. The size of the population that is needed to predict ADRs in clinical trials is such that it would be almost impossible to carry them out. This is why most licensing authorities pursue a policy of early licensing of drugs, when only some 3,000 subjects or so have been studied. Naturally, if such a policy exists, one has to have very good post-marketing surveillance. What is more, if one licenses early one must not be surprised that occasionally a so-called drug disaster occurs. Provided your post-marketing surveillance is good, the disaster can usually be largely averted. Thus the occasional revocation of licences is the fault neither of industry nor of regulatory authorities; they are inherent in a system which licenses drugs early.

Today I need hardly enlarge on matters of post-marketing surveillance. A number of other contributors to this conference will address these problems. I would merely remind you that methods of post-marketing surveillance are of two kinds, namely alarm signals and quantitative methods. Geoffrey Venning wrote an excellent article in the *British Medical Journal* around 1983 to show that most of the major adverse drug reactions were first spotted by means of case reports, the most notorious being the thalidomide disaster. In his paper he gives some 17 examples of clinical acumen giving the first evidence of serious adverse drug effects. Apart from case reports, the other alarm systems are the voluntary reporting schemes. The Yellow Card scheme in the United Kingdom has now been going for a long time and has given us much help in raising alarm signals. It must never be forgotten that it is not a quantitative system. Neither enumerators nor denominators are reliable.

Rather than detailing methods of post-marketing surveillance, which I leave to others to do, I want to make two general points. Firstly, most post-marketing surveillance is funded by the pharmaceutical industry itself and it is, therefore, difficult for outsiders to regard it as unbiased. I have often felt that there was a need for an independent body to oversee post-marketing surveillance. Secondly the WHO International Centre, whose 25th anniversary we are celebrating today, stores adverse-reaction data from all over the world. It is a most valuable data-base, but we do need to be aware that pooling of adverse-reaction data, even from countries as near to each other as in Europe itself, can be a dangerous business. John Griffin pointed out the differences in perception of adverse reactions in different parts of the world and the difference in reporting rates of different types of adverse reaction. Thus in Australia reporting rates of dermatological adverse effects are far in excess of those in other countries as a percentage of total reported adverse effects, whereas cardiovascular adverse effects are much more commonly reported from the United States and from Britain. What this illustrates is that there are natural differences in perception of what constitutes an ADR. Thus, I must conclude that, whereas ADRs can be recorded and stored centrally for easy access, they must not be pooled.

Finally I wish to address the problem of communication and education as a means of reducing adverse reactions to medicines. Communication between the industry, the regulatory body, the patients and the doctors is of vital importance in increasing the benefit and reducing the risks of medication. How can we make ourselves clear across national, ethnic and linguistic barriers? Once a month or so I retreat from the city of London to a tiny cottage in South Wales and I always have great pleasure in taking a Sunday morning walk in the countryside nearby. In Springtime I not infrequently notice a local farmer who has a very simple notice on his farm gate. It simply says "Eggs". To me, that notice, which was cheap to make and didn't

involve any publicity agents, conveys a great deal of information. It tells me that this farmer's eggs are probably still warm, snatched from beneath the hen; they are probably brown and they probably still have the feathers stuck on them. Now all that information is conveyed in that one word "Eggs". It should teach us all to keep the message simple. That is the best way to educate consumers and prescribers alike so as to reap greater benefit at less risk from the many wonderful drugs we have available today.

SESSION I

**25 YEARS OF INTERNATIONAL
DRUG SURVEILLANCE**

Chairman: John F. Dunne

**The WHO Programme for International
Drug Monitoring**

- **The formative years**
- **Current activities**
- **Future prospects**

The Broader Perspective

What Has Been Achieved?

THE WHO DRUG MONITORING PROGRAMME: THE FORMATIVE YEARS (1968-1975)

Jan Venulet*

It is with some emotion that I address you about the beginning of a programme of which we are today celebrating the 25th anniversary, and of which for its first 7-1/2 years I was in charge of planning, development and operations. Of course, WHO had been for long concerned with drug safety but it is only 25 years ago that WHO's hitherto mainly consultative and advisory role was complemented by a major programme under its direct responsibility and operated by its own staff.

Doubts about tolerability of drugs are as old as mankind but in modern times they began to attract particular attention largely because of disasters associated with certain drugs. In 1932 a book was published on dangers in everyday foods, drugs and cosmetics. The consumer movement had begun.

The first scientific book on adverse drug reactions (ADRs) — that of Myler — appeared in 1952. It may be worth recalling some major accidents of those times.

In 1937, 107 people died of poisoning by an elixir of sulfanilamide containing the solvent diethylene glycol. In 1954, 100 people died of poisoning by Stalidon, an organic compound of tin used in the treatment of boils. It took 47 years to discover that aminophenazone was a potent marrow poison; and it took 39 years to incriminate aspirin as a cause of gastric haemorrhage, and another 20 years to have this generally recognized. Blood dyscrasias related to chloramphenicol were first reported in the early 1950s but it took nearly 20 years to have this association accepted as standard knowledge.

In 1961 came news of the thalidomide disaster. Thousand of babies had been born with phocomelia and micromelia, in many countries. More and more, this bleaker side of therapeutics began attracting attention among physicians and pharmacologists. Health authorities in several countries began collecting reports on adverse drug reactions, and various systematic drug-monitoring programmes were initiated, and the World Health Organization was requested to take an active role in assuring the safety of drugs.

In 1962, six months after the thalidomide disaster became known, the World Health Assembly recognized the seriousness of drug safety problems and recommended first measures for dealing with them. Afterwards, each World Health Assembly adopted a more specific resolution than the previous, culminating in 1967 in Resolution 20.51, which laid the basis for the international system of monitoring ADRs.

* CIOMS Consultant and formerly Chief, WHO International Drug Monitoring Programme, Geneva, Switzerland.

WHA20.51 The Twentieth World Health Assembly

Having noted the report by the Director-General, and
Recalling resolutions WHA18.42 and WHA19.35 on the monitoring
of adverse reactions to drugs,

1. NOTES with appreciation the agreement reached between the Organization and the Government of the United States of America concerning a grant for the WHO pilot research programme on the modalities of an international system of monitoring adverse reactions to drugs; and

2. REQUESTS the Director-General to take the necessary measures for that pilot project to be carried out and to report on its results to the World Health Assembly.

May 1967 160,29

Under the grant referred to in the Resolution the US Government provided, for the duration of the pilot project of three years, office space and equipment, computer facilities and advice and financial support. It is of some interest that this grant was the subject of a statement by President Lyndon Johnson.

THE WHITE HOUSE

Letter from the President to the Secretary of Health, Education and Welfare, John W. Gardner (Excerpts)

Dear Mr. Secretary:

I authorize you to perform the functions as may be required to provide assistance by the United States in the World Health Organization International System to Monitor and Report Adverse Reactions to Drugs.

I am pleased that the grant made possible by this delegation of authority will enable the World Health Organization to develop a worldwide early warning system for drugs, similar to the system now in development in the Food and Drug Administration. The World Health Organization's international drug reactions monitoring system will help prevent widespread tragedy of the sort which resulted from the use of thalidomide.

Sincerely,
/s/ LYNDON B. JOHNSON

As soon as it was decided to implement the project an immense amount of preparatory work began at WHO headquarters in Geneva, sorting out technicalities with the US Food and Drug Administration,

planning, and the recruitment of staff. This was in the hands of Dr. Bruce Royall, Chief of the Drug Safety Unit, who for some years had been preparing the necessary background papers, reports and other documentation, and Dr. Hans Halbach, Director of the Division of Prophylactic and Therapeutic Substances. Without any doubt it was the quality of these preparatory steps, and the recruitment of the right people, which assured the successful development of the project.

The result was the establishment of the WHO Drug Monitoring Centre. It was first called the WHO Pilot Research Project for International Drug Monitoring, and was located at Alexandria, Virginia, USA. It began its operations on 7 February 1968 as an inter-regional project under the authority of WHO in Geneva. Its purposes were to develop an international system of drug monitoring; devise a system for recording case histories of adverse reactions to drugs, and analysis and feed-back of data to national centres; permit searches by WHO staff and national centres of types and patterns of adverse drug reactions to individual drugs; and study the contribution of drug monitoring to research in pharmacology and therapeutics.

Twelve positions were assigned to the project: two medical officers, one pharmacist, one statistician, two programmer-analysts, one technical officer, one administrative technician, and secretarial and clerical staff. Ten nationalities were represented: Canada, Finland, Colombia, Mexico, Philippines, Poland, Sweden, Trinidad & Tobago, the United Kingdom and the United States. For a few months we also had an Indian colleague. It was thus a very heterogenous group, even by WHO standards, mostly newcomers to the US, with different command of English, different backgrounds, etc. but with a lot of competence, good will and enthusiasm to take up the challenge.

Ten countries, all with national drug monitoring centres, participated in the pilot phase: Australia, Canada, Czechoslovakia, the Federal Republic of Germany, the Netherlands, Ireland, New Zealand, Sweden, the United Kingdom and the United States of America.

During the two years of the pilot phase the Centre received 24,719 case reports. The original reporting form required cumbersome transcribing and was soon replaced by an improved version suitable both for national centres reporting and for the monitoring centre's coding and card-punching. With minor modifications this reporting form is still used except where it has been replaced by direct computer input.

The participating centres were using the adverse-reaction terms used by the reporting doctors, translated into English if necessary. For computer input at first a more restrictive list of terms, prepared before the inception of the project, was used; it was later extensively revised. A three-tier terminology was developed, with so-called "high-level terms" as the group terms, "preferred terms" representing the main working level, and "included terms" as synonyms of "preferred terms". Terms

describing adverse reactions affecting different body systems — e.g., cardiovascular, renal, central nervous system or skin — or certain types of suspected ADR such as resistance-mechanism disorders or application-site disorders were grouped into system-organ classes, with the provision that a term could be part of up to three system-organ classes. This added flexibility for output and retrieval, allowing for print-outs at different levels of specificity and a more diverse array of variables according to various needs of users. In the development of the ADR terminology the contribution of Lloyd Christopher was notable. The WHO Adverse Reactions Terminology, in its structure and contents, has remained largely unchanged. Time has proved it a useful tool but it now obviously needs revision.

A complex problem to handle was that of drug names. The project had to develop a system for thousands of names of active substances marketed under even more trade names, as single-active-ingredient drugs or as combinations of ingredients. Margaretha Helling-Borda, the pharmacist of the project, designed a very efficient system for this purpose to permit a more sophisticated analysis of data: two classifications of drugs were devised, a pharmacological one for mechanism or site of action, and a therapeutic one for clinical application. The drug reference list is still continued according to the same principle, but after the transfer of the Centre to Sweden the therapeutic and pharmacological classifications were replaced by the Anatomical-Therapeutic-Chemical classification, developed in Norway.

Practical operations of the project — input of case reports, quality checking of different items of data, and the development and maintenance of different files and retrieval formats — would not have been possible without the immense contribution of the project's programmer-analyst, Sam Molander, assisted by Esko Ahlroth. In those days these were difficult tasks, practically without software packages, and every operation had to be analysed, designed and programmed from scratch. It took some time for those of us less acquainted with modern data-processing to acquire the minimum essential knowledge in this domain, indispensable for mutual understanding. Ted Webster had the difficult task of seeing that the administrative procedures were strictly followed.

The proper use of data as numerous and varied as those processed in the Centre required a retrieval system capable of satisfying predetermined needs, but flexible enough to enable the staff to retrieve other information as indicated by changing interests and to follow up various leads and suspicions generated by the scientific approach. Two types of reference report were developed. They contained basic information on all drugs and all adverse reactions reported to the system. Report Type A had *drug name* as a main entry, followed by a list of suspected ADRs associated with each drug. Report Type B contained the same

information, but the main entries were the adverse-reaction terms. Today, 25 years later, document Type A is still produced.

One purpose of the programme was to aggregate single-case reports of rare and unusual reactions from different countries, which otherwise would not attract attention.

A considerable effort was devoted to the identification of changes in the flow of data and of types of individual case-report that might indicate a drug-safety problem, and to translate this into computer programmes so that the occurrence of any such event would be signalled automatically.

This led to the development of a group of signalling reports. The first signal was "Increase in reporting" on a drug in general or on an association between a drug and an adverse reaction. It was based on statistical testing proposed by our statistician, Alvaro Aldama, and developed further by Guillermo Belleno Patwary. Another signal listed the most reported drugs — namely, drugs responsible for 30 per cent and more of the reports. Still another signal designed to draw attention to single-case reports of serious or new and unexpected ADRs, was that called "New to the system". The computer was programmed to retrieve and print from every new batch all adverse-drug-reaction combinations not already known to the system. These were communicated to all national centres with the request to check combinations of interest to them. These, in turn, were reintroduced into the computer in such a way that whenever reported again a signal would be generated up to a certain total or during the following twelve months. Still another group of signals represented case reports with certain types of ADR, such as death, malformation, drug dependence. Some of these signals are still operational and in use.

Ad hoc needs for information, in particular of participating national centres, could be satisfied by means of "special search" procedures specially developed for that purpose.

All output documents were circulated to participating national centres and evaluated by the Centre's staff.

The outcome of the pilot phase was positively evaluated by the World Health Assembly in 1970, which requested the Director-General to develop the activities of the project into a primary operational phase aimed at establishing an international system for monitoring adverse reactions for alerting Member States in case of urgency.

The immediate consequence of this decision was the transfer of the Centre to WHO, Geneva. The central location, in the premises of WHO headquarters, and access to computer facilities were the main reasons for this decision, but more independence, resulting from not being located in one of the participating centres, played a part also.

With the satisfactory completion of the pilot phase more countries became members. These were Bulgaria, Denmark, Finland, Israel, Japan, Norway, Poland and Yugoslavia.

With more emphasis placed on alerting in case of urgency, the Centre's staff became more involved with the analysis of the accumulated data. An important regular addition was so-called "Drug comments", based on clues derived from our signalling system, compared with the data from the literature and commented upon. Here, the contribution of Dr. Edmund de Maar was of particular importance.

The Centre did not publish or report on associations between drugs and adverse reactions; this was not its responsibility. It did however publish papers on methodology of drug monitoring, epidemiology of drug use, economics of adverse drug reactions, and related topics, as it felt an obligation to share its experience. Up to 1974 eight papers were published.

Table 1. Reports and other documents regularly produced by the centre

REPORT TYPE	MAIN DATA CONTENTS
A (reference)	Drug names, followed by associated adverse reactions
B (reference)	Adverse drug reactions, followed by associated drug names
H (signalling)	Survey on increase in reporting on a drug or a drug/adverse reaction combination
K (signalling)	Drug/adverse reaction combinations new to the system (first time reported)
L (signalling)	Drug/adverse reaction combinations of possible interest. Selected in cooperation with National Centres.
M (signalling)	Most reported drugs (responsible for 30% of total input)
N (signalling)	Reports with "death" as outcome or as suspected adverse reaction
P (signalling)	Reports with foetal disorders
D (signalling)	Reports with drug dependence
Drug Reference List	List of all reported active substances, INNs and trade names cross-referenced and with additional information
ADR Terminology	Structured list of adverse reaction terms used for computer input and retrieval
Drug Comment	Prepared by Centre's staff; the first step in evaluation of a drug safety problem
Search Request	A document containing retrieved information based on specific parameters

There is of course the big question of what all of this was good for. What were the results? To answer these questions several aspects of the activity need to be considered: general and specific, immediate and delayed.

A particularly valuable, though unforeseen, effect has been the creation of a network of people in regulatory agencies who know one another well and are ready to discuss matters and advise one another. The industry at first deeply mistrusted the programme. Certainly the data were weak, and fears that unjustified alarms would do more harm than good were widespread. Well, the system stood the test and the Centre was never blamed for an unjustified action. And the respect was mutual. In those days I was advised to avoid any contact with industry. Now there are many joint projects as well as other forms of cooperation.

The Centre did not lag behind the professional media in recognizing drug-safety problems, except of course when case reports were sent elsewhere. The Centre did identify through its signalling system several associations between drugs and adverse reactions, and brought them to the attention of national centres, which at times recognized the validity of the signal and took necessary steps.

Single-case reports are frequently criticized as not being substantial enough to reveal a new drug-safety problem. I disagree. The potential of single-case reporting was best demonstrated some years ago by Venning¹. In a long list of recently discovered adverse drug reactions the first signal was a single-case report in a medical journal. This confirms the value of single-case reports and of alert observers. Publication in a medical journal is likely to attract more attention among doctors than the submission of a report to a manufacturer or drug regulator. I suppose that not enough attention is given to the differences in "alerting power" of a case report according to where it is submitted.

Table 2. Examples of recognized drug safety problems (up to 1974)

Drug/Adverse reaction	Date of signal recognition by the WHO Centre	Follow-up by national Centre	Action
1. Clindamycin/colitis	30.03.1973	16.08.1974	Dear Doctor letter (USA) Regulatory warning in 1976 (UK)
2. Erythromycin estol./ jaundice	30.03.1973	28.11.1973	Warnings by CSM(UK) and ADRAC (AUS), withdrawal in SWE
3. Penicillamine/ nephropathy	30.09.1972	1974	Warning publication in Deutsches Aerzteblatt, 1974, 71:197
4. Tilidine/dependence	31.12.1972	1974	Publication in The Pharmacologist, 1974, 16; 247. Registration refused in FIN
5. Heparin/syncope, dizziness	30.09.1972	20.01.1973	Manufacturer returns to formerly used preservative
6. Oral contraception;/ pregnancy unintended	30.09.1972 (interact.through enzyme induction)	01.06.1974	Article in The Lancet 1974, 2; 1113 (similar findings reported)

The Programme was to me a particular challenge. As a physician specialized in experimental pharmacology, I had worked for many years with the rigour of experimental sciences, characterized by clear hypotheses, standardized conditions, statistical evaluation of results, etc. — in other words, trying to approach the ideal situation of studying the effects of a single variable. And then, in this Project I was exposed to the other extreme, of a retrospective analysis of frequently incomplete and poorly documented case-reports of suspicions, sent in by health professionals from different countries, cases of patients frequently taking many drugs, etc. — in short, an unknown number of unknown variables. Hoping to find among this mass of reports cases of medical significance amounted to what Bill Inman compared to looking for nuggets of gold in a huge pile of garbage. It took me some time to convince myself that it was possible. Our objective was to devise methods to find these nuggets of gold, if there were any! Though fortunately there were no tragedies of the dimension of that caused by thalidomide, the Centre made some valuable contributions, in some cases in raising valid suspicions, and, in others, in providing additional data supporting the original observation and amplifying awareness of a particular drug-safety problem.

All of this was possible thanks to the competence and enthusiasm of all of my colleagues, first at Alexandria, Virginia, and later here in Geneva, the advice of numerous consultants over the years, and the help and understanding of participating national centres. Let me thank all of them on this particular occasion again.

Reference

1. Venning, G.R. Identification of adverse reactions to new drugs. *British Medical Journal* 1983; 286; 289-92.

THE WHO DRUG MONITORING PROGRAMME: CURRENT ACTIVITIES

I.Ralph Edwards*

In 1978 the operational activities subserving the international data-base for the monitoring of adverse reactions to drugs were relocated from WHO, Geneva to a WHO Collaborating Centre at Uppsala, Sweden. The Centre is situated within the Swedish Department of Drugs, and the operative costs are met by the Government of Sweden. The staff consists of four pharmacists, a computer programmer and a medical director.

Sources and channels for ADR data

Voluntary reporting systems are dependent upon observant health professionals who are well informed about the possibility of pharmaceuticals to cause untoward effects and who are prepared to inform others about their observations. Individual countries have different rules as to what should be reported by the medical profession to the national monitoring centre. For the purpose of the WHO programme an adverse reaction has been defined as one which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of a physiological function. Some countries have asked the medical profession to concentrate their reporting on severe or unexpected reactions and on reactions to drugs which have recently been marketed. Special forms for ADR reporting have been developed at the various national monitoring centres. These are distributed to those who are asked to report, for instance as inserts in a national medical journal.

Usually the adverse reaction case reports come to the national monitoring centre directly from physicians and other health professionals. In a few countries the majority of reports come via the pharmaceutical industry. A small amount of reports emanate from clinical trials or special surveillance studies. In most countries the individual case reports are subjected to medical assessment of the cause-effect relationship between the suspected drug and the adverse reaction. This assessment is often made with the assistance of an advisory committee constituted of medical specialists. The report material forms the basis for an evaluation of the national situation with regard to drug safety.

* WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

Reporting to the WHO Drug Monitoring Scheme

At present, 36 countries are participating in the WHO scheme. The information on an individual case transmitted to the Collaborating Centre can be divided into four categories:

1. Case identification and patient data
2. Description of the adverse reaction
3. Information about administered drugs
4. Background data and comments by the national centre

A computerized procedure checks all case reports arriving at the Collaborating Centre for completeness and technical correctness. Adverse reaction terms and drug names are also checked by the programme and new terms for adverse reactions and drugs not previously reported are coded separately to update their respective dictionaries.

The reports are then added to the data base INTDIS (International Drug Information System). This data base contains over 1 million individual case reports. It has been possible to cope with the significant increase in reporting in recent years thanks to the very efficient and flexible data-base system developed at the Uppsala University computer centre.

Adverse reaction terminology

The adverse reaction terminology was created in 1968 by amalgamating terms from relevant dictionaries already in use in some countries. It is an open-ended terminology with new terms added as necessary and it comprises approximately 1300 so-called Preferred terms. The adverse reaction terminology is built up as a tree structure. All terms pertaining to the same body organ are grouped into a System Organ Class (e.g. respiratory system, cardiovascular system). There are altogether 30 system organ classes. The Preferred terms, with Included terms as synonyms in order to help reporters find the right Preferred term, are the terms used at the input side. Preferred terms are grouped into High Level terms, which are more general terms for similar conditions. Preferred terms, High Level terms or System Organ Classes are used at the output side, depending on the purpose of the particular document.

Drug dictionary

The drug dictionary contains data on all drugs presented on adverse reaction reports since the beginning of the project in 1968. Drugs are usually reported as trade names. At the end of 1991 the drug dictionary contained approximately 24 500 different trade names as well as 6 300 names of active substances. Around 2 000 new names are added annually. Drugs containing the same active ingredient(s) are grouped

under a “preferred” drug name. In the case of single-ingredient drugs the INN-name is used as the preferred name, while for multiple-ingredient drugs the first reported drug name of a given combination is chosen as the preferred name. In addition, information is stored on the name of the manufacturer of each drug, the national drug list where it has been described and the pharmacological group of the drug.

The ATC-system (Anatomical-Therapeutic-Chemical classification) is used for pharmacological coding. This system allows accurate classification of both single and multiple ingredient drugs and retrievals of adverse reaction reports by pharmacological or therapeutic groups.

Use made of the WHO data-base

The material collected is available to national centres participating in the WHO scheme. This unique source of information on drug experience may be used in various ways. Originally, the prime objective of the international drug monitoring scheme was the early warning function. The scheme was established to assist in the detection of adverse drug reactions not revealed during clinical trials. By pooling drug experience reports from many countries, it was considered possible to detect also the very rare adverse reactions. This idea is still valid.

To this end the material received is screened four times a year for serious reactions and associations not previously reported. Documents based on this screening are distributed to the national centres. They comprise the following:

- * All drugs associated with death, fetal malformations, neoplasms or dependence
- * Adverse drug reaction associations not previously reported
- * Follow-up of reporting frequency of interesting associations chosen by national centres or staff of the Collaborating Centre.
- * All suspected reactions to new drugs

In recent years the efforts to identify previously unknown drug-reaction associations have been intensified. Specialists at national centres have been nominated to intensively review new associations reported to WHO within their specific fields of interest. They are asked to consult relevant literature and provide brief comments on their findings. Some of these findings may be suitable for bringing to the attention of the medical profession through an article in a medical journal^{1,2,3}. A recent article described quality criteria for adverse reaction signals to be published.

The WHO data-base INTDIS with its 1 million case reports is a unique reference source for strengthening or refuting suspicions about new adverse reactions that arise at national centres. On average, two to three requests per week for special data-base searches are received at the Collaborating Centre. Twelve national centres have passwords to

the WHO computer, allowing them to consult the data-base on-line from their own offices. In addition an annual reference document, the Report Type A, containing all suspected associations occurring in the previous four years, is distributed to all national centres.

Frequently the adverse reaction profile of a specific drug is requested, especially when a country contemplates the registration of a product that previously has been marketed elsewhere. A summary of all reactions reported is then provided in the form of a tabulation supplemented with a graph. It is often of interest to compare the adverse reaction spectrum of newer drugs with that of older established therapies. Of course, this only gives a rough overview, owing to the heterogeneity of the data.

The adverse reaction pattern of a pharmaceutical preparation may vary from one country to the other. The reasons for such variations are multifold — e.g. the use of different excipients in the preparation, different dosages employed or different indications for the use of the drug. It is important to be able to demonstrate such inter-country differences in order that reasons for variations may be investigated. This can easily be done through the WHO reporting scheme. Unfortunately information on drug sales is not readily accessible from most countries, which often makes interpretation of the findings difficult. However, a pilot collaboration with Intercontinental Medical Statistics is under way and may provide valuable data in this area.

Risk factors predisposing to adverse reactions may be studied by use of the WHO data-base, since frequently a large cohort of patients may be identified. Such factors as age, sex, dosage, duration of treatment, and indication for drug use may be studied in relation to the unwanted effect. Accordingly it is of great importance that submitted reports are as complete as possible.

Other functions and developments within the WHO Collaborating Programme

An increasingly important aspect of the international programme and the Collaborating Centre is its role as a communication centre, a clearinghouse for information on drug safety. National centres provide the Collaborating Centre not only with individual case reports but also with information on regulatory measures taken, problems under investigation, drug bulletins, scientific articles etc. On the basis of this information the Collaborating Centre produces an Adverse Reaction Newsletter for participating national centres four times a year. Topics raised in the Newsletter are supplemented with figures from the WHO register. The Adverse Reaction Newsletter has been very well received by the national centres and constitutes an important exponent of the clearinghouse function.

Annual meetings of representatives from national centres, arranged since 1978, have been very well attended and have been of great

importance for the maintenance of international communication in this field. At the meetings, current drug problems are discussed as well as methodological and technical issues. These meetings thus contribute to a harmonization of definitions and methodology in drug monitoring as well as to the development of the international monitoring scheme.

The terminologies developed within the WHO programme for coding adverse reactions and pharmaceuticals have been adopted by numerous parties outside the programme. A number of pharmaceutical companies using different adverse reaction terminologies, all based on the WHO terminology, have formed a group with the aim of attaining optimal compatibility with the terminology used within the WHO scheme. There is a proposal for further joint work within the Council for International Organizations of Medical Science (CIOMS) to produce a new single international adverse reaction terminology with definitions or guidelines for use of the main terms. This harmonization effort, already begun in part, will significantly enhance understanding and exchange of adverse reaction data.

General terms used in the adverse reaction area such as 'signal' and the causality terms 'certain', 'probable', etc. have been used differently, with confusing results. The Programme has already agreed and published several definitions and will continue to work on others. These agreed definitions will help solve many misunderstandings between professionals.

More and more countries implement national drug policy programmes, and adverse reaction monitoring becomes integrated as a natural part of such programmes. A considerable demand for advice and expertise in setting up national adverse-reaction reporting programmes is coming from the more advanced developing countries. National centres and the WHO Collaborating Centre are frequently involved in the education of fellowship holders from such countries.

As more and more countries join the Programme it is essential that communications be as easy and rapid as possible, both in general and in the transmission of adverse reaction reports. To this end the Collaborating Centre now offers free on-line access to the data-base for all member countries, which includes an advanced electronic mail conferencing service — DISNET.

Recent years have seen a more open attitude to the data-base. There are still some understandable restrictions to access by parties outside the Programme, but, more and more, the pharmaceutical industry and others with a genuine interest in public health make use of the safety data.

Since the pharmaceutical industry collectively holds international adverse reaction data within each company there is a need to be able to see how much is duplicated with the WHO data. This unknown amount of duplication can only be determined easily, even on an *ad hoc* case-by-

case basis, if there is harmonization of information held by all data bases. Better still, a single international data-base for all adverse reaction information would allow for easier checking of both accuracy in a uniform manner and duplication between various sources.

Generally, the Programme aims not only to develop the existing signal generation potential, but also to ensure that analysis and investigation of all important safety signals proceed consistently. This can only be done through cooperation with many people throughout the world with an interest in pharmacoepidemiology and drug safety.

References

1. Biriell C., McEwen J., Sanz E. Depression associated with diltiazem. *Br Med J* 1989; 796.
2. Lindquist M, Edwards I.R. Endocrine adverse effects of omeprazole. *Br Med J* 1992; 305: 451-452.
3. Olsson S., Edwards I.R. Tachycardia during cisapride treatment. *Br Med J* 1992; 305: 748-749.
4. Edwards I.R., Lindquist M., Wiholm B-E. Quality criteria for early signals of possible adverse drug reactions. *Lancet* 1990; 336: 156-158.

FUTURE PROSPECTS OF INTERNATIONAL SURVEILLANCE OF DRUG REACTIONS

Folke Sjöqvist*

The purpose of this presentation is to emphasize present and future possibilities of preventing concentration-dependent adverse drug reactions in the perspective of the new pharmacogenetics and the recently discovered interethnic differences in drug metabolism.

Drug surveillance or pharmacoepidemiology may be subdivided into drug-oriented and utilization-oriented research. The former is usually aimed at evaluating the safety of a drug product, while utilization-oriented studies are aimed at improving the quality of drug therapy by identifying factors involved in irrational prescribing. The former is of central interest to the drug industry and to drug regulatory agencies; the latter is the more important for health care, because many problems may be prevented by education and by therapeutic auditing.

The late Sir James Crooks was one of the first to introduce the concept of auditing in health care. He defined therapeutic audit as a "searching examination of the way in which drugs are used in clinical practice, carried out at intervals frequent enough to maintain a generally accepted standard of prescribing"¹. Crooks was undoubtedly ahead of his time in emphasizing the importance of setting up therapeutic audit. Today the concept has been broadened to the auditing of all kinds of procedures and technology used in health care delivery². Already, some ten years ago, an international symposium documented amazing differences in drug usage between and within countries³. A distinguished colleague concluded that differences in drug utilization to a large extent lacked rational explanation and that "doctors differ more than patients"⁴. Research into drug utilization has to a large extent been descriptive but its analytical aspects could be strengthened by including established and new clinical-pharmacological concepts⁵. As an example, dose/effect relationships are very important in understanding the mechanisms involved in adverse drug reactions (ADRs). There is a marked interindividual variability in these relationships, of which doctors have to be aware. Some patients suffer ADRs already at subtherapeutic doses. The population is not homogeneous but includes phenotypes at risk of developing ADRs and other undesirable drug-effects.

Already in 1538 Paracelsus wrote: "Everything is a poison; the dose alone makes the thing not a poison". It appears that the dose/effect relationship, which is a key concept in basic and clinical pharmacology,

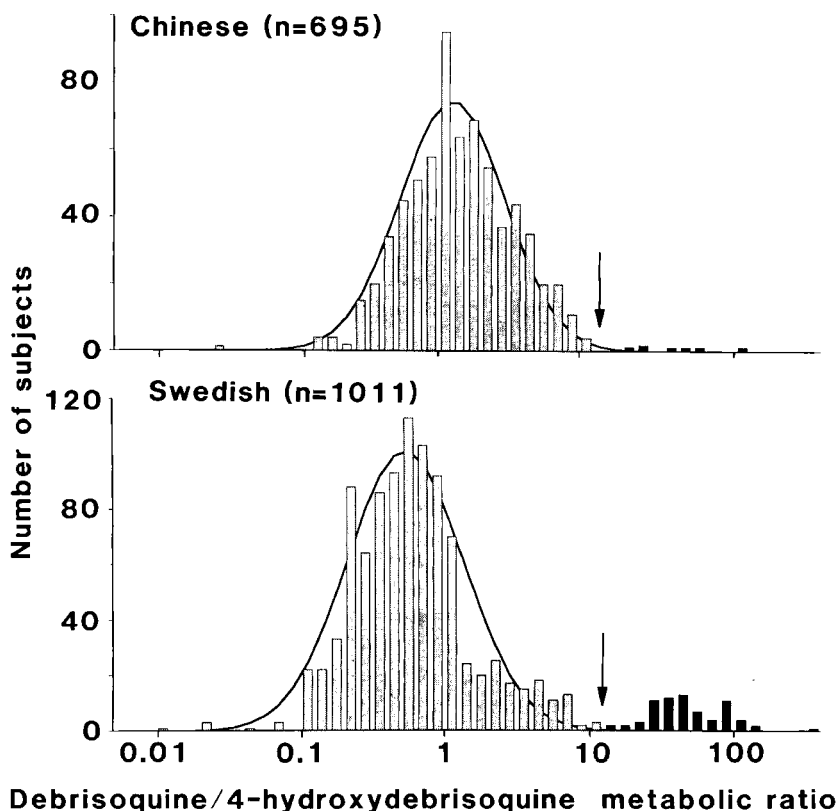
* Department of Clinical Pharmacology of the Karolinska Institute, and WHO Collaborating Centre on Drug Utilization Research and Clinical Pharmacological Services, Huddinge University Hospital, Huddinge, Sweden.

has been disregarded so far in pharmacoepidemiology, which too often uses vague terminology such as “drug exposure”. Paracelsus would still be at the front of research if the word “dose” were exchanged for “concentration”. Thus, the ultimate level of sophistication in drug surveillance is to establish concentration-effect relationships for any ADR. Indeed, steady-state plasma concentrations of many drugs that are metabolized may vary up to thirty-fold between patients treated with a fixed dosage schedule. On such a regimen, only a fraction of the patients will reach optimal therapeutic plasma-concentrations. Therefore, it is high time to exchange the term “drug exposure” for “dose” or, even better, for “concentration” in drug surveillance. It is perfectly possible to perform concentration-effect studies in the clinical situation, even in psychiatry. For example, Gram and his associates have succeeded in characterizing the concentration-effect responses of imipramine in endogenous depression, nocturnal enuresis and diabetic neuropathy⁶. They found excellent relationships between the concentrations of the parent drug and its active metabolite and these clinical effects. However, it is still an exception rather than the rule that such studies have been performed when new drugs are registered, and many drug control agencies fail to realize the importance of such studies as a basis for proper drug-utilization.

The secretary of the Swedish Adverse Drug Reaction Committee, Dr B. Wiholm, has compiled literature suggesting that about 75% of all ADRs occurring in hospitalized patients and of those causing admission to hospitals are of type A — the so-called pharmacological type, in which the side-effects are concentration-dependent and, therefore, should be avoidable by more appropriate drug-utilization⁷. However, we have to realize that the concept of individual dosage is rather complex, because the patient has several individualities — psychological, biochemical, pathophysiological and age-dependent. The most important individuality is related to interindividual differences in drug metabolism, particularly in hydroxylation catalyzed by cytochrome P450-enzymes.

The different members of the cytochrome P450-(CYP) family of enzymes have their own favourite substrates, which include such diverse xenobiotics as therapeutically important drugs, caffeine, ethanol, and some natural toxins. One of these isoenzymes, CYP 2D6, has been shown to metabolize several important groups of drugs, including neuroleptics and antidepressants, which are notoriously difficult to use in an optimal dosage-schedule. CYP 2D6-activity varies markedly between individuals, but it is now feasible to phenotype individuals with respect to this drug-metabolizing activity⁸. This is done by measuring the hydroxylation of a small oral dose of a probe drug such as debrisoquine, sparteine, codeine or desmethyl-imipramine. The ratio between the parent drug and its hydroxylated metabolite is determined in a urine sample. These ratios are bimodally

distributed in Caucasian populations, with hundred-fold interindividual differences⁸. Using debrisoquine as a probe drug in more than 900 healthy Swedish subjects⁹ we found an antimode of the ratios at 12.6 separating the two phenotypes, extensive (EM) and poor (PM) metabolizers (Fig 1).



Phenotypic distribution of the urinary debrisoquine/4-hydroxydebrisoquine metabolic ratios in a Chinese and a Swedish population. The arrows indicate the antimode (metabolic ratio of 12.6) which separates the two modes in Swedes, with approximately 7% in the right mode (poor metabolizers, PM) and 93% in the left mode (extensive metabolizers, EM). Heterozygous EM are not distinguishable from homozygous but can be "diagnosed" with genotyping methods. The frequency of PM among the Chinese is considerably lower (about 1%) than among the Swedes. At the same time there is a right shift in the Chinese distribution, suggesting that they in general have a slower debrisoquine hydroxylation than Swedes (and other Caucasians). From Bertilsson *et al*⁹ with permission of the publisher.

The latter group constitutes 7% of Caucasians and represents the phenotype at risk of developing concentration-dependent ADRs of most drugs that are metabolized by CYP 2D6, if they are prescribed in normal therapeutic doses, unless the drugs have a very broad safety range. Moreover, patients at the extreme right end of the EM mode may also suffer such side-effects unless the dosage is reduced. A clear association between phenotype and steady-state plasma concentration of drugs used in long-term treatment has been shown for, e.g., antidepressants¹⁰. Drugs metabolized by CYP 2D6 with a relatively narrow therapeutic range include classical tricyclic antidepressants, the new serotonin uptake inhibitors such as fluoxetine, most neuroleptics and several potentially toxic antiarrhythmics.

Studying the debrisoquine hydroxylation ratios in volunteers from different parts of the world, we have recently demonstrated profound differences between Chinese and Swedish subjects (Fig. 1). Among 695 medical students at Beijing University, we found only about 1% of extremely slow metabolizers, but there is a right shift in the ratios in the Chinese compared with the Swedes (and other Europeans). This implies that Chinese generally hydroxylate drugs at a slower rate than Europeans. This is one example of a profound interethnic difference in the hydroxylation of drugs. Another example is the much higher incidence of poor metabolizers of mephenytoin among Chinese (15%) compared with Swedes (3%)⁹. Mephenytoin is a probe drug for another polymorphic P450-hydroxylase, CYP 2C19, which metabolizes important drugs such as diazepam¹¹. Accordingly diazepam is metabolized slower in Chinese than in Swedes¹¹ and therefore has to be prescribed in lower doses for Chinese than for Caucasians¹².

The genetic basis for these interethnic differences in drug metabolism is now being explored with the help of molecular biological techniques developed by Dr Urs Meyer and his associates¹³. The mutations in the CYP 2D6 gene that cause defective enzyme activity have been mapped out in different Caucasian groups and recently in several other ethnic groups¹⁴. It turns out that the most abundant point mutation of the Caucasian CYP 2D6-gene is rarely seen among Chinese, while another mutation associated with slow but not entirely defective metabolism is common among Chinese and missing among Caucasians^{15, 16}. These pharmacogenetic studies imply that the same dose of CYP 2D6 and CYP 2C19 substrates given to different ethnic populations may result in different mean steady-state plasma concentrations and hence in other incidence figures of concentration-dependent ADRs.

After 30 years as a clinical pharmacological consultant to the Swedish Medical Board of Health I dare to define the weakest aspects of the documentation of new drugs in terms of the possibility of preventing concentration-dependent ADRs. Firstly, dose-response studies are often missing or poorly designed. Secondly, concentra-

tion-response studies are the exception rather than the rule. Thirdly, in spite of pronounced interindividual variability in pharmacokinetics and drug metabolism many drug companies insist on recommending practising physicians to prescribe fixed dosage schedules; obviously the intellectual focus of the doctor should be to vary the doses to patients in a manner that corresponds to the drug metabolic variability in the population. Fourthly, there is poor realization of the importance of genetically determined variability and interethnic differences in drug metabolism. All these deficiencies contribute to the maintenance of concentration-dependent ADRs as an important problem in health care delivery, which sometimes also results in the withdrawal of useful drugs from the market.

At the First World Conference on Clinical Pharmacology, some 15 years ago, Dr Richard Crout, then an important decision-maker at the FDA, concluded that during his tenure there had been an explosion of knowledge in the fields of pharmacokinetics and drug metabolism. Regrettably, we still do not use this knowledge systematically in clinical practice.

References

1. Crooks, J. Methods of audit in drug use. In: *Advances in Pharmacology and Therapeutics*. Proceedings of the 7th International Congress on Pharmacology, Paris, 1978, Vol 6, Clinical pharmacology, ed. P. Duchêne Marullaz.
2. Richards, C. Impact of medical audit advisory groups. *Br Med J* 1991; 302: 153-5.
3. Sjöqvist, F and Agenäs, I Drug utilization studies: implications for medical care. Proceedings of ANIS symposium, Sönga-Säby, Sweden, June 1982, *Acta Medica Scand (Suppl.)* 1984; 683.
4. Hjort, PF, Holmen, J and Waaler, HTh. Relation between drug utilization and morbidity pattern: antihypertensive drugs. *Br Med J* 1991; 302: 83-93.
5. Sjöqvist, F. Auditing drug therapy, why and how? In: *Auditing drug therapy. Approaches towards rationality at reasonable costs*. International symposium, Oct. 24-25, 1991, Stockholm. Swedish Pharmaceutical Press, 1992.
6. Gram L. Dose-effect relationships for tricyclic antidepressants: the basis for rational clinical testing of new antidepressants. In: *Clinical pharmacology in psychiatry*. Psychopharmacology Series 10, 1993; 163-73.
7. Sjöqvist, F. The impact of clinical pharmacology in enhancing benefit-cost ratios of drug therapy. In: *Clinical pharmacology*, eds. Abshagen, U, Münnich, FE. Zuckschwerdt Verlag, München, 1990, pp 21-9.
8. Mahgoub, A, Dring, LG, Idle, JR, Lancaster, R and Smith, RL. Polymorphic hydroxylation of debrisoquine in man. *Lancet* 1977; ii: 584-6.
9. Bertilsson, L, Lou, Y-Q, Du, Y-L, Liu, Y, Kuang, T-Y, Liao X-M, Wang K-Y, Isefius, L and Sjöqvist, F. Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxylations of debrisoquine and S-mephenytoin. *Clin Pharmacol Ther* 1992; 51: 388-97.
10. Dahl, M-L, Johansson, I, Palmertz, M, Ingelman-Sundbert, M and Sjöqvist, F. Analysis of the CYP 2D6 gene in relation to debrisoquine and desipramine hydroxylation in a Swedish population. *Clin Pharmacol Ther* 1992; 51: 12-17.
11. Zhang, Y, Reviriego, J, Lou, Y-Q, Sjöqvist, F and Bertilsson, L. Diazepam metabolism in native Chinese poor and extensive metabolizers of S-mephenytoin: interethnic differences in comparison with white subjects. *Clin Pharmacol Ther* 1990; 48: 496-502.

12. Kumana, CR, Lauder, IJ, Chan, M, Ko, W, and Lin, HJ. Differences in diazepam pharmacokinetics in Chinese and white Caucasians — relation to body lipid stores. *Eur J Clin Pharmacol* 1987; 32: 211-5.
13. Heim, M and Meyer, U, Genotyping of poor metabolisers of debrisoquine by allele-specific PCE amplification. *Lancet* 1990; 336: 529-32.
14. Kalow, W and Bertilsson, L. Interethnic factors affecting drug response. *Advances in drug research* 1994; 25: 1-53.
15. Johansson, I, Yue, QY, Dahl, M-L, Heim, M, Säwe, J, Bertilsson, L, Meyter, UA, Sjöqvist F and Ingelman-Sundberg, M. Genetic analysis of the interethnic differences between Chinese and Caucasians in the polymorphic metabolism of debrisoquine and codeine. *Eur J Clin Pharmacol* 1991; 40: 553-6.
16. Johansson, I, Oscarson, M, Qun-Ying, Y, Bertilsson L, Sjöqvist F and Ingelman-Sundberg M. Genetic analysis of the Chinese cytochrome P450 2D locus. Characterization of variant CYP 2D6-genes present in subjects with diminished capacity for debrisoquine hydroxylation. *Mol Pharmacol*. In press.

THE BROADER PERSPECTIVE

Michael D. Rawlins*

I have been asked to examine the evolution of forces of cooperation in drug surveillance. In doing so I will be considering cooperation in its broadest sense, and encompassing cooperation between scientific disciplines as well as between scientists, cooperation between methodologies, and cooperation between stakeholders (drug regulatory authorities, consumers, and the pharmaceutical industry) all in pursuit of the public health. My talk will be in three parts — the reasons behind the need for cooperation, the approaches to drug surveillance and the scope of cooperation, and some of the issues that have been addressed over the past 25 years and how these have been addressed.

1. The Problem

Pharmaceutical companies spend US\$ 150 million or more to bring a new active substance to the marketplace. Why, then, do problems arise?

The premarketing safety data-base, when a new active substance is brought to the market, consists traditionally of preclinical data and clinical data.

The preclinical pharmacological data provide us with some idea of the safety margins between the primary pharmacology of the drug and its secondary pharmacological properties (which are those that are most likely to cause toxicity). The general toxicology studies, broadly speaking, tell us whether a new drug is likely to be widely toxic in a range of species. The special toxicology studies, which include carcinogenicity and reproductive toxicity studies, may help us to identify and predict specific problems.

The clinical data-base provides us with information on adverse reactions and, perhaps more importantly, on adverse events. It should also offer us insights into the results of target-organ monitoring if we have interpreted the general and specific toxicological studies sensibly. And we may obtain important information about special subgroups such as patients with renal or hepatic impairment, or the elderly.

The preclinical safety data-base, however, has many weaknesses. General toxicology studies have been widely estimated to have a predictive value of around 65 to 70%. The predictive value of special toxicology studies is much less certain, and the predictive value of carcinogenicity studies, for example, is almost unknown. Thus, whilst we know that the predictive value of human toxicology studies in

* Wolfson Unit of Clinical Pharmacology, Department of Pharmacological Sciences, University of Newcastle, Newcastle-upon-Tyne, and Committee on Safety of Medicines, United Kingdom.

predicting cancers is high, we have very little information about the reverse. In terms of the clinical data-base, other speakers have already pointed to the limitations and weaknesses of our dose-ranging and dose-response studies. The laboratory screening methods that we use in seeking evidence of target-organ toxicity are those adapted from tests used in the diagnosis of disease and were never designed for predictive purposes. We do not yet have a rigorous biostatistical approach to systemic overviews of safety, and the duration of treatment is inevitably limited. There are also, inevitably, limitations to our studies of subgroups, and the British Paediatric Association believes we are creating a new class of therapeutic orphan by neglecting the needs of children when new drugs are first marketed.

There is moreover a clear limitation to the numbers of patients who have been treated with the drug at the time it is first marketed. Thus, the median number of patients that have been exposed to a new drug at the time of its licensing in the United Kingdom is about 1,500, though the range is extremely wide. Such numbers, in the context of safety studies, present us with four major problems, and pharmacovigilance, I believe, thus has four major objectives. These are the detection of previously unsuspected adverse reactions, the identification of predisposing factors for known adverse reactions, the detection of long-latency adverse reactions, and (of equal importance) refutation of “false-positive” adverse drug reaction signals.

2. Pharmacovigilance methods

Broadly speaking, pharmacovigilance methods are either observational or experimental in design.

Observational studies require a very considerable degree of expertise in their execution, and fine judgement in their interpretation. There are at least four criteria for surmising a causal association in observation studies: a strong statistical association; consistency between studies; a biological gradient (i.e., a dose-response effect); and biological plausibility.

The main types of observational study used in pharmacovigilance (spontaneous reports, case-control studies, and non-experimental cohort designs) are discussed by other speakers. I wish to limit my remarks to two other approaches — vital statistics and case registry.

We sometimes neglect the power and value of vital statistics as a means of pharmacovigilance. Thus, there has been a suggestion, over the last 10 to 15 years, that there is a rising mortality, in many countries, that correlates with the increasing use of inhaled beta-agonists. However, when one corrects the UK mortality data for asthma (by taking account of factors such as changes in disease classification and changes in the coding rules) the mortality from the condition in patients under 65 has stayed virtually constant, whilst the prescription volume has increased threefold. This does not, to me,

suggest that the use of beta-agonists is a significant and major cause of death in asthma. Of course, it is possible that a small number of asthmatic patients may be suffering as a result of their medication. But, overall, from a public health point of view, a causal relation is not sustained, at least for the beta-agonists on the British market and the way that they are used in the United Kingdom.

Registries are, I believe, likely to play an increasingly prominent role in pharmacovigilance. When clozapine was introduced to the United Kingdom, and to the United States, a few years ago there was great anxiety about its risk of producing agranulocytosis. There were also concerns that, when it had been previously marketed (in the 1970s), there appeared to be marked racial differences in the incidence of this reaction. Because of the way in which clozapine was introduced into the US and UK markets, all patients receiving it have had routine blood counts, which have been carefully documented. This particular form of surveillance confirmed that the incidence of agranulocytosis amongst patients receiving clozapine in the United Kingdom is similar to that anticipated from the pre-marketing data base.

3. Some past pharmacovigilance issues

Earlier this morning, Sir William Asscher talked about the drugs that had been withdrawn from the United Kingdom market. I divide these into two groups. First, there are those drugs that have been withdrawn on safety grounds but which were introduced onto the market since modern drug regulation came into force (i.e., in 1972). Of the 400 to 500 new active substances that have been licensed during the past 21 years, 15 have been withdrawn for safety reasons, giving a withdrawal rate of somewhere between 3% and 4%. Whether or not this is an acceptable proportion is a matter for debate but I am sure that all of us involved in drug research, development and regulation would wish it to be reduced.

Since 1972 there have also been, for safety reasons, a significant number of withdrawals of products that were originally marketed prior to 1972. These included drugs which were first marketed around the turn of the century. It is important that these safety withdrawals are separated from those involving more recently marketed drugs.

During the last 21 years there have also been other major drug-safety issues. These remind us that at the time a drug goes on the market we can only make provisional assessment of its safety. Examples include the behavioural and withdrawal effects of benzodiazepines, which have caused considerable suffering in many parts of the world. The contamination of blood products with human immunodeficiency virus has caused unknown misery. The Jacob-Creutzfeldt disease in recipients of human pituitary extracts is causing, and will probably continue to cause, suffering. All these are testimony to our relative inability to predict adverse reactions.

There have also, during the same period, been a number of what I would call “false-positive” signals. The alleged carcinogenicity of cimetidine, the claimed teratogenicity of debendox, and the alleged association between the use of human insulin and sudden death, have all caused very great (and unnecessary) anxiety for patients. Similarly, the allegations that whooping cough vaccination could cause permanent neurological damage, first made in the 1970s, produced a profound fall in vaccination rates and a consequent rise in the annual incidence of whooping cough. It was only during the 1980s that convincing evidence demonstrating the absence of an association between permanent neurological damage and pertussis vaccination appeared, with a subsequent rise in vaccination rates and a fall in whooping cough cases. False-positives may thus not only cause embarrassment to regulatory authorities and pharmaceutical companies, and concern to consumers, but also major public health problems.

The importance of post-marketing drug safety surveillance is unquestioned. Much has been achieved by cooperation between disciplines, methodologies and stakeholders. But there is a continuing need for international cooperation and I, like many other people here, am much encouraged by the determination of the European Commission to promote research in pharmacovigilance. Their example will, I hope, be replicated within member states and be accompanied by analogous initiatives elsewhere in the world and in the industry.

WHAT HAS BEEN ACHIEVED?

PANEL DISCUSSION: Chairman John F. Dunne

J.F.Dunne

We have eight panellists. Three of them — Dr. Bruppacher, Dr. Juillet and Dr. Tilson — come from industry. Two, Dr. Kreutz and Dr. Lumpkin, are representatives of regulatory authorities. Dr. Laporte has had a great deal to do with the development of clinical pharmacology in Spain and given a great deal of thought to the educational aspects of adverse-reaction surveillance. There are two people from WHO: Dr. ten Ham from our division, who has been responsible for coordination with the Collaborating Centre for International Drug Monitoring, and Dr. Phillips-Howard from the Division of Control of Tropical Diseases, who is concerned with furthering drug surveillance in developing countries. We should hear first a voice from industry, because so far we have had no comments from this quarter. I suggest that Dr. Juillet might start the discussion. Dr. Juillet, who now holds an administrative position in Roussel Uclaf, previously worked within the French national organization representative of research-based pharmaceutical companies.

Y. Juillet

Taking stock of 25 years of activity can lead to two different attitudes: to congratulate ourselves on what has already been accomplished; and, more realistically, to compare the successes with what remains to be done. I think we can say that what has been done is impressive but what has to be done is enormous and will be difficult.

The first speeches today have reminded us of the essential role of the World Health Organization in the emergence of pharmacovigilance. I would pay homage also to a great precursor, Dr. Desarmenien, at that time Director-General of the *Syndicat National de l'Industrie Pharmaceutique (SNIP)*, who was one of the first in France to pay attention to this question and who, after his first contacts with WHO, was responsible for setting up a system in France to gather reports of adverse effects. This system consisted of the *Centre National de Pharmacovigilance* created jointly with the *Conseil de l'Ordre des Pharmaciens* and the *Conseil de l'Ordre des Médecins* and *SNIP*. This structure, which still exists, was the origin of the organization in our country of pharmacovigilance, now the responsibility of the Ministry of Health.

As a member of the pharmaceutical industry, I recall that the pharmaceutical industry was aware early on of the necessity of active pharmacovigilance in each company. After some initial reluctance, it

became evident even to the marketing departments that informing and defining, even limiting the use to optimal conditions, were the best means of not only protecting but also of promoting a drug effectively. The logical consequence was the establishment, within each company, of a pharmacovigilance structure able to collect and evaluate the notified cases, to propose to management any necessary consequential action, and to serve as intermediary with the government authorities.

During the years since then, two major difficulties have appeared, one technical, the other political. Technically, it was necessary to create a new medical speciality. The collection, evaluation, validation and quantification of adverse drug reactions, the demonstration of a relationship between administration of a medicine and the occurrence of a reaction, all require special investigative methods non-existent 25 years ago. These have had to be created, and they are still far from definitive.

Politically, the difficulty lies in the decision, which is based on the well-known benefit/risk ratio. This decision should be as objective as possible, and based only on scientific and medical aspects and the patient's interest. It is unacceptable that any other consideration, be it political, industrial or related to the mass media, exert an influence.

The consequence of these difficulties has been the setting up of dialogues and exchanges as much technical as political and administrative. Technically, on a national and international level, a sort of club of specialists in pharmacovigilance has been created, bringing together representatives of the universities as well as of industry and the health authorities. Politically, health authorities from different countries have realized that frequent contacts are essential. In the European Community most pharmacovigilance decisions are now taken together, even though member states still diverge in implementing them. For example, a system of urgent alert, by fax, has been set up between member states.

The present evolution of pharmacovigilance appears to me to take place around three axes: evaluation of safety during development, harmonization, and improvement of methods.

Evaluation of safety has become one of the pivots of the decision to authorize the marketing of a drug. The search for maximum security, sometimes at the expense of efficacy, has led health authorities to request more and more complete and precise information. Consequently, special safety departments have been attached to the development divisions of pharmaceutical companies.

For products marketed internationally, the development safety department and the post-marketing department are bound to collaborate, especially during the critical period when a product begins to be marketed in some countries and awaits registration in others.

Harmonization has begun, but the road is still long. We should be thankful to CIOMS for the results already obtained. This topic will be taken up by other speakers.

Improvement in methods implies previous agreement on definitions: what are we talking about? A great deal has been achieved, thanks particularly to the efforts of Dr. Bénichou, but these efforts must go on. This question will also be taken up later.

For the future I would hope that the marketing of interesting products is not obstructed by a requirement for absolute safety, which does not exist; that the pharmaceutical industry as well as the health authorities know how to resist media pressures, which can impede objective medical and scientific evaluation; that the decisions taken are scientifically rather than politically motivated; that regulatory authorities consider the cost of the additional studies they request, in relation to the information these studies can provide (this refers to their tendency to ask for increasing numbers of patients to be treated before the marketing authorization, or for post-marketing studies to be carried out on numerous cohorts); and that greater attention is given to the good use of a drug, allowing optimal utilization at least risk.

If these conditions are met, pharmacovigilance will contribute even more in the future to the availability of products which will bring patients the relief and treatment they need. If not, pharmacovigilance will have missed its goal and will be used to support a restrictive policy which will dry up the potential of clinical research, to the detriment of public health.

J.F. Dunne

One of issues that we may need to delve into later is to what extent we can expect more open exchange of information between regulatory authorities and industry. That is a difficult one, but let's perhaps attack a simpler issue: collaboration on the methodological front. Dr. Bruppacher has been responsible in two of the major companies in Basel for the teams that Dr. Juillet has been describing. He has also worked very closely with CIOMS over the past two or three years in the ADR definition programme and various other activities related to adverse reactions. Could we hear your viewpoint, Dr. Bruppacher?

R. Bruppacher

There is a surprising parallelism between the work of the headquarters of an internationally operating company and the headquarters of an international organization. We all are grappling with national differences, so we have looked to WHO in our efforts to optimize pharmacotherapy and try to have hazards detected as early as possible; we have perceived WHO as an ally in our own efforts. Some international organizations have a logo or a flag, like the Olympic

Committee's with its five rings. I would give a flag to the WHO initiative, not the complete five rings, but five Cs. The first C stands for 'centre'. Spontaneous reports are very valuable, especially if they are well documented, but for drug monitoring on the broadest possible basis the information has to be collated at a central focal point. This basic idea of WHO's drug monitoring initiative has been consistently pursued for 25 years and, though one might hope for more, it is impressive how many countries have linked up, in view of the difficulties in bringing these countries together. The second C is for 'coordination'. Data can be reviewed only after they have been standardized in a certain way, so one has to coordinate how these data are collected, transmitted and so on. In this respect also the success of the past 25 years should not be underestimated. Coordination is very demanding, as we know from our own work, and the terminology that has come into very wide use, even though competitive terminology has always crept up, has been a big contribution from this initiative. The third C stands for 'coaching'. It is a good tradition of WHO to let all nations profit from the developments and achievements of well-developed nations. The WHO initiative has helped greatly in raising the methodological standards of many countries, and we in industry are very grateful for that, as it makes for easier communication with these countries. The fourth C is for 'collaboration', of course, and Dr. Dunne has mentioned it. The WHO initiative has also had great merit in its support and facilitation of the CIOMS effort on international adverse-drug-reaction reporting. I have myself been a member of at least four of the CIOMS working groups over almost eight years, and the opening up into a wider spectrum in less formal and more pragmatic, but highly successful, approaches to dealing with this problem is also part of the achievements that we can point to. And, if we look to the future and to CIOMS, the last C should stand for 'cooperation'. Drug safety does not stop at national boundaries, as WHO recognized at the beginning; it does not stop at the boundaries of different stake-holders, of different scientific disciplines, or for that matter at the boundaries of the different divisions of WHO. So we look with great hope and expectation to the further development of this cooperation that has started between different disciplines, but also between industry, regulators and academia, on the basis of WHO. We in industry are very ready to open our doors and cooperate in these efforts.

J.F. Dunne

The message is one of encouragement, at least from the methodological viewpoint. Dr. Tilson is the last member from industry on the panel. He is at the sharp end of the business within Burroughs Wellcome. He has also been a leader in opening discussion of this topic within the Drug Information Association, as many of you will know. I wonder if he might tell us a little about validation of reports, because most

regulatory authorities simply don't have the resources to become involved on the scale that they might wish. Industry has the resources, but it may not have access to the patients, at least here in Europe, because, when private doctors report, the issue of confidentiality is invoked. In the United States the situation is somewhat different. There, companies are directly involved in gathering the data. Reliance is placed largely upon sales representatives to assure reporting, and this must imply that companies have greater access to information concerning patients. Does this raise problems of confidentiality in the United States? And if it doesn't, does it enable you to obtain information that is not available to your colleagues here in Europe?

H. Tilson

You asked if industry could help to move us forward in our knowledge — that is to say, is industry really a partner in trying to overcome problems, which our keynote speaker pointed out, about adverse experience signals that come in, unclear, confusing, and incompletely analysed? Each country has its own approach to that. In the United States, industry is in full partnership, thanks to the leadership of the Food and Drug Administration — our regulatory authority — on this matter. It is estimated that industry generates more than 80% of all adverse-reaction signals that derive from the spontaneous reporting system in the United States. This is because our sales representatives are out in contact with the field. A fundamental principle applies in gathering epidemiological data of any nature. If you want to know what is going on in the field, provide a service to the field; do not just ask people to do you a favour, but respond with a favour in kind. The favour, in this case to the physician who wishes to prevent preventable illness, is help, information, contact. Therefore if you have representatives who ask doctors whether they have a patient with a particular problem and a doctor says yes, the representative will offer information about that. In this way we learn more about this experience so that we may help others who have the same adverse experiences in their practices. I can promise you, as an epidemiologist, that this is the key to gaining the information that you need. So, responsible manufacturers in the United States train field representatives to be the eyes and ears of this system for us, and to elicit adverse-experience information so that we may know what we need to know as quickly as possible.

A component of this, of course, has to be an intelligent drug-information service. The industry in the United States is progressively turning to the drug-information pharmacist and to the pharmacy community to train pharmacists so that they can provide proper drug information in response to an enquiry; then we train them to be our epidemiological intelligence officers as well, so that when a call comes in for information the pharmacist gives not only information but also help. Then finally of course, if we have information to collect, we do so

by phone, letter or whatever way is easiest, the most user-friendly, for the reporter. There is concern about over-zealous pursuit of information, and of course that sometimes is true; we love our field and care about the people whose health we are charged with protecting, and so we may be over-zealous, just as governments and academics may be over-zealous, in trying to get information.

One last point: recently the FDA has tried to increase the volume of reports of severe or serious adverse experiences, through the Medwatch Programme. Here is the most extraordinary statement of partnership — I think the one for which you are looking — for in establishing the programme the FDA also established a precedent that any report submitted to a regulator would, given the reporter's permission, be forwarded to the manufacturer for follow-up. In this system, the need to harness available resources to respond to evident concern to pool available pharmacological knowledge and to act in true partnership is fulfilled. It is an exciting time in the United States in this field.

J.F. Dunne

Thank you very much. That sounds very encouraging. Can I draw you out on one point, just to tie in with what Professor Sjöqvist was saying to us this morning, that it is very important to try to determine a mechanism for an unexpected reaction. Through your close relationship with the clinicians, on the one hand, and the FDA, on the other, can you get back to a particular patient and, say, get interested in the phenotype and whether he is a fast excretor, slow excretor, this sort of thing? If *you* are not in a position to do that, no one else is likely to be. This could mean that a drug gets discarded because of idiosyncrasy which, if explained, might not result in the rejection of the product and might, indeed, render us more knowledgeable about that product and many others.

H. Tilson

The simple answer is that it is always possible, if the physician is still in contact with the patient, and willing and able, and if science can yield. Remember we are talking about busy doctors in the mainstream of medical practice, who may not be in a position to do this sort of work. First, of course, we need to find signals or cues or patterns — the so-called risk-factor analysis, and learning about risk factors is part of epidemiological intelligence. Secondly, if there seemed to be cues coming from academia or the laboratory, that would help us, and a blood sample might be helpful. Then, it is not only possible, but we would quite frequently ask for blood samples if they were still available from that patient, or even ask that one be taken. But we are talking about a voluntary system with busy doctors whom one does not want to overburden with excessive requests. One would only do that if one

were working on a specific lead — for example, pseudocholinesterase deficiency, where screening was already documented as having some value for a particular patient or for that patient's family. Thirdly, of course, we have to turn to our academic colleagues to do the broader, prospective population monitoring, and there I think the great advantage of having an enlightened industry is that we are in the forefront as well of commissioning such academic studies, and would do so to follow up such a signal.

J.F. Dunne

Before we broaden the discussion could we have a view from the FDA, from Dr. Lumpkin, on the positive aspects, perhaps the negative aspects as well, of collaboration with industry?

M. Lumpkin

We at the FDA have noted over the last several years, as regards the types of adverse-event reporting and the various mechanisms we have, that two things have changed a great deal, and have changed greatly some of our perceptions. One is that, both at the FDA and in many other places, regulatory authorities realize that the assessment of safety and the definition of a safe drug are dynamic matters. This is something that does not fit very well into some of our old conceptions. When we look at our job of trying to make drugs available as soon as possible, with well-documented directions for use, we have to realize that the perception of what is a safe drug changes according to the perceiver. A patient with HIV infection or a parent with Alzheimer's, or someone who has cancer or multi-resistant tuberculosis, has a somewhat different perception of what a safe drug is from that of a group sitting around a table in Geneva or a regulatory authority. This brings to a head the premier question: how does one draw the line between legitimate pharmaceutical help and pharmaceutical exploitation? This is truly the bottom line as regards safety and drugs. It is a hard question to answer, and the only way that we as a society can begin to deal with it is by data and trying to get as much data as possible, as much validated data as possible, as quickly as possible, available to all the stakeholders, and that means down to the patient, who clearly is the most important stakeholder. One thing we have seen from an international perspective is that the revolution in technology and information exchange has made it possible to come up with the kinds of system we have talked about in the last few hours. These are some of our biggest challenges. We have had very good results working with the CIOMS I Working Group, the CIOMS II Working Group and the CIOMS III Working Group, the International Conference on Harmonization, some of Dr. Bénichou's groups, talking about common terminology, and it is imperative that we continue as

individual regulatory groups to be part of these activities. If we can come up with electronic systems for transfer of data that allow compatibility, we clearly will be able to meet the regulatory challenges that face us. In this modern world of limited resources within both the pharmaceutical and the regulatory agencies, duplication of effort, from both a regulatory and a development perspective, is wasted money and wasted time. Drug development and drug usage are not national issues — they are international issues.

The other issue I would like to raise is that most of us tend to talk about drug safety in the context of traditional Western pharmaceuticals. Now, in 1993, approaches to help often involve other products — medical devices, vaccines, biological products, homoeopathic drugs, herbal medicines — and all of these play large roles in adverse-event and safety issues. One of our challenges internationally in the next decade is to broaden our perspective on the safety of medicinal products and not just limit it to pharmaceutical products as we have done in the past.

J.F. Dunne

Can we have a quick overview from the other side of the Atlantic, from Dr. Kreutz of the Federal Health Office in Berlin, emphasizing the sorts of links you have with industry, the international system and so on?

G. Kreutz

Thank you for the question about the relations between the different players in the game. I am speaking as the person responsible for almost a decade for the evaluation and follow-up of ADR reporting, and the evaluation of benefit and risk of marketed drugs. The idea of looking at the objectives which were put forward when the national centres were established and what their objectives should be is interesting, especially in relation to communication with others concerned with drug safety. The objectives of national centres have been, first, to identify as early as possible serious adverse drug reactions, and second, to attempt to establish the causative relationship between the drug and the adverse reaction. Different approaches have been mentioned as to how these objectives could be tackled. Countries implement these objectives in different ways. We have heard about two or three at this meeting but we haven't heard about all the different means of implementation. The problems of communication between national centres, between industry within a country and the national centre, and maybe also between industries on the international level should not be overlooked by someone sitting in only one country. My perception is that there are no clear information channels; they are very different in different countries — for example, the network system now implemented in the United States has been operational in other countries for many years,

and there are very important new developments in other countries, but there is still no agreement on what is good practice in communication between regulators, between companies and regulators, and within companies. So there is urgent need of a standard according to which all concerned should communicate their own decisions, their own evaluations. We have during recent years had several opportunities in certain small, defined areas to get a better understanding of the problems, and also to come forward with recommendations which could be internationally accepted, but they are still not implemented, and that is another problem. Whenever we come up with recommendations, it is very difficult to implement them in a national setting, where the responsibilities of drug-safety surveillance may be distributed in completely different ways from those in another country, and this is a second very important aspect which must be looked at. As long as these responsibilities are not shared responsibilities but clear-cut responsibilities assigned to different bodies in different countries, it is almost impossible to work out one uniform way which everyone could use for communicating and for making decisions according to common criteria, with the aim of reaching the same conclusion. This seems to be my experience. The positive side of my experience has been the greatly improved possibilities in recent years of communicating with others; this results in more certainty in decisions one has to take and defend.

J.F. Dunne

That sets a challenge for us all in the international sector. After all, one of the reasons we are here is to try to improve communication, nationally as well as internationally, and one of the things at the back of each of the minds of those of us within WHO, on occasions like this, is how to propose a resolution to the World Health Assembly to move these things forward. I think that we shouldn't just leave this issue as it now stands; it is so important that we ought to throw the point open for further discussion. Are there persons here working within industry who are frustrated because information in the hands of regulatory authorities, relating to the safety of products for which they are responsible, is not routinely available to them, or do they accept that there is a better flow from governments than there used to be? Dr. Tilson.

H. Tilson

Let me start by picking up on an earlier comment, by Professor Bruppacher. It is interesting to hear this group talking about organizing and communicating. Dr. Kreutz is right when he says that the ground rules must be clear, and at least one part of that is that industry also has to organize itself so that communication will work. So one of the most

encouraging things many of us have witnessed over the last decade has been industry creating forums for people from industry to get together and talk about our shared commitment to the prevention of preventable drug-injury, to talk openly about the methods we use, to build the game plan and the capacity to do something about it, and then to create a forum where regulators can meet comfortably and safely and appropriately with us. This happens at the national level through epidemiology working-groups. The Pharmaceutical Manufacturers Association in the United States, for example, holds a dinner-meeting twice a year with our regulatory colleagues from the FDA, where we talk about our common agendas, and when there are urgent matters of communication there is a forum into which to put those matters, and an opportunity to convene more rapidly and more regularly than that if necessary.

J.F. Dunne

Is Dr. Lowrence here, because there is another such initiative that was started here in Geneva, namely RAD-AR (Risk Assessment of Drugs — Analysis and Response)? Would he say one or two words about that initiative?

W. Lowrence

We are not purely an industry group. I am director of a new foundation called the International Medical Benefit-Risk Foundation. A number of people here in the room are among our leadership. We have been careful to involve people from government, academia and journalism, and so on throughout in our thinking about medical benefit and risk.

Y. Juillet

Just a comment about the limits of cooperation. Of course there is now well-established cooperation on the technical side — on how to improve the system, the definitions, the way of reporting. But the difficulties arise when we have to discuss the problem of a drug, and I would like to let you know, and Professor Royer will also be in a position to give information on that, that in France cooperation is still present when there is an enquiry about the drug. As you know, information comes from the physician, who reports directly to the health authorities. And what is important to know is that in France, at the time of the enquiry, all the cases are put together, with the people in industry and the regulatory people at the same table to analyse the problem. And then, of course, there is the assessment and the decision, which are the health authorities' responsibilities. This system works well, and has been working for years, and it could be an example for other countries, and perhaps at the international level.

J.F. Dunne

A lot of us have long been persuaded that the decentralized system adopted in France has many advantages, particularly for exchange of information.

J.-R. Laporte

I would like to respond to your question on the exchange of information. For me, when I look at safety problems with drugs used in the community, it is difficult to think about safety and to decide about safety without referring to efficacy, registration, criteria for registration and use of the drug, the indications for use of the drug, the level of use, etc. And one of the problems, at least for academia, is that some of us as professors of pharmacology or therapeutics or clinical pharmacology are blind, and others among us are blinded by the information existing in some countries. Many professors of pharmacology and therapeutics in many European medical schools refer in their teaching to drugs that are not those most used in their own countries; they just refer to the drugs that appear in textbooks of pharmacology and therapeutics. So, at least in my opinion, one of the problems with drug safety is that, at least in academia, we do not have enough information on the criteria for registering the drugs, on the grounds on which certain indications were accepted or even the actual registration of the drug, on how the drug is used and by which groups of the population it is used, and which doctors are prescribing the drug and for what problems as seen by them.

J.F. Dunne

That brings us to another very important issue. The FDA already produces “summary bases of approval”, which give some of that information. Others of you, here in Europe from other regulatory authorities, do not give as much information. Is any other regulatory authority moving toward offering more information about newly-approved drugs, the basis on which indications have been accepted or rejected, the type of information that has been developed, the types of patients on which that information has been generated, and so forth? Or do you feel that that is not your job? Many people here tell us that the “summary bases of approval” issued by FDA are very useful. They certainly give me an insight into things that I would otherwise not know about. Dr. Laporte, again.

J.-R. Laporte

I will show you six or seven examples of drug safety problems that have appeared in Spain in the last 10 or 12 years with certain drugs which were marketed in our country. I think you are familiar with most of

them. One is Parkinsonism and depression caused by cinnarizine and flunarizine; the second is agranulocytosis caused by a so-called vasodilator drug, cinepazide, for which we evaluated the risk of agranulocytosis as three per 1000 person-years of treatment, and the efficacy had not been demonstrated. The third is acute dystonia associated with the use of clebopride, for which the registered doses were too high. Another is hepatotoxicity caused by bandazac, a non-steroidal anti-inflammatory drug which has been used for the treatment of cataracts but without any evidence of efficacy from clinical trials. The fifth is bronchospasm caused by citiolone, which is a drug that has been marketed in some countries as a liver protector and in other countries as a mucolytic. Philandelo would say that it is a drug in search of an indication. And the last and most recent one is the problem of acute motor polyneuropathy associated with the use of gangliosides. For these drugs, estimating the risk of these reactions would be more or less nonsense, because what resulted when we reviewed the data for these drugs was that the evidence for their efficacy was very tenuous. For cinnarizine there was, of course, some efficacy demonstrated for the treatment of motion sickness but not for the main indication in Spain, which was arteriosclerosis; for flunarizine there is some efficacy, as shown in clinical trials, for the preventive treatment of migraine, but it is also very tenuous and the clinical trials were not very good. For example, for clebopride what we discovered was that simply the Phase II studies — the dose-finding studies — were very weak, very badly done; it had to be reformulated, so after the problem the drug was reformulated to half the dose, and we do not have any evidence of efficacy of the dose which is consumed now. So these are the kinds of problem to which I was referring when I said that we need the safety data and summary safety data; otherwise we can not have reliance on health authorities, at least in certain countries, of course not in all countries. But I would say to finish that this is not a specific Spanish problem — many of these drugs are marketed in most European countries. Also, this situation, which is one of the three or four main lessons we have learned from 10 years of experience with drug surveillance in Spain, may indicate for us the realities of the less developed countries, or of developing countries, where drug controls and criteria for drug registration are much looser than in more developed countries.

J. F. Dunne

We sympathize with that concern. It is extremely important that the drug be shown to be efficacious when it is registered. It is not acceptable that a drug be put on the market unless one has got the risk/benefit situation straight. If one does not know about the benefit, the drug should not be registered.

J. Schou

We often find in our attempts to harmonize an approach to a safety problem occurring in a member state of the European Community that the same international manufacturer has marketed a drug in a number of member states, but at different times, with different indications, and with differences in dosage and in ADR information. Also, there can be national priorities because a national company is producing the drug. This indicates to me, at least, that the industry should see if it could harmonize its marketing in the different countries in which its products are approved. We have found also when investigating problems with a certain product that companies from the same industry-group in different countries do not know what their products are sold for in other countries. Therefore each international company needs to have an international branch to deal with these problems. So it's not only a matter of industry saying to the regulators: "Now go home and try to be helpful to the industry and harmonize"; industry should also go home and harmonize for itself.

J.F. Dunne

Well, there must be a response from industry to that. Is this simply a question of being capricious or are these differences inflicted upon you by rigorous regulatory agencies that all have rather different requirements, and might this whole issue not be harmonized on both sides? What is the response to that?

Y. Juillet

I should like to give an answer. It is true that for all products there are some differences between countries and in industry. But I have to say that nowadays, for international products, industry is looking for international information, if we look at the European Community, for instance, where the opinion of the Committee for Proprietary Medicinal Products (CPMP) is not yet binding. If the CPMP is providing summaries of product characteristics (SPCs), each country has the possibility of modifying the SPC, and each country modifies the SPC which is proposed by the CPMP. In the future, therefore, with the binding opinion of the European Community, harmonization will be easier. So if it is true that for the old products there could be better management on the part of industry, for the international products nowadays I think that regulatory authorities have part of the responsibility.

J.F. Dunne

Can I just ask what proportion of new products goes through CPMP channels in Europe these days?

Y. Juillet

For a new chemical entity, perhaps 25%. But of course, from 1 January 1995 most products will go through the European Union.

O. Doi

I have two comments. In Japan, we are also introducing summary bases of approval, from next year. As to harmonization, when I was director of the New Drugs Division of the Ministry of Health and Welfare we did try to promote harmonization, from the standpoint of benefit of patients, not from the standpoint of industry, and in the context of Research and Development. But when I became director of the Drug Safety Division, one year ago, I found that there had been no effort to promote harmonization, and I learned from industry that it had been facing difficulties because of different standards, different formats, and so on. As for adverse drug reactions, most companies are interested in getting information from other countries, but ADR criteria are not the same, and they have no idea whether the information has been derived by means of scientifically correct measures. Therefore we should start discussions on the promotion of harmonization from both scientific and administrative points of view.

S. Shapiro

What I find about the panel discussion in general is that there has been insufficient concentration, in viewing the achievements over the past 25 years, as to what the purpose of drug surveillance is. As I understand it, it is to determine the incidence of adverse reactions to drugs among persons exposed to the drugs, both overall and in specific sub-populations; Professor Sjöqvist has mentioned that we are interested in incidence rates in different ethnic groups. We are interested in incidence rates according to metabolic pathways, according to genetic determinants, and according to the prevalence or absence of other risk factors. Adverse-reaction reporting systems to my mind have value in two circumstances. The first is that they remain not only adverse reaction systems but adverse reaction reporting; they remain among the most sensitive and effective means of identifying previously unsuspected reactions. They also are of great help, as Professor Laporte has pointed out, when there is no benefit from the drug, and therefore any toxicity or any adverse-reaction-rate is unacceptable. What I have missed from the discussions has been an epidemiological and quantitative insight into how we use adverse-reaction reporting.

J.F. Dunne

I am sure we all agree with that. We must ensure that we accommodate that request. We should now hear from Professor Laporte about educational aspects of reporting — how he makes doctors aware of

their responsibility to report and so forth. You have been teaching medical students for a long time — have you some comments about the educational aspects? I notice that you also want to reply to Professor Shapiro.

J.-R. Laporte

My view on academically-based pharmacovigilance or drug surveillance activities may be naïve. We started in 1982 and tried to develop for the first time a voluntary reporting system in Spain in the framework of a wider programme which included such other activities as describing patterns of drug use, and carrying out drug utilization studies. One of our aims was to identify educational priorities. Another was to produce independent and problem-oriented information for prescribers, which we did in different ways. Thus, we prepared a therapeutic formulary for general practice, issued drug bulletins, broadened the programme of postgraduate continuing education for prescribers, extended postgraduate training in clinical pharmacology, which is now officially recognized, and devised complementary methods of drug surveillance, including not only voluntary reporting but also formal epidemiological studies. Things have improved very much in Spain in terms of consumption of drugs, kinds of drugs consumed, prescribing habits, and number of drugs prescribed per patient visit to the clinic. However, I cannot say to what extent our activities, and of course the activities of other universities which have followed our way of working in pharmacology and clinical pharmacology, have influenced these patterns of use, because societies are stochastic and unpredictable models that behave in ways that are not totally predictable. We know we may have had some influence not only on the regulators, but also on the drug industry, which tends to present the products in a different way. However, they may have been influenced also by our entering the European Community, by having more international relationships, by participating more broadly in conferences for harmonization, criteria etc. So it is very difficult to say that one factor or another had a given weight of influence in one's society; and any academic who would try to say that his or her activities had any influence on the society would be saying something that is very difficult to measure.

I should like to comment on something that Dr. Shapiro said. I think that when we discuss the taking of decisions on safety problems, and when we look at who is developing the voluntary reporting system and other epidemiological methods for the evaluation of drug safety, we see that all the systems for drug surveillance which are by now developed in Europe are based on the voluntary reporting of adverse drug reactions. There is no system which is a common system or at least the embryo of a common system for the evaluation of risks. I have here an example of the risk of incidence of the most severe drug-induced diseases in

relation to the use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDS). It shows that many of the drug-safety decisions made in the last ten to twenty years in many of our countries were taken because of blood dyscrasias or because of the risk of hepatotoxicity in some cases or of hypersensitivity reactions. But the incidence of, for example, upper gastrointestinal bleeding is two orders of magnitude higher than the incidence of agranulocytosis and aplastic anaemia, and also of pseudoallergic reactions, and most probably also acute hepatitis caused by hepatotoxic drugs. Now, in regard to case fatality numbers, even taking mortality as an indicator of the severity of these reactions, gastrointestinal bleeding and end-stage renal disease stand first. The problem is that we, in academia, in regulatory agencies, in the pharmaceutical industry, tend to focus our attention more on very rare events, in which we suppose, through with little evidence, that drugs have a high etiological fraction. The etiological fraction of, for example, aspirin and NSAIDS in the production of upper gastrointestinal bleeding is 37% in our country. So we can say that in our country more than one-third of all upper gastro-intestinal bleeding is caused by aspirin and NSAIDS. No one pays attention to this because this is no news, but in terms of public health this is much more a problem than agranulocytosis or aplastic anaemia, for example.

J.F. Dunne

Thank you very much. That is extremely interesting. Perhaps we could leave until another session the further discussion of the educational aspects. One topic we must discuss, however: what are we doing for all of those countries that are not subscribing directly to our international monitoring programme — those white areas on the map that Professor Edwards showed us? I think we can claim that we have done one or two creditable things within WHO. One thing we have done, in collaboration with Professor Awadzi, on ivermectin is a series of focused studies on the safety aspects of using ivermectin to suppress the clinical sequelae of onchocerciasis. Ivermectin is a new drug for onchocerciasis, as most of you know, which has been developed by Merck, and it is remarkably efficacious in suppressing the microfilarial load if given once a year. An aspect of the development of the product is that it needed to be used from the outset in a community setting in countries without highly-evolved regulatory authorities. WHO took part in what we considered to be a suitable monitoring exercise. I have been rather surprised that nobody has talked much about post-marketing surveillance studies, for what we did was in fact a post-marketing surveillance study on ivermectin. We have also taken part in field studies of eflornithine, a new drug for African sleeping sickness developed by Merrill Dow. I believe they have provided us the sort of information that Professor Shapiro was wanting with denominators and so forth. WHO sponsored one study in Liberia on 60,000 patients

who received ivermectin, and I wonder if Dr. ten Ham could say something about the relevance of voluntary monitoring and focused monitoring, in relation particularly to developing countries. He will do that together with Dr. Phillips-Howard, and he will concentrate on experience gained with the recent admission of additional countries into the international scheme. Some of these do not, as yet, have highly-evolved regulatory machinery. Is this an international system, as it now exists, a utility which we can confidently recommend to countries at every level of development?

M. ten Ham

Well, first of all, we do not have answers to all the questions raised this afternoon on information, monitoring, and so on. One problem, of course, well-known in monitoring, is that it is just the beginning of a series of activities. It needs to be followed up by a regulatory authority. Regulatory authorities need information on adverse effects to be able to decide whether regulatory action is needed. This implies the existence of a regulatory agency, of course. If there is none, then probably the monitoring of adverse effects is a rather vain activity. However, many of the countries that have recently joined our programme, such as Morocco, Tanzania, Costa Rica, Republic of Korea, Tunisia and the Slovak Republic, have a regulatory agency in place; perhaps, less sophisticated than in most European countries but certainly some kind of regulatory activity. And it seems that these countries do benefit from the experience of the Programme, and from help they receive from others.

Apart from that, we try outside the direct activities of the monitoring programme to inform these agencies of regulatory activities in other countries. These drug alerts and the pharmaceutical newsletter, *WHO Drug Information*, are directed mainly at the developing countries — EEC member states and other highly developed countries have other mechanisms to exchange their information, and they are more providers of information, which we can pass on to others in need of it. Dr. Lumpkin has referred to the other products associated with adverse effects. Of course, we cannot cover everything; we have a small staff and very little money. But we are doing something about adverse effects of immunization, which have been of concern to many vaccination programme managers. The methodology at the basis of a reporting system for such reactions is basically similar to that of adverse-drug-reaction programmes, and, as a consequence, we have brought the two together at a meeting in Ottawa, and we are having very soon a meeting, co-sponsored by the USFDA, to try to develop methods of monitoring these kinds of adverse effect. This becomes, of course, important not only because of the examples provided by Dr. Rawlins on whooping-cough and other

instances, but also in view of quality control of vaccines used in developing countries.

This brings me back to the monitoring of drug effects in developing countries. There is a joint effort going on within WHO headquarters between several units concerned with these problems, and Dr. Phillips-Howard is in a better position to give details on these activities.

P.A. Phillips-Howard

We have not done so well with regard to developing countries. WHO's mandate is to serve all countries, including the developing countries, and this has enormous public health implications. I would urge that one of the outcomes of this meeting be a recommendation to set up a working group to better define the needs of developing countries and how to go about setting up a drug-safety monitoring scheme. There has been much discussion on technology transfer, cooperation, communication, and collaboration, but little reference to developing countries. We need to turn some of our expertise, and the wealth of expertise in this room is huge, towards the needs of developing countries.

Case management is a major element in the control of most tropical and communicable diseases in developing countries, and safety data are mostly gathered by the developed countries, which may provide some insight but are of little help in interpretation for risks, costs and benefits. Also, as we have heard, there are ethnic differences in metabolism of drugs. Taking malaria as an example, our mandate is to set up a mechanism to establish the safety of antimalarials in developing countries, and there is wide-scale uncontrolled use of anti-malarials, as of most antimicrobials, in developing countries. The problem is getting very much worse now, because of the rapid evolution of resistance, which Dr. White will describe tomorrow. One important point to consider is that not only are there very few systems in most developing countries to protect vulnerable populations against harmful effects of drugs, but also we must anticipate that the ever-increasing rise in HIV seroprevalence will compound the problem of drug toxicity in developing countries: about 40% of pregnant mothers in Uganda are HIV positive, and nearly one in three in Kenya. In many countries up to 20% of children seen in outpatient clinics are seropositive. This has important public health implications related to the use of drugs, drug-use practices, and drug safety.

The governments of some African countries have asked us to assist them in setting up a cost-effective mechanism for monitoring toxicity associated with the antimalarials. In such countries the concern is the switch now from chloroquine to the long-acting sulfa drugs, which are freely available over the counter, as first-line medication for malaria and upper respiratory tract infections.

We are trying to develop guidelines based on technical documents, many of which we are still in search of, and would be very happy to

provide an outline of these guidelines. We would be most obliged to people here for any further information they could provide. The guidelines will have to be extremely practical and adapted to the health infrastructure of the countries. For example, we have talked a lot about educating doctors, but in many developing countries most drugs are not issued or administered by doctors. So we welcome your expertise, your advice and your support on how to deal with the methodological issues associated with monitoring in developing countries without suitable infrastructure, and how we can set up some simple form of sentinel site monitoring and post-marketing surveillance appropriate to developing countries.

M. Hassar

Pharmacovigilance is very important for developing countries but requires a certain degree of development of medical practice; to be able to report certain adverse drug reactions some tests may be needed and often they are not available, or sometimes they add to the cost of medical care, and this can be an important constraint. However, pharmacovigilance would have the advantage for such countries that it can improve medical care; doctors would have to improve their practice in order to report adverse drug reactions. Another problem for these countries is that reports of adverse reactions may not be adequately documented to permit sometimes important decisions to be taken after reviewing reports.

S. Oksüz

I completely agree with Dr. Phillips-Howard's suggestion of a separate working group on drug-safety monitoring in developing countries. Though my own country, Turkey, is a large one with ample resources and manpower, it does not have the infrastructure for post-marketing surveillance. For example, it is almost impossible to find reliable statistical data on many aspects of health care in the population, and this includes the surveillance of drug safety. It must be possible to prepare some common guidelines for developing countries, despite their diversity, to undertake drug-safety surveillance.

J.F. Dunne

Dr. White, you have had experience of working in the most sophisticated of national medical infrastructures. You have also given many years of your career to working in developing countries. You have planned and executed many studies concerned with the efficacy and safety of antimalarial preparations, in particular, in field conditions. Could you offer a few general comments on how you see the way ahead?

N. White

We have got to accept that there are double standards. We have heard today about harmonization and many other words that imply that we are going for a single standard. That is just pie in the sky for most of the world, since for the large portion of the map we saw this morning countries have an annual per capita health expenditure of less than US\$ 10. Most of the drugs taken in these countries are not prescribed — they are bought from shops and not through medical channels — so it is impossible to obtain denominators.

I think a powerful organization such as WHO could encourage a separate method of trying to obtain information, one that involves manufacturers, for instance. Perhaps the actual amount of a drug produced in or imported into a country might provide a useful denominator. It is simply impossible to obtain reliable data on drug usage through hospital or rural health-care facilities.

We must also accept that the drugs generally available in the tropics are evidence of a double standard. Many of the drugs shown on the list we saw this morning to have been withdrawn in developed countries, or drugs with comparable adverse effects, are still being used in developing countries. Most of the anti-parasitic drugs were invented over 100 years ago. Who in the West would tolerate malarsapil, a drug with a 5% mortality associated with it? Well, there is nothing else available to treat African trypanosomiasis.

One of the reasons for maintaining an adverse-drug-reaction reporting system is to identify among many contenders those with the most unfavourable adverse-drug-reaction profiles. There are always others to take their place. In developing countries the option of choice rarely exists; there are no new drugs made for the tropics, because there is no money to be made by the pharmaceutical industry in investing in new drugs. The Third World simply cannot afford the new treatments.

I am not denying the value of monitoring systems; they are important in regulating the use of many of the unnecessary drugs that are also widely used in the tropics, but I would also hope that we could incorporate in all of this a plea for mechanisms which would allow the pharmaceutical industry to obtain sufficient benefits to again turn to the Third World as it did during the colonial era and consider that there are great pharmaceutical challenges there, if not a lot of money to be made. Some form of creative accounting is needed in the richer countries to encourage their pharmaceutical industries to invest in the Third World. Also, somehow, we have got to come to terms with the legitimacy of double standards, because it may well be that a drug which would not be acceptable in the West because of its adverse-reaction profile would be acceptable in a country which needed it, had no alternative, simply because nothing else is affordable. These are difficult concepts to come to terms with, but we cannot just ignore them.

SESSION II

**METHODOLOGICAL APPROACHES:
CONTRIBUTION TO
DRUG SURVEILLANCE**

Chairman: Michael D. Rawlins

**Spontaneous Reporting
Case-Control Studies
Randomized Controlled Trials
Causality Assessment**

SPONTANEOUS REPORTING

René-Jean Royer *

Introduction

Spontaneous notification is a general term covering sporadic, voluntary, compulsory monitoring, as defined by Napke¹². Its main goal is the detection and notification of events or side-effects by the patient, the practitioner, or prescribers in general. Often, adverse drug reactions (ADRs) are centralized nationally and assessed before being stored in a data bank for further comparison and analysis of the alert signal. WHO undertakes the international collection of national reports. The difficulty is in obtaining as many notifications as possible and maintaining and, if possible, strengthening the collaboration between the professionals and the spontaneous reporting schemes.

Spontaneous reporting will probably remain the most appropriate alert system for the surveillance of drug safety. It is still the fastest and the cheapest system for supervising the drugs on the market.

Most developed countries and the European Community have initiated at different levels a drug surveillance programme, designed mainly to compile spontaneous notifications from health professionals and marketing-authorization holders. The goal is to detect an alert signal which could be further analysed.

The advantages of spontaneous notification

The main advantage of spontaneous notification is that no other method has the same capability to oversee all drugs all of the time in a whole population. Moreover, it is easy to operate, does not interfere with medical habits, and, as it covers a large population, can quickly produce an alert signal¹⁶.

An expert group convened in 1992 by the European Commission on Pharmacovigilance in the European Community¹⁴ agreed that such systems were of proven and established value in generating ADR signals of previously unsuspected reactions — for example, hypothesis generation; identifying previously unsuspected reactions — hypothesis testing, particularly for disorders that commonly have an iatrogenic basis; identifying factors that predispose to ADRs (the dose, for example) in susceptible populations (age, sex, underlying disease, medical history, etc.); providing information about comparative ADR profiles of products in the same therapeutic class; monitoring the continued safety of pharmaceutical products through the duration of

* Commission nationale de Pharmacovigilance, Ministère de la Santé, Paris, France.

their use and after significant extensions to their indications; and identifying drug-drug interactions.

The disadvantages of spontaneous reporting schemes

Underreporting. The main disadvantage is underreporting, which makes it difficult to determine the true incidence of side-effects. Moreover, the rate of notification can vary from one drug to another in the same period of time. It is related to the drug's marketing life: higher during the first three years, and decreasing afterwards. Adverse reactions also tend to increase when the attention of doctors is drawn to specific problems. This relationship was explored by Rawlins, who gave as an example the reporting of the neuromalignant syndrome to the Committee for the Safety of Medicines, in the United Kingdom¹³.

The media often introduce an involuntary bias in the course of exposing an alleged problem with a particular medical product. Griffin gave the example of triazolam⁸, which, following the published report of Van der Kroef, was given extensive exposure on Dutch television, with a consequently large increase in notifications of side-effects. He gave a further example of the same phenomenon in the United Kingdom, with the triple vaccine (diphtheria/tetanus/pertussis).

Medical publications have similar, though less extensive, consequences.

Specific monitoring requirements can also induce bias. In New Zealand, intensive monitoring increases the relative number of cases from the products concerned. The French system systematically avoids this kind of bias¹⁵.

Inaccurately low incidence rates. Underreporting introduces major bias in the estimation and comparison of frequencies¹⁻², and it is hazardous for estimating relative risk²⁰. Usually the incidence rate is undervalued, owing to the overvalue of the denominator (number of treatments) and the undervalue of the numerator (underreported ADRs). Of course, this maintains the value of the alert signal² but is a disadvantage if one wants to determine true incidence.

Inability to identify long-latency ADRs. Spontaneous reporting is inherently unable to identify ADRs with a long latency, though a report may occasionally generate a signal⁷⁻¹⁴.

The separation of ADR signals from background noise depends on the reporting schemes, on the quality of the notification, on the quality of the selection of the reports, and on the accuracy of drug assessment. There is a great diversity of such schemes even within the European Community, and the interpretation of data they provide fluctuates widely between member states and pharmaceutical companies.

Consequently, pharmacovigilance has to use methods other than spontaneous notification, especially epidemiological methods.

Reasons for underreporting

Underreporting is the major disadvantage of spontaneous reporting. The reasons for underreporting are now well recognized. They are related to the patient, the doctor, the medicinal product, and the adverse drug reaction itself.

The patient. Drury⁴ has the impression that there are two types of patient: those who attribute every evil to the drugs given by the doctor, and those who will follow advice implicitly through every sort of adverse reaction until “death us do part”. Of course, the first group is the more vocal.

The doctor. Doctors are the main cause of blockage. Some reasons are understandable, such as difficulties of diagnosis, a great number of side-effects, time constraints, lack of knowledge of pharmacology in general and of drugs in particular, and low patient-reporting. Others are more psychological: guilt feelings, denial, poor understanding of the objectives and logistics of reporting, a doctor's reluctance to attribute the patient's trouble to his own actions, diffidence, laziness, and the feeling of working for an anonymous system instead of for patients.

Sometimes a psychological barrier can limit the acknowledgement of the relationship between a drug and a side-effect. For example, for a long time doctors believed that bismuth salts did not cross the intestinal barrier, and probably some encephalopathies were attributed to viruses that were undetectable at that time. In France, after the Australian publication, it was surprising suddenly to receive a number of reports of encephalopathies related to bismuth.

Our inability to imagine the possible transport of bismuth from intestine to blood blocked the recognition of the causal relationship.

The medicinal product. Some drugs present a specific risk related to the class of drug, and adverse reactions are generally notified. Examples are:

- hepatological, or haematological disturbances with antidepressants,
- haematological disturbances with analgesics, and
- cough from angiotensin-converting enzyme (ACE) inhibitors.

The same applies to side-effects related to the pharmacodynamic properties of the drug. But more trivial and less known effects are less likely to be reported.

The marketing life of a medicinal product also affects the rate of notifications. It increases during the first three years, and then decreases slowly. For a comparison between drugs of the same class it is necessary to take into account the date of marketing¹³.

We also have to take into account the sales and the efficacy of marketing, which influence directly the number of side-effects and indirectly the perception of their frequency.

The adverse drug reaction. An ADR can be confounded with a customary complication of the disease. It can be too new or too common to be notified. The evaluation of severity is sometimes

difficult. Also, it is necessary to have better statistics on mortality and morbidity. Those established for general health purposes may be modified to serve as a valuable indicator for new ADRs. This requires close cooperation between the statistical offices and the drug surveillance authorities¹⁰. In general, severity and novelty of ADRs increase the likelihood of notification^{4,8,10,14,15}.

Trends in rates of underreporting of adverse drug reactions.

There are few studies of rates of underreporting of ADRs. Griffin⁸⁻⁹, in a survey of ADR reporting in 15 countries, based on the maximum number of reports received in any single year, used two methods of expressing the rate of ADR reporting: the absolute number of ADRs year by year for each country surveyed; and the rate of ADR reporting per million of the population per annum. This rate varied considerably among countries. In general, the rate of ADR reports $\times 10^{-6}$ population per annum showed an inverse correlation with the number of drugs prescribed per caput per annum.

In a study in the United Kingdom, reported by Walker and Lumley¹⁹, 100 practitioners observed and reported 576 ADRs from 36 470 consultations. Only 35 (6%) of them were notified to the Committee for Safety of Medicines. The reporting rate varied with the seriousness of the reaction: 10.6% of the severe reactions and 3.5% of the more trivial.

In France, in the region covered by the Lorraine Regional Centre, from a panel of private practitioners using the same method, 1.8% of the cases were notified to the Centre (22% of severe and 0.6% of trivial reactions). Total notifications to both regional centres and industry are estimated at about 3.6 to 4%. It is not surprising to find the same rate of reporting in France as in the United Kingdom, since their populations and the annual number of reports are similar.

Many of the authors referred to, and others such as Faich^{5,6}, have noted that the rate of underreporting has varied relatively little from year to year.

Proposals for improving rates of spontaneous notification

It seems difficult to influence the reporting of ADRs and other drug-related problems; the main target is the doctor. To improve spontaneous notification we need to¹⁶:

- train students in clinical pharmacology and pharmacovigilance;
- inform the doctors as often and as completely as possible about new severe side-effects;
- persuade them to contribute individually to knowledge useful to everybody, by participating in inquiries and notifications; and
- stimulate their active participation in the system by providing them with feedback and an easy system of consultation.

The French system, which is decentralized and open to practitioners, is a means of achieving this aim. The number of queries by practitioners to the regional centres has increased rapidly and now numbers over 25,000 a year¹¹⁻¹⁶⁻¹⁷.

We also ought to be conscious that to medical doctors time is not only money but also care; we should limit their regular participation to the reporting of new or severe side-effects, and we should urge doctors and pharmacists to become conscious of their social responsibility.

Nevertheless, it would be wrong to think that spontaneous reporting could provide epidemiological data and permit a determination of frequencies. It is only an alerting system, generating hypotheses or permitting in emergencies the making of some public health decisions.

The size of the surveyed population

Motivating practitioners to increase their reporting rates would increase the number of observed patients.

Another way leads to increasing the pool of side-effects by using larger areas such as the European Union or countries world-wide with developed national spontaneous reporting schemes. For this purpose, some such schemes require from the manufacturers reports of foreign individual ADRs suspected to be related to their products.

Under the auspices of CIOMS, a working group has developed and implemented a standardized method for reporting post-approval ADRs. The method is based on a set of uniform definitions and procedures and the use of a single reporting form. The objectives are to standardize national foreign reporting and to limit the waste of time due to the repetitive submission of reports to numerous countries.

The WHO Collaborating Centre at Uppsala compiles in a large data bank and analyses the individual reports sent by national regulatory authorities. A lot of data can be obtained through the WHO system, and this could make the use of foreign individual notifications by national authorities superfluous.

References

1. Bégaud B., Pere J.C., Tubert P., Barat C., Haramburu F., Albin H. Centres de renseignements sur les effets indésirables: une fonction d'alerte aussi. *Thérapie* 1987; **42**: 231-237.
2. Bégaud B., Tubert P., Haramburu F. et al. Comparing toxicity of drugs — Use and misuse of spontaneous reporting. *Post Marketing Surveillance* 1993; **5**: 69-76.
3. Dangoumau J., Lagier G., Royer R.J. A drug information ADR collection network: The French system. *Drug Inform. J.* 1986; **20**: 337-346.
4. Drury V.W.M. Monitoring ADRs in general practice. In: Gross F.H. and Inman W.H.W. *Drug Monitoring* 1977; Academic Press Ed.
5. Faich G.A. Postmarketing surveillance of prescription drugs: current status. *Clinical real life studies program*, Oct. 1986.
6. Faich G.A. Massive under-reporting of adverse drug reactions continues. *Reactions* 7 Sept. 1991; **367**:5486.

7. Fletcher A.P., Griffin J.P. International monitoring for adverse drug reactions of long latency. *Adverse Drug Reaction and Toxicology Review* 1991; **10**: 189-210.
8. Griffin J.P. Survey of the spontaneous adverse drug reaction reporting schemes in fifteen countries. *British Journal of Clinical Pharmacology* 1986; **22** Suppl 1: 835-1005.
9. Griffin J.P., Weber J.C.P. Voluntary systems of adverse reaction reporting: Part II. *Adverse Drug Reaction Acute Poison Review* 1986; **1**: 23-55.
10. Kimbel K.H. Thirty years after thalidomide still plenty to do. *International Journal of Risk and Safety in Medicine* 1993; **4**: 1-12.
11. Moore N., Biour M., Paux G., Loupi E., Boismare F. and Royer R.J. Adverse drug reaction monitoring. *Lancet* 1985; **8463**: 1056.
12. Napke E. Present ADR monitoring methods in drug monitoring, Gross F.H. and Inman W.H.W.. 1977; **1 vol.**: 311pp. *Pergamon Press Ed.*
13. Rawlins M.D. Spontaneous reporting of adverse drug reactions. II: Uses. *British Journal of Clinical Pharmacology* 1988; **26**: 7-11.
14. Rawlins M.D., Fracchia G.N. and Rodriguez-Farré E. EURO-ADR: Pharmacovigilance and Research — A European perspective. *Pharmacoepidemiology and drug safety* 1992; **1**: 261-268.
15. Royer R.J., Lagier G. *La Pharmacovigilance*. 1986; **1 vol.**: 79 pp. *Spécia Ed.*
16. Royer R.J. *Regulatory Affairs* 1990; **2**: 449-453.
17. Royer R.J. Clinical pharmacology and pharmacoepidemiology. Challenges by the European Community after 1992. *International Journal of Clinical Pharmacology Therapy and Toxicology* 1992; **30**: 449-452.
18. Stephens M.D. The detection of new adverse drug reactions. 1988; **2^e édition, 1 vol.**: 366 pp. *Stockton Press Ed.*
19. Walker S.R., Lumley C.E. *Reporting and under-reporting of adverse drug reactions*. R.D. Mann (Ed.), Parthenon Publishers 1987; **198**: 115-126.
20. Waller P.C. Measuring the frequency of adverse drug reactions. *British Journal of Clinical Pharmacology* 1992; **33**: 249-252.

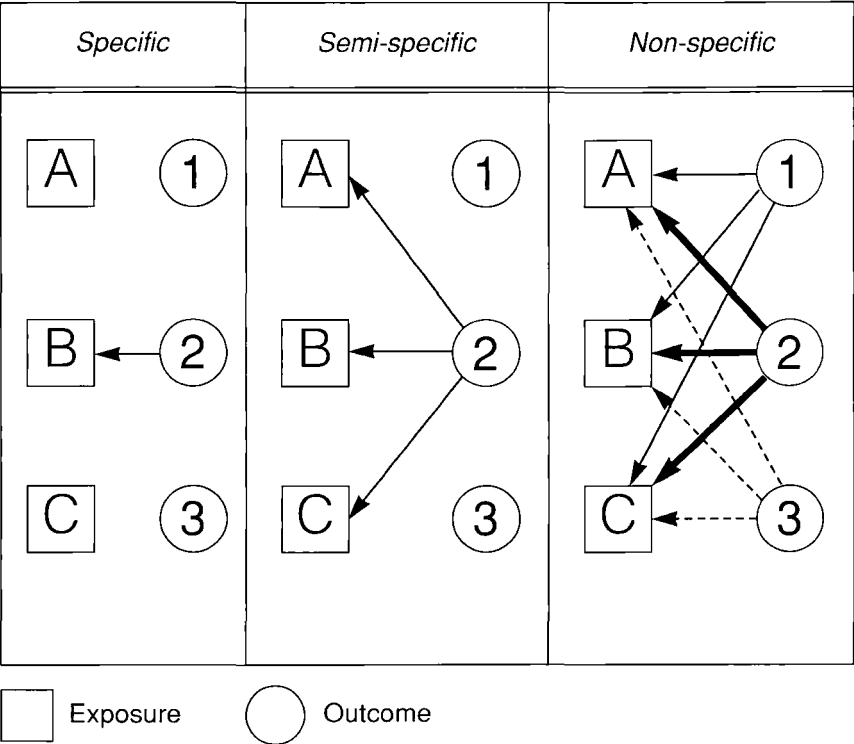
CASE-CONTROL STUDIES

Samuel Shapiro*

It is entirely appropriate on the 25th anniversary of the WHO reporting system to talk about case-control studies. One reason why I consider it appropriate is that case reports optimally used constitute an informal case-control study methodology: the reporter assumes that among putative controls there is a very low frequency of exposure. Hence, one can reach or approach a reasonably valid inference of causality from a small series of case reports, particularly if the clinical documentation is thorough.

Conceptually, there are three types of case-control study. In Figure 1, the circles represent outcomes (cases), and the squares represent exposures. For simplicity, the controls and the nonexposed are omitted, and should be understood. Three types of case-control study are presented: specific, semispecific and nonspecific.

Fig 1. Types of case-control studies



* Slone Epidemiology Unit, Boston University School of Medicine, Brookline, MA, USA

In a specific case-control study a single disease, e.g. lung cancer, is evaluated in relation to a specific exposure, e.g. cigarette smoking. No other information is recorded. Such a study is a conceptual abstraction, and in practice it would seldom be valid. In this instance, for example, one would want to know not only about smoking but also about age, or about exposure to asbestos, or about urban or rural environment, which might be, e.g., A and C. And indeed we must know about A and C in order to assess properly the role of B.

A semispecific study is one in which a single disease, or a single set of diseases, is evaluated in relation to a wide range of exposures: B might again be cigarettes, and A might be, once again, asbestos, and C might be rural or urban environment; and now, in evaluating B, allowance is made for the potentially confounding effect of A and C. Similarly, in evaluating C allowance is made for A and B, and in evaluating A allowance is made for B and C. This is the conventional *ad hoc* type of case-control study.

A method that our group developed some 15 years ago was to extend case-control methodology to the third example in the figure, i.e., the nonspecific surveillance of many diseases, all monitored at the same time, in relation to multiple exposures. Thus, we now monitor not only disease 2 as in the first two parts of the figure, but also diseases 1 and 3 in relation to exposures A, B and C. That is, we now monitor multiple diseases in relation to multiple exposures. In this situation, case-control methodology can now generate and test multiple hypotheses — as with cohort studies; and an advantage over cohort studies is that, for commonly used drugs, case-control surveillance is more robust.

Next, I would like to consider a few comparative features of cohort and case-control studies (Table 1). The first consideration is that, if an exposure is exceedingly rare, the case-control approach is not an efficient method for determining risk. However, if the outcome is exceedingly rare, that methodology is just about the only one that's available. With regard to minimizing bias in the ascertainment of exposure, case-control studies can sometimes do this, but since cohort studies ascertain the exposure before the event has taken place they have an absolute advantage. In ascertaining diseases (outcomes), case-control studies can frequently achieve much greater precision than cohort studies. In the measurement of absolute risk (that is, the incidence in the exposed minus the incidence in the nonexposed) cohort studies have an advantage. However, that advantage is not absolute: if the incidence of the disease at issue is known, absolute risk can also be estimated from case-control data. In minimizing cost, case-control studies have the advantage. Cohort studies, in general, tend to have more dropouts than case-control studies, particularly when the follow-up needs to continue for 10, 20, or even 30 years, as may be the case in the evaluation of carcinogenic hypotheses, for example. Finally, a disadvantage of case-control studies is that they can be beset by the

inappropriate choice of controls; but if sufficient care is taken to ensure their proper selection this problem can be avoided or at least minimized.

Table 1. Comparative features of cohort and case-control studies

	Cohort	Case-control
Study of rare exposure	+	
Study of rare diseases		+
Minimizing bias in ascertaining exposure	+	
Minimizing bias in ascertaining diseases		+
Measuring absolute risk	+	
Minimizing cost		+
Special problems		
Dropouts	+	
Choice of appropriate controls		+

Next, I would like to consider the various types of bias that may exist in case-control studies (Table 2). Selection bias occurs when there is non-independence of the outcome and the exposure. This happens if the disease influences, or is otherwise related to, the exposure. An extreme example of how this may happen is when the diagnosis is conditional on the exposure. The disease might influence the exposure before it has been formally diagnosed, so that, for example, a patient with as yet undiagnosed cancer might begin to use some particular drug because he's feeling sick; the drug is then falsely implicated as the cause. Information bias may occur when there is unequal recording of the information (among cases and controls) on the part of either the observer or the subject. Confounding bias is the central and most important problem in epidemiological research. Some confounders (e.g., age) can be precisely recorded, and hence precisely controlled. Certain confounders, however, can only be incompletely recorded (e.g., socioeconomic status), or they may be unknown. It is because confounding may be incompletely recorded, or even be unmeasurable, that randomized control trials retain the absolute advantage relative to any of the nonexperimental methods used in epidemiology.

One further point to make about confounding is that the problems confounding are exactly symmetrical, whether the methodology is based on a case-control or a follow-up approach.

Table 2. Case-control studies: types of bias

1. Selection bias	Nonindependence of outcome and exposure <ul style="list-style-type: none">• if disease influences exposure• if diagnosis is conditional on exposure
2. Information bias	Unequal recording of information <ul style="list-style-type: none">• observer• subject
3. Confounding bias	Factors related independently to outcome and to exposure <ul style="list-style-type: none">• known – completely recorded<ul style="list-style-type: none">– incompletely recorded• unknown

How do we deal with selection bias in case-control studies (Table 3)? Good case-control methodology relies very much on incident cases only, so that one can be reasonably reassured that the exposure antedated the outcome; this means that the case-control approach tends to be rather unsatisfactory when it comes to the evaluation of chronic conditions of insidious onset, such as hypertension or hypercholesterolemia. I've already referred to the need for the careful selection of controls. Another source of selection bias in this type of study is failure to enrol 100% of the cases or the controls, giving rise to the possibility that those that are not enrolled may be different from those that are. This possibility can be minimized or avoided by first specifying the sampling frame, and then by making strenuous efforts to attain 100% enrolment, or as close to 100% as possible.

Table 3. Case-control studies: selection bias

<ul style="list-style-type: none">• Incident cases only• Comparable controls• Specified sampling frame with 100% enrolment• On the null assumption, independence of outcome and exposure

Finally, it is worth re-emphasizing that case-control studies must be designed so that on the null assumption the exposure and the outcome are independent. The principle of independence can perhaps best be illustrated by reference to the large literature on analgesic nephropathy: in many studies a patient with end-stage renal failure who has been heavily exposed to analgesics is given that label; a patient who has not been exposed is given another label. To assess correctly whether analgesics cause nephropathy, the exposure and the outcome must be kept independent.

How do we deal with information bias (Table 4)? Information bias tends to be the Achilles heel of case-control studies. Sometimes, however, that bias can be avoided — for example, by reviewing medical records from which the diagnostic information has been removed. The observer then decides on exposure status without knowledge of whether the patient is a case or a control. But that is the exception; more often than not, possible information bias cannot be ruled out in case-control studies, and any association must be judged in that light. One potentially powerful contribution of automated data bases, or of general practitioner records in other settings, is that it may be possible, independently, to validate the accuracy of the drug-exposure histories ascertained by interviewing cases and controls. Validation of exposure in that way would enormously strengthen the validity of case-control methods.

Table 4. Case-control studies: information bias

-
- Standard procedures
 - “Blind” observation if possible — observers
 — subjects
 - Validation — independent source
 — independent observer
-

How do we deal with confounding bias (Table 5)? The first observation, of course, is that we can never be sure we have dealt with it in nonexperimental studies, whether of the case-control or the cohort type. The second observation is that a minimum requirement for dealing with confounding is the standardized, complete, and symmetrical recording of known or potential confounders among cases and controls. Beyond that there are the usual methods used in epidemiology, which are exclusion, matching, stratification, and standardization either by weighting or by multivariate analysis.

One point that needs to be stressed at this meeting is that the most important failing of automated data bases, as currently used, has been their failure to adequately control confounding. I mention this point

because it bears on case-control methodology. I believe that the method by which control of confounding might be improved in automated data-bases would be to use them to mount nested case-control studies. The exposure information for cases and controls would then be augmented by the recording of confounding data obtained directly from the patients.

Table 5. Case-control studies: confounding bias

-
- Standard recording
 - Adjustment for confounding factors by:
 - exclusion
 - matching
 - stratification
 - standardization
-

Concluding remarks

Over the past 20-30 years the case-control approach has played an indispensable role in the quantitative elucidation of some of the most compelling problems related to drug safety. Examples abound: oral contraceptives and thrombosis, estrogens and endometrial cancer, NSAIDs and peptic ulcer disease, to mention just a few.

Our own contribution has been to extend case-control methodology from the *ad hoc* evaluation of specific hypotheses to a comprehensive drug surveillance system. The next task is to improve and extend the methodology still further. One obvious way to go is to bring about an effective application of that methodology to automated data-bases, as discussed above. Another way is to extend case-control surveillance to the monitoring of rare diseases known to be caused by many drugs (eg. blood dyscrasias, acute renal failure, severe cutaneous reactions, etc.). [This topic is considered at this meeting at greater length by Dr. Wiholm]. It is also to be hoped that the critical application of case-control principles will make case-reports more informative.

THE CONTRIBUTION OF CONTROLLED CLINICAL TRIALS TO DRUG SAFETY

Michael J.S. Langman

An initial judgement would suggest that controlled clinical trials present an inappropriate format for assessing drug safety. The archetypal clinical trial includes carefully selected patients, where the drive is towards judging clinical efficiency. Those included, though having the disease to be studied, may nevertheless be selected according to such rigorous criteria that they cannot be considered generally representative of drug recipients in practice. Thus they may not include the very elderly, or those receiving other treatments, whether for the same or for other diseases, simultaneously.

These features make the classical exploratory trial a generally unsuitable format, but the pragmatic trial bears a greater relationship to practice, with the emphasis not upon “can treatment be shown to work?” but upon “does treatment ordinarily work?”.

A second feature of a clinical trial which limits value in safety assessment is that studies are often too small to be likely to detect unexpected hazards. Anticipated pharmacological actions on systems outside those to be modulated may well be assessable, however.

Controlled clinical trials can nevertheless contribute to drug safety in at least four ways. Firstly, standard clinical trials may make useful contributions, in particular by confirming that dosages required to produce pharmacological effects are well judged. Secondly, larger trials with wide entry criteria may have particular value in judging safety in practice. Thirdly, it may sometimes be possible by combining data by meta-analysis to demonstrate safety issues which are not discernible in individual small studies. Fourthly, the deliberate design of randomized trials of large size specifically to assess safety may make a valuable contribution.

Standard clinical trials

Provided they are conducted in sufficient detail they may, for instance, have special value in establishing firmly the lowest doses required — typically of hypotensive drugs. Thus, with hindsight, insufficient attention may have been paid to the lowest possible doses of angiotensin-converting enzyme inhibitors in treating hypertension and cardiac failure. The result was that when released for general use there was an undesirable level of adverse effects, typically with over-dosage, such as hypotension and renal failure.

* Department of Medicine, Queen Elizabeth Hospital, University of Birmingham, England.

One could speculate that such events could arise from anxiety to ensure an effective dose rather than to establish that which was least effective and thus most commensurate with drug safety.

Large trials

Balance between advantage and disadvantage — hypertension.

The balance between advantage and disadvantage is sometimes clearly assessable. Thus, the Medical Research Council (MRC) trial for mild hypertension randomly assigned treatment in general practice by beta blockade, propranolol or placebo, and examined benefits as well as drawbacks.

Table 1 displays patterns of adverse effects in the male entrants. Treatment was clearly not without its drawbacks. At the same time the rates of stroke occurrence were reduced by nearly 50%. This apparently satisfactory result has to be placed in the context of requiring nearly 1,000 patient years of treatment to stop one such event.

It then has to be asked whether the treatment regime is one that should be accepted as a standard rather than as one that demonstrates achievable benefit, but probably better obtained by another route, using less unpleasant remedies.

Table 1. Medical Research Council trial of treatment of mild hypertension¹

% [men]	Bendrofluazide	Propranolol	Placebo
Impaired glucose tolerance	7.7	3.4	3.3
Gout	12.8	6.3	1.3
Raynaud's phenomenon	0	5.1	0.2
Lethargy	3.6	5.3	0.5
Patients	2236	2385	4525
Stroke rates			
Active Treatment	1.4		
Placebo	2.6		

(per 1000 patient years)

Results obtained by the MRC trial can be compared with those in the Systolic Hypertension in the Elderly Programme (SHEP). This also

used a diuretic (chlorthalidone rather than bendrofluazide, and a beta blocking agent (atenolol rather than propranolol). Treatment was demonstrably effective, with a 36% reduction in stroke rates by active treatment. Adverse effects (Table 2) were not prominent, despite the fact that the stepped programme allowed combination of the active agents.

The contrast between the outcomes of the two studies in terms of adverse effects is quite striking, and difficult to explain. Nevertheless, one possibility derives from the rigorous entry criteria of the SHEP study². This randomized 4927 individuals, but they were drawn from an initial possible entry group of 447,921. It could be asked whether the entry and conduct criteria, apparently reasonable in themselves, resulted in the inclusion of a group of highly motivated, stoical, and atypical individuals in acceptance of drug problems. The criteria included four blood-pressure measurements on two separate visits, physical examination, twelve-lead electrocardiogram, behavioural assessment, and measurement of blood levels of cholesterol, uric acid and others, as well as repeat measurements.

The application of quality-of-life analysis is often, and very reasonably, advocated. It is not always immediately obvious what the outcome means. Thus a recent study compared the effects of captopril and enalapril on quality of life³ and established differences which, in the authors' opinions, were "substantial" and "clinically meaningful". Examination of the paper showed that the basis included a

Table 2. Systolic Hypertension in the Elderly (SHEP)²

Identified 447,921 individuals

Met criteria	11.6%	Base-line visit 1	2.7%
Eligible base visit 2	1.7%	Eligible randomize	1.2%
Randomized 1.1%			

Adverse effects (%) in SHEP

	Active	Placebo
Postural faintness	12.8	10.6
Tiredness	25.8	23.8
Cold hands	13.6	9.8
Any intolerable effect	28.1	20.8
Patients	2365	2371
Stroke rate per 100 per 5 years	2.5	8.2

comprehensive self-administered questionnaire which included *inter alia* psychological well-being and general perceived health. In addition, the degree of distress due to side-effects and other effects was assessed. “The conceptualization of quality of life and the rationale for choosing these scales were based on previous studies”.

Difficulty inevitably arises for the ordinary clinician in deciding just what changes in responsiveness index units mean (Table 3). This does not necessarily imply criticism of the authors. Rating scales are accepted tools in psychological assessment. It is more that their transposition to the field of blood-pressure measurement is novel, and weighting is problematic. Thus a rise of 18.1 for low-dose captopril looks impressive, and may be, with confidence intervals which do not overlap zero. However, a rise of 18.1 from a base of 427 is a change of less than 5%.

Table 3. Quality-of-life analysis³

**Use of angiotensin converting enzyme inhibitors
in mild to moderately severe hypertension**

	Captopril	Enalapril
<i>Dose:</i>		
Low	+ 18.1	+ 5.9
Medium	- 6.8	- 4.3
High	- 0.5	- 10.7
Number of subjects	184	178

Scores represent overall quality of life changes from baseline in responsiveness units.

Expected untoward effects — thrombolytics and aspirin.

Aspirin has clearly demonstrable effects in the prophylaxis of transient ischaemic episodes. Aspirin is also well known to exacerbate peptic ulceration. The UK TIA (transient ischaemic attack) trial included 2463 patients who received placebo, aspirin 300 mg or 1200 mg daily for a mean period of four years, with overall beneficial effects⁴. Later examination of the data showed clear differences in the frequency of upper gastrointestinal bleeding, with evidence that aspirin 300 mg is above the no-effect level⁵ (Table 4). Episodes were markedly more common in the first three months of treatment than later. However, difficulty arises in deciding whether this represents weeding out of a population of susceptibles, gastric adaptation, or perhaps reduced

dosage with continued use. The trial itself showed an 18% reduction in vascular events with a 7% (non-significant) reduction in disabling stroke, or death.

Thrombolytics are now well established as treatment for acute myocardial infarction. Amongst potential adverse responses are haemorrhagic stroke and reperfusion arrhythmias.

Table 4. Upper gastrointestinal bleeding in UK-TIA study⁵

	Placebo	Aspirin 300 mg	Aspirin 1200 mg
<i>Bleeding from:</i>			
Gastric ulcer	nil	1	8
Duodenal ulcer	nil	6	9
Unknown site	2	8	11
Odds ratio (all causes)		7.7 1.7 – 33.8	14.4 3.4 – 60

The International Study of Infarct Survival (ISIS)⁶ was conducted to a very simple protocol, and therefore likely to give generalizable results. Table 5 shows the overall outcome and clearly illustrates that the chances of haemorrhagic stroke or major bleeding were outweighed by the reduced chances of vascular death.

If treatment is effective there is logic in administering it as early as possible. The ISIS-2 study was conducted in hospital, and it is noteworthy that a range of side-effects, including arrhythmias, hypotension and bradycardia as well as allergic and gastrointestinal reactions, were more common in drug than in placebo recipients. Pre-hospital thrombolytic therapy could arguably therefore be less safe.

A recent randomized study in 5469 patients compared feasibility and safety of therapy by “well equipped, well trained mobile emergency

Table 5. Streptokinase for myocardial infarction⁶ (ISIS – 2)

Stroke, haemorrhagic	7	0
Major bleed	46	18
Vascular death	791	1029
Total	8592	8595

medical staff' with that given in hospital⁷. Table 6 shows the results. The pattern of arrhythmia occurrence differed but overall was, if anything, more frequent in late (in hospital) recipients than in those treated before admission. Whether this would imply safety in less skilled hands before admission and in less vigorously selected patients is unclear.

Table 6. Thrombolysis for myocardial infarction⁷
Occurrence of ventricular fibrillation

Event occurrence	Treatment	
	pre hospital	in hospital
A. Preadmission	69	44 *
B. Admission to injection 2	34	43
C. Rest of hospital stay	100	145 **
Total treated	2750	2719

* $P < 0.02$ ** $P < 0.002$

Unexpected adverse effects — azathioprin.

Occasionally, clinical trials yield unexpected information, although generalization can be difficult. The National Crohn's co-operative trial, in comparing azathioprin, prednisone and placebo in treating Crohn's disease had six patients in a total of 113 who developed acute pancreatitis within a month of azathioprin prescription; none of the other treatment groups had similar problems⁸. Generalization is difficult; inflammatory bowel disease may constitute a special risk since treatment with mesalazine, and also olsalazine and sulphasalazin, occasionally has been associated with pancreatitis. On the other hand, post-transplant pancreatitis during immunosuppression is also well recorded⁹.

Meta-analyses

The importance of including all data sets; steroids and ulcer.

Three studies of ulcer occurrence in steroid recipients have been conducted in which data were aggregated, and they illustrate the differences in conclusions which can be reached when data sets are included, or excluded¹⁰⁻¹². Conn and Blitzer¹⁰ initially examined 50

controlled trials and found no significant association. Messer and colleagues used 71 studies and, by contrast, detected an association. Conn and Poynard in a further analysis claimed that 28 of the studies in the analysis of Messer *et al* were inappropriately included, and that in 12 studies other factors could have explained ulcer occurrence, whilst a further group of seven studies was inappropriately omitted. In the circumstances ultimate truth is difficult to define. However, overall ulcer rates were quite low in all data sets. One could ask whether rigorous exclusion/inclusion criteria made it possible to underestimate the true burden of disease.

Conclusions which appear to differ from clinical experience.

Divergence from expectation is brought out by a meta-analysis of 123 trials of nonsteroidal anti-inflammatory drug (NSAID) therapy¹³ (Table 7). Compared with the results of case-control analyses the risks seem strikingly underestimated. It is difficult to tell whether such underestimation could arise because trials were generally of short duration, so that side-effects did not occur, or because of rigorous selection criteria, or because the severity of arthropathy diverted attention from possible gastrointestinal effects.

Table 7. Meta-analysis non-aspirin NSAIDS¹³
123 trials

	Treated	Controls
Proven ulcer	2	0
Gross bleeding	24	8
Abdominal pain	175	118
Indigestion	116	64
Total	6460	6355

Unexpected conclusions about the general value of treatment.

Examination of data obtained in cholesterol-lowering treatment trials has generally shown disappointing overall results. The statistical overview presented by Ravnskov is one of the largest, and Table 8 summarizes the data. Taken overall there was no evidence of a reduction in death rates, although fatal coronary heart disease and non-fatal coronary events were marginally reduced. These trends were associated with a markedly raised frequency of non-medical deaths and cancer deaths, reported in subsets of studies. The bases of these findings are unclear but they cast doubt upon the wisdom of general attempts to lower serum-cholesterol levels by the methods used.

Table 8. Overview of cholesterol lowering trials¹⁴

Measurement	No. of trials	Odds ratio	95% ci
All deaths	24	1.02	0.97 – 1.07
Fatal coronary heart disease	27	0.94	0.88 – 1.00
Non-fatal coronary heart disease	24	0.90	0.84 – 0.96
Non-medical deaths	12	1.55	1.11 – 2.16
All deaths*	12	1.05	0.95 – 1.17
Cancer deaths	14	1.15	0.91 – 1.45

* In the same trials where non-medical deaths were separately recorded.

Trials designed to examine safety issues

Data obtained in comparisons of salmeterol and salbutamol present a good example. 25,170 asthmatic individuals were randomized 2:1 to these respective drugs¹⁴. Table 9 summarizes the outcome during the

Table 9. Outcome in Serevent Nationwide Surveillance Study¹⁵

No. included	Salmeterol 16787	Salbutamol 8383	
	%	%	relative risk
All deaths	0.32	0.24	1.35
All admissions	1.89	1.97	0.95
Other serious events	2.09	2.09	1.00
Asthma related			
Deaths	0.07	0.02	3.00
Admissions	1.15	1.22	0.95
Other serious events	1.18	1.19	0.99
Withdrawals	2.91	3.79	0.77**
Mild events	3.50	4.60	
Moderate events	4.40	5.00	
Severe events	9.90	11.60	
Total No. with non-fatal events	879	520	

** P < 0.001

16-week period of surveillance. Such information could not have been gathered during routine surveillance, where potential biases would include a likely inclusion preferentially of severe cases in the new-drug group. The slight (non-significant) excess of deaths in those given salmeterol contrasts with somewhat lower proportions of asthma-related events in the same group. Taken overall the picture is reassuring.

Conclusions

Randomized controlled trials can make valuable contributions to drug safety but their defects must be recognized. Defects include degrees of selection which can make generalization difficult, failure to include high-risk groups or concurrent other-drug users, and failure to mirror market-place practices.

References

1. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Brit med J* 1985, 291, 97-104.
2. SHEP Cooperative Research Group. Prevention of stroke by anti-hypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA*. 1991, 265, 3255-3264.
3. Testa MA, Anderson RB, Nackley JG, Hollenberg NK and the Quality-of-life Hypertension study group. *N Engl J Med* 1993, 328, 907-13.
4. Peto R, Gray R, UK-TIA Study Group. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. *Brit Med J* 1988, 296, 316-320.
5. Shorrock CJ, Langman MJS, Warlow CP and UK-TIA Study Group. Risks of upper gi bleeding during TIA prophylaxis with aspirin. *Gastroenterology* 1992, 102 A165.
6. ISIS-2 Second International Study of Infarct Survival Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither during 17187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988, 2, 349-360.
7. The European Myocardial Infarction Project Group. Pre-hospital thrombolytic therapy in patients with suspected acute myocardial infarction. *N Engl J Med* 1993, 328, 383-9.
8. Sturdevant RAL, Singleton JW, Deren JJ, Law DH, McCleery JL. Azathioprin related pancreatitis in patients with Crohn's disease. *Gastroenterology* 1979, 77, 838-886.
9. Corrodi P, Knoblauch M, Binswanger U, Scholzel E, Largiader F. Pancreatitis after renal transplantation *Gut*, 1975, 16, 285-9.
10. Conn HO, Blitzer BL. Non-association of adrenocorticosteroid therapy and peptic ulcer. *N Engl J Med* 1976, 294, 473-9.
11. Messer J, Reitman D, Sacks HS, Smith H Jr Chalmers TC. Association of adrenocorticosteroid therapy and peptic-ulcer disease *N Engl J Med* 1983, 309, 21-4.
12. Conn HO, Poynard T. Adrenocorticosteroid administration and peptic ulcer: a critical analysis. *J Chronic Dis*. 1985, 38, 457-68.
13. Chalmers TC, Berrier J, Hewitt P, Berlin J, Reitman D, Nagalingam R, Sacks H. Meta-analysis of randomised controlled trials as method of estimating rare complications of non-steroidal anti-inflammatory drug therapy. *Aliment Pharmacol Therap*, 1988 2S 9-26.
14. Ravnskov U. Cholesterol-lowering trials in coronary heart disease: frequency of citation and outcome. *Br Med J* 1992, 305, 15-19.
15. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *Brit Med J* 1993, 306, 1034-7.

ADVERSE DRUG REACTIONS: CAUSALITY ASSESSMENT

Jan Venulet*

The assessment of whether a given drug is the cause of an adverse event — in other words, whether an adverse event is a true adverse drug-reaction — remains the most controversial issue in all considerations of drug safety. Indeed, all warnings and precautions about a particular drug imply at least that it has in the past caused an adverse reaction.

Epidemiological studies are not controversial — if the incidence of an adverse drug reaction is significantly higher in a treated group than in a control group it is a good reason for postulating a causal relationship on epidemiological and statistical grounds. As long as causality is not an issue in an individual case, agreement on the medical importance of the findings of the study is not difficult.

Causality assessment in individual cases is a radically different matter, as it can easily turn into an endless argument of pros and cons of a relationship between a drug and an adverse reaction.

Why are attitudes to epidemiological studies so different from those to single-case reports? The fundamental difference between evidence based on statistical calculations and not based on assessment of an individual case is that statistical probability of a causal relationship applies in the same degree to all patients in the affected group — which of course is impossible in a medical sense. Epidemiological studies usually indicate some “false positives” — cases with signs and symptoms identical to those caused by the drug.

For single case reports, every case is assessed separately, and the evaluation can range from ‘definitely related’ through ‘probable’, ‘possible’, and ‘unlikely’ to ‘not drug-related’. In reality, however, only ‘definitely related’ and ‘not drug-related’ can be true. The intermediate assessments contradict biological truth.

The importance of assessment, with all its practical consequences, is confounded by the biological fact that the drug either did or did not cause the reported adverse reaction. Therefore, in reality only two assessments are possible: ‘not related’ and ‘definitely related’. The intermediate degrees of causal relationship, though frequently used, reflect paucity of information in a case report and sometimes also insufficient knowledge and experience on the part of the assessor. Also, the assessment is retrospective and no further information can be obtained than that available.

While every organization concerned with safety is interested in causality there seems to be much reluctance about applying the concept

* CIOMS Consultant and formerly Chief, WHO International Drug Monitoring Programme, Geneva, Switzerland

of causality or even imputability. There might be less reluctance if there were better understanding of the nature and potential of causality assessment and its relation to other types of information.

Causality assessment is of particular value in regard to reports that are 'serious', with 'high causality rating', and 'frequent'. In practice the relative importance given to these criteria depends on what is known about the drug and its safety profile (new, old, life-saving, known ADR, unexpected, etc.). Thus, causality assessment should be regarded primarily as a means of drawing attention to cases that need investigation rather than as a definitive means of assigning causality.

Once the need for assessment is accepted the question of how to do it arises. In general there are three approaches: unstructured or conventional, semistructured, and standardized.

The first, *the unstructured approach*, is based on the medical experience and knowledge of the assessor, who exercises judgement in a completely unstructured way after considering the information contained in the case report. It amounts to a judgement by an expert of a particular case. If the judgement is not supported by a detailed discussion of the case, the grounds on which it was reached will not be clear, yet it is the most authoritative form of assessment. It is paradoxical that the most authoritative form of assessment is left to the completely subjective opinion of an assessor.

The semistructured approach provides for every causality level a descriptive and more or less loose list of what should and what should not be in the case report to assign it to a given causality level. It is a sort of *aide-mémoire* of what to look at and how to interpret it. The semistructured approach shows how assessment was reached, even if the rules are not very specific and are mostly qualitative. Several such lists of items of information leading to different levels of causality have been proposed in the past, most recently by the World Health Organization.

The third approach, *standardized assessment*, consists of a set of questions and decision rules which result in the same answers always leading to the same final assessment. The term *standardized assessment* implies that the same operational logic is always applied.

Numerous standardized methods have been described in the last 15 years, which indicates that many are aware of such a need. They are distinguished mainly by the specificity and number of items of information taken into consideration, and the weight attached to different items.

Standardized assessment with regard to certain problems related to the work of a drug-safety section has the following advantages:

1. Improvement of communication between users, because it indicates clearly how judgement was reached; thus the message relative to causality becomes less equivocal.
2. Reproducibility of results. Standardized assessment makes it more likely that different assessors treat the same report in the same way.

3. Validity of results. Like medical judgement in general, the extent to which results obtained with standardized methods reflect true causality is difficult to demonstrate. This applies equally to expert opinion and lists of criteria. Working retroactively, and usually with a finite amount of detail, the assessor will determine true causality only in the rare cases in which the evidence is unequivocal — i.e., either definitely related or not related. Such assessments as 'possible', 'probable' or 'unlikely' can not reflect true causality, as they are biologically untenable. They are only the closest possible approximation to the truth.
4. Double-checking of case reports. Some organizations use standardized assessment in addition to unstructured medical judgement to identify differences of opinion for purposes of follow-up.
5. Standardized assessment will never apply equally to all cases, as some information not obtainable by this method (e.g., blood level of a drug) may be a decisive factor in particular instances.

Lawyers, particularly in the United States, warn against assessing causality in individual cases because of the risk of legal consequences. However, this risk will vary with method of assessment. Assessment made by a standardized method carries much less weight and is less disputable in law than the assessment of an expert. Assessment by a standardized method means no more than that certain fixed criteria were met in a particular way, thus permitting the assignment to the adverse event of a given level of causality.

The expert does a specific assessment for a particular case, taking into account many more factors than any standardized method could cover. Should it come to litigation it would be much more difficult to reopen a case assessed by an expert than one assessed by a standardized method.

Table 1 (Annex) shows the place of causality assessment in routine drug monitoring. Almost all 25 respondents assess causality, 16 by either an unstructured or a semistructured approach, 8 by a standardized method, and only one by the use of a prescribed official method.

National drug monitoring centres have stressed their interest in standardization by establishing, in the WHO Collaborating Centre at Uppsala, a set of definitions of terms for different degrees of causal relationship.

The European Community, recognizing the wide use of causality assessment in its member states and the consequent need for standardized equivalents of the variety of terms in different countries, resulting from various approaches to causality assessment, has introduced a 'translating list'.

A questionnaire survey of 25 large European companies carried out by Dr. Danan of Roussel UCLAF showed that all 25 assessed causality in one way or another — 19 by either an internal (unpublished)

procedure or an unstructured method, and only 6 by a standardized method. Several companies indicated that they needed a more structured method for assessing severe or new adverse drug reactions than the methods they were then using. A questionnaire survey carried out by the Active Permanent Workshop of Imputologists (APWI) in 1989 found that 60 of 82 respondents used standardized assessment. Altogether nine methods were listed, of which three predominated. Evidently several companies had responded to both questionnaires.

This paper demonstrates the importance of causality assessment of single case reports; analyses the pros and cons of the three basic methods of assessment, viz. unstructured medical judgement, the use of descriptive criteria, and standardized assessment; and describes the attitude of drug regulators and pharmaceutical companies to these approaches. What lessons are to be learned?

It is time to dedramatize in the eyes of the public the role of causality assessment and to explain what it really is — a means of sorting out cases that require particular attention. An educational effort is essential to make the public and lawyers alike understand the inherent limitations of single reports, so as to avoid over-interpretation. In general, it seems that causality assessment is accepted. Regulatory authorities and pharmaceutical companies, which 10 or 15 years ago gave no thought to causality assessment, have come to accept the assessment of causal relationship of single case reports as part of their daily routine.

However, progress in causality assessment has been uneven. No one approach is generally accepted, and general acceptance may not even be desirable, for different reasons. Perhaps we are so individualistic that, so long as a particular approach is not imposed, as it is in France, there will be no standardization. However, in view of the active exchange of information between different organizations, and of the need for clear communication and interpretation of case reports of suspected adverse drug reactions, a degree of standardization of approach would seem to be beneficial. Any loss of accuracy associated with standardization in assessing causality should be weighed against the fact that true causality can only rarely be determined by any method.

In conclusion, it might be asked, what is to be done? We should, I suggest, give priority to an approach that is reasonably well founded, provides good documentation, is clear and well defined, is operational, and is based on the information usually requested in a single case report. Computer support would be an asset. Unambiguous communication between users is essential in the present globalization of drug monitoring. And the help of experts will be required anyway should a case, for medical or other reasons, become of particular interest.

Annex

Table 1 — National drug monitoring centres and causality assessment. Compilation of answers to a questionnaire distributed in 1991 to centres in the following 25 countries: Australia, Austria, Belgium, Canada, Czechoslovakia, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Japan, Netherlands, New Zealand, Norway, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, United Kingdom, United States, Yugoslavia. (Responses in *italics*.)

1. Does your centre require that case reports submitted by the pharmaceutical companies include an assessment of causality?
1.1 *8 Yes* 1.2 *9 No* (Six centres did not receive reports from industry)
2. If Yes, do you require that the assessment be done with a particular method?
2.1 *1 Yes* 2.2 *9 No*
3. If Yes, please indicate which one: *French method*
4. If your answer to question 1 was No, please indicate the reason (s) for your lack of interest in causality (check as many as are appropriate)
 - 4.1 *7* The details in the case report allow you to make your own judgement and you do not want to be influenced
 - 4.2 *—* Causality is a minor parameter in your considerations of individual case reports
 - 4.3 *2* General scepticism about the validity of causality assessment (whether with a method or by an expert)
 - 4.4 *7* Other reasons:
 - Done regardless of whether the company has asked or not
 - Copies of case records required
 - Causality may change with further information
 - Broader net preferred
 - Considered a luxury to ask industry to make the assessment
 - Lack of time
 - Some companies tend to disavow causality whenever possible or would tend to provide biased interpretation
 - Few reports from industry
5. Are you assessing causality of single case reports within your centre?
5.1 *22 Yes* 5.2 *3 No*
6. If Yes, is it done:
6.1 *21 Routinely* 6.2 *3 Occasionally*
7. If causality assessment is done, (check as many as appropriate):
7.1 *8* With a method. Please indicate which one.
For details see below
7.2 *14* Solely by using your knowledge and experience or according to descriptive criteria

* List of national drug monitoring centres that assess causality of single ADR reports with indication of method used:

Australia	(5)	Greece	South Africa	(2)
Austria		Ireland	Spain	(4)
Belgium		Italy	Sweden	(1)
Czechoslovakia		Japan	Switzerland	(4)
Denmark		Netherlands	Thailand	
Finland	(6)	New Zealand	USA	
France	(3)	Norway	Yugoslavia	(2)
Germany				

Key to the above: (1) Methods of Venulet *et al.*,^{1,2} or Stephens,³ or BARDI⁴; (2) Venulet *et al.*,^{1,2} (3) French method,⁵ (4) Karch and Lasange,⁶ modified; (5) Australian, personal information; (6) Certain algorithms.

UK, Turkey and Canada do not assess causality. All the other countries assess according to knowledge and experience or according to descriptive criteria.

References Table 1

1. Venulet, J., Ciucci, A. C. and Berneker, G. C. Standardized assessment of drug adverse reaction associations — rationale and experience. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 1980; **18**: 381-338.
2. Venulet, J., Ciucci, A. G. and Berneker, G. C. Updating of a method for causality assessment of adverse drug reactions. *Int. J. Clin. Pharmacol. Therap. Toxicol.* 1986; **24**: 559-568.
3. Stephens, M. D. B. Assessment of causality in an industrial setting. *Drug Inform. J.* 1984; **18**: 307-314.
4. Venulet, J. APWI: Past and Present. *Drug. Inform. J.* 1991; **25**: 229-243.
5. Lane, D. A., Kramer, M. S., Hutchison, T. A., Jones, J. K. and Naranjo, C. A. The causality assessment of adverse drug reactions, using a Bayesian approach. *Pharmaceut. Med.* 1987; **2**: 265-283.
6. Dangoumeau, J., Evreux, J. C., and Jouglard, J. Méthode d'imputabilité des effets indésirables des médicaments. *Thérapie* 1978; **33**: 373-381.
7. Karch, F. E. and Lasagna, L. Toward the operational identification of adverse drug reactions. *Clin. Pharmacol. Therap.* 1977; **21**: 247-254.

