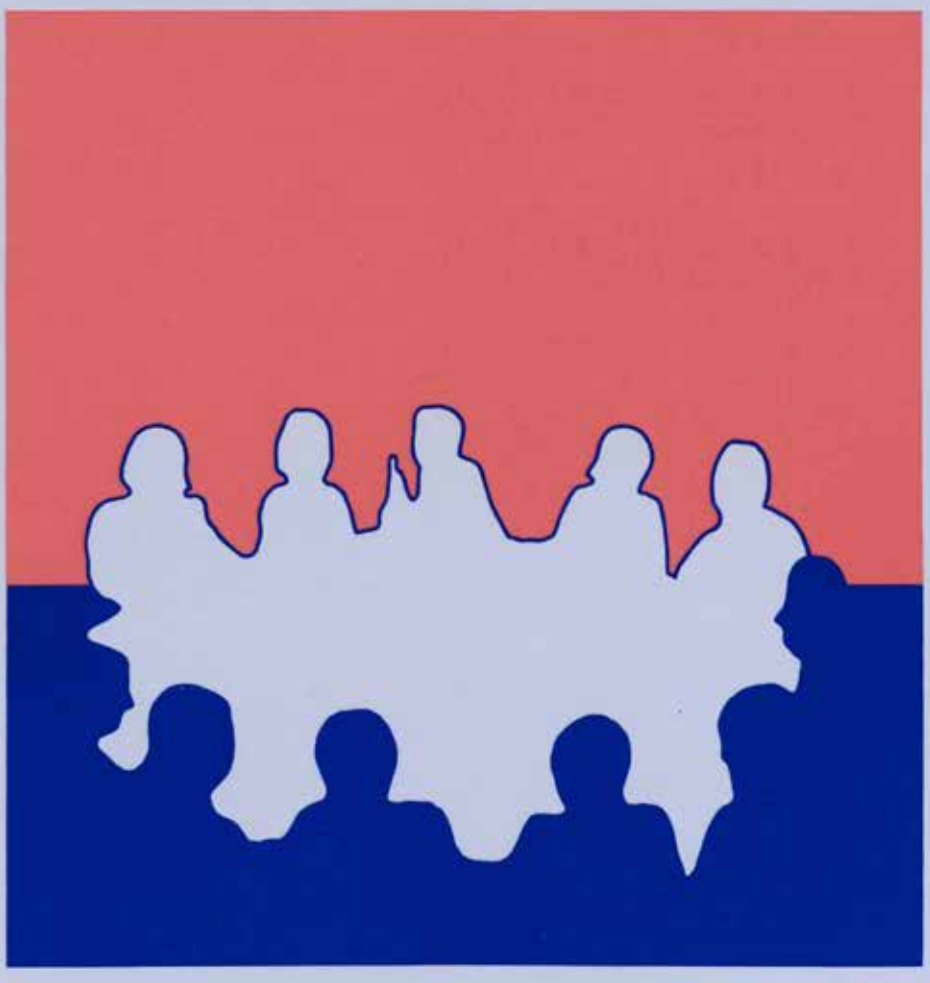
DRUG SURVEILLANCE: INTERNATIONAL COOPERATION PAST, PRESENT AND FUTURE

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

Edited by Z. Bankowski and J.F. Dunne



CIOMS

DRUG SURVEILLANCE: INTERNATIONAL COOPERATION PAST, PRESENT AND FUTURE

Proceedings of the XXVIIth CIOMS Conference
Geneva, Switzerland
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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

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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 Kindom 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 Stalinon, 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 Asembly.

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 betwen 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 Venning[1]. 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 Deutches 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.

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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 delivery[2]. Already, some ten years ago, an international symposium documented amazing differences in drug usage between and within countries[3]. 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 concepts[5]. 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,

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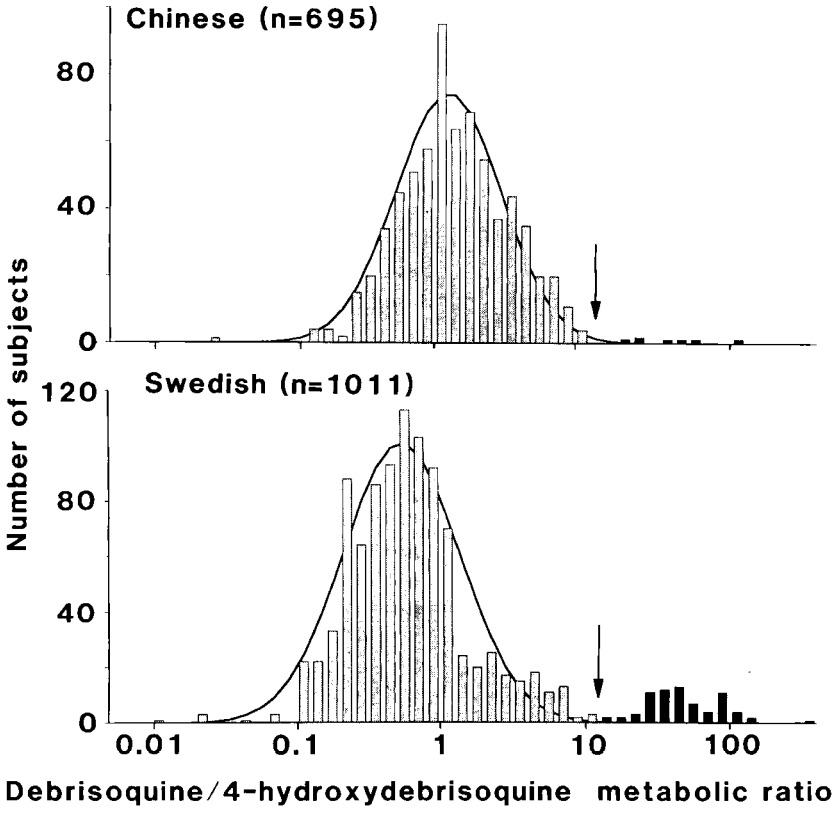
has been disregarded so far in pharmacoepidemiology, which too often uses vague terminology such as "drug exposure". Paracelsus would still be at the front of research if the word "dose" were exchanged for "concentration". Thus, the ultimate level of sophistication in drug surveillance is to establish 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 neuropathy[6]. 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-utilization[7]. 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 activity[8]. This is done by measuring the hydroxylation of a small oral dose of a probe drug such as debrisoquine, sparteine, codeine or desmethylimipramine. 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 differences[8]. Using debrisoquine as a probe drug in more than 900 healthy Swedish subjects[9] 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 goup 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., antidepressants[10]. 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 diazepam[11]. Accordingly diazepam is metabolized slower in Chinese than in Swedes[11] and therefore has to be prescribed in lower doses for Chinese than for Caucasians[12].

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 associates[13]. 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 groups[14]. 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. Duchène 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, Sånga-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. Zuckswerdt 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, Iselius, 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

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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 benzodiazopines, 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. Julliet, 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 idiosyncracy 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 symphatize 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 reponse 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 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 quantitive 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 naive. 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 gastro-intestinal 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 recommandation 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 antimalarials, 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 Napke[12]. 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 signal[16].

An expert group convened in 1992 by the European Commission on Pharmacovigilance in the European Community[14] 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

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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 Kingdom[13].

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 triazolam[8], 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 bias[15].

Inaccurately low incidence rates. Underreporting introduces major bias in the estimation and comparison of frequencies[1-2], and it is hazardous for estimating relative risk[20]. 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 signal[2] 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 signal[7-14].

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. Drury[4] 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 ars 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 marketing[13].

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 authorities[10]. 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. Griffin[8-9], 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 x 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 Lumley[19], 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 to[16]:

- 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 year[11-16-17].

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 JC.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; **2e 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.

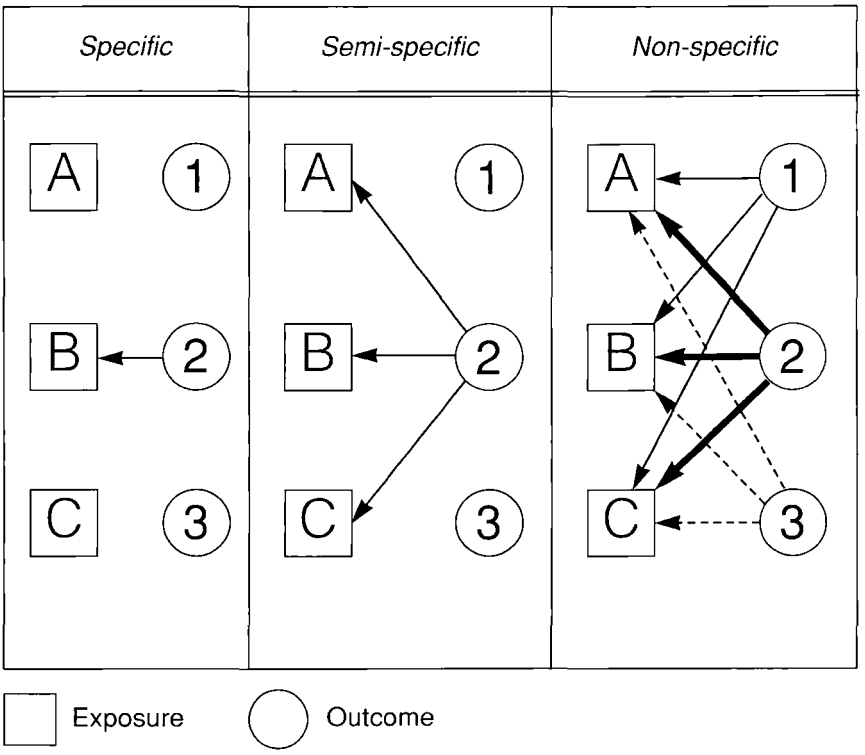
CASE-CONTROL STUDIES

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**



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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 reasearch. 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 • if disease influences exposure • if diagnosis is conditional on exposure
2. Information bias	Unequal recording of information • observer • subject
3. Confounding bias	Factors related independently to outcome and to exposure • known – completely recorded – 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 possiblity 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

- 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, howerer.

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 overdosage, such as hypotension and renal failure.

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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, porpranolol 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 hypertension[1]

% [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 study[2]. 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 captopnil and enalapril on quality of life[3] 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 analysis[3]

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

	Captopril	Enalapril
Dose:		
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 priod of four years, with overall beneficial effects[4]. 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 level[5] (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 study[5]

	Placebo	Aspirin 300 mg	Aspirin 1200 mg
Bleeding from:			
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 infarction[6] (ISIS - 2)

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

medical staff" with that given in hospital[7]. 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 infarction[7]
Occurrence of ventricular fibrillation

Event occurrence	Treatment pre hospital	Treatment 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 problems[8]. 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 recorded[9].

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 excluded[10-12]. Conn and Blitzer[10] 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) therapy[13] (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 NSAIDS[13]
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 trials[14]

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	084 - 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 drugs[14]. Table 9 summarizes the outcome during the

Table 9. Outcome in Serevent Nationwide Surveillance Study[15]

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. Azathrioprin 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

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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

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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 aproach 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 distingushed 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. Reproductibility 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

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* 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 BARDI[4]: (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.

SESSION III

HARMONIZATION OF REPORTING AND TERMINOLOGIES OF ADVERSE DRUG REACTIONS

Chairman: Ronald D. Mann

HARMONIZATION OF REPORTING AND TERMINOLOGIES OF ADVERSE DRUG REACTIONS

Introduction

Ronald D. Mann*

There are three principal issues involved in the harmonization of reporting requirements and the provision of suitable terminologies relating to reporting of adverse drug reactions. These are:

1) The reporting requirements of drug regulatory agencies.
2) Classification systems by which ADR reports can be computerized.
3) Nomenclatures or dictionaries defining adverse-drug-reaction reporting terms.

1. Reporting requirements

There has, in the past, been great difficulty because individual national drug regulatory agencies and governments have put forward rules and regulations for reporting of adverse drug reactions, and these requirements are not harmonized. Each drug regulatory body tends to disseminate rules and regulations of its own and this leads to pharmaceutical companies having to report precisely the same information in a number of different formats. This duplicative and entirely unnecessary work risks erosion of the data-base through multiple reporting. It is also wasteful of resources and it does nothing to enhance patient-care, which is the prime object of adverse drug reaction reporting.

It is essential that we work towards international agreements regarding reporting requirements, and useful steps in this direction have been made by the CIOMS I and II agreements. Further work is in progress in the CIOMS III working group.

The CIOMS I agreement was concerned with the international reporting of adverse drug reactions. It did not interfere with national reporting requirements, but ensured that there would be one form, with one set of definitions, to be completed in one language for international reporting. The idea was that drug regulatory agencies could define their reporting requirements as they wished for use within their own countries, but pharmaceutical companies, which had to undertake international reporting, would do this by means of the CIOMS I form and procedure.

The CIOMS II agreement is concerned with periodic safety updates. Many regulatory authorities require that, from time to time, pharma-

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ceutical companies should provide a summary of the adverse reaction experience which had occurred since the date of the last report. These requirements also vary from one regulatory body to another, and the CIOMS II agreement provided a format allowing one unified report which could be sent to all regulatory authorities that were willing to participate in the scheme.

There remain a number of current needs:

(a) It is necessary to increase the number of countries and pharmaceutical companies that use the CIOMS I and II procedures. It also seems perfectly sensible to use the same procedures for internal reporting within individual countries, and further consideration needs to be given to this possibility. Certainly it is desirable to bring national reporting requirements into some sort of uniformity.

(b) It is necessary to make sure that countries setting up drug regulatory authorities should have the CIOMS I and II agreements drawn to their attention so that they can seriously consider participating in these schemes from the beginning. This will apply particularly to Eastern European countries and developing countries, and their adoption of the CIOMS I and II procedures would avoid their generating independent and non-harmonized regulations.

(c) It is necessary to differentiate validated from non-validated reports. Data quality is important and we do need to evolve a means of showing which reports have been validated by further follow-up and can therefore be accepted as authenticated.

(d) It is also desirable to indicate reports for which biological samples have been stored. As we move towards increasing capability regarding phenotyping and genotyping, the usefulness of storing biological samples for subsequent examination increases. Central adverse-drug-reaction registers should record which reports have been handled in this way.

(e) It seems clearly necessary to develop the World Health Organization's international drug safety monitoring data-base at Uppsala. This will avoid the setting up of unnecessary data-bases in the European Community and elsewhere. It seems very difficult to justify duplicative data-bases in scientific terms and this matter would seem to be of some importance.

2. Classification systems

There are clear advantages in using a classification system. These include:

(a) Data can be recorded more quickly and more accurately.
(b) Data can be retrieved far more easily.
(c) Data can be analysed far more thoroughly.
(d) Data can be communicated more regularly in a standardized form.

There are a number of different classification systems in extensive use; they include ICD (International Classification of Diseases) 8/9/10, OXMIS, READ, ADROIT, WHOART and COSTART.

The first part of Volume 1 of the ICD ninth revision provides a list of three-digit categories. The bulk of the volume then goes on to expand this classification in terms of four-digit sub-categories. The ICD classifications are in widespread use and are considered by most workers to be indispensable. They would seem to be at their strongest in classifying diseases rather than symptoms and less well defined clinical conditions.

The OXMIS problem codes are based on the International Classification of Diseases (8th Revision) and the Classification of Surgical Operations (1975) of the Office of Population Censuses and Surveys in the United Kingdom. Entries are cross-referenced, where possible, to the disease coding system of the Royal College of General Practitioners (RCGP) and the International Classification of Health Problems in Primary Care (ICHPPC) of the World Organization of National Colleges, Academies and Academic Associations of General Practitioners and Family Physicians (WONCA). The system, which is currently in use on the VAMP database in the United Kingdom, links the RCGP WONCA/ICHPCC Codes to a series of unique numerical and alphabetical identifiers which provide codes for the clinical conditions listed. The system is non-hierarchical, but is extremely useful in the hands of general practitioners because it permits the easy recording of symptoms and less well-defined clinical conditions.

The READ clinical classification became Crown copyright in the United Kingdom in April 1990 when the National Health Service Centre for Coding and Classification was established to develop the READ codes for use throughout the British National Health Service.

Unlike OXMIS, the READ Classification System is hierarchical in structure; it is also capable of considerable extension as the need arises to add further codes. The dictionary itself comprises the Read code (the main or "preferred" medical terms — that is, the nomenclature) and "synonyms", which are linked to the preferred terms. Care is needed to ensure that such systems do not force data entries so that they receive a somewhat erroneous specificity or precision — it is important that if the doctor wishes to record an incident as having been a "heart attack" then this is not forced into the rather more precise and well-defined condition of "myocardial infarction".

ADROIT is a classification system developed by the Medicines Control Agency of the Department of Health in the United Kingdom and intended to provide, on a hierarchical basis, a composite and all-embracing classification system which embodies the codes of many other systems. It has not yet received usage outside the UK and few details are available in the scientific literature.

WHOART and COSTART are the hierarchical classification systems brought forward and used for a considerable number of years in the World Health Organization's international reporting scheme and, in respect of COSTART, in the offices of the Food and Drug Administration in the United States. Those concerned are considering the possibility of linking or uniting these very important systems and updating them.

3. Dictionaries

Having accurate definitions of individual reporting terms is clearly essential if classifications of these terms are to mean anything and if data from different sources are to be recorded on the same data-base. At least two initiatives have been undertaken in attempts to secure internationally acceptable definitions of terms used in reporting adverse drug reactions. One is being led by Dr Christian Bénichou, who has organized a number of meetings which have proposed definitions of terms in a series of publications put forward in France. Bénichou's group has also produced, in English, a series of definitions covering liver problems and blood dyscrasias. The second initiative under the auspices of CIOMS has taken place under the chairmanship of Dr Mann. It has been sponsored by seven German and three Swiss pharmaceutical companies. This effort started with a 1980 list of critical terms and has developed a standard format in which each term is treated by means of a "preamble", a "definition" and "basic requirements for use of the term". The definition is intended to provide a description which will be useful to those validating reports of adverse drug reactions. The preamble sets forth a short list of the specific points that should be borne in mind in determining whether a report satisfies a definition. The section on basic requirements is also intended to facilitate validation listing points of special relevance to the definition. This initiative is continuing and is now beginning to define the terms used in the system-organ classifications of WHOART.

The terms which have recently been defined by the CIOMS group of workers have been published in a series of four papers in *Pharmacoepidemiology in Drug Safety*. The terms defined are the following:

I *Anaphylactic shock, arrhythmia, cardiac failure, hypertension, thrombosis, embolism.*

II *Colitis, gastrointestinal haemorrhage, hepatocellular damage, peptic ulcer, pancreatitis.*

III *Aplastic anaemia. bone marrow depression, coagulation disorders, agranulocytosis, thrombophlebitis.*

IV *Dyskinesia, depression, myopathy, neuropathy, paralysis, convulsions.*

TOWARDS A DICTIONARY OF ADVERSE DRUG REACTIONS OR SHOULD EXISTING TERMINOLOGIES BE HARMONIZED?

Christian Bénichou*

It seems timely and even crucial to turn our attention to the need for one universal worldwide terminology for adverse drug reactions. This is essential to allow exchange of information between the different parties involved in drug safety within the same country and between different countries. Indeed, owing to cultural or nosological differences, terms apparently very close to one another may be applied to different situations. For instance, the French term *thrombophlébite* applies to any venous disorder associating thrombosis and inflammation, including deep vein thrombosis, while the English term *thrombophlebitis* designates superficial phlebitis. Worldwide data-banks centralizing information from many countries are the best way to accelerate knowledge on the safety of new drugs. But this centralization can be effective only if the same terms are used for the same disorders. A few adverse-reaction terminologies have been proposed, such as WHOART and COSTART. None has been associated with definitions or precise guidelines for the use of the terms. Therefore, it is impossible to be sure that each user always uses the same term for the same abnormality. This reservation applies to those using the terminologies in a central data bank as well as to the notifying reporters who originate the information. Thus a dictionary with definitions of all terms or guidelines for their use could be the solution to ensuring that different users "speak the same language".

The nature of adverse drug reactions is not very different from that of the non-drug-induced diseases, except for a very few uncommon and well-known reactions, e.g., fixed drug eruption. Therefore, theoretically the definitions given by medical dictionaries of diseases should suffice. However, at least three main reservations must be made:

- Definitions given by different medical dictionaries are not always concordant and not all dictionaries take into account variations related to age, sex or ethnic origin.
- Dictionary definitions are not always usable in practice and are not adapted to the level of information contained in spontaneous notifications reporting adverse drug reactions attributed to marketed drugs. Histological, biochemical or virological data are rarely available.
- Most ADR terms refer not to diseases but to physical signs, which much more than diseases need precise definitions, not often found in dictionaries.

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To solve these three problems, it would be necessary to create an international dictionary of adverse drug reactions, giving definitions precise enough to reduce to a minimum the risk of wrong assignation to a term. A margin of error is inevitable since the information is usually not sufficient to assure 100% specificity and sensitivity. Such a dictionary of adverse reactions should be constructed in such a way as to take into account up-to-date knowledge about non-drug-induced diseases — that is, with the help of experts from each medical field. Such a project could appear extremely ambitious: how many years would be needed to rethink completely a medical dictionary, universally accepted and adapted to drug safety? The work is probably not insurmountable, since it is a question of redefining not all diseases, but only those likely to be induced by drugs. Moreover, certain system organs are more frequent targets of drug toxicity, such as the liver, blood, skin and kidney, and should be dealt with as top priorities. In each medical field lists should be drawn up of abnormal conditions liable to be induced by drugs. One term should correspond to one condition, and the different terms retained should correspond to different conditions. All the conditions likely to be encountered should be anticipated in the list of terms. To sum up the two essentials for a terminology:

1. For each condition, one term
2. When two different terms are retained, they should correspond to conditions that have a significant clinical difference for the patient — that is, involving different seriousness, prognoses and risks.

Experience shows that all languages have several terms to designate the same condition, or conditions that are not very different. The criterion for a good terminology is to retain only the terms that deserve to be included. It is possible, however, to give for each of these terms a list of synonyms (or included terms). But outdated terms from the past, representing physiopathological or nosological conceptions no longer accepted, must be progressively eliminated from current use.

Knowing that an ADR dictionary cannot be built without the support of experts from the different medical fields, we organized consensus meetings for definitions and causality — assessment criteria of ADRs, gathering university experts in the principal domains of medical toxicity, and specialists in pharmacovigilance from industry and regulatory authorities. This effort was carried out first in France, and then, at the request of the Council for International Organizations of Medical Sciences, at the international level. All of the conclusions have been published (1-10). The international meetings covered liver disorders and blood cytopenias. For liver disorders, experts came from six different countries. First they listed the specific abnormalities which enable the existence of an hepatic disorder to be verified. Then they proposed a classification of these abnormalities into several categories. They proposed a new ratio which facilitates the distinction between hepatocellular and cholestatic injuries (Table 1). And, finally,

they made comments on the different terms retained by WHOART for the system organ: liver and biliary tract disorders.

Table 1. Designations of drug-induced liver disorders on basis of abnormalities shown by liver tests

Terms requiring histological data:	*Type of liver injury:*
Hepatitis	Hepatocellular: increase of over 2N in ALT alone, or $R \geqslant 5$
Hepatic necrosis	Cholestatic: increase of over 2N in AP alone, or $R \leqslant 2$
Chronic liver disease	Mixed: increase of both ALT over 2N and AP, and $2<R<5$
Cirrhosis	Acute: elevation of liver tests lasting less than three months
In the absence of histological data:	
Abnormalities of liver tests: • any increase between N and 2N in – ALT – or AST – or AP – or TB	Chronic: elevation of liver tests lasting more than three months Fulminant: rapid (days to weeks) development of hepatic encephalopathy and severe coagulation disorders
Liver injury: • increase over 2N in ALT or CB • or combined increase in AST, AP and TB, providing one of them is above 2N	Severe: liver injury complicated by, in order of increasing severity: jaundice, prothrombin <50%, hepatic encephalopathy.

Symbols: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; N = Upper limit of the normal range; AP= Alkaline phosphatase; CB = Conjugated bilirubin; TB = Total bilirubin.

$$R \text{ (ratio)} = \frac{\text{Serum activity of ALT}}{\text{Serum activity of AP}}$$

(Each activity is expressed as a multiple of N. Both should be measured together at the time of recognition of liver injury.)

From the initial set of definitions it was possible to draw up recommendations for the use of all of these terms. Later, in collaboration with the WHO Collaborating Centre for International Drug Monitoring at Uppsala, it was possible to work on what could be a new terminology of adverse drug reactions, cleared of obsolete terms, enriched with new terms which the evaluation of drug effects and progress in knowledge had justified adding, and always accompanied by practical definitions or recommendations for use. Then the

definitions were submitted to different countries, collaborating with WHO, and their comments were taken into account. It has now been offered for publication as a trial example for general opinion. The conclusions of the international consensus meeting (9), published four years ago, did not produce any fundamental criticism and are widely used. If this holds true for this first chapter of a new dictionary, it may be concluded that it fulfils the conditions necessary for a world-wide standardized terminology.

This standardization will probably make unnecessary the harmonization so often called for between the different terminologies. Harmonization could only be accomplished by passing through an initial phase of definition in order to verify the equivalences between the terms of the different terminologies. It will be superfluous if the dictionary is well constructed, since it should be sufficient to attach to each term the different synonyms existing in each terminology. Obsolete terms should be eliminated from current use. New terms should be added. Finally, certain terms may be assembled in larger entities, allowing regrouping of common mechanisms to investigate certain conditions of drug toxicity.

Therefore, the war between terminologies should not take place: the dictionary of adverse reactions, drawn up with the help of international experts and adapted in accordance with the comments of specialists in pharmacovigilance, should make harmonization of the various terminologies unnecessary.

References

1. Bénichou C, Danan G, Lack of definitions of adverse drug reactions. *Drug Inform J.* 1989; **23**: 7174.
2. Danan G, Consensus meeting on causality assessment of drug-induced liver injury. *J. Hepatol* 1988; **7**: 132-136.
3. Solal Céligny P, Bénichou C, Boivin P, et al. Critères d'imputation d'une cytopénie granuleuse ou plaquettaire à un médicament. Résultats de réunions de consensus. *Nouv Rev Fr Hematol* 1987; **29**: 265-270.
4. Habibi B, Solal Céligny P, Bénichou C, et al. Anémies hémolytiques d'origine médicamenteuse. Résultats de réunions de consensus. *Therapie* 1988; **43**: 117-120.
5. Vigeral P, Baumelou A, Bénichou C, et al. Les insuffisances rénales d'origine médicamenteuse. Résultats de réunions de consensus. *Nephrologie* 1989; **10**: 157-161.
6. Fournier M, Camus P, Bénichou C, et al. Pneumopathies interstitielles. Critères d'imputation à un médicament. Résultats de réunions de consensus. *Press Med* 1989; **18**: 1333-1336.
7. Guillaume JC, Roujeau JC, Chevrant-Breton J, et al. Comment imputer un accident cutané à un médicament. Application aux purpuras vasculaires. *Ann Dermatol Venereol* 1987; **114**: 721-724.
8. Roujeau JC, Béani JC, Dubertret L, et al. Photosensibilité cutanée médicamenteuse. Résultats d'une réunion de consensus. *Therapie* 1989; **44**: 223-227.
9. International Consensus Meeting. Criteria of drug-induced liver disorders. *J Hepatol 1990;* **11**: 272-276.
10. Bénichou C, Solal Céligny P, Standardization of definitions and criteria for causality assessment of adverse drug reactions. Drug-induced blood cytopenias. Report of an International Consensus Meeting. *Nouv Rev Fr Hematol* 1991; **33**: 257-262.

THE THREE CIOMS WORKING GROUPS ON DRUG SAFETY

Win M. Castle* and Diane Chen**

This paper describes how the Council for International Organizations of Medical Sciences (CIOMS) became involved in the three working groups on drug safety: the first on expedited case reports; the second on the periodic safety review of drugs; and the third on safety elements in core data sheets.

The beginning

The working parties originated from a CIOMS working group in 1985 on the monitoring and assessment of adverse drug effects. One of its purposes was to make proposals for the reporting of adverse drug reactions, with particular reference to the needs of developing countries. However, it became evident that even among the more developed countries, such as the Federal Republic of Germany, the United Kingdom and the United States, with reasonably efficient systems, there was disharmony in international reporting, and manufacturers were concentrating on paper-flow instead of following up important case reports.

Not only were the requirements different between countries, but the items of information required by the regulatory authorities differed markedly. Table 1 (Annex) shows 14 items of information required at that time by the regulatory authorities of the Federal Republic of Germany (BGA), the United Kingdom (MCA), and the United States (FDA), and this was only a third of the information which was required by any of them.

Therefore, a decision was made to convene a group of interested people from regulatory agencies and the pharmaceutical industry, as well as observers from the World Health Organization, to discuss the feasibility of standardizing international reporting of adverse drug reactions. They were invited by either Dr Gerry Faisch (FDA) or Dr Win Castle (ICI) to attend a week-end meeting. Their selection was arbitrary; nobody was officially representing any organization. They agreed on the following: the definition of a reportable individual reaction; the data elements which should be in the report, and a procedure and format for submitting the same report to all interested regulatory authorities. So that the initiative and the consensus reached would not be wasted, Dr Bankowski suggested that the group become

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the first CIOMS working group on international reporting of adverse drug reactions. At each subsequent meeting from 1987 through 1989 the group reviewed its set of agreements and procedures and examined progress.

CIOMS I — Expedited case reporting

The agreements reached

- Reports were to be submitted by all manufacturers to all regulatory bodies on the same prescribed CIOMS form (Figure 1, Annex).
- Local reporting requirements would be unchanged.
- Cases requiring international reporting were defined as those which were serious, medically substantiated, and unlabelled (in the product core data sheet), and which occurred in patients in foreign countries. In addition, the reports should be reactions and not events — i.e., the physician or other health-care professional had judged with a reasonable possibility that an observed clinical occurrence had been caused by a drug. The working group took the view that all spontaneous reports were of suspected reactions, otherwise they would not be reported. In clinical trials the physician had the responsibility of identifying those which were "possibly" or likely to be drug-related.
- There had to be a minimum standard of information before the case was reported: an identifiable source, a patient (even if not precisely identified by name and date of birth); a suspect drug and a suspect reaction. If any of these essential elements was missing, no report needed to be submitted until the missing information had been obtained through follow-up inquiries. However, it was essential that manufacturers made genuine efforts to follow up reports of a possibly serious nature.
- The reports had to be sent no later than 15 working days after being identified as "CIOMS reportable".

A retrospective look at CIOMS I

The CIOMS I agreement was remarkably successful and the drug regulatory authorities of the United Kingdom, Italy and Germany have incorporated CIOMS I reports in their regulations. Although the FDA in the United States is now changing the format of its internal domestic reports in its MEDWATCH initiative, it is agreeing to accept CIOMS I reports for overseas cases, and all regulatory authorities requiring expedited overseas reports accept them. Nevertheless, the CIOMS working party is not complacent and is anticipating the time when the information will be sent from the manufacturer electronically, instead of by hard copy, through regulatory authorities' databases to WHO.

Several factors contributed to the success of the working group. Firstly, its relatively small size encouraged open dialogue. Secondly, all

members were encouraged not to focus on their own organizations but to strive for a consensus view. Having reached consensus, members agreed to accept responsibility for trying to put the agreement into effect both within their organizations and elsewhere. Finally, CIOMS working groups are, as the name indicates, working groups, not debating societies. Nowhere was this more true than in the CIOMS second working group.

The CIOMS II Working Group — International reporting of periodic drug-safety update summaries

CIOMS Working Group I had focused on reports of adverse drug reactions occurring in countries other than the country of the particular local national regulatory authority, but regulatory authorities also require safety updates, based on both domestic and foreign data, and this was the subject of CIOMS Working Group II. A safety update is an interim report and by its nature is not an alert. Rather, it should review information accumulated from various sources since the previous report and put it into context against previous information. As with CIOMS I, it was the aim of CIOMS II that each regulator requiring a periodic safety report would receive the same update at the same time. Any new important safety issues should continue to be brought immediately to the attention of prescribing physicians through the regulatory authorities, according to current procedures.

Background

Just as the first CIOMS Working Group had been motivated to try to harmonize the various regulatory requirements, the second CIOMS Working Group also tried to harmonize the multitude of requirements for periodic safety updates, as shown in Tables 2 and 3 (Annex). Work began in Amsterdam towards the end of 1989, and by the middle of 1990 the working group had proposals for the content and format of the periodic updates. At the 1990 October meeting, it was agreed that all representatives from industry would follow the draft CIOMS II proposals and compile a pilot safety-data-update for at least one drug. Each update would then be circulated individually to the regulators in the working group for review. The evaluation of the pilot safety update reports followed largely the formats suggested by Dr Hugh Tilson.

By the middle of 1991 and on the basis of the results of the manufacturers' ten prototypes, the proposals for periodic safety updates were clarified, refined, and agreed. A draft report was prepared describing the proposals, and a mock-up prototype written by Mrs Sue Roden of Glaxo was included. The lesson learned from the pilot project was to balance brevity and reader-friendliness whilst ensuring that the information was sufficient to enable regulators to fulfil their public health role of monitoring drug safety. The group

regards the final CIOMS II proposals as a practical, achievable, standardized format for meeting these goals.

CIOMS II proposals

The CIOMS II Safety Update contains nine items:

- The brief *introduction* is to ensure that the reviewer cannot misinterpret the scope of the report.
- The *core data sheet* is a document prepared by the manufacturer, containing all relevant safety information, such as adverse drug reactions, which the manufacturer stipulates should be included in all countries where the drug is marketed. It is the reference document by which "labelled" and "unlabelled" are determined internationally for CIOMS I reports.
- The *drug's licenced status for marketing* describes the number of countries where the drug is approved and marketed.
- The *update of regulatory* or *manufacturer actions taken for safety reasons* should include descriptions of any drug licence suspensions, restrictions on distribution, or any clinical trial programmes leading to significant alterations in label or package insert, such as lowering of the recommended dosage, for safety reasons. There should be a brief narrative stating the reasons for any significant regulatory or manufacturer action.
- *Patient exposure* is not always easy to ascertain, but the manufacturer is obligated to give the best estimate possible and describe the method used for its estimate.
- *Individual case histories* are presented in the safety updates on one line each as a line listing. For clinical trials the unlabelled serious adverse reactions that are required as expedited reports according to the CIOMS I criteria are included. For spontaneous reports, the CIOMS I criteria were expanded to permit all serious (i.e., labelled and unlabelled) cases to be included on the line listing as well as non-serious unlabelled cases. Consumer reports that cannot be medically confirmed but considered relevant by a medical professional in the industry and published individual case histories should be included. Although reports from regulatory authorities to the manufacturer were not specifically required in the original CIOMS II line listing, subsequent experience has shown that these are useful. CIOMS line listings of case reports require all relevant cases to be presented in body-system order, giving the country, source (e.g., study/prescribing physician), the age and sex of the patient, dose of the drug, duration of treatment prior to the event, the time to onset, the description of the reaction as reported, the outcome (e.g., fatal/resolved), and any comments that the company wishes to make, as well as the case's company reference number in case a regulator wants more information on a particular patient.

- A section on *studies* includes newly analysed studies containing important safety information; the manufacturer is asked to include any new signals or important findings from any studies involving patients, as well as from newly completed animal toxicology studies: the format requires that all studies reviewed be listed and any signals mentioned. A separate focus of attention is any targeted new safety studies, which should be described as they are initiated, in addition to describing the results when they are first analysed.
- The *overall safety evaluation* is the most important part of the CIOMS II update. In a short report (i.e., no more than 8 to 10 pages) the manufacturer is asked to not only describe any specific safety issues relating to the drug, but specifically address any increased frequency of known toxicity, drug interactions, overdose and its treatment, drug abuse, positive and negative experience during pregnancy or lactation, effect of long-term treatment, and any specific safety issues relating to the treatment of specific patients groups, such as the elderly or the very young. The "bottom line" is whether the interim safety data remain in line with the cumulative experience to date and the manufacturer's core prescribing information.
- The final part of the CIOMS II Periodic Safety Update is any *important information received after the "data lock point"* (i.e., the time when the tables were generated from the data-bases for inclusion in the CIOMS II Safety Update). The CIOMS II report specifies the data lock-point and it should be no more than 45 calendar days before the completion and submission of the safety update.

CIOMS II reports are interval reports (i.e., non-cumulative) and they are required or submitted six months from a drug's International Birth Date (which is the date on which the first regulatory authority approved a particular drug for marketing). The idea was that the manufacturer's data are temporarily frozen for review for that particular drug every six months subsequent to the International Birth Date and that all regulatory authorities that wish to have safety updates accept the same cut-off date and time of submission.

A retrospective look at CIOMS II reports

People would no doubt agree that the CIOMS II Periodic Safety Update is not an easy undertaking for any manufacturer, for it is usually difficult to collect together all the different pieces of information from the different departments within the organization. Once written, they are very user-friendly and informative to people within the corporation as well as to those regulatory authorities that require them.

The UK and the Swedish regulatory authorities have been the most forthcoming in requesting written safety updates in CIOMS-II format.

It is interesting to see that the periodic updates which the European Union regulations require are to be submitted in the CIOMS-II format. Meanwhile, in the US, the CIOMS II format seems to be gaining increasing acceptability, although we all hope that the FDA will agree to substitute CIOMS-II reports for other current requirements, rather than asking for CIOMS-II updates in addition to their other periodic reporting needs!

The CIOMS III Working Group — Core data sheets

The first and second CIOMS working groups had to refer to a core data sheet. Whereas most companies had some sort of core data sheet for each drug, there was no consistency among manufacturers on how these should be formatted, and there are also wide differences between the Layout of the Summary of Product Characteristics as defined in Europe and in the U.S. Package Insert.

CIOMS Working Group III is considering why there should be a standard format and specifying, as far as feasible, what should be included, both in the initial core data sheets (at the time of product licence for marketing application) and subsequently as post-marketing information on the safety of a product becomes available. The group is also addressing ideas of when and where the information should be included, and other ideas which describe how best to put the information into the core data sheet, i.e. general ideas concerning good working practices. As would be expected, the third CIOMS Working Group is concerned only with safety aspects of the core data sheet.

CIOMS III home-work

As part of the exercise, each regulator and manufacturer representative in the working group produced two borderline scenarios in which it was debatable whether the data sheet should be amended. Each scenario was then evaluated by each member of the working group, who was asked to comment on his or her decision about changing the data sheet, any problems concerning "what", "when" and "where", and the wording suggested.

The working group is at present producing an early draft of its conclusions, looking at factors affecting the weight of the evidence (i.e., the threshold above which it should be decided that the drug does cause an adverse reaction), considerations about the sufficiency or importance of the information, and aspects of good practice.

Summary

Figure 2 (Annex) represents the core data sheet, and shows how safety statements can vary between countries A, B and C, whilst there is a central core. This could be the logo of the three CIOMS working

groups. The first group related expedited case reports and labelling to the core. The second gave periodic safety updates and comments on the adequacy of what is included in the core data sheet. The third is dealing with the content of the core data sheet.

What of a fourth CIOMS working group? It could be that such a group would revisit the conclusions of the first three working groups, once the regulations in Europe are clear. However, it could work on specifying in more detail the information items which are considered important for sending information from source to WHO through the intermediate data-base. You may have some other specific ideas, in which case we should be glad to hear from you.

Table 1. Information required by the regulatory authorities of the Federal Republic of Germany[a]. the United Kingdom[b] and United States of America[c] (1986)

a) Required by all three regulatory authorities:

- Patient identification, sex, weight
- Observed unwanted effect, date of onset, outcome
- Identification of suspected drug
- Drugs given, mode and dates of administration, indication
- Name of reporting doctor, address, date of report

b) Required by only one or two of the three regulatory authorities:

Date of birth (BGA, CSM)
Age (FDA)
Race (BGA, FDA)
Height (BGA, FDA)
Occupation (BGA)
Parity (FDA)
Month of pregnancy (BGA)
Week of pregnancy (FDA)
Duration of effect (BGA)
Laboratory tests (FDA)
Drug brand name (CSM, FDA)
Dosage form (BGA)
Duration of treatment (FDA)
Prior exposure to suspected drug (BGA, FDA)
Previous tolerance (BGA)
Re-challenge (BGS, FDA)
Past medical history (BGA, FDA)
History of allergy (BGA, FDA)
Smoking/drinking habits (BGA)
Progress and treatment of observed unwanted effect (BGA)
Cause of death (BGA, FDA)
Date of death (FDA)
Assessment of causality (BGA only, but required from three sources)
Information about who has been informed (BGA)
Whether information may be released (FDA)
Speciality of reporting doctor (BGA)
Signature (BGA, CSM)

[a] Bundesgesundheitsamt (BGA) (Federal Health Agency)
[b] Committee on the Safety of Medicines (CSM)
[c] Food and Drug Adminstration (FDA)

Table 2. Requirements for Periodic Safety Updates (Countries represented in CIOMS Working Group II)

Country	Before submission of marketing application dossier	After submission before approval	While drug marketed (Time post-launch, in years)	Formal post-marketing surveillance requirements
Canada	N	N	N	N
Denmark	N	N	N	N
France	N	N	0.5, 1.0, Yearly	M, Local
Germany	N	N	2, 5; then every 5 years	N
Italy	N	N	January & July every year	N
New Zealand	N	Y*	N	Y**
Sweden	N	N	N	N
United Kingdom	M	N	N	Y, "Voluntary"
United States	Y	Y	0.25 for 3 years; then yearly	M

Y = Yes; N = No; M = Maybe
* Often but not always requested by the Department of Health
** Only as requirement for reimbursement status approval

Table 3. Requirements for Periodic Safety Update Reports (Countries not represented in CIOMS Working Group II)

Country	Before submission of marketing application	After submission, before approval	While drug marketed (Time post-launch, in years)
Australia	N	N	Yearly for 3 years
Japan	N	N	Yearly; special 6 year report
Korea, Republic of	N	N	Yearly for 3 years
Netherlands	N	N	0.5 for 5 years then every 5 years
Philippines	N	Y	Yearly
Switzerland	N	N	0.5, 1.0*
Taiwan	N	N	0.5 for 3 years
Thailand	N	N	0.2 for 2 years
Proposed EC 1993)	N	N	0.5 for 2; yearly for 3, then every 5, years

Y = Yes; N = No
* Only for drugs approved under "monitored release"

Figure 1. The CIOMS form

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

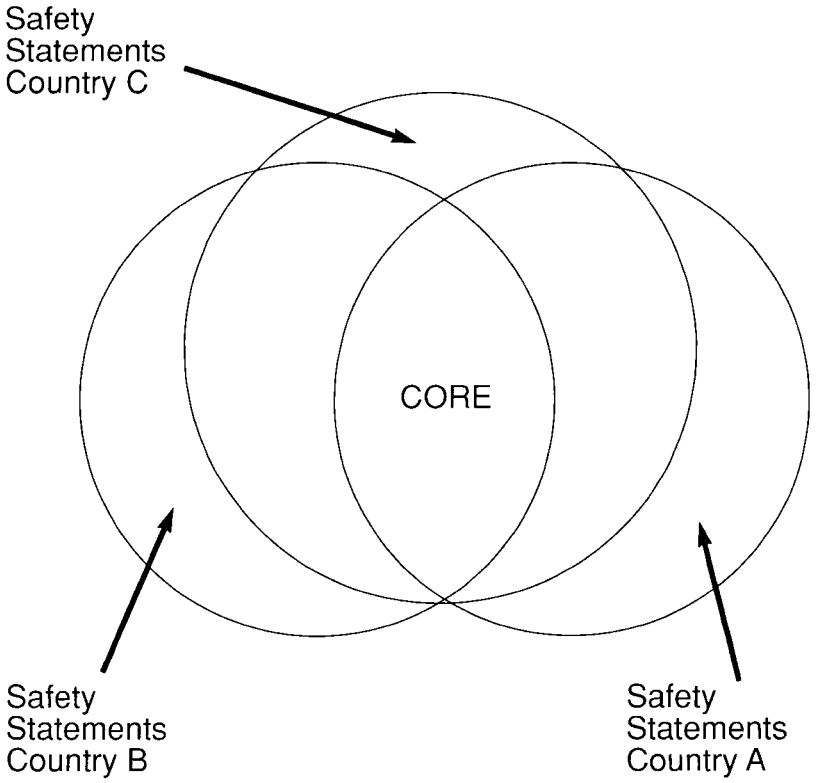
III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

Figure 2. The Core Data Sheet

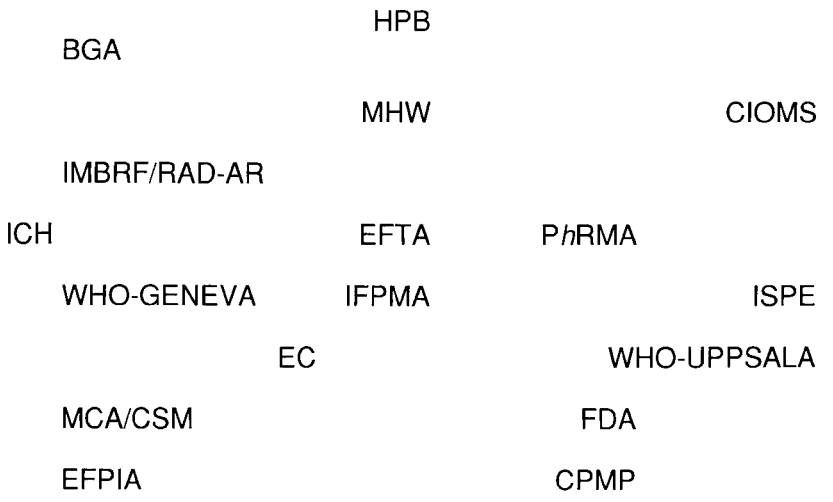


THE INTERNATIONAL CONFERENCE ON HARMONIZATION: EXPEDITED REPORTING OF ADVERSE DRUG REACTIONS

Arnold J. Gordon*

Before addressing the specific subject of my comments, I would like to share with you a situation (Fig. 1) that represents some of the frustration that many, if not all of us, experience in the field of drug safety: just who is responsible for what; who has the authority to issue guidelines or regulations or create definitions; who is important; who speaks to whom?

Figure 1. *JUST WHO*: is responsible for what? has authority? is important? speaks to whom?



This is an embodiment of the communication issues that previous speakers have raised. We all seem to be submerged in an alphabet soup of organizations, most of which you will recognize immediately. The CIOMS Group, which of course, is not an "official" group, as Dr Castle has indicated, has generated useful proposals, which have created important precedents for standardization of adverse-reaction reporting and monitoring for marketed drugs. Another significant "unifier" is, of course, the International Conference on Harmonization (ICH), which began several years ago. The regulatory authorities in the three geographic areas of the United States of America, the European

* Worldwide Harmonization, Pfizer Inc., New York, NY

Community and Japan agreed to attempt a harmonization of the technical requirements for drug development and registration (pre-marketing activities). Observers are the EFTA countries, Canada and WHO. The ICH secretariat is the International Federation of Pharmaceutical Manufacturers Association (IFPMA). The three technical branches of ICH are preclinical safety (toxicology, etc.) formulation quality issues (stability testing, excipients, etc.), and clinical efficacy and safety. Major ICH gatherings are held every two years to present accomplishments to, and obtain feedback from, a wide audience of affected parties.

Standardization of clinical-safety data

I have had the privilege of coordinating one of the ICH2 efficacy topics, referred to officially as Topic E2, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting," which I will describe in some detail. As with each ICH topic, the expert working group (EWG) consists of a regulatory and an industry representative from each geographic region, plus an observer, if appropriate.

There is an important need for standardization in this area, which, after all, deals with key clinical safety information on a new medicine. The WHO Collaborating Centre (Uppsala) is now receiving some 100,000 reports annually from its member agencies, of which 20% are deemed "critical". The US FDA alone processes more than 80,000 adverse event reports on US marketed drugs per year, 20% on an expedited basis (15-day); about 30% of the latter are fatalities. Many factors can influence the need for rapid reporting on important safety issues. For example, is the event "serious" or non-serious; is it unexpected (not previously documented) or expected (labelled or previously reported); is it a local case or a foreign case; does the case come from a clinical trial or from another source? Unfortunately, the definitions of terms and the requirements for reporting are different in most of the 20 or so countries that do have such regulations, including how quickly to report and how to report — some countries require special local forms, some will accept a CIOMS form, and in many cases no forms are required (Fig .2).

Fig. 2. Current multiplicity of definitions and requirements for expedited reporting on drugs in development

Regulations/Guidelines:	About 20 countries
Factors governing *what* to report:	Serious vs. Non-Serious Unexpected vs. Expected Related vs. Not related Domestic vs. Foreign Clinical trial vs. Other source
When to report:	Immediately, promptly, 72 hours; 3, 10, 15, or 30 days; without delay.
How to report:	Local form, CIOMS form, no form.

Although the pre-marketing environment differs in special respects from the marketing environment, one of the important issues we had to face was the following: at least over the lifetime of those of us in this room, it is safe to say that most drugs will be approved at different times in different parts of the world, so that while a drug is under development in some countries it may very well be on the market elsewhere. So it would be ill-advised and possibly dangerous to consider only the pre-marketing environment when trying to establish regulations or guidelines for safety reporting, because the information that is collected on marketing experience surely will be of direct interest to those regulators in countries where the drug is in development or under market-application review. Therefore, the two stages should not be separated from the point of view of important safety-reporting. This is a slight departure from the ICH mandate, which is directly concerned with technical requirements during the developmental stage of a product.

Proposal for standardization of expedited reporting

As we have been hearing from other speakers, to make sure that everyone is receiving the same kinds of information in the same way, we do need agreed definitions and standards. Under E2 we chose to limit requirements for expedited reporting to those reports that are of "serious, unlabelled, adverse reactions"; each term in the quotes has been carefully defined. The proposal by our EWG has reached Step 4 (June 1994) in the ICH process (sign-off by all three regulators). It was officially released as a Step-2 paper in June 1993 for critical review and comments; the Step-4 version emerged following the October 1993 ICH-2 Conference (Orlando, Florida).

In developing the proposal we drew heavily on definitions already developed by WHO for application to marketed products. An adverse

event refers to any occurrence of an adverse finding whether or not drug-related; "reaction" refers to the fact that there is thought to be a causal relationship between drug and event. We also had to distinguish between the terms "serious" and "severe"; the former is a medical/administrative determinant for reporting, the latter a relative intensity (as in mild, moderate, or severe headache). The definition of "serious" is very similar to, but not identical with, the definitions now in place in other parts of the world, such as under CIOMS I for marketed drugs, under FDA regulations, and under other regulatory bodies.

"A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*"

Regulator and industry parties in ICH have, I believe, captured the meaning and the spirit of all of them. Note the expression in the first sentence, "at any dose"; it was inserted specifically to cover the use of a drug in overdose. When a drug is under development and not on the market anywhere in the world, manufacturers are expected to have a standard Investigators' Brochure, which will be the same everywhere the drug is studied; the Investigators' Brochure, when appropriately constructed and updated, will contain all important safety information and will serve as the relevant source document for expectedness.

The primary reports are of single cases of serious, unexpected adverse drug reactions. As under CIOMS I rules for marketed drugs, it was decided that a spontaneous report would have implied causality. In a clinical-trial case, one usually has access to much more detailed information and is required to perform a causality assessment. If either the reporting physician or the sponsor believes the drug is causally related, expedited reporting is required. In general, it is not important to report in an expedited fashion anything except serious, unexpected, adverse drug reactions (ADRs); expedited reporting of all other categories have the effect of diluting the attention needed for those very important cases, particularly for a drug still under development. Other criteria also have been established for expedited reporting. For example, new cases with greater severity or more specific pathophy-

siology would be "unexpected" (fulminant hepatitis vs. hepatitis). A clinically significant increase (without strict definition of this phrase) in the rate of occurrence of an "expected" (known) serious ADR is also reportable. Other observations involving medical and scientific judgment on reporting include a significant hazard to a study population, such as lack of efficacy of a drug used to treat a life-threatening condition, or a major safety finding from an animal study (carcinogenicity, for example).

Reporting to regulators

How should the information be submitted to regulators? It is suggested but not required by the proposal that the CIOMS form be used as a simple, standard summary to capture the basic facts on the case; but primarily, the key is the inclusion of basic data elements on each case (the subject, incidentally, of a new CIOMS initiative known as CIOMS-IA). The basic data elements are: *patient details, suspected product, other treatments, details of suspected ADRs, details on reporter of events, and administrative/sponsor details.* However, a company should feel obligated to report a case even if all the details are not available, as long as four minimum criteria are satisfied; these criteria are: *an identifiable patient, a suspect medicinal product, an identifiable reporting source, and an event or outcome identifiable as serious and unexpected, and for which in clinical investigation cases there is a reasonable suspected causal relationship.* Thus, regulators are made aware initially of a potential serious ADR, with details to follow in subsequent reports.

Agreement was also reached on the timing for reporting to all appropriate health authorities relative to the first time anyone within a company has sufficient knowledge that a case qualifies:

Fatal and life-threatening reactions — 7 calendar days
All other serious ADRs — 15 days.

For the rapid alert, 7-day reports, follow-up with as much detail as possible is required within eight additional calendar days. With regard to the situation involving a blinded-study report, the EWG proposal advised that the code should be broken for an individual case that qualifies for reporting. This is not expected to compromise the integrity of the study and it facilitates better understanding and communication of risks, especially when the Investigators' Brochure and informed consent are involved.

Further harmonization tasks

It is expected that the E2 proposal will be implemented at the regulatory level within all three ICH regions during 1995. However, harmonization of many other aspects of safety reporting is needed. Examples include the reconciliation of differences that still remain between certain definitions and reporting standards for pre-marketing

and marketing phases; development of international standards and specifications for paper and electronic reporting and exchange of individual AE/ADR cases; and consideration of the nature and amount of information for periodic, summary reporting that should be gathered and assessed on a medicine while under development. It is hoped that these and other issues will be addressed as topics under ICH3.

[*Note:* This paper is an updated version of the author's presentation at the Conference]

STANDARDIZATION OF ADVERSE EXPERIENCE TERMINOLOGY

Raymond Herman*

As President of the COSTART Users Group in the United States, and having been involved in drug safety in the pharmaceutical industry for the past 14 years, I should like to share my views with you regarding the standardization of adverse-experience terminology. COSTART is the official post-marketing adverse-experience dictionary of the US Food and Drug Administration, and more than 70 pharmaceutical companies in the US use COSTART in its pure or a modified form. These companies are members of the Users Group, whose main functions are to educate the user for COSTART use and to liaise with FDA on areas of concern with the dictionary.

Needless to say, there are concerns with COSTART, just as there are with WHOART, as both dictionaries were heavily derived from a dictionary called DART, which was in place for both the World Health Organization and the FDA in the mid-1960s. Besides the common complaint that some therapeutic areas (e.g. infectious diseases) have been given little coverage, as well as placements that could be more medically correct, the concern of late is why we need two major different dictionaries or thesauri, when so much attention has been given to international standardization efforts. I refer, of course to the initiatives of WHO, CIOMS, the International Conference on Harmonization (ICH) and other bodies.

A COSTART or WHOART dictionary is, in effect, a thesaurus of adverse-experience terms. And these terms are the result of a distillation of natural language into a workable subset for simple data-base retrieval and analysis. This process is known as vocabulary control. One must be very cautious of any vocabulary control system as it provides only a rapid and partially accurate picture of the actual events reported. Hence we must constantly remain suspect of the thesaurus and not ascribe to it more credibility than it deserves. The authors of the 1970 COSTART manual stated in the preface: "it cannot be emphasized too strongly that COSTART is not designed to be an end in itself. Its entire construction is predicated upon the capability to provide selective, consistent and inclusive retrieval of data entered into the computer". While we must be prepared to lose a degree of specificity when employing COSTART, we must also remember the reasons for this loss. The results allow a consistency, albeit a loss of specificity, to achieve a simplified safety-profile with the ability to raise questions or concerns. It is the consistency aspect of an adverse-drug-experience vocabulary control system which begs for international standardization.

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What must we do, and, if we do it, what will be the final result?

First, the proprietors of the major dictionaries need to accept the concept of universal standardization. Professor Edwards has been pursuing this for a few years now, so the idea has been well disseminated to members of WHO. On the other side of the Atlantic, I, representing the COSTART Users Group, as well as Professor Edwards, have met with the FDA and spelled out what it is we should like to accomplish. Those proposals have received general acceptance along with a promise of active participation in the near future.

This commitment by the FDA implies that in the US a concurrence needs to happen within the FDA for submission of reviews of adverse experiences in both the pre- and the post-marketing areas. The concurrence means that all FDA reviewers will accept and use the same agreed-upon thesaurus.

Action of this type would be a major impetus to the standardization effort and would certainly be welcomed by pharmaceutical manufacturers, who constantly have to modify terminology to suit the regulatory registration reviewers' own preferences. Of course, for this project to be fully successful, it would be not only advantageous but also advisable to have the acceptance of the other regulatory reviewing agencies of major adverse-experience reporting countries.

Another area that requires consideration for this project to succeed is definitions of terms — the words behind the words. Are we using adverse-experience terminology in the same way? Does "the event which is reported" mean the same thing, medically and universally? Those of us who work in the drug safety areas, internationally, know the answer already. And that answer is "not in all cases". Once one crosses country borders, it is not unusual to find differences in medical definitions. And this will occur even though the spoken language is the same! Even yesterday, we heard Dr Rawlins tell us to ignore the data on leukopenia in the UK/US study because the definitions of the adverse experience were different.

The consensus definitions that have been put forth by CIOMS and Dr Bénichou have been pivotal for medical science but, as we are aware, an iron-clad diagnosis requires considerable information for precision. Regrettably, we usually do not obtain that degree of information in the conduct of clinical trials or in the body of spontaneous reports received after a drug has been marketed. However, this is not to say that definitions of adverse-experience terms are unnecessary. On the contrary, we need to look towards clinically descriptive definitions that can be useful for even the anecdotal data we receive in post-marketing reports, if we are to have international acceptance of a standardized terminology.

The COSTART Users' Group has previously presented what we believe constitutes the ideal system and what we should work towards. I should like to share these ideas and goals with you:

1. The system should embrace the concept of one world-wide thesaurus.
2. It should have world-wide regulatory acceptance.
3. It should contain clinically descriptive terminology.
4. It should have appropriate categories and terminology so that:
   - one can derive easy labelling-information
   - a safety profile can be clearly presented
   - it is appropriate for international pharmacovigilance — it is appropriate for pre- and post-marketing use
   - it can avoid the deficiencies in the current terminology.
5. It should be developed with the assistance of medical and coding experts.
6. It should provide authorized translations in major languages.

If we can help to achieve these objectives, drug safety, as we know it, will become considerably more understandable.

SESSION IV

CHALLENGES FOR DRUG SURVEILLANCE

Chairman: John H. Bryant

Educational Aspects

Needs in Developing Countries

Management of:

- ***malaria***
- ***onchocerciasis***
- ***tuberculosis***

Monitoring the Safety of Biological Products

DRUG SURVEILLANCE AND EDUCATIONAL CHALLENGES

Molly Thomas*

Early tragedies of drug use have taught us the need to monitor drug safety, efficacy and quality. The ease with which drugs can today reach any part of the world makes this all the more important.

Problems of drug surveillance in India and other developing countries

Various post-marketing surveillance techniques have been used and much has been published on this. The spontaneous monitoring of adverse drug reactions, widely popularized in the United Kingdom and Sweden and in many other Western countries, has yielded sustained interest and has aided in many pharmaco-epidemiological pursuits. However, the developing countries have not kept pace with those countries mainly because of lack of recognition, evaluation and notification of ADRs. In many developing countries, indigenous systems of medicine have a major role and self-medication with them is very common. The composition of these indigenous products is obscure and many contain allopathic drugs as well. Hence if reactions occur, it is difficult to identify the possible causative ingredient. As access to over-the-counter drugs is unlimited and there are no means of monitoring prescriptions, drug reactions cannot be easily traced to a particular drug. Many drug reactions simulate clinical conditions. The severity of illness in a grossly malnourished population makes recognition of a reaction all the more difficult. Patients flit from doctor to doctor and pharmacy to pharmacy, thus adding to the confusion.

Physicians are not sure whether it would be to their advantage to report reactions. Fear of enquiries and misguided notions that drug reactions are evidence of therapeutic inadequacy prevent them from reporting.

There is no organized continuing medical education and often the only updates come from pharmaceutical representatives. Experience from the West has shown that the success of drug surveillance depends particularly on education and awareness among doctors, consumers and drug regulatory authorities.

The programme of monitoring ADRs is limited and it is only recently that, in addition to industry-directed surveillance, voluntary reporting has been encouraged by private or voluntary and governmental agencies.

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Conventional educational benefits of post-marketing surveillance

The traditional value of post-marketing surveillance in generating or testing hypotheses and quantifying hazards of drug treatment in the outpatient setting is well known. Results have been used to look for associations between drugs and disease, such as aspirin and gastrointestinal bleeding, or coffee and non-fatal myocardial infarction.

ADRs can be used to identify hazards, establish causality and estimate incidence. The estimation of incidence may be a difficult task as the drug-use denominator is not readily ascertained.

Risk/benefit judgment of new classes or groups of drugs introduced can be made from ADR data. However, for the developing countries, the greatest educational challenge of ADR monitoring is improvement of drug use in the community.

Drug surveillance can be used as a challenge to educate the parties concerned in a number of ways.

1. Awareness building

An adverse reaction is often thought of only as an inconvenience to patients and doctors. Awareness building should start early in both medical and community education. For largely illiterate populations, maximum use should be made of audiovisual and traditional forms of dissemination of information.

Medical education should give more attention to ADR recognition and evaluation as well as to communication skills. Too little time is spent with patients and in explaining drug use to patients, and means of communicating with "illiterate" patients are neglected.

The importance of taking a drug history and looking for drug reactions must be stressed. Most undergraduate teaching does not stress adverse reactions to drugs in terms of drug safety, efficacy or risk/benefit.

Simple visual reinforcement by means of videos that depict typical drug reactions can be used to enhance education. The stress should be on selection of drugs for a disease from the large range of drugs available. Scoring techniques to assess selection of drugs in which safety and efficacy are included are useful. Problem-solving exercises can be worked around ADRs to emphasize drug safety.

2. The cooperation and education of physicians

Primary care physicians are the backbone of health care in any country. To enable them to participate in post-marketing surveillance, early exposure and follow-up are needed. Good rapport with the physician and the use of simple ADR-reporting forms could give a reasonable response. The use of practitioners' own reports as educational tools could also improve reporting.

i. Through easily read **newsletters** or other forms of feedback issued periodically, practitioners can be notified about the ADRs being reported. An acknowledgement by name in the newsletter of doctors who respond might motivate them to report more frequently.

ii. Analysis of ADR reports can reveal doctors' **prescribing patterns**. It is most difficult to get this information direct from physicians but, if it can be gathered in a non-threatening way from the reports, the offending drugs and the conditions for which they are used can be revealed. Some reported reactions have been caused by drugs of which the efficacy and safety have been questioned elsewhere. A newsletter can use such information to illustrate the need to avoid selecting a potentially dangerous drug when safer alternatives are available; also it can highlight drug interactions.

Many irrationalities of drug use can be gathered from ADR reports and these can be used to promote rational drug use. The newsletter and feedback should open up easy communication channels between the doctors and the reporting centre.

iii. **Containing the cost of treatment**. Mostly patients pay for their treatment. ADR reports can be correlated with length of treatment or hospital stay to assess the economic burden that ADRs impose upon the patient and the community. This can be very significant for poorer countries with meagre health-care resources and no health insurance coverage.

iv. **Curbing the inappropriate use of antibiotics**. A major problem in developing countries is the indiscriminate use of antibiotics. ADR reports can indicate prescribing patterns and trends in using antibiotics for viral fever, diarrhoeal diseases etc., and these can be brought to the notice of physicians.

New antibiotics still untried in tertiary-care hospitals are very often freely available in the community; for example, four years ago when ciprofloxacin was used only in selected cases of enteric fever, it was the most commonly used drug for fever in urban general practice; not only was its use an unnecessary expense, but its indiscriminate use resulted in multi-drug-resistant *salmonella typhi*.

There has been similar inappropriate use of mega-dose vitamins, tonics and injections. Once such problems are identified, doctors may be educated by such means as workshops and lectures, through medical associations or other agencies. Workshops have the advantage of bringing people together and are an educationally ideal means of introducing and updating concepts in therapeutics and the rational use of drugs and improving clinical competence. It is essential to establish good rapport and give primary support with drug information. The participation of general practitioners gives them a sense of involvement and accountability, and boosts their morale and self-esteem.

3. Training of pharmacists

In most developing countries, pharmacists are the first point of contact for patients and hence play a pivotal role. Since transactions cover diagnosis, prescribing and advising on the effective use of a prescribed medicine or self-medication, and over-the-counter drugs are expected, pharmacists should be trained in the necessary expert knowledge and skills. Pharmacists are the first health professionals likely to receive reports from patients about possible reactions to medicaments purchased with or without prescription. Hence, primary-care pharmacists can do much to ensure that maximum information on possible ADRs is made available to central reporting centres and in educating the public.

Printed information or a training manual on drug use, with emphasis on post-marketing surveillance, would be useful, as well as workshops for physicians and pharmacists.

4. Educating the community

The community at large is ill-informed about drugs and their uses or side-effects. Where self-medication is common and many drugs can be bought over the counter, communities should be educated about drug use. They should be taught to recognize early reactions and report them to the nearest physician if possible. Since levels of literacy may be low, visual communication media such as videos and television shows in community halls are likely to be more useful than print media. "Street drama" performances depicting drug-related events can be enacted to retain interest and educate. In view of the growth of consumer protection associations and of awareness of individual rights, information about ADRs should be disseminated impartially. Early teaching about drug use and the hazards of medication could be encouraged in schools.

5. Manufacturers

Manufacturers should stress quality assurance and update drug datasheets. Adverse reactions to a drug should be the same in developing and developed countries, except where genetic differences occur. Industry is very influential and can reach practitioners in remote areas. It is very important that medical representatives be trained to give rational promotional material. Industry can do much to improve drug use and can be a good resource for notifying drug reactions and for education.

6. Health authorities and regulatory agencies

Health authorities can use information on ADRs in ascertaining risk/benefit ratio and safety assessment of drugs. Epidemiological profiles

that can be constructed from ADR reports could be used to introduce drugs cautiously among vulnerable populations, and could help also in checking for quality assurance and spurious drugs.

7. The mass media

The education of this group is of paramount importance, as irresponsible reporting can do much harm. There should be a mechanism for informing them responsibly so that they give wide publicity when necessary to educate doctors, patients and the community.

In conclusion, the crucial challenge of education from drug surveillance lies in ensuring its relevance to community health, promoting the principles of rational prescribing, and cultivating a discerning attitude towards cost of treatment.

NEEDS IN DEVELOPING COUNTRIES: CURRENT STATE OF ANTIMALARIAL DRUG RESISTANCE

Nicholas J. White*

Introduction

Although malaria is estimated to infect about 5% of the world's population at any time, and to kill between one and two million children a year, there are remarkably few drugs available for its prevention and treatment. Research during the Second World War and the conflict in Viet Nam brought us most of the drugs we have today. The list is short, and the development of new compounds has not kept up with the parasite. *Plasmodium falciparum* has developed resistance to all of our available drugs, and *Plasmodium vivax* has developed resistance to chloroquine in some parts of New Guinea. Multi-drug resistance in *P. falciparum* is particularly serious in South-East Asia, and the possibility of completely untreatable malaria in the near future must be considered seriously.

All antimalarial treatment regimens are associated with some failures (Bruce-Chwatt, 1981). In the last three centuries, the bark of the cinchona tree was the only specific remedy available for the treatment of malaria in the Americas and Europe. Laveran's discovery of the malaria parasite in 1880, and his subsequent demonstration that quinine killed these intra-erythrocytic organisms, finally characterized the specific antimalarial action of the alkaloid content of cinchona bark.

Research stimulated by the two world wars led to the introduction of mepacrine (quinacrine) and chloroquine, and the discovery of the antimalarial biguanides proguanil (chloroguanide), chlorproguanil and, somewhat later, amodiaquine and pyrimethamine (Covell et al., 1955; Coatney, 1963); it also laid the foundations for the development of other antimalarial quinolines and acridines, and also the hydroxynaphthaquinone compounds. There have been only a few more recent additions.

Between 1963 and 1976 the US Army screened over 250,000 potential antimalarial compounds, which led to the discovery and development of mefloquine and halofantrine. The first reports in 1961 of chloroquine resistance in *P. falciparum,* in both South America and South-East Asia, were further incentives to research. By then chloroquine had become the standard antimalarial for treatment and prophylaxis of all the human malarias and, as a consequence, one of the most widely-used drugs in the world. At first, resistance to chloroquine was low-grade and geographically focal, but during the ensuing years

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treatment failures increased in number and degree. By the beginning of the 1980s, chloroquine was no longer effective for the prevention or treatment of falciparum malaria in many parts of South-East Asia and South America, and the ominous first reports of chloroquine resistance were emerging from the east coast of Africa. Over the past ten years, resistance has spread inexorably from the east to the west coast of Africa. Most countries in the tropics are now affected (World Health Organization, 1990a). Only central America (North of the Panama canal) and North Africa are still free.

The development of antimalarial drug resistance

How do malaria parasites develop resistance to the antimalarial drugs? The selective pressure exerted by drugs takes place during asexual multiplication in the human host. The sexual forms (gametocytes) of *P. falciparum* but not the other malaria parasites of man are relatively resistant to the antimalarial drugs (with the exception of primaquine). Parasite meiosis takes place following random mating between the sexual forms in the gut of the female anopheline mosquito. After sporogony (the development of sporozoites) in the mosquito, the genetically-mixed variants are then redistributed to humans at subsequent feeding. Naturally-occurring populations of *P. falciparum* are genetically diverse, with heterogenous sensitivity to the antimalarial drugs (Thaithong, 1983). Infections are usually polyclonal. Resistance probably results from spontaneous chromosomal point mutations (this is thought to be independent of drug pressure), followed by selection of the more resistant mutants under antimalarial drug pressure. Although resistance to the dihydrofolate reductase (DHFRT) inhibitors (pyrimethamine, proguanil) can arise from single or two-point mutations, epidemiological and laboratory observations suggest that resistance to the quinoline compounds is likely to require a series of unlinked additive mutations. Significant resistance to the artemisinin derivatives has not been confirmed yet. Models of the development of drug resistance have been developed (Curtis & Otoo, 1986; Cross & Singer, 1991) and have some important practical implications. These models predict that resistance will develop rapidly if maximally effective antimalarial treatment is given to more than 25% of the population in areas of intense transmission (e.g. sub Saharan Africa, New Guinea). In theory, the use of antimalarial combinations delays the onset of resistance, but only if the parasite resistance genes are rare and free recombination can occur between them, and if less than 20-25% of the population is treated (Curtis & Otoo, 1986).

Selection of the resistant parasites is most likely if the heterogenous parasite population is exposed to a sub-therapeutic level of drug. For resistance to spread, the selected more resistant parasites must then survive to produce gametocytes, and these parasites must be transmitted. There should not be a major survival disadvantage for

these resistant parasites. Anopheline mosquitoes differ in their receptivity to different parasite strains; in some circumstances the principal vectors are more receptive, and in others less receptive, to resistant parasites (Wernsdorfer, 1991).

In practice, antimalarial drug resistance is likely to develop in three sets of circumstances: (a) widespread and extensive antimalarial drug use; (b) generally inadequate dosing (doses too low, or more usually treatment courses that are too short); and (c) adequate dosing with drugs that are eliminated slowly from the body. Inadequate dosing occurs commonly because of poor compliance with prescribed antimalarial treatment regimens, or unregulated antimalarial drug distribution and self-prescribing. Both are common. The greatest pressure occurs when the whole population has low antimalarial drug concentrations constantly in the blood.

There has been considerable progress in recent years in characterising the mechanism of antimalarial drug resistance. The precise molecular basis for resistance to the dihydrofolate reductase inhibitors has been identified to single or double base pair mutations. The gene or genes responsible for chloroquine resistance have been localised to a 4 000 base segment of the parasite's chromosome 7 (but not as yet characterised). The importance of the multiple drug resistance (mdr) genes and their products which pump drugs out of cells has been a subject of considerable interest and debate but their overall contribution to drug resistance is not yet resolved. Many important practical questions need to be addressed. For example, would it be possible to preserve or regain chloroquine efficacy? Perhaps drug sensitivity would return if chloroquine were no longer used, thereby removing the selective pressure on resistance? This has been suggested but never proved. Indeed most data suggest that the chloroquine-resistant phenotype is stable. In practice it is very difficult to restrict use of chloroquine, particularly as it remains the antimalarial drug of choice for the other three human malarias. Cross-resistance between antimalarial drugs of the same group is another potential source of drug pressure, but one which has not been quantified adequately. For example, could use of the 4-aminoquinoline amadiaquine drive chloroquine resistance? Does widespread use of co-trimoxazole for treating bacterial infections encourage resistance to antimalarial antifolates? Does use of mefloquine drive quinine resistance? We do not have answers to these questions.

Chloroquine resistance

In the past, there has been a tendency to declare falciparum malaria in a country 'chloroquine-resistant' if returned (non-immune) travellers with the infection fail after chloroquine treatment or if *in vitro* sensitivity tests indicate resistance. These reports do not assess the usefulness of the drug in the indigenous population, which usually has

some immunity, and in which the drug may still retain efficacy. Even though nearly all countries in sub-Saharan Africa now have evidence of chloroquine-resistant *P. falciparum*, chloroquine remains the most widely-used antimalarial on the continent, and is still a most valuable drug. In Africa, transmission is usually intense and, as a consequence, malaria is largely a problem of childhood. In 1988, 91 metric tons of chloroquine were consumed (World Health Organization, 1990a), corresponding to approximately 500 million child-treatment doses. Chloroquine can be purchased readily without prescription, and is used as a cure-all for fevers and a variety of minor ailments. It has an extremely long (c. 1-2 months) terminal elimination half-life (White, 1985). In many places the majority of the population has detectable blood concentrations of chloroquine at any time. This is the 'drug-pressure' that drives resistance. Where transmission of malaria is intense, reinfection occurs rapidly after treatment and the newly acquired parasites are exposed to low blood concentrations of chloroquine. If there is low-grade resistance and some background immunity, there will be a satisfactory symptomatic response to chloroquine treatment (Brandling-Bennett et al., 1988). Severe infections will respond reliably to treatment, i.e. the drug is still very useful. Unless children are followed up for several weeks after chloroquine treatment, the full adverse effects of resistance will not be appreciated. There is now clear evidence from Africa that the main adverse effect of rising chloroquine resistance in endemic areas is anaemia in childhood. This has serious consequences but can be overlooked easily if the immediate clinical and parasitological indices of response are relied upon as the sole indicators of drug efficacy. As resistance worsens in areas of high transmission, the therapeutic response slows, and increasing numbers of infants with severe anaemia are seen. Eventually the number of infections with an unsatisfactory response to treatment rises to the point where chloroquine is no longer useful, and alternative drugs are recommended. In most countries quinine has now replaced chloroquine as the treatment of choice for severe malaria (although there is some evidence that in fully sensitive infections chloroquine is the better drug). The decision when to change treatment recommendations is difficult and depends on knowledge of the local therapeutic response *in vivo*, and the cost and availability of alternative drugs. Chloroquine is still a very useful antimalarial drug in Africa; indeed in many areas, it is still the only drug available for uncomplicated malaria, but resistance will continue to increase and more and more countries will be forced to find alternatives in the near future.

After chloroquine; what next?

What are the alternatives to chloroquine? Amodiaquine is structurally similar but is more active against moderately chloroquine-resistant

strains, although the difference is not great. Prophylactic use of amodiaquine has been discontinued because of the high incidence of agranulocytosis (1 in 2000) and hepatitis (Hatton et al., 1986), and this has cast a shadow over its role in treatment. The combination of a long-acting sulphonamide (sulfadoxine, sulphalene) with pyrimethamine or antimalarial biguanide (proguanil, chloroproguanil) together with a sulphone (dapsone) are synergistic and active against *P. falciparum* in some areas where pyrimethamine alone is not. These combinations are well tolerated and have the practical advantage of single-dose therapy. Unfortunately, resistance to these drugs has developed rapidly in South-East Asia and South America, although both sulphonamide-pyrimethamine and sulphone-biguanide combinations are still very effective in East Africa (Watkins et al., 1988b) and have replaced chloroquine in some countries.

Despite over 350 years of continuous use, quinine remains an effective treatment for malaria. Quinine sensitivity in *P. falciparum* has decreased in some areas but there is still no convincing evidence of high-grade resistance, i.e. complete failure to respond in the presence of adequate blood levels (Looareesuwan et al., 1990). *In vitro* tests of antimalarial sensitivity of *P. falciparum* in Thailand, where multi-drug resistance is a particular problem, are now indicating a worrying increase in the rate at which quinine resistance is increasing (H.K. Webster, personal communication). In Thailand, the therapeutic response to quinine in severe malaria did not change significantly in the 1980s, but in the past three years there has been a significant decline in the therapeutic response (Pukrittayakamee et al., in press). Thus the cinchona alkaloids, quinine or quinidine, can still be relied upon in severe malaria (World Health Organization, 1990b), but in some areas this may change relatively soon.

Several antibacterial drugs have antimalarial activity, although most are not reliably effective when used alone. The new macrolides, particularly azithromycin, have excellent antimalarial activity *in vitro*, and will be evaluated for both prophylactic and treatment efficacy in the near future. Rifampicin also has weak antimalarial activity, and has been shown to be active against vivax malaria in man, but its value in combinations is not know.

Mefloquine is a quinoline-methanol compound active against most multi-drug-resistant strains of *P. falciparum* , although some West African strains appear to be intrinsically resistant (Simon et al., 1988). Resistance has developed rapidly over the past four years since 1989, despite strict regulation of mefloquine use (Nosten et al., 1991). There is also concern that mefloquine resistance may encourage resistance to quinine — the only drug available for the treatment of severe chloroquine-resistant malaria. Fortunately, mefloquine is still effective in most tropical countries, and those infections which recrudesce after

mefloquine treatment will usually respond to the quinine-tetracycline combination.

The immediate future

The immediate prospects are not good. There are very few new antimalarial drugs, and most countries cannot afford to buy them anyway. Halofantrine is intrinsically more active as an antimalarial than mefloquine (ter Kuile et al., 1993) and, apart from occasional diarrhoea, is generally very well tolerated in comparison with other drugs (Watkins et al., 1988a). In particular, halofantrine does not have adverse central-nervous-system effects and for this reason patients often prefer it to mefloquine. However, it has variable oral bioavailability and it is structurally similar to mefloquine. Cross-resistance is seen *in vitro* and may be a problem in clinical use (Webster et al., 1985). The standard one-day, three-dose halofantrine regimen (24 mg/kg) is effective in semi-immunes, or where parasites are highly drug-sensitive, but longer courses are required for the treatment of multi-drug-resistant malaria (ter Kuile et al., 1993).

The Chinese drugs related to ginghaosu (artemisinin) are the most important antimalarial drugs to be discovered since chloroquine. They are structurally unrelated to the other known antimalarials. Several different preparations and formulations are available for parenteral, rectal and oral administration. All have a common biologically-active metabolite, dihydroartemisinin. This is also the starting point for the synthesis of derivatives. They have proved safe and effective in China (Quinghaosu Antimalaria Coordinating Group, 1979), and over the past 15 years it has become clear that they are more rapidly acting than either quinine or chloroquine in severe malaria (World Health Organization, 1990b).

The Chinese scientists have developed other antimalarial drugs too, notably pyronaridine and nitroquine, but these have not been used outside China, and their potential role in treatment remains to be determined (Ding, 1988).

Unfortunately, despite the considerable amount of research conducted in the US Army's antimalarial drug development programme in the 1960s and 1970s, and the extensive work in China over the past 20 years, antimalarial drug development has not kept pace with resistance in the parasite. It is hoped that improvement in existing drug regimens, the cautious introduction of the new antimalarial compounds and, if necessary, a return to quinine, will buy some time, but if no more new drugs are forthcoming (which seems likely) there is a real prospect of completely untreatable malaria within the next ten years.

Which drugs?

Prophylaxis

This is a most difficult area. In many situations there are no right answers, and recommendations on antimalarial regimens are a compromise which must be under constant scrutiny and review. Where sensitive *P. vivax* or sensitive strains of *P. falciparum* only are seen, chloroquine is an appropriate prophylactic. As resistance begins, an increase in the usual weekly chloroquine dose from 5 to 10 mg base/kg (or daily administration of 1.5 mg/kg) will prove more effective, but this will be only a temporary holding measure. On what will happen afterwards opinions have diverged. The European practice has been to recommend chloroquine and proguanil for most places, in the knowledge that this combination would not be completely effective everywhere but at least would prevent severe disease and death. The combination is well tolerated and remains effective over much of Africa, southern Asia, and some parts of Oceania and the Americas. Where multi-drug resistance is more prevalent in South-East Asia, there are three options: (a) weekly mefloquine; (b) daily doxycycline; and (c) presumptive treatment with either mefloquine, halofantrine or quinine plus tetracycline. Recent evidence from two large prospective studies of the use of mefloquine prophylaxis suggests that mefloquine is reasonably well tolerated, and is more effective than other regimens in areas with resistance (Lobel et al. 1993; Steffen et al. 1993)

. Indeed the incidence of neurotoxicity in one study ($\approx$ 1:10 000) was similar to that associated with chloroquine — i.e. ten times less than with treatment. As a consequence many authorities are now recommending weekly mefloquine as a first-line choice for prophylaxis over short periods (< 3 months). In all cases, local knowledge of transmission areas and of antimalarial drug sensitivity is essential in giving the appropriate advice. Antimalarial prophylaxis is often not needed at all — for example, most tourists who visit South-East Asia do not need to take it. Even if prophylaxis is only partially effective, it will probably attenuate the development of the resistant infection, and thus reduce the risk of death (provided the patient and the physician consider the possibility of malaria in the differential diagnosis of subsequent fever). Poor compliance is a major confusing factor in all these assessments, and is an important factor contributing to 'apparent drug resistance' and malaria fatalities in returned travellers.

Treatment

Travellers returning home from the tropics with malaria are likely to have little or no immunity, and may not know the antimalarial drug sensitivity patterns of parasites in the area where they contracted malaria. In such cases, to be on the safe side, falciparum malaria should be considered resistant, if there is any doubt. In most countries in the

tropics, cost is probably the major factor in determining treatment policies and therapeutic practice locally. The other important factor is information on antimalarial drug sensitivity. *In vitro* testing of antimalarial drug sensitivity has been refined and simplified over the past ten years, and is now available to most countries with malaria problems. The information provided by *in vitro* testing is interesting for the scientist and tropical epidemiologist, but not very useful in clinical practice. It has never led to a change in treatment recommendations. What health authorities and workers need to know are the *in vivo* responses to antimalarial treatment and it is these that they act on. The sources of information on *in vivo* response vary from detailed prospective research assessment of drug efficacy in a particular community (and usually patient group) to the clinical impressions of health workers, who may notice that, more and more, patients seem to be coming back with malaria again within a few weeks of treatment. These impressions can be very insensitive; a high incidence of low-grade drug resistance (R_I) can easily go unnoticed. As there are so few antimalarial drugs available, their effectiveness needs to be monitored carefully and repeatedly, and the compliance with an adverse effects of different drug regimens evaluated.

The failure of a malaria infection to respond to antimalarial treatment results either from host factors (pharmacokinetics, compliance) which result in an insufficient concentration of the drug in blood available to the parasites or from the intrinsic resistance of the infecting parasite population to the drug treatment. All these factors can be characterized. The pharmacokinetic properties of most antimalarial drugs in a variety of patient groups have been defined in recent years because of the availability of precise (usually HPLC) drug measurement techniques. These assays are now available more widely, and antimalarial blood levels should be measured in studies investigating drug resistance.

As resistance develops, increasing numbers of late recrudescences occur. The initial therapeutic response is satisfactory, the patient recovers but the infection returns later. Patients whose parasitaemia declines slowly may be more likely to have a subsequent recrudescence; in the case of mefloquine, persistence of parasitaemia beyond day 4 following treatment in Thailand predicts subsequent failure reliably (ter Kuile et al., 1992). As resistance increases, progressively more patients are seen whose infections do not resolve (RII and RIII; high-grade resistance).

It is at this point that treatment recommendations must change if possible. Recommended antimalarial drug regimens have changed in recent years with a greater understanding of the pharmacokinetic and pharmacodynamic properties of these compounds (Winstanley & Watkins, 1992; White, 1992). There is probably some room for further improvement of current regimens, but the basic problem

confronting the tropical world is that there are not enough new drugs, and not enough research is being conducted on antimalarial drug development.

Treatment studies

Detailed guidelines for the conduct of *in vivo* clinical evaluations of chloroquine sensitivity have been published (Bruce-Chwatt, 1981). A recent World Health Organization Scientific Group (World Health Organization, 1990a) advised that 'simple and sustainable systems for the identification and reporting of antimalarial side-effects should be developed' and that the 'frequency of treatment failures should be carefully monitored and reported to health authorities', but it does not say how these recommendations could be effected. Most tropical countries have not the academic or health infrastructure to comply with these recommendations.

If *in vivo* testing stations could be set up in malarious areas, conducting simple *in vivo* studies of antimalarial drug efficacy, the results provided would give health authorities and the medical profession the information they need to decide upon appropriate antimalarial treatment. More detailed assessments of drug toxicity, blood concentration measurements, and determination of other malariametric indices could be added where necessary. The costs and benefits of newer, and nearly always more expensive, drug regimens could be gauged with certainty and the inexorable march of drug resistance defined.

References

1. Brandling-Bennett AD, Aloo AJ, Watkins WM, Boriga DA, Kariuki DM, Collins WE. Chloroquine treatment of falciparum malaria in an area of Kenya of intermediate chloroquine resistance. *Trans R Soc Trop Med Hyg* 1988; **82**: 833-847
2. Bruce-Chwatt LJ,. Ed. (1981). *Chemotherapy of Malaria,* 2nd edn (WHO Monograph Series, 27). World Health Organization, Geneva
3. Coatney GR. Pitfalls in a discovery: the chronicle of chloroquine. *Am J Trop Hyg* 1963; **12**: 121-128
4. Covell G, Coatney GR, Field JW, Singh J. *Chemotherapy of Malaria.* (WHO Monograph Series 27). World Health Organization, Geneva 1955
5. Cross AP, Singer B. Modelling the development of resistance of *Plasmodium falciparum* to antimalarial drugs. *Trans R Soc Trop Med Hyg* 1991; **85**: 349-355
6. Curtis CF, Otoo LN. A simple model of the build-up of resistance to mixtures of antimalarial drugs. *Trans R Soc Trop Med Hyg* 1986; **80**: 889-892
7. Ding GS. Recent studies on antimalarials in China: a review of literature since 1980. *Inter J. Exp Clin Chemother* 1988; **i**: 9-22
8. Hatton CS, Peto, TEA, Bunch C, Pasvol G, Russel SJ, Singer CR et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet* 1986; **i**, 411-444
9. Lobel HO, Miani M, Eng T, et al. Long term malaria prophylaxis with weekly mefloquine. *Lancet* 1993; **341**: 848-851
10. Looareesuwan S, Charoenpan P, Ho M, White NJ, Karbwang J, Bunnag D, Harinasuta T. Fatal *Plasmodium falciparum* malaria after an inadequate response to quinine treatment. *J Infect Dis* 1990; **161**: 577-580

11. Nosten F, ter Kuile F, Chongsuphajaisiddhi T, Luxemburger C, Webster HK, Edstein M, Phaipun L, Thew KL, White NJ. Mefloquine-resistant falciparum malaria on the Thai-Burmese border. *Lancet* 1991; **337**: 1140-1143
12. Pukrittayakamee S, Supanaranond W, Looareesuwan S, Vanijanonta S, White NJ. Quinine in severe falciparum malaria: evidence of declining efficacy in Thailand. *Trans R Soc Trop Med Hyg* 1994; **88**(3):257-368
13. Qinghaosu Antimalaria Coordinating Group. Antimalarial studies on qinghaosu. *Chinese Med J* 1979; **92**: 811-816
14. Steffen R, Fuchs E, Schildknecht J, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* 1993; **341**: 1299-1303
15. ter Kuile F, Nosten F, Thieren M, Luxemburger C, Edstein MD, Chongsuphajaisiddhi T, Phaipun L, Wester HK, White NJ, High dose mefloquine in the treatment of multi-drug resistant falciparum malaria. *J Infect Dis* 1992; **166**: 1393-1400
16. ter Kuile F, Dolan G, Nosten F, Edstein MD, Luxemburger C, Phaipun L, Chongsuphajaisiddhi T, Wester HK, White NJ, Halofantrine versus mefloquine in the treatment of multi-drug resistant falciparum malaria. *Lancet* 1993; **341**: 1044-1049
17. Thaithong S. Clones of different sensitivities in drug-resistant isolates of *Plasmodium falciparum*. *Bull WHO* 1983; **61**: 709-712
18. Watkins WM, Oloo JA. Lury JD, Mosoba M. Kariuki D, Mjomba M. et al. Efficacy of multiple-dose halofantrine in treatment of chloroquine-resistant falciparum malaria in children in Kenya. *Lancet* 1988a; **ii**: 247-250
19. Watkins WM, Brandling-Bennett AD, Nevill CG, Carter JY, Bariga DA, Howells RE, Koech DK. Chlorproguanil-dapsone for the treatment of non-severe *Plasmodium falciparum* malaria in Kenya: a pilot study. *Trans R Soc Trop Med Hyg* 1988b; **82**: 398-403.
20. Webster HK, Boudreau, EF, Pavanand K, Yongvanitchit K, Pang LW. Antimalarial drug susceptibility testing of *Plasmodium falciparum* in Thailand using a microdilution radioisotope method. *Am J Trop Med Hyg* 1985; **34**: 228-235
21. Wernsdorfer WH. The development and spread of drug-resistant malaria. *Parasitology Today* 1991; **7**: 297-303.
22. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10**: 187-215
23. White NJ. Antimalarial pharmacokinetics and treatment regimens. *Brit J Clin Pharmacol* 1992; **34**: 1-10.
24. Winstanley PA, Watkins WM. Pharmacology and parasitology: integrating experimental methods and approaches to falciparum malaria. *Brit J Clin Pharmacol* 1992; **33**: 575-582
25. World Health Organization. *Practical Chemotherapy of Malaria* (WHO Technical Report Series, 805). World Health Organization, Geneva. 1990(a).
26. World Health Organization. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990 (b); 84 Supp. 2: 1-65.

NEEDS IN DEVELOPING COUNTRIES: ONCHOCERCIASIS AND SURVEILLANCE FOR RESISTANCE TO IVERMECTIN

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Introduction

Onchocerciasis is a filarial disease caused by *Onchocerca volvulus* and transmitted by blackflies of the genus *Simulium*. The disease is a chronic process punctuated by episodes of acute exacerbation. It produces much morbidity (pruritus, disfiguring skin lesions and weight loss) and is an important cause of blindness, especially in the savannah areas of tropical Africa, where socioeconomic consequences have been severe. An estimated 18 million people throughout most of tropical Africa, in the Americas (Guatemala, Venezuela, Ecuador, Colombia, Brazil and Mexico) and the Eastern Mediterranean (Sudan, Yemen and Saudi Arabia) are afflicted. At least 350 000 are blind and a further one million suffer from significant visual loss (WHO, 1987).

The bite of an infected female *Simulium* fly deposits infective larvae in the skin. These develop into adult male and female worms. The female worms produce microfilariae, which invade principally the skin and the eye. When taken up subsequently by the fly they develop into infective larvae, thus completing the cycle. The pathology of onchocerciasis results predominantly from the death of microfilariae in the skin, eyes, and lymph nodes and at other sites.

Drug treatment of onchocerciasis

Drugs act on both the microfilariae and the adult worms. Those available for treatment include suramin, diethylcarbamazine (DEC) and ivermectin. Suramin is curative while DEC and ivermectin are suppressive. Both DEC and suramin have been used for more than four decades. However, their administration in mass therapy is not recommended (WHO, 1987) on account of severe reactions (DEC) or toxicity (suramin), the need for close medical supervision, and lack of enthusiasm in the target communities.

Ivermectin (Mectizan) is a safe, effective, single-dose microfilaricide which is eminently suitable for community therapy. The standard dose is 150g/kg given once or twice a year. It achieves prolonged suppression of skin and ocular microfilariae by an additional, unique effect of blocking their release from the adult female worms. Repeated dosage may however be required indefinitely in the absence of *Simulium* control.

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Ivermectin has replaced DEC and further limited the indications for the use of suramin. Thus, for practical purposes, drug surveillance in onchocerciasis implies the monitoring of the adverse effects and of the development of resistance to ivermectin.

Resistance to anti-onchocercal drugs

Despite their use over several decades and in various dosage schedules (Hawking, 1978; Awadzi & Gilles, 1992), there is little evidence that *Onchocerca volvulus* has developed resistance to DEC or suramin. It is therefore unlikely that resistance will occur with ivermectin, which is given very infrequently, but the possibility can not be dismissed entirely, in view of its occurrence in veterinary practice by *Haemonchus contortus* (Echevarria & Trindade, 1989) and *Trichostrongylus colubriformis* (Giordano et al., 1988).

The development of significant resistance to ivermectin would be disastrous for onchocerciasis control, since mass ivermectin distribution can be used to supplement, or instead of, vector control (Remme et al., 1990; Greene, 1992). Therefore the sensitivity of *Onchocerca volvulus* to ivermectin must be monitored so that appropriate measures may be taken if required and also to develop a macrofilaricide suitable for mass treatment.

Monitoring sensitivity of *Onchocerca volvulus* to ivermectin

Two aspects need to be considered: a) the sensitivity of the microfilariae; and b) the ability of ivermectin to block the release of microfilariae from the adult female worms. Both can be investigated by direct and indirect means.

The microfilariae

Ivermectin causes rapid and near total reduction in skin microfilariae, followed by more gradual elimination of ocular parasites. This is accompanied by improvement in skin manifestations, ocular symptoms and anterior segment lesions, and a reduction in the incidence of optic nerve disease (Pacque et al., 1991; Dadzie *et al.*, 1991; Abiose *et al.*, 1993). Thus failure of increasing numbers of patients to benefit from ivermectin treatment or a less than expected reduction in skin microfilaria counts would suggest the development of resistance to the drug.

The sensitivity of microfilariae to ivermectin can be studied *in vitro* by the exposure of the parasite to graded concentrations of the drug and then determining their viability by suitable techniques, such as motility. A baseline sensitivity needs to be established which can then be monitored periodically. The requirement of increasing drug concentrations to obtain a given effect would then provide direct evidence of the development of resistance. In pursuance of this, baseline

data have been obtained by Townson *et al.*, (in press) for four geographical isolates of *O. volvulus* microfilariae obtained from Ghana (West African forest and savannah strains), Cameroon (West African forest strain), and Guatemala (Central American strain).

Ivermectin reduces the uptake of microfilariae and their development into infective larvae in the vector. This can be studied in feeding experiments on treated human volunteers (Cupp *et al.*, 1986, 1992; Trpis *et al.*, 1990; Chavasse & Davies, 1990). Failure to interrupt the uptake of microfilariae and to suppress their development into infective larvae on repeated dosage would suggest the development of resistance to ivermectin. The experiments however need to be carefully controlled as results may be influenced by a rapid return of microfilariae to the skin in areas of intense transmission (Remme *et al.*, 1990) and by population migration (De Sole & Remme, 1991; Cupp *et al.*, 1992). In non-endemic areas sensitivity can be studied by pretreatment of *O. volvulus* microfilariae with graded concentrations of ivermectin followed by their intrathoracic injection into surrogate vectors. The ability of these microfilariae to survive and develop into larval forms is then a measure of the degree of sensitivity to ivermectin (Tagboto *et al.*, in press). These *in vivo* experiments complement direct *in vitro* assessment of the sensitivity of *O. volvulus* to ivermectin.

The adult worms

The prolonged suppression of skin and ocular microfilarial counts is due to the blockage of their release from the adult female worms. A rapid return of skin microfilariae in a defined population would suggest resistance to the effect on the female worms. This can be confirmed directly by the examination of nodules excised from treated patients. The effects of intense transmission will have to be taken into account.

Surveillance for ivermectin resistance in developing countries

More than 17 million of the estimated 18 million people infected worldwide with *O. volvulus* live in tropical Africa, the worst endemic area being in the Volta river basin. Onchocerciasis is essentially a disease of rural populations in remote and sometimes inaccessible areas, beyond the last motorable road and the outermost health facility. Several countries lack trained medical and technical personnel. The distribution of ivermectin in some of these areas has been possible only through the efforts of the Onchocerciasis Control Programme (OCP), The River Blindness Foundation, Sight Savers and other non-governmental organizations. Surveillance for ivermectin resistance will require a similar effort on the part of the same or other organizations.

The monitoring of the effects of ivermectin in the skin and eye and the parasitological techniques involved in skin snipping and nodule

examination require highly trained personnel. The determination of ivermectin sensitivity by *in vitro* methods and the conduct of *in vivo* transmission experiments using *Simulium* species require specialized laboratories and personnel. Thus most such work has necessarily been done by visiting scientists from developed countries, aided by a handful of local experts. The transfer of technology and training to the endemic areas will be necessary if local scientists are to assume responsibility for these activities.

The major challenge to surveillance for ivermectin resistance is that it will not be undertaken because resistance is not expected to occur. However, a number of factors will tend to favour its occurrence. These include the use or projected use of repeated and high-dosage regimes in an attempt to obtain macrofilaricidal effects (Duke et al., 1990, 1991, 1992), and the unapproved use of ivermectin in endemic areas for conditions such as epilepsy and failure to thrive. Ivermectin is widely believed to be an anti-convulsant (Kipp et al., 1992), and failure to thrive has been attributed to 'worms', commonly *Ascaris*, the expulsion of which, during previous treatment, has left a lasting impression. There is also the regrettable practice of selling ivermectin as a cure for a wide spectrum of skin disorders.

Ivermectin is supplied free of charge by Merck for all who need it, and for as long as they need it. Monitoring for adverse effects is an essential part of distribution. Surveillance for the development of resistance, however improbable, should be instituted to ensure that the drug remains effective as long as it is needed.

References

Abiose, A., Jones, B.R., Cousens, S.N., Murdoch, I., Cassels-Brown, A., Babalola, O.E., Alexander, N.D.E., Nuhu, I., Evans, J., Ibrahim, U.F. & Mahmood, A.O. (1993). Reduction in incidence of optic nerve disease with annual ivermectin to control onchocerciasis. *Lancet*, **341**, 130-134.

Awadzi, K. & Gilles, H.M. (1992). Diethylcarbamazine in the treatment of patients with onchocerciasis. *British Journal of Clinical Pharmacology*. **34**, 282-288.

Chavasse, D.C. & Davies, J.B. (1990). The effect of ivermectin on the uptake and development of *O. volvulus* microfilariae in *S. damnosum* s.l *Acta Leidensia*, 59, No. 1 and 2, 227-230.

Cupp, E.W., Bernado, M.J., Kiszewski, A.E., Collins, R.C., Taylor, H.R., Aziz, M.A. & Greene, B.M. (1986). The effects of ivermectin on transmission of *Onchocerca volvulus*. *Science*, **231**, 740-742.

Cupp, E.W., Ochoa, J.O., Collins, R.C., Cupp, M.S., Gonzales-Peralta, C., Castro, J. & Zea-Flores, G. (1992). The effects of repetitive community-wide ivermectin treatment on transmission of *Onchocerca volvulus* in Guatemala. *American Journal of Tropical Medicine and Hygiene*. **47(2)**, 170-180

Dadzie, K.Y., Remme, J. & De Sole, G. (1991). Changes in ocular onchocerciasis after two rounds of community-based ivermectin treatment in a holo-endemic onchocerciasis focus. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. **85**, 267-271.

De Sole, G. & Remme, J. (1991). Importance of migrants infected with *Onchocerca volvulus* in West Africa river valleys protected by 14 to 15 years of *Simulium* control. *Tropical Medicine and Parasitology*, **42**, 75-78

Duke, B.O.L., Zea-Flores, G., Castro, J., Cupp, E.W. & Muñoz, B. (1990). Effects of multiple monthly doses of ivermectin on adult *Onchocerca volvulus*. *American Journal of Tropical Medicine and Hygiene*, **43(6)**, 657-664.
Duke, B.O.L., Pacqué, M.C., Muñoz, B. Greene, B.M & Taylor, H.R. (1991). Viability of adult *Onchocerca volvulus* after six 2-weekly doses of ivermectin. *Bulletin of the World Health Organization*, **69(2)**, 163-168.
Duke, B.O.L., Zea-Flores, G., Castro, J., Cupp, E.W. & Muñoz, B. (1992). Effects of three-month doses of ivermectin on adult *Onchocerca volvulus*. *American Journal of Tropical Medicine and Hygiene*, **46(2)**, 189-194.
Echevarria, F.A.M. & Trindade, G.N. (1989). Antihelminthic resistance by *Haemonchus contortus* to ivermectin in Brazil: a preliminary report. *Veterinary record*, **124(6)**, 147-148.
Giordano, D.J., Tritschler, J.P. 2d & Colles, G.C. (1988). Selection of ivermectin-resistant *Trichostrongylus colubriformis* in lambs. *Veterinary parasitology*, **30(2)**, 139-148.
Greene, B.M. (1992). Modern medicine versus an ancient scourge: Progress toward control of onchocerciasis. *The Journal of Infectious Diseases*, **166**, 15-21.
Kipp, W., Burnham, G. & Kamugisha, J. (1992). Improvement in seizures after ivermectin. *Lancet*, **340**, 789-790.
Pacqué, M., Elmets, C., Dukuly, Z.D., Muñoz, B., White, A.T., Taylor, H.R. & Greene, B.M. (1991). Improvement in severe onchocercal skin disease after a single dose of ivermectin. *American Journal of Medicine*. **90**, 590-594.
Remme, J., De Sole, G., Dadzie, K.Y., Alley, E.S., Baker, R.H.A., Habbema, J.D.F., Plaisier, A.P., van Oortmarssen, G.J. & Samba, E.M. (1990). Large scale ivermectin distribution and its epidemiological consequences. *Acta Leidensia*, **59**, No. 1 and 2, 177-191.
Townson, S., Tagboto, S.K., Castro, J., Lujan, A., Awadzi, K. & Titanji, V.P. (1994). Comparison of the sensitivity of different geographical races of Onchocerca volvulus microfilariae to ivermectin: studies in vitro. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **88(1)**, 101-106.
Trpis, M., Childs, J.E., Fryauff, D.J., Greene, B.M., Williams, P.N., Munoz, B.E. Pacque, M.C,. & Taylor, H.R. (1990). Effect of mass treatment of a human population with ivermectin on transmission of *Onchocerca volvulus* by *Simulium yahense* in Liberia, West Africa. *American Journal of Tropical Medicine and Hygiene*, **42(2)**, 148-156.
World Health Organization (1987), WHO Expert Committee on Onchocerciasis Third Report. *WHO Technical Report Series* No. 752 61-64.

NEEDS IN DEVELOPING COUNTRIES: SURVEILLANCE OF RESISTANCE TO ANTI-TUBERCULOSIS DRUGS

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I. Resistance to anti-tuberculosis drugs

This paper will summarize the current state of knowledge about resistance to anti-tuberculosis drugs in the developing world and discuss the critical role surveillance for drug resistance should play in the control of tuberculosis world-wide.

Anti-tuberculosis drug resistance — causes

What is generally understood by drug resistance is that a patient infected with resistant strains of *Mycobacterium tuberculosis* will fail to respond to treatment with the drug concerned. There are more precise and complex laboratory definitions[1,2], but they are less suitable for the purposes of this paper.

Resistance to anti-tuberculosis drugs is the inevitable result of poor management of tuberculosis control[3]. Poor management takes many forms, including the prescription of regimens with an insufficient number of drugs to which the patient's organisms are likely to be susceptible; inadequate dose or duration of therapy; or, most commonly, poor supervision of the patient's drug-taking, or poor supplies of drugs, resulting in drugs being taken irregularly. In the past, patients have taken much of the blame for poor compliance[4], but it is now recognized that tuberculosis services and their staff are not entirely innocent[5,6]. Either way, such deficiencies lead to patients acquiring resistance. If they then transmit the resistant organisms to their contacts, and if those contacts later develop tuberculosis also, then these latter cases are said to have primary resistance.

The impact of anti-tuberculosis drug resistance

Whatever tuberculosis programmes might do to cause drug resistance it is clear that drug resistance can also do considerable harm to tuberculosis treatment. Failure of treatment, which is commonly defined as the persistence of positive cultures for *M. tuberculosis* at the end of the treatment period, is more likely if the initial organisms were resistant. Moreover, the more potent the drug, and the more drugs to which an organism is resistant, the greater the risks of treatment failure. In the British Medical Research Council (BMRC) trials in Africa, Hong Kong and Singapore[7], of 11 patients with isolates resistant to

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rifampicin, of whom 9 also had organisms resistant to one or more other drugs, 5 (45%) patients failed on treatment and a further 3 (27%) had a subsequent relapse. On the other hand, resistance to just isoniazid and/or streptomycin led to chemotherapy failure in only 12% of 264 patients.

Multi-drug resistance

In recent years attention has focused on multi-drug resistant (MDR) strains of *M. tuberculosis*. MDR strains are usually defined as those that are resistant to at least rifampicin and isoniazid, and often to other drugs as well. While occasional MDR strains have been isolated from time to time, it was outbreaks of MDR tuberculosis in the United States that brought MDR into the limelight[8-15]. These outbreaks were characterized by an association with the human immunodeficiency virus (HIV) and by an alarmingly high mortality of over 80%, despite the availability of a full range of reserve drugs. Widespread occurrence of MDR, especially primary MDR, would constitute a major threat to tuberculosis control, particularly to resource-poor countries, since effective treatment would become impossibly expensive[16].

However, there are grounds for some optimism. Rates of resistance do not rise inexorably. In Styblo's classic study in Kolin, ex-Czechoslovakia[17], the introduction of stronger control measures, especially supervision of all patients in hospital, ensured that almost all patients completed their therapy. The prevalence and incidence of resistance declined rapidly. Nevertheless, the most important measure against resistance is to ensure that it does not happen. This is achieved by making certain that all patients complete a full course of adequate treatment.

The role of HIV

The impact of HIV on drug resistance is not yet fully understood. The MDR outbreaks in the US suggest that HIV might be associated with resistance to anti-tuberculosis drugs. HIV-associated tuberculosis is some societies, such as part of the US[11] and Zaire[18], is associated with poorer adherence to therapy than that of patients with tuberculosis alone, and this could lead to the acquisition of resistance. HIV-infected tuberculosis patients are up to 20 times more likely than HIV-negative patients to have household contacts who are themselves HIV infected[19], and these contacts are particularly susceptible to contracting tuberculosis[20,21], which would likely be resistant if the source case also had resistant disease. However, the few studies, in the US[12,22], Haiti[23] and Africa[24,25], that have so far measured resistance levels in more representative cohorts of patients have not found an excess of resistance in the HIV-positive groups.

One can intuitively see that the impact of resistance will depend on the number and efficacy of the drugs available to treat tuberculosis. Six main drugs are in current use in the developing world: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S) and thiacetazone (T). The first three are the most essential. Streptomycin is given parenterally, and therefore constitutes a risk for HIV and hepatitis-B-virus transmission in those areas where sterilisation of injection equipment cannot be guaranteed. However, the risk has never been adequately quantified for tuberculosis control programmes with sufficient supplies and equipment. The cost of streptomycin has also increased considerably over the past few years. WHO does not therefore recommend it for use in areas with a high prevalence of HIV infection[26]. In addition, HIV infection has been shown to increase greatly the risk of severe, and potentially fatal, cutaneous hypersensitivity reactions in patients treated with thiacetazone[26-29]. It is therefore advised not to use this drug in patients known or suspected to be infected with HIV. The armamentarium available for the fight against resistant tubercle bacilli is thus somewhat reduced in areas of high HIV-prevalence.

Furthermore, withdrawal of thiacetazone might create resistance to more powerful drugs. If the commonly used regimen of 2SHRZ/6TH (an initial phase of 2 months of daily SHRZ, followed by 6 months of a continuation phase of T and H) is altered to 2EHRZ/6EH in some areas, then a proportion (unknown) of those patients with isoniazid resistance will, in effect, receive monotherapy in the continuation phase. Ethambutol resistance is therefore likely in a percentage (unknown) of patients so treated. Since the re-treatment regimen recommended by the International Union against Tuberculosis and Lung Disease[30] and WHO consists of 2SHRZE/HRZE/5HRE, the continuation phase will again, in effect, be monotherapy, this time with rifampicin. Rifampicin resistance in a proportion (again, unknown) is the likely result. This is the domino theory of resistance. Surveillance will, at the very least, help to determine the present unknowns in this scenario.

It is already clear however that new, effective, low-cost anti-tuberculosis drugs are urgently needed in the fight against tuberculosis in both the developing and the industrialized world.

II. Surveillance for resistance to anti-tuberculosis drugs

Current situation in the industrialized world

Until recently, very few countries, rich or poor, considered it necessary to carry out systematic surveillance for resistance to anti-tuberculosis drugs. The USA ceased surveillance in 1986, but resumed it in 1993. It was maintained in the industrialized world that the recommended treatment regimens were designed to succeed even in the presence of

resistance to one or two of the commonly used drugs; the minority of patients who failed to respond to treatment could be investigated for resistance as the need arose; surveillance was expensive, resources were limited, and, in any case, tuberculosis was disappearing fast. The occurrence of MDR, and the rising incidence of tuberculosis in many Western countries[31-33] due to HIV, immigration and the failure to maintain adequate health services in deprived inner cities, has led to a re-examination of this position.

Resource-poor countries

Likewise, in the developing world, in spite of a general failure to control tuberculosis, surveillance for drug resistance was not an issue until recently. Nevertheless, a number of countries such as Kenya[34], Tanzania[35] and Korea[3] conducted nationwide surveys at 5 or 10 year intervals to assess the extent of their tuberculosis problems. These generally included some representative information on drug resistance. In East Africa it was clearly not a major problem, with resistance to one or more drugs varying from 7-10% between 1964 and 1984. In Korea primary resistance to one or more drugs rose to 31% of isolates tested in 1960, but fell to 15% in 1990 with the introduction of improved tuberculosis control. Acquired resistance was as high as 75% in 1980, falling to 47% in 1990. Apart from these three studies, which also had their share of methodological problems, most published work has suffered from at least one of three major deficiencies which make interpretation difficult, if not impossible: selection bias (in favour of patients referred to major hospitals and thus more likely to have resistant disease), failure to distinguish clearly between those patients who had had previous treatment, or the use of non-standard or unclear laboratory methods. Our current level of ignorance of the scale and nature of drug resistance in the developing world is therefore profound, although we do know that HIV is plentiful, and MDR exists there (M. Kinyanjui and W. Githui, personal communication).

Aims of surveillance

The potential benefits of suitable surveillance for drug resistance are many. At an international level, surveillance could determine the geographical extent and severity of resistance in given countries or regions, and thus determine the need for major international changes in treatment policy. Such information would also determine the extent of the need for international research into new chemotherapeutic agents or new combinations of drugs. At a national level a surveillance system would provide a useful indicator of performance of a tuberculosis control programme and assessment of the need for changing current treatment policy, identify districts or health centres in need of support, and determine the risk factors for resistance.

But there are potential disadvantages. The diversion of scarce resources to resistance surveillance could jeopardize the essential tuberculosis control targets of curing 85% of all new smear-positive cases diagnosed, and finding 70% of all cases. However, it is in precisely those countries with poor programme performance that resistance could be predicted. National resources should then, perhaps, focus on achieving the targets, and donor agencies on resistance surveillance.

Recommendations

The Tuberculosis Programme of WHO has therefore developed a strategy which will determine the nature and extent of resistance to anti-tuberculosis drugs in regions of the developing world. Countries with viable tuberculosis-control programmes will be encouraged and assisted to develop their own surveillance system, using guidelines for surveillance drawn up by the Programme, which avoid the defects, mentioned above, of many previous resistance surveys. With the collaboration of the International Union against Tuberculosis and Lung Disease, it is intended to establish a network of supra-national reference laboratories to provide the quality control and standardization of susceptibility testing that will be essential for international comparison. At the same time, much-needed support will be given to national reference laboratories in developing countries to develop their own capacity for work on drug resistance.

Conclusion

Resistance to anti-tuberculosis drugs, and especially multi-drug resistance, is a major threat to tuberculosis control programmes. This danger is amplified by the presence of HIV. Our current state of knowledge about the extent and severity of resistance, especially in the developing world, is woefully inadequate. Surveillance for drug resistance is therefore needed in those countries with tuberculosis control programmes sufficiently developed to be able to support such a system. WHO is taking the initiative, together with the International Union against Tuberculosis and Lung Disease, to set up such a system.

References

1. Canetti, G, Fox W, Khomenko A, et al. Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. *Bulletin of the World Health Organization.* 1969; **41**: 21-43.
2. Vareldzis B, Grosset J, de Kantos I, et al. Laboratory issues in drug-resistant tuberculosis: WHO Recommendations. *Tuberc Lung Dis* 1994; 75:1-7.
3. Kim S, Hong Y. Drug resistance of Mycobacterium tuberculosis in Korea. *Tuberc Lung Dis* 1992; **73**: 219-224.
4. Fox W. Compliance of patients and physicians: experience and lessons from tuberculosis. *Br Med J* 1983; **287**: 33-35.

5. Sumartojo E. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Amer Rev Respir Dis* 1993; **147**: 1311-1320.
6. Rubel AJ, Garro LC. Social and cultural factors in the successful control of tuberculosis. *Pub Hlth Rep* 1992; **107**: 626-636.
7. Mitchison D, Nunn A. Influence of initial drug resistance on the response to short chemotherapy of pulmonary tuberculosis. *Amer Rev Respir Dis* 1986; **133**: 423-430.
8. Centers for Disease Control. Transmission of multidrug-resistance tuberculosis from an HIV-positive client in a residential substance-abuse treatment facility — Michigan. *MMWR* 1991; **40**: 129-131.
9. Centers for Disease Control. Nosocomial transmission of multi-drug resistant tuberculosis to health-care workers and HIV-infected patients in an urban hospital — Florida. *MMWR* 1990; **39**: 718-722.
10. Centers for Disease Control. Nosocomial transmission of multi-drug resistant tuberculosis to health-care workers and HIV-infected patients in an urban hospital — Florida. *MMWR* 1990; **39**: 718-722.
11. Pitchenik AE, Burr J, Laufer M, et al. Outbreaks of drug-resistant tuberculosis at AIDS centre. *Lancet* 1990; **336**: 440-441.
12. Chawla P, Klapper P, Kamholz S, Pollack A, Henrich A. Drug resistant tuberculosis in an urban population including patients at risk for Human Immunodeficiency Virus infection. *Amer Rev Respir Dis* 1992; **146**: 280-284.
13. Centers for Disease Control. Transmission of multidrug-resistant tuberculosis among immunocompromised persons in a correctional system — New York, 1991. *MMWR* 1992; **42**: 507-509.
14. Beck-Sagué C, Dooley S, Hutton M, et al. Hospital outbreak of multi-drug resistant *Mycobacterium tuberculosis* infections. *JAMA* 1992; **268**: 1280-1286.
15. Frieden T, Sterling T, Pablos-Mendex A, Kilburn J, Cauthen G, Dooley S. The emergence of drug-resistant tuberculosis in New York City. *N Eng J Med* 1993; **328**: 521-526.
16. Mahmoudi A, Iseman M. Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. *JAMA* 1993; **270**: 65-68.
17. Styblo K, Dankova D, Drapela J, et al. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia: Report for the first 4 years of the study, 1961-64. *Bulletin of the World Health Organization* 1967; **37**: 819-874.
18. Perriens JH, Colebunders RL, Karahunga C, et al. Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with "standard" chemotherapy in Kinshasa, Zaire. *Amer Rev Respir Dis* 1991; **144**: 750-755.
19. Nunn PP, Mungai M, Nyamwaya J, et al. The effect of human immunodeficiency virus type 1 on the infectiousness of tuberculosis. *Tuberc Lung Dis* 1994; **75:** 25-32.
20. Di Perri G, Cruciani M, Danzi MC, et al. Nosocomial epidemic of active tuberculosis among HIV-infected patients. *Lancet* 1989; **2**: 1502-1504.
21. Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. *N Engl J Med* 1992; **326**: 231-235.
22. Shafer RW, Chirgwin KD, Glatt AE, Dahdouh MA, Landesman SH, Suster B, HIV prevalence, immunosuppression, and drug resistance in patients with tuberculosis in an area endemic for AIDS. *AIDS* 1991; **5**: 399-405.
23. Long R, Scalcini M, Manfreda J, et al. Impact of human immunodeficiency virus type 1 on tuberculosis in rural Haiti. *Am Rev Respir Dis* 1991; **143**: 69-73.
24. Githui W, Nunn PP, Juma E, et al. Cohort study of HIV positive and HIV negative tuberculosis, Nairobi, Kenya: Comparison of bacteriological results. *Tuberc Lung Dis* 1992; **73**: 203-209.
25. Braun M, Kilburn J, Smithwick R, et al. HIV Infection and primary resistance to anti-tuberculosis drugs in Abidjan, Cote d'Ivoire. *AIDS* 1992; **6**: 1327-1330.

26. World Health Organization. Severe hypersensitivity reactions among HIV-seropositive patients with tuberculosis treated with thioacetazone. *Wkly Epidemiol Rec* 1992; **67**: 1-3.
27. Eriki PP, Okwera A, Aisu T, Morrissey AB, Ellner JJ. Daniel TM. The influence of human immunodeficiency virus infection on tuberculosis in Kampala, Uganda. *Am Rev Respir Dis* 1991; **143**: 185-187.
28. Pozniak AL, MacLeod G, Mahari M, Legg W, Weinberg J. The influence of HIV status on single and multiple drug reactions in Africa. *AIDS* 1992; **6**: 809-814.
29. Nunn P, Kibuga D, Gathua S, et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337**: 627-630.
30. Enarson D, Jentgens H, Oberhoffer M, et al. *Tuberculosis guide for high prevalence countries*. Paris, France: International Union against Tuberculosis and Lung Disease, 1991; 1-72.
31. Tuberculosis, final data — United States, 1986. *MMWR* 1988; **36**: 817-820.
32. World Health Organization. Secular trends of tuberculosis in Western Europe. *Wkly Epidemiol Rec* 1993; **68**: 65-72.
33. Raviglione MC, Sudre P, Rieder HL, Spinaci S, Kochi A. Secular trends of tuberculosis in Western Europe. *Bulletin of the World Health Organization* 1993; **71**: 297-306.
34. Swai OB, Edwards EA, Thiong'o R, et al. Tuberculosis in Kenya 1984: A third national survey and a comparison with earlier surveys in 1964 and 1974. *Tubercle* 1989; **70**: 5-20.
35. Tanzanian/British Medical Research Council. Tuberculosis in Tanzania — a national survey of newly notified cases. *Tubercle* 1985; **66**: 161-178.

MONITORING THE SAFETY OF BIOLOGICAL PRODUCTS

Susan S. Ellenberg*

Biological products

The definition of a biological is given in the US Code of Federal Regulations (600.3(R)): A biological product is any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man. Biological products are regulated by the Centre for Biologics Evaluation and Research (CBER), while drugs and other medical interventions are regulated by the Center for Drug Evaluation and Research or the Center for Devices and Radiologic Health. A list of some of the types of product that CBER regulates is given in Table 1. Some, such as blood

Table 1. ***Types of biological product regulated by CBER***

Allergenic extracts	Diagnostic agents
Antitoxins	Gene therapies
Cytokines	Growth factors
Blood derivates for therapy	Monoclonal antibodies
Blood products for replacement	Thrombolytic agents
Coagulation factors	Vaccines

derivatives, are traditional products that have been available for many years; others represent newer products of biotechnology. ("Biotechnology" refers primarily to recombinant DNA technology-produced products, monoclonal antibodies, and some somatic-cell and gene therapies and vaccines.) The number of investigational biological products has increased rapidly over the last decade.

The special case of vaccines

Some of the most important types of product regulated by the Center for Biologics are vaccines. The surveillance system for vaccines is separate from that for biological therapeutic products. It is called the Vaccine Adverse Event Reporting System, and it is implemented by the FDA together with the Centers for Disease Control and Prevention, in Atlanta, Georgia. The system has been in operation only since November 1990. The reporting form is specific to the system; the

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MedWatch form recently introduced by the FDA for reporting adverse events in connection with therapeutic products is not used for reports on vaccines. In contrast to therapeutic products, on which most adverse-experience reports are submitted by manufacturers, more than 50% of the reports on adverse events associated with vaccine use are submitted direct to the FDA by health professionals. This is one of a number of differences between monitoring vaccines and monitoring therapeutics. One major difference is that vaccines are given to healthy individuals, mostly children. The "mind-set" on the acceptability of adverse events in this population is quite different from that on therapeutic products. The assessment of causality in regard to vaccines is even more difficult than with drugs because, when immunizations are given universally, almost any kind of adverse event that happens to an infant during the first year of life will be not too far removed in time from a vaccination. Experts in this area believe that a very, very small proportion of the serious adverse events that are reported are truly caused by the vaccine; such events are reported primarily because of temporal coincidence. This is a difficult issue to study, however, because the rates of exposure to the vaccines are so high. In a sense, with vaccine adverse-event-reporting we have problems of over-reporting as well as under-reporting, because most of the reports probably do not reflect vaccine-induced events.

The regulation of biological products

At present there is no formal regulation requiring the reporting of adverse events or biologicals; biological adverse events have been reported voluntarily by manufacturers for some time. CBER will soon issue its adverse-event-reporting regulations. Requirement for 15-day alert reports, periodic reports, and increased-frequency alert reports will be specified. We shall also be collecting data on the amount of each product distributed. These data will provide a crude estimate of the number of individuals exposed to a product, permitting calculation of bounds on rates of adverse events. There is a strong intent, in both the Center for Biologics and the Center for Drugs, to move toward international standards of reporting as initiated by CIOMS and the International Conference on Harmonization (ICH); while for technical reasons this will not happen immediately, it is planned to bring the regulations for both Centers into harmonization simultaneously with the recommendations of these groups.

The Center for Biologics participates in the MedWatch programme along with the Center for Drugs and the Center for Devices and Radiological Health. The forms are received centrally, and rapid feedback of direct reports (that is, reports sent direct to the FDA for health professionals, parents, consumers, etc.) is provided to the manufacturers. The MedWatch Programme has been widely pub-

licized, and we hope it is going to increase the level of reporting, particularly of serious, unexpected events.

Special challenges for the monitoring of biological therapeutic products

These are in four different areas:

(i) *The patient populations that receive biological products*
Patient populations for biological products tend to have serious and complex disease. In many instances it is difficult to distinguish the effect of the drug from the effect of the disease. Also, because the patients are often quite ill, they are usually taking a variety of medications, which will complicate interpretation and assessment of causality for the events reported. Of course, not all biological therapies are administered in such contexts, and certainly some drug or chemical therapies also are given to such populations; but it is probably true that, on average, this is more of a problem for biologics.

(ii) *The magnitude of the drug development programmes*
Drug development programmes are often limited in size because for many indications the population is quite limited; for example, studies of genetic disorders, rare cancers, and certain neurological diseases such as amyotropic lateral sclerosis. Biological therapies tend to be developed in these smaller but seriously ill populations, because with serious, often life-threatening diseases there is more leeway for moving promising products rapidly through the drug approval process. (There is now a special programme called "Accelerated Approval", which allows us to do just that in these special situations.) A practical problem is that many of the new products, particularly biotechnology products, are being developed by small companies with limited resources. We have the difficult task of trying to encourage the development of exciting new products in the creative atmosphere of these small companies without compromising the standards that we require for proof of efficacy and safety.

(ii) *The broad spectrum of activity of most biological products*
Biologicals are pleiotropic. Biologics can have many different kinds of effect, some of which may well be adverse. Many unusual types of adverse event — cancers, neurological and psychiatric problems, endocrine disorders — have probably been associated with biological therapies to a greater proportional extent than with other types of therapeutic product. It is difficult to predict what is going to happen when these products are put into human beings, so that there is a need to monitor for both acute and long-term effects. Many biologicals are what we call biological response modifiers: they are directed not at the disease itself but at the body's biological response to the disease. Therefore, the disease

process may continue, or even accelerate or become more severe. In addition, biologicals are immunogenic. Immune-complex disease has occurred with certain biological products. There is also an increased risk of some common adverse events such as allergic reactions that are related to the immune system.

(iv) Some manufacturing issues

The complexity of the manufacturing process for these products raises special issues for quality control with regard to the purity of the product, storage issues, stability, and sterility. The surveillance is lot-specific; that is, each lot must undergo certain kinds of testing and be individually approved for release. Further, the lot is something that we have to take into account as we monitor the adverse-event reports received for products after they are put on the market.

Conclusion

I have tried to raise some of the challenges that confront surveillance programmes for biological products. Despite the differences between biologics and drugs, there seems no reason why the general approach to monitoring should not be the same for biologics as for other therapeutics. The increased efforts that are being made toward international harmonization of adverse-event reporting are going to be important to the development of more efficient surveillance programmes.

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NEW APPROACHES TO PHARMACOVIGILANCE AND ALTERNATIVE STRATEGIES

Bengt-Erik Wiholm*

I am honoured to have been invited to this 25th anniversary, and to have been charged with looking into the crystal ball and to suggest new approaches to pharmacovigilance. However, to those who know history new thoughts are rare. Some 3,700 years ago King Hammurabi decreed that any physician who hurt his patients through treatment should be severely punished and today lawyers uphold that tradition. Hippocrates introduced a code of ethics in medicine and we should be wise to follow it. Paracelsus in 1538 introduced the concept of dose-effect relationship but we still lack good data in this area for most medicines. Longmoore (1978) described salicylate toxicity in a case-series study, and although this knowledge has been rediscovered many times aspirin is still an over-the-counter drug. Mendel in the 19th century described the laws of genetic variation and now we are slowly accepting the concept in drug metabolism. A registry for drug-induced diseases was instituted in the United States in 1952 and now I shall suggest it again as one of the methods of the future.

The scenario for the rest of the '90s in drug development and regulation is influenced by several major factors. The internationalization of drug development and marketing, as well as the rapid expansion of international cooperation between drug regulatory agencies, including moves towards supranational decision-making, e.g. the European Commission, provide a scenario in which new medicines will be introduced on to the world market at more or less the same time in all countries.

This evolution is essentially rational with regard to development costs and the need for rapid access to effective new medicines. However, it also results in rapid and massive exposure of patients to medicines with inadequate evidence of safety. It is widely recognized that the clinical trials programmes have not been sufficient to prove safety, because of their inherent limitations. The result has been that during the last 20 years 3% of new drugs have been withdrawn and another 10% have had to be seriously limited in their use because of adverse effects.

Imporovements in the design, methodology and monitoring of clinical trials and the possibilities of integrating results from different single trials mean that today frequent short- and medium-term adverse drug reactions to a new chemical entity are well characterized in the populations studied, prior to general marketing.

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The challenge that we face is how best to follow up all these new medicines to ensure their safety in clinical practice — that is, in patients who differ in many important aspects from those on which the medicine was tested, such as ethnic origin, age distribution, disease patterns, concomitant therapy, and therapeutic environment.

Our common problem thus relates more to the identification of uncommon reactions, reactions induced by long-term treatment, and problems emerging as a result of new patient groups being treated — e.g., increased susceptibility or new interactions.

Experience shows that very many of the problems associated with new medicines surface only several years after their introduction. It took 30 years to detect the association between aminopyrine and agranulocytosis, and more than 100 years to detect the association between salicylates and Reye's syndrome. In a recent survey performed by Professor Auriche and Dr Spriet-Pourra in France, it was shown that the median market-life for new chemical entities withdrawn from the European market during the period 1982-86 was nine years. Only 15% of these products were two years or less of the market.

Clearly some of the problems were known long before the product was finally withdrawn, and some of the withdrawals may be questionable. The point to make, however, is that new problems tend to surface also long after the introduction of the medicines.

The evaluation of new potential adverse effects of medicines is a multifaceted and complicated procedure, which includes the following steps:

- Detection and hypothesis generation
- Verification or refutation of the hypothesis
- Quantification — estimate of relative and attributable risk
- Exploration of mechanisms
- Identification of possible high-risk populations and the search for markers of increased susceptibility
- Evaluation of the clinical impact of the reaction on the individual and the population
- Identification of possible preventive strategies — including, as a last resort, regulation of the use of the medicines
- Information to the prescribers, the patients and those concerned in the medical community.

The responsibility of this task should be shared between the producers, the regulators, the scientific community, the prescribers and the users of the products. There is no single method which can encompass and answer all these necessary questions. Therefore, we must build up a portfolio of supplementary methods, each designed to handle most effectively the different parts of the safety evaluation.

Specific suggestions for detection

We need to develop rapidly the signals of new potential adverse effects of new medicines. Therefore, the reporting systems have to become more efficient. This can be done by increasing the sensitivity and the specificity of the spontaneous reporting systems or by creating new mechanisms. Unfortunately, the kind of automated signal generation that Dr Mann suggests is yet a long time ahead for most societies. Until then I hold that motivation and imagination are key elements in the development of efficient reporting systems, but neither can be introduced and maintained by legislation and regulation.

In an area where progress is dominated by these human characteristics, I believe that the most profitable approach is to increase the size of the carrot instead of the use of the whip. In Sweden we have taken this path, and by decentralizing the reporting to a regional level and linking it with the drug information units we have obtained a 43% increase in the reporting rate — from some 300 to 550 reports/million inhabitants/year. The quality of the reports also has improved markedly as most of the reports of potential new reactions have contained copies of case records, laboratory lists, etc. Similar experiences have been reported from France, Spain and Thailand.

This could not have been done in an environment where the reporting was directed to drug companies. because in most countries manufacturers cannot store the identities of patients and it is therefore more or less impossible to follow up on the single cases — especially since the manufacturers cannot force the clinicians to give them supplementary background information.

Specific suggestions for quantification

In the process of verification, quantification is a key issue. Spontaneous reporting systems have several weaknesses in this respect. The most important drawback is that ADRs by nature are not unique events but rather mimic diseases from other causes, and that several diseases, such as rheumatoid arthritis, can induce symptoms that are also often seen as adverse drug reactions. The only way to solve these issues is by adopting an epidemiological approach, thereby creating comparative data on the incidence of the occurrence of the symptom in people exposed and not exposed to the drug of interest. This can be done by two different approaches: the cohort and the case-control approach.

They differ mainly in that the cohort approach is the more efficient for describing the total risk profile of one medicine as compared with no treatment or an alternative treatment, whereas the case-control design is the more efficient for comparing the risk of a certain type of reaction with different medicines. For rare reactions the case-control approach is almost always the more efficient, provided the exposure is reasonably common. This poses a special problem for new drugs before

they are widely used, and to meet this situation Professor Inman created a new approach — the Prescription Event Monitoring Scheme — which has much potential if further developed. However, traditional postmarketing monitoring by means of unfocused cohorts is rarely cost-effective, but the New Zealand scheme, in which initial patients are tagged but not followed up unless a signal arises, is probably a cost-effective solution that should be further explored.

However, not too uncommonly the outcome under study is rare and exposure to the medicine is also rare. Then, as exemplified by acetazolamide and aplastic anaemia, and dapsone and agranulocytosis, neither of the above methods can work at an affordable cost or within an acceptable time. In these circumstances the only practical way to get a rough estimate of the frequency of the problem is good collection of case information in spontaneous reporting systems or disease registers, and the intelligent use of sales and prescription data. One advantage of disease registers is that they involve clinical specialists, which guarantees the necessary diagnostic precision, and therefore may provide the foundation for diagnostic developments such as those reported yesterday at the first meeting of the European Society of Pharmacovigilance.

Most often, however, information from controls is needed to make valid comparisons, and a case-control design is the most effective way of analysing a signal. Such studies can be done in several ways and in countries with limited economic resources. In Barcelona, Professor Laporte is running an emergency-room case-control survey, which can serve as a model. Also, problems linked to non-compliance and drug resistance could probably be studied on a similar basis in developing countries, around sentinel posts where patients seek medical care.

In the previously mentioned survey of drug withdrawals it was found that the reasons for withdrawing medicines were not only of type B, and being rare they were also concentrated in a limited number of clinical expressions. Of 79 withdrawals due to clinical adverse reactions, about 75% related to serious skin reactions, blood dyscrasias, liver damage, general allergic reactions, kidney failure and neurological reactions. Therefore, a scheme has been suggested, based on an international network of case-control surveillance covering those serious but rare diseases that can be caused by many drugs and that often cause drug withdrawal.

Such a scheme would meet most demands of a future pharmacovigilance system as it would yield continuous and timely information on the clinical expression of serious reactions to old and new drugs. Moreover, it would yield risk estimates of sufficient precision to make valid risk comparisons between existing and new medicines. The system could also form a basis for mechanistic research and a data-bank for DNA from patients experiencing serious idiosyncratic reactions, which in the future could help in elucidating the mechanisms and risk factors

for such reactions. Moreover, a data-base on detailed drug intake in relation to life-style habits and diseases from the controls would permit international comparison of the rationality of drug use. With a large common pool of controls such a system could easily tackle other types of signals as they come — e.g., *torsade de points* arrhythmias and the use of antihistamines.

During the last 20 years a number of multi-purpose record-linkage data-bases have been created, first in North America but now increasingly also in Europe. Such data-bases, if properly used, can be very valuable. They can be used to make quick but rough analyses of potential problems in emergencies, but because of selection bias and misclassification problems they are not well suited for detailed studies of adverse reactions that can be elicited by sporadic drug intake. For studies of long-term risks and teratogenicity they should be of immense value in the future unless the new laws on the confidentiality of medical data contemplated by the European Parliament and the European Commission will make use of such data-banks impossible.

Funding of drug-safety studies

Many countries are becoming increasingly market-oriented and have a declining amount of society-dominated research funds. The pharmaceutical companies have money but are naturally oriented more to products than to problems. Society has the problem but no funds are allocated. For example, it is quite unacceptable that we spend millions of dollars on lipid-lowering drugs without knowing whether they save lives or only lower a biochemical marker. Thus, we need to create some common funds for society-oriented drug-safety problems, and why not place these under CIOMS auspices?

SESSION V

ACCESS TO INFORMATION: PATIENTS AND COMMUNITIES

Chairman: Robert J. Levine

ACCESS TO INFORMATION: PATIENTS AND COMMUNITIES

Introduction

Robert J. Levine

Dr Bankowski has asked me to open this session with some remarks which reflect my perspectives as an ethicist and as a clinician. Since time is short I will limit my remarks to some suggestions about the scope of our agenda for this session. They will be a sort of impressionistic overview of the potential scope of our discussions on access to information. We may, for example, talk about providing information to patients and to research subjects. Much of this discussion has gone on here at CIOMS earlier under the topic of informed consent, and for those who would like to see a good bit of writing relevant to that topic it appears not only in the 1993 CIOMS publication, *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* which Dr Bryant mentioned, but also in the 1991 CIOMS publication, *International Guidelines for Ethical Review of Epidemiological Studies.*

Another topic we might consider is conditions under which transmission of information to the public might be either withheld or delayed. Sir William Asscher, when he spoke of his seven deadly sins, identified one as ambition. Ambition might stand in the way of somebody publishing a case report. As he put it, the one who first identified an adverse drug reaction might want to wait to publish a report on it until he or she found another two or three so that the report would become a full-fledged publication. On a much larger scale we sometimes see enforcement of what has come to be the Ingelfinger Rule standing in the way of timely delivery of information to the public, as journals such as the New England Journal of Medicine have held up, for varying periods of time, publication of the reports of important clinical trials or case-control studies.

We might also consider the way in which access to information by epidemiologists may be impeded by legal or ethical barriers or by the actions of research ethics committees. For example, yesterday John Dunne spoke about the inability to get into contact with patients because of policies designed to protect the privacy of patients. I have also noticed of late that the development of privacy legislation in Europe threatens the destruction of large areas of epidemiology, including the destruction of registries that have been maintained by epidemiologists to do very important work. In my view, almost all of the interpretations of the ethics and law of privacy that lead to barriers to the conduct of epidemiological work are based upon some ill-considered reasoning.

Another topic we might consider is whether steps might be taken to prevent the premature release of preliminary information, or in some cases preliminary speculations, to the public. Not only does this result in tragedies like what occurred with pertussis vaccine, as described yerterday by Professor Rawlins, but sometimes it makes it very difficult to begin a randomized clinical trial when people, including members of research ethics committees, hold the belief that it is already known that a drug is effective or ineffective, or more effective than whatever it is being compared with. And the final case I will mention is that called first to our attention by Dr Phillips-Howard, the deprivation of people in communities in developing countries — they are deprived perhaps unjustly, I believe unjustly, of access to such benefits as new drugs, and access to knowledge about adverse drug reactions, and I think that this could also become part of our agenda this afternoon.

LEGAL ASPECTS OF ACCESS TO INFORMATION ON DRUG REACTIONS

Bernard M. Dickens*

Introduction

Legal concerns in drug surveillance studies arise at individual, public and institutional levels. Individual interests concern the conventional legal issues of patients' adequately informed, non-coerced and not unduly induced decisions about whether to accept drugs they are offered for therapeutic or preventive care, and preservation of personal confidentiality. Information about prospective treatments and uses of data serves patients' autonomous choices in care. The legal duty of disclosure of information about therapies is based on legal criteria of what responsible health-care providers know and reasonably ought to know about the effectiveness, side-effects, contraindications and, for instance, limits of prevailing knowledge of administration of drugs they recommend or are willing to prescribe. A limit of knowledge may be due to the lack of long-term follow-up studies of populations of patients to whom a drug has been administered. These are often described as post-marketing surveillance studies or Phase IV studies.[1]

Public interests arise from considerations of public safety and drug licensing authorities' need to make benefit-to-risk assessment in determining whether a drug is safe for marketing. Extreme caution will deny for many years the benefit of a drug to those it could help, and compel exhaustive pre-marketing tests that will drive up research and development costs, which pharmaceutical companies will reflect in their prices for drugs when they are approved for marketing. In both developed and developing countries, such costs may fall on government health care systems when they supply therapeutic drugs or subsidize their costs. Speed of approval of licensure of a drug may expose to undue risks patients for whom long-term follow-up studies would show the drug to be ineffective or contraindicated. A judicious middle path is to approve licensure on reasonable demonstration of a drug's effectiveness and safety, but to make marketing conditional on post-marketing surveillance studies and diligent reporting and analysis of adverse drug reactions, which may include apparent ineffectiveness as well as untoward outcomes of use of the drug.

Institutional interests arise when investigators who develop or administer drugs or are responsible for post-marketing studies hold positions in universities, hospital research institutes or similar institutions: their contracts of employment will often require or imply the application of ethical guidelines for research involving human

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subjects as individuals or populations. These private contractual agreements reinforce or provide legal enforceability of ethical guidelines for the conduct of research on individual human subjects and populations, and indeed on the use of animals in research.

This chapter identifies three issues that require legal resolution in drug post-marketing surveillance studies, and concludes with observations on how courts are likely to approach the employment of knowledge that arises or ought to arise from such studies.

1. The conflict between confidentiality and the right to know

Patients traditionally have been recognized to enjoy legal rights of confidentiality regarding not only the outcome of their medical treatment, but also the conditions for which treatment is sought and applied. Rights may be based in law on contracts for medical services, duties of care that physicians assume on entering a relationship of doctor and patients, whether or not the relation is based on contract and, for instance, on the fiduciary duty the physician owes the patient. This duty is to protect the patient's confidences and employ information arising from the relation only in the patient's best interests or with the patient's prior informed and free agreement. Patients' rights are not absolute, and legal systems recognize that, on occasion, higher interests may prevail that mandate, justify or excuse limited disclosures, often to public agencies that must themselves guard information that they receive. Public health laws often compel or justify disclosures, such as when notifiable diseases are diagnosed. If post-marketing surveillance studies fall under the protection of explicit legislation, this will usually prevail over patients' individual claims of confidentiality.

Surveillance studies rarely enjoy this level of protection. The legal duty to report adverse drug reactions may have a legislated basis, but reports may be statistical and informational, not naming or otherwise identifying individual patients. If a physician makes it a condition of administering a drug that the patient consent to identifiable outcome data subsequently being made available to, for instance, the drug manufacturer, consenting patients may accordingly be held in law to have waived or surrendered their rights to confidentiality to that extent. However, when patients feel they have no option but to accept such conditions in order to obtain drugs essential to their care, courts may find the consent to have been coerced, and to be an unenforceable but severable condition of patients' acquisition of treatment. Anonymous single case reports to manufacturers may be upheld, since patients' confidentiality is not then involved.

Some medical disorders may raise patients' special apprehensions about identifiable disclosures occurring, such as infections with a sexually transmitted disease or the AIDS virus, malignancies, sexual dysfunctions including infertility, and psychiatric disorders. Even when

disclosure of a disorder is not sensitive, stigmatizing or otherwise prejudicial, patients are entitled to preservation of their privacy. There is no difference between disclosures that patients suffer from named disorders that are being treated and disclosures that certain conditions such as depression, impotence or dependency have been caused by drug treatments, or indeed that some such conditions have been successfully treated. Patients are entitled in principle to control what information about them is made available to others, and not to have their names given to drug companies or independent investigators for surveillance studies, which some investigators might want to pursue for decades or generations following initial drug administration. Patients are also entitled not to be pressured or unduly induced to consent to such disclosure of their names, or to fear prejudice in care if they decline to consent.

As against this, however, patients for whose care a drug may be appropriate have a strong interest in their physicians and the manufacturers who advise prescribing physicians learning as much as possible about the drug, including its long-term effects, and having access to earlier users' medical information for that purpose. Acquisition of data sets and anonymous anecdotes may be insufficient, since precision in safe prescription may depend on determination of whether an earlier patient's adverse outcome was due to the drug, an unrelated cause or the interaction of the drug with a predisposing factor, such as genetic characteristics or, for instance, other earlier or concurrent drug treatments. Clinical scrutiny of the patient who experienced the single-case adverse outcome may be the essential condition of future safe prescription of the drug.

A prospective patient's interest in this level of study of other patients' medical experiences is shared and amplified by national drug licensing or importing authorities that have approved the drug for prescription. As guardians of the public welfare in the safe prescription of drugs, accountable to the public for their diligence and efficiency, they want harmful effects that may be due to an approved drug to be probed. The manufacturers and commercial promoters and distributors of the product are similarly interested in its demonstrable effects and contraindications that single-case examinations and wider surveillance studies may provide.

Patients' rights to protection of their personal data may have been founded on customary or judge-made laws, but a number of jurisdictions have now protected the right to confidentiality by legislation on confidentiality itself or by wider laws on patients' rights and health professionals' obligations. However, legislatures may find that they are also interested in patients' medical records being available to governmental and private agencies, such as pharmaceutical manufacturers, for the purpose of post-marketing surveillance studies. The balance between the competing claims of individual

confidentiality, on the one hand, and, on the other, the public interest in appropriate disclosures of anonymous and identifiable data may be struck on grounds of public policy by governmental and legislative agencies or by the courts. Legislation that permits agencies to obtain identifiable information without patients' consent or knowledge may also have to impose strong obligations of data protection on such agencies in order to receive judicial or public approval.

Where surveillance studies cannot be conducted by non-consensual access to patients' identifiable medical records, courts will not be able to impose duties of conducting comprehensive follow-up studies on physicians or drug manufacturers in litigation by patients attributing harmful outcomes to drugs. The extent to which courts require expenditures on consensual or non-consensual surveillance studies will be a matter of judicial policy influenced by economic factors, degrees of harm and risk, and judicial concern with drug pricing practices. The background law will determine the standard of vigilance to outcomes of drug use that physicians and drug manufacturers will be expected to observe. If governments or legislatures want a higher standard, or a standard more respectful of individual confidences, they may promote and enact legislation for this purpose.

2. Levels of information disclosure in surveillance studies

Patients may be made aware of others' interests in the results of their taking of prescribed drugs at the time the drugs are recommended or administered, or, more usually, after they have taken the drugs and effects have been produced, such as adverse drug reactions. This raises the legal question of their consent to involvement in studies, and in particular what level of information must be disclosed to them for their agreement to participation to meet legal standards.

Physicians' compilation of aggregated statistics of results of their care of their own patients will not usually be considered to be human research. Informing drug companies that given volumes or dosages of a drug were prescribed to a total number of patients and that a percentage or number responded favourably, that a percentage or number did not appear to respond at all, and that there was a percentage or number of adverse reactions, will not involve individual patients in research as such. Their care will conform to clinical practice directed solely to their welfare, and data resulting from their care will be presented anonymously. No examination or monitoring that exceeds or departs from that therapeutically indicated will be undertaken, so that neither patients' management nor confidentiality will be affected. This is accordingly not research that involves human subjects in any way that requires individual patients' consent. Information is used for a purpose for which it is not directly given, namely to contribute to the comparative compilation, but patients will

know in advance that their physicians have access to their medical records.

When some departure from or variation of routine management of a patient is proposed for the sake of a surveillance study, however, the patient's consent will usually be legally required, or authorization from an appropriate source regarding patients unable to give legally effective consent for themselves. The law reflects the ethical principle that standards of disclosure for consent in therapeutic practice and in research are not necessarily the same.[2] The purpose of disclosure in both cases is to contribute to individual autonomy of patients and subjects respectively, but in therapy there is the so-called "therapeutic privilege" of non-disclosure of information that routinely should be given, because it is feared, in clinical judgment, that it might jeopardize success of a proposed method of therapeutic care for a particular patient. The privilege has been formulated in a variety of ways by legislatures and courts,[3] but its essence is that patients' care should not be compromised by disclosures that might induce physical or psychological reactions that would impair their therapy or welfare. It is not a sufficient ground for non-disclosure that a physician simply fears that relevant information would deter a patient from making a decision the physician considers best advised.

Uncritical language sometimes describes the law as requiring patients' "fully" informed decisions on medical treatment, but the legal standard is one of adequacy. Decisions on both therapy and research must be adequately informed, but criteria of adequacy require more disclosures for research than for therapeutic recommendations. Adequately informed decisions are responses to disclosures of information material to the choices that patients have to make. Patients who are competent to exercise choice are presumed to be possessed of common intelligence and to understand, for instance, that not every proposed treatment is guaranteed to be effective, or without risk of adverse effect.

Accordingly, the law does not hold physicians to guarantee the effectiveness of treatments they recommend, or to promise that there will be no idiosyncratic or reasonably unpredictable adverse reaction. For instance, courts do not require disclosure of the risk of a routine blood transfusion transmitting hepatitis B, because the risk, although real, is too low to be material to the choice to be made by a patient for whom transfusion is therapeutically indicated. Indeed, courts have held that over-informing is as much malpractice as inadequately informing, since both may deny patients their autonomous right to exercise choice on the basis of relevant information. In some legal systems this means information that is material to the choice of a reasonable person in the patient's circumstances; in others it means information that physicians usually provide. Whatever the legal orientation, however, courts do not require that everything known about a proposed treatment be

disclosed, but that physicians will determine on reasonable grounds how much of what is known, and unknown, should be disclosed, and what routinely will not be disclosed unless a particular patient makes the information material, notably by asking a relevant question.

The "therapeutic privilege" of non-disclosure concerns information that routinely should be given according to the legal test of materiality or professional practice, but that an attending physician decides should not be given to a particular patient on the basis of that patient's personality, characteristics and, for instance, history, because it might compromise the patient's care. Courts treat therapeutic privilege restrictively, for fear that it may subvert not only a patient's autonomy but the general rule of disclosure. The burden of establishing the legal propriety of exercise of non-disclosure, for instance, falls on the physician, who must justify the decision not to give information that routinely should be given. It follows that where an intervention into a patient's treatment or confidentiality is requested for a surveillance study and not advised on therapeutic grounds, there is in law no therapeutic privilege of non-disclosure.

Controversy continues to surround innovative treatment, such as administration of an unapproved drug or of an approved drug on an untested indication that a clinician advises on therapeutic grounds. The recommendation may be, for instance, because of the novel combination of medical features presented by a patient or because standard therapeutic options have been discredited or are clinically contra-indicated. Unproven treatments may be proposed on therapeutic grounds with preservation of the therapeutic privilege, even though the treatment will produce an outcome that will be of secondary but significant interest and service to the research community. Descriptions such as therapeutic research are unhelpful in distinguishing therapeutic treatment from instances of human experimentation or research, as is the medical professional practice of describing unproven procedures undertaken to address patients' health problems as clinical experimentation.

It may be observed, however, that when treatment and subsequent monitoring are undertaken on an exclusively therapeutic basis but clinical outcome data will contribute to research knowledge, for instance through extraction of data from the medical file, the research is distinguishable from the therapy. Information for consent to inspection of the medical record by investigators does not have to address any intervention that was part of the therapy and follow-up care unaffected by any intention to produce research data, whether the intention arose in advance of the therapeutic recommendation or subsequently.

Post-marketing surveillance studies are not essential to therapeutic care of individual patients, although designed to benefit the population of present and prospective patients in general. They rank as research, even though they may be limited to secondary use of outcome data

from therapeutic treatment, and information must be fuller than is required for therapy. For instance, risks of which people of common intelligence may be unaware but that are inconsequential in proportion to the prospective benefit of therapeutic treatments, such as of contracting hepatitis B from an essential blood transfusion during or following surgery, need not be disclosed. However, the same risks should be disclosed when a subject is invited to participate in the medical procedure for non-therapeutic reasons.

Further, patients who are prescribed drugs on therapeutic grounds usually will be aware of the drugs' names only on receipt, for instance, of the packaging and package inserts, but the names of the manufacturing companies will be immaterial. Patients receiving drugs by injection will know their purposes but not necessarily their names. Physicians are not required to name manufacturers of the drugs they recommend. In contrast, however, a subject who is asked to accommodate a physical intervention or compromise of medical-file confidentiality for the sake of a post-marketing surveillance study or of an investigation of an adverse drug reaction is entitled to know not only what is being requested that departs from therapy, but also on whose immediate behalf that accommodation is requested. Subjects willing to assist one manufacturer or type of manufacturer may be less accommodating of another, even on irrational grounds. Prospective subjects must be informed about why they as opposed to others are being approached, who will have access to any information they may provide and, for instance, the reasonably foreseeable consequences for them and their future care of participation in the study.

In some countries, such as the United States of America, legislation or subordinate regulations ritualize the processes of making disclosures and receiving consent for purposes of research. Surveillance studies will have to conform to such legislation or regulations, although non-conformity may expose investigators to administrative sanctions or legal accountability such as for breaches of contract or institutional employment, but not necessarily give legal claims to subjects recruited to studies by irregular processes.

3. Classification of surveillance studies — clinical and epidemiological studies

It has been seen that ethical codes for research may achieve legal enforceability through their express or implied incorporation in private contracts, such as of institutional employment or between product manufacturers and investigators they engage to conduct surveillance studies. Ethical codes may also be material when public authorities or governments agree to permit studies, or require that studies be undertaken, for instance as a condition of continued approval of a product for use. The expectation is that such studies will reflect ethical considerations. Accordingly, the classification of a surveillance study as

either a clinical study or an epidemiological study, bound by the ethical principles relevant to clinical studies[4] or to epidemiological studies respectively,[5] is of legal as well as ethical significance.

It has also been seen that purely statistical surveillance studies, carried out by patients' physicians, that employ data gathered or presented anonymously and that cannot be linked back to identifiable individual persons, such as data aggregated at their source and applied in cohort studies, will not be classified as human-subject research that requires individual consent from the persons whose data are used.

Nevertheless, it cannot be concluded that, because these studies do not have to conform to guidelines on clinical research, no consent is required to conduct them. When epidemiological studies are conducted that involve or affect identifiable populations or communities at large, some input from and approval of members of such populations or communities may be an ethical requirement that will receive legal recognition.

It is only relatively recently that collectivities of people have been acknowledged to have interests in preservation of their confidentiality and dignity, and in control of interventions that may affect their resources, capacity to pursue their self-determined priorities, and their members' social and individual health.[6] This has long been implicit in the legal origin of public health legislation, which arose not in the health but in the policing powers of states. Like those who render more obvious police services, public health officials possess legal powers to oblige the public to provide information, to detain individuals on suspicion and hold them in quarantine pending investigation, to compel individuals to make disclosures of their contacts and for officers to trace contacts, and to oblige those found dangerous to the public to undergo treatment or restraint.

Because public health powers have historically been founded on the authority and responsibility of governments to protect populations, the aspect of consent to its exercise has been obscured. However, following "steps towards the democratization or laicization of the field" of bioethics in the last two decades,[7] recognition has grown that collectivities may assert their interests independently of government, seek consultation on studies likely to affect them, and claim powers to approve or disapprove such studies. Members of groups concerned with HIV infection and AIDS have recently been most visible in several countries in advancing this understanding.

Consent to epidemiological studies that involve individuals' identifiable data should in principle include that of each individual concerned, consistent with principles governing clinical interventions. There may be good reasons, however, for this requirement to be waived by an authorized, independent ethical review agency, such as impossibility or excessive cost when failure to conduct the study would prejudice public health, or when prospective benefits of the

knowledge gained convincingly outweigh irreducible loss of confidentiality. Too much should not be made of the historic principle *salus populi suprema lex* (the health of the people is the highest law), but when risk to individuals is minimal, such as marginal reduction in confidentiality of medical data of no special sensitivity, and the risk to many more is considerably greater if a surveillance study is not conducted, the public interest may justify conduct of the study without individual consent. Approval should be subjected to stringent safeguards of confidential information in the hands of investigators.

Endorsement of a study may be sought at a public or political level through due prior publicity and notification. This is illustrated when drug licensing authorities approve prescription of a drug subject to subsequent surveillance studies of outcomes and reactions. It is recognised that individual consent of patients may not always be practically obtainable. Further, it is unlikely that a manufacturer required to conduct such a study could decline on the ground of lack of consent to access to data by individual patients. A governmental sanction against the manufacturer of withdrawal of approval to marketing of the drug would be dysfunctional to the public interest when the drug had been conditionally approved earlier because of its therapeutic function.

When drug manufacturers initiate surveillance studies without governmental request, it may be more difficult for them and their investigators to claim legal authority to gain access to individuals' identifiable medical information without the individuals' prior, adequately informed consent. Legal distinctions are recognized, however, between nonconsensual access to information that is considered not to constitute a breach of confidentiality, breaches of confidentiality that are justifiable, and breaches that are not justifiable but that are excusable. This last category is legally wrong in principle, but such breaches warrant no punishment or compensation because they serve a tolerable conscientious purpose. At worst, surveillance studies that are bona fide and competent attempts to identify, for instance, contraindications to use of an approved drug may come in this category. In contrast, a purposed "study" of which the primary goal is to promote a practice of prescription of a drug among physicians by offering them free introductory supplies in exchange for outcome information will not. In any event, some attempt should be made to obtain study approval on behalf of any identifiable affected community.

When a community exists independently of a study, with an authentic social structure and group self-awareness, cohesive interaction and discernible leadership, contact may be made with the group at the planning stage of the study. Its views can be sought through individuals able to represent or speak for the group, and its collective approval can be gained. Beyond inhabitants of an area, common sufferers from a disorder, for instance, or family members of sufferers,

may form themselves into a society or group of this nature. When a group is a purely statistical construct, however, defined only by the admission criteria of a scientific research protocol, whose members have no relationship to one another and do not identify themselves with one another, this level of group representation and participation is impossible. Individuals can be engaged in relevant discussions, but their approval carries no more than individual weight.

Even the former groups, involved through credible representatives, cannot give legally effective consent to invasions of individual group members' bodily integrity or confidentiality. Their significance is that they may facilitate surveillance-study investigators in discharging their legal duties to observe ethical guidelines on epidemiological studies by demonstrating respect for collectivities of peoples and for collectivities' ethical rights to autonomy. Like other ethical rights, of course, these are not necessarily absolute, but have to be weighed against other ethical values, such as beneficence, non-maleficence and both distributive and compensatory justice.

4. Legal standards of care and negligent non-disclosure

"Informed consent" is a legal term of art relevant to medical decision-making; it possesses different meanings, applications and implications among different jurisdictions.[8] Those that deny that they apply the doctrine in a form familiar in another jurisdiction have a variant of it in their own, since no jurisdiction denies the principle that individuals of adult years and intellectual competence enjoy bodily and personal self-determination, subject to specific legal limits on such grounds as emergency, morality, public health and public order. Laws that limit self-determination tend to restrain positive actions that individuals may wish to undertake for themselves, but leave considerable scope for individuals to restrain bodily or other interventions against themselves that others may wish to impose. The legal condition of any such interventions is the prior consent to those proposed to be subject to them, and the consent must be adequately informed of the nature and quality of the proposed interventions.

Interventions that lack consent or that depart from or exceed any consent given will be legal wrongs that merit punishment and compensation. In addition, however, many legal systems recognize that the duty to give proposed subjects of interventions adequate information for their decision-making is part of a general duty of care, violation of which constitutes legal negligence. Breach of the duty of care consists in failure to act according to the legally determined standard of care. The negligent breach of duty may become legally actionable when it causes damage. Negligent disclosure causes damage if it results in decisions that lead to harm when, with appropriate disclosure, informed individuals would have made different decisions.

For instance, administration of a drug will usually bear an irreducible minimum risk of an adverse reaction that no amount of care can prevent. If a patient gives adequately informed consent to take the drug and suffers an adverse outcome, it will be very difficult for the patient to show that negligence was the cause. If, however, the patient was negligently not informed about the drug or, for instance, about alternatives to its use, and therefore consented to take it and can show that, with proper information, a different decision would have been made, the adverse outcome will be held in law to have been caused by the negligence. This is so even if the patient was adequately aware of the risk of the actual harm that resulted, and the risk was inherent in the product and not a result of faulty design, manufacture, prescription or, for instance, administration. Causation in law is the result not of a fault in the drug, but of the negligence that led the patient to the decision to take it.

The standard of required medical disclosure is set by the law, but not in the abstract. Courts will not usually set unrealistic standards. They will be guided, although not governed, by disclosure practices within the medical profession and the pharmaceutical industry, in their domestic and other relevant markets, judges' perceptions of what patients need to know to make decisions that protect their interests, and in particular by what information is actually available and is feasible and necessary to acquire. The significance of post-marketing surveillance studies is that they demonstrate what information of outcomes of drug use is considered feasible and necessary to obtain, and what information actually exists.

There is no legal duty to provide patients with information that does not exist or that is not reasonably suspected to be true. Patients must be informed, however, of such facts as that a drug, though approved for use, has not yet been subjected to long-term follow-up studies of its safety and efficacy. It may not be long before courts, particularly in developed countries, require women — of reproductive age, for instance — to be informed that drugs or dosages of drugs proposed for them have not been tested on women if they have not been, and geriatric patients to be similarly informed if drugs or proposed dosages have not been proven safe and effective for elderly patients.

Courts will attend to post-marketing surveillance drug-studies that have been conducted, required or recommended in order to determine standards of disclosure of information to which prospective users of drugs are legally entitled, and to identify which non-disclosures are negligent. Single-case adverse reactions associated with drugs that have been in widespread use will not have to be disclosed unless further studies or suspicions have linked the reactions to the drugs. When a contraindication is responsibly identified, however, drug companies will be expected to warn physicians rapidly, and they in turn will be

expected to warn patients for whose conditions they propose to recommend or to continue to recommend such drugs.

Modern electronic techniques of rapid collection and analysis of massive volumes of data will improve possible means of surveillance. Courts will not set standards of performance by requiring nothing less than the best that science or the pharmaceutical industry can achieve, but will be conscious that standards are improving and that companies fall behind in vigilance and proficiency not only at their competitive peril but at their peril of legal liability too. Standards will be influenced not necessarily by the performance of a defendant company but by expert testimony of standards conscientiously considered appropriate in the industry for a fair balance between consumer protection and competitive economy. Beyond setting standards of surveillance that companies should undertake, courts will consider accessible information that has been produced by other manufacturers, at home and relevantly abroad, and by international organizations and academic contributors to the relevant literature.

Accordingly, manufacturers of prescription drugs will be expected to conduct surveillance studies of their own and make material findings available to physicians, pharmacists and other relevant health professions. They will also be expected to know and apply findings that are reasonably available to them from other manufacturers' studies, to participate in national, regional and international means of exchange of information and to monitor the evolving relevant literature. In particular, a subsidiary of a parent company will be hard put in court to explain that it was unaware of information available to a twin subsidiary or to the parent company's head office but was not negligent. It is a legal principle of criminal liability that information available to officers of a company is imputable to the company itself, which is deemed to know what each of them knows, and courts may be persuaded to adapt the principle to product liability and duties of care to disclose information.

As electronic-data-processing techniques advance and become economically accessible, and as rapid transfer of information becomes increasingly possible, courts will expect them to be used for the protection of patients. Manufacturers that maintain contemporary efficiency in conduct and awareness of surveillance studies, and that equip physicians and others with the information to use their products to maximum benefit and minimum harm, will satisfy legal standards of care that bind them in disclosures to which prospective consumers are entitled.

End-notes

1. Phases of drug development studies in human subjects are described in *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Council for International Organizations of Medical Sciences, 1993, Annex II, pp.51-2.

2. See Robert J. Levine, "Informed Consent in Research and Practice: Similarities and Differences" 143 *Arch. Intern. Med.* (1983), pp. 1229-1231.
3. See Dieter Giesen, *International Medical Malpractice Law* (Dordrecht: Martinus Nijhoff, 1988) pp. 376-392.
4. See the CIOMS Guidelines, note 1 above.
5. See *International Guidelines for Ethical Review of Epidemiological Studies,* Council for International Organizations of Medical Sciences, 1991.
6. See Z. Bankowski, J.H. Bryant and J.M. Last,(eds) *Ethics and Epidemiology: International Guidelines* (Geneva: CIOMS, 1991).
7. John H. Bryant in Z. Bankowski, J.H. Bryant and J.M. Last, *ibid.* at p.9
8. See generally, Dieter Giesen, note 3 above, Part II Disclosure Malpractice, pp. 252-369.

THE PARADOX OF WIDELY AVAILABLE AND RESTRICTED INFORMATION

Judith K. Jones*

We have a paradox of information. We have both too much information, as I implied in my remarks yesterday, and access to information through a number of different channels. They are widely available, so to a certain extent the notion that we can protect information — that is, as regulators and others — may be a fallacy. it is widely available to patients. We should recognize that. Even scientific information is widely available. Computer networks such as Internet are now becoming the new channels of information, which go around all the formal gatekeepers of information. So we are in an era of open information, and this is probably why we are breaking down boundaries throughout the world in the political arena, and I would say there is definitely an analogy here, as I will mention in a minute.

The other part of the paradox is that there is closed information. There is growing interest in restricting access to information. This is a major threat to our understanding of what is happening. There is a great need to foment responsible use of information. The charge is that we have to have a system in which we can have both proper management of good information and responsible use of the information, with protection of privacy, somewhat as discussed by Professor Dickens. How do we do this? I think we have to think about a somewhat different design of where we are. This is apropos of the time, certainly in the current political environment. It is very clear from the participants here that we live in a global village. We are redefining, and we need to redefine, the community in which we live.

One of the ways — when I came to the FDA and looking at the adverse reaction system — we approached this was by looking at it from a systems standpoint. We are very much in the environment of evolutionary systems. A systems approach is to look at input, process and output and ideally at what one's goals are. Obviously our goals are to have informed patients who can manage their drug therapy and, more largely, their health. Everyone would agree with that. How do we do it? I think we do have to redefine the community, as is being done. Because of the dissemination of information the hierarchies of all of our relationships are flattening, for everyone has access to the information. The hierarchy based on information is no longer there. We have also seen examples, and very successful ones, of the decentralization of that hierarchy, in the French and Swedish adverse-drug-reaction systems, but such decentralization through information and exchange of information probably needs to extend all the way down to the

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physician and the patient exchanging that information. We need in this redefined community to redefine some roles and responsibilities, and the important thing is not to leave out any of the participants.

There are some participants, I think even in this discussion, who have been left out to a certain extent or have left themselves out. One group has to do with academia and their responsibility in recognizing the rest of this community, in recognizing the output. If medical schools had to be as responsible as manufacturers for their products they would fail terribly in their physicians' use of drugs. So we have to involve the academicians and call upon their level of responsibility. We also in this coming age of managed care, particularly in the United States, and perhaps in other areas, have to call upon the responsibility of those who make decisions about use of drugs and are administratively responsible for doing so. We have to involve those people and we have to co-opt and involve all participants in this process, which is a much more flattened process than it has been.

I would leave you with an analogy that perhaps is not appropriate but I think does represent a shift of responsibility. If you look at the transportation systems in most developed countries I would say that in the past, and decreasingly perhaps the present, they have been operating a little like the air transportation system, which is quite paternalistic. Our therapeutic system is to a certain extent paternalistic — both the regulators to the manufacturers and the physicians to the patients. We are seeing that diffuse, and the regulators and manufacturers, as evidenced by the CIOMS effort, are talking around the same table and sharing in consensual decisions. The future vision may be analogous to surface transportation, particularly cars, because everyone who drives a car takes a lot of responsibility for the use of that product. It does have a policing action analogous to the public health issue that Professor Dickens mentioned, and perhaps there is an analogy there. It cannot be carried too far but I would say there does need to be a restructuring of responsibility and involvement of everyone in the community.

ACCESS TO PATIENT INFORMATION

Charles Medawar*

Access to patient information is the stuff of whole conferences and it is going to be very difficult to deal with it in the very limited time available this afternoon. I shall necessarily make sweeping generalizations. Inevitably I shall confine myself to matters relating to the overall context of this meeting — that is to say, access to information in the context of adverse-drug-reaction monitoring. I shall emphasize also, I hope, where I want to be in future rather than dwelling on, in some ways, the rather sad past.

I want to pick up where I left off yesterday by restating that it is clear enough that adverse-drug-reaction monitoring systems must be regarded as an integral part of the drug licensing system. If the original licensing system was the car, the addition of post-marketing surveillance system might be compared by analogy to the introduction of disc brakes; cars should not be driven without them, not these days anyway. However, it is clear that such systems are not without their dangers. I have already mentioned the problem of under-reporting, and perhaps with so much obviously superfluous data flying around it might be better to rely on collecting better-quality information from fewer physicians — when in any case the majority do not report adequately anyway. And that is the kind of solution I would think might be more meaningful to less developed countries, which have of course enormous, almost insuperable, problems with resources. Dangers include also, as I hinted yesterday, the temptation to skimp on pre-marketing approval and a fair example of this was the drug nomifensine. This case has been cited as a classic example of a drug the ill-effects of which were detected through adverse-drug-reaction systems and it was withdrawn in 1986 — but do not forget that the Swedes had never approved it; they decided in 1984 that this drug had an unacceptable incidence of allergic reactions.

There is also a problem with time lag. I am now revealing a secret, by telling you that when the drug regulatory authorities in my country became alarmed about triazolam in 1989 they negotiated with the manufacturers a post-marketing surveillance study, the results of which would not be complete until 1994. Professor Shapiro made a plea, which I can well understand, for no quick fixes — but my plea would be for no slow fixes either. I think the challenge for post-marketing surveillance is not to refine the technologies in order to look for even smaller needles in even larger haystacks: to my mind the challenge for the future is to develop faster and more reliable systems, and then to overcome the enormous problems of communicating the hard, often

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excellent, data that derive from well-planned studies. At present, prescribers often do not use that information at all.

I was pleased, but also perplexed, to hear with Judith Jones had to say. She kept on saying "we" and I think she was talking about the United States, for she was describing a situation which in some respects is totally unfamiliar to me. About 25 years ago (give or take probably 10) I saw a New Yorker cartoon of which I was reminded when thinking about what I was going to say today. In the bottom right corner was a missionary, in a jungle clearing, and the missionary was pointing up to the sky to an aeroplane. There were two natives leaning on their spears looking slightly perplexed, one talking to the other saying: "Holy Father says that is a great white bird but it looks to me like an extended-bodied DC-3!" For "missionary" read "medical establishment".

The challenge for the future as I see it is for the medical establishment in general, and for epidemiologists and clinical pharmacologists in particular, to develop much greater responsiveness, an acceptance of the notion of accountability and more of the disciplines of democracy. What medicine needs is to pass some test of public acceptance and that has got to be an informed acceptance. There is a great deal more to explain, there is a great deal more for the public to understand. Medicine needs a greater degree of public trust; this is now lacking and arguably is fading.

Professor Asscher mentioned at the beginning of this conference the absolute inevitability of another drug disaster, and having listened to Professor Sjöqvist you have a pretty good idea how it is going to happen and also the time-scale. But what is the public going to think when they are told yet again, with bland reassurances: "but of course no drug is safe, all drugs have adverse drug reactions"? It really is not good enough. The secrecy that still blights medicine today seems to me to be a hangover of the clinical freedom that blighted medicine certainly in my adult lifetime and, in some parts of the world, continues to do so today. That secrecy is also the stuff of political advantage; it is also the stuff of commercial gain.

Now commercial gain within limits is acceptable and desirable; beyond those limits it is totally unacceptable; in medicine, I am afraid, there is a good deal of transgression and it leads in my view to an abuse of public trust. The traditional reason given for secrecy in medicine, and thank God I have not heard it said at this conference — for I think I would have screamed — is that the public would be alarmed, would be confused, if they were to get too much information. But evidence on this is slight. I did a MEDLINE search before I came here, conjoining the words "public" and "alarm": I got 11 citations, not one of which had anything to do with drugs. What patients are you talking about when you talk about patients being alarmed?

The problem with secrecy is that it prevents the development of an infrastructure of understanding and trust — and this is to me so perplexing when medicine in so many ways is so great today. It is as perplexing for me to hear there must be secrecy because the public cannot understand, just as it would be perplexing for many of you to hear me urge secrecy over the benefits of medicine on the grounds that many physicians might get carried away. It's clearly absolutely absurd. The reason for openness is best explained in the excellent WHO report, *New Approaches on Health Education and Primary Health Care,* 10 years ago (WHO Technical Report Series 690, 1983):

> "...science and technology can contribute to health standards *only* if the people themselves become full partners of the health care providers in safeguarding and promoting health... People have not only the *right* to participate individually and collectively in the planning and implementation of health care programmes, but also a *duty* to do so."

It was followed up with a statement which makes a fundamental point about the need for openness:

> "Openness and effective communication are basic to the success of a drug policy ... Public participation is crucial to the attainment of health for all by the year 2000; it is needed to provide checks and balances in decisions relating to the allocation of resources and acceptability of drug risks."

We are not talking here about patients' rights; we are talking about a discipline that medicine in particular and science in general needs. It is discipline that it must have if it is to work as effectively as it might.

Obviously there is a need to protect patients from risk, and that risk will be reduced with better understanding and with greater intelligent compliance. Intelligent compliance may sometimes include non-compliance, in my view.

There is another aspect to openness and the need for it, and that is simply consumer rights — and I distinguish here between "patients' rights" and "consumer rights" because patients increasingly claim rights to have some say in the organization of services for which they pay and which in political and in many other ways may deeply affect the way they lead their lives. In 25 years time I think I can see, but I hope it will come sooner than that, a yellow-card system which is in fact consumer-led, perhaps as Professor D'Arcy would like, with the pharmacist holding the hand of the consumer — so it is the consumer who may have suffered the adverse reaction who prompts the doctor to do what so many doctors do not do nowadays. I believe that one of the reaons for secrecy, one that has not been touched on so far, is not to disguise evidence that is held in files — deep damaging secrets, smoking guns — but to hide evidence of how much is not known. To use Stephen Evans' lovely phrase, the problem is that greater disclosure would make uncertainty explicit. But it would be more scientific to do so, it would be

more humane to do so, it would be more intelligent to do so, and it is a better way of making progress to do so. It has to be. It is the first responsibility of all professions and all professionals not to exceed their limitations — which is always a danger if you do not know what your limitations are.

Let me summarize what I have to say by quoting from the resolution of Health Action International (Europe) in November 1992 — a statement which explains why secrecy is becoming, deeply, politically incorrect:

> "Secrecy in medicine is pervasive, largely unnecessary, and an obstacle to health. Lack of information limits freedom of choice, diminishes science and inhibits constructive participation. Secrecy also tends to hide evidence of inefficiency, incompetence and inappropriate behaviour, and therefore tends to reduce levels of public confidence and trust."

Dr. Lumpkin made the point that the patient is clearly the most important stakeholder, and if there is an important challenge before this conference — and indeed to medicine in general — it is to make that, not lip-service, but much more of a reality in the future. I have felt at times in this conference rather like a statistic and, as you know, statistics don't bleed. I would prefer to have felt at times more like a person and certainly not to have my prospective death compared with that of a drug. The challenge for medicine is very simple: it is simply to explain and justify what it does and thereby to earn public trust. I think that can be achieved in the next 25 years but we really have to make progress at a far faster rate, with far greater determination, than we have done so far. We need much more openness, please, in the next 25 years. It is wonderful medicine.

THE USE OF ANONYMIZED PATIENT DATA

Norman Taylor*

We have all been assuming over the last two days that the data we need will be readily available — sometimes expensive and difficult to obtain but available nevertheless. However, we could imagine a situation in preclinical research in which the animal rights campaign denied toxicologists the laboratory animals they needed. We could also foresee epidemiologists and other workers in the post-marketing field being denied access to the data they required. The issue is no less than the balance to be struck between the needs of society and the rights of the individual. This is a problem which has been troubling philosophers and jurists for the last 3000 years, so we are hardly going to solve it today. But we are left with the problem of an imperfect balance between these competing needs and rights, and particularly the problem of deploying society's resources most effectively. The Chairman invited his discussants to consider his paper on informed consent and research in practice, which deals with the problems of informed consent in research and the problems of informed consent in practice. I want to talk about information issues in research *on* practice. In this area, just as much an important data subject is the doctor, as important as the patient and the patient's response to drug therapy. I want to cover some of the coming problems in access to patient data in observational studies.

Real life means observing the world outside the area of randomized control trials — it includes a concern for miscommunication, misunderstanding and misuse, just as much as data-sheet compliant use. Here I want to identify, for the purposes of data access, a couple of the issues. Retrospective studies pose problems in obtaining patient consent to the use of personal data; patients may be difficult to contact, they may have moved or died, or they may not be competent to give consent. In the use of multipurpose data-bases, such as Dr Jones referred to, in the computerized administration of medicine we have a different problem. It is impossible to know in advance what the nature of the problem to be studied will be and therefore impossible for the patient to give in advance informed consent to the use of information. What are some of the applications of observational research? We have thought about several of them during the last two days — the natural history of disease, particularly some of the issues related to ADR testing, and Dr. Edwards has referred to the use of observational data to set up denominator values. But I would like also to refer to the last three items, which may be somewhat surprising in that they are economic issues. Dr. Antezana has invited us to think about cost-

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benefit analysis of drugs and procedures, and in a world in which the cost of health care is rising these are just as important issues for society as concern about analysis of adverse drug reactions. Therefore many groups have a legitimate interest in anonymized output from observational studies. They are not limited to researchers and clinicians; they include pharmaceutical manufacturers, drug regulators, health planners, health funders — extremely important, patients' organizations, social researchers, the media, and politicians, for policy formation.

Let me change gear here for a moment and say that we all have great sympathy with patients who are caught up in the gears of the media machine. The identities of such patients are obviously to be protected. In this regard we can all agree that there is a need for regulation and data protection. But there is a growing body of regulation which has the capacity to impede the many worthwhile purposes of observational research. I have identified three levels and three processes: *data protection at the national level,* which is designed to protect individual privacy and will be implemented by legislation, and which is fairly benign as far as anonymized data are concerned; *data protection at the supra-national level,* such as is typified by the EC data directive, which is somewhat more intrusive; and *data control,* which is yet more intrusive and malign.

National data protection in the United Kingdom

The Data Protection Act 1984 in the UK and the guidelines issued by the General Medical Services Committee of the British Medical Association permit anonymized use of data: "data when anonymized are no longer personal and their use is not a disclosure". Doctors are given the sensible advice that they should explain to patients the practices involved in research and that it is wise to reassure patients that they cannot be identified by use of their anonymized data.

The European Commission Directive on Data Protection

This Directive was presented to the European Parliament in 1992 and amended as a result of that presentation, and is now expected to be adopted by the member states without substantial change. Its purpose is relatively benign but it is wide-ranging and in some aspects imprecise in its operation. Interpretation can be provided by Commission staff, but of course the interpretation is not binding and we will have to wait the arrival of cases in the courts for the final resolution of imperfections. The start-point is essentially unpromising and the freedoms which we need have to be clawed back in the sub-paragraphs. First, the Directive covers personal data, and the sub-para starts off by saying "processing personal data requires written patient consent". Written patient consent across 350 million people in the European

Community presents some logistic problems. Data could be depersonalized; obviously this is what we would like but the Directive indicates that depersonalization itself is data-processing and therefore forbidden, and that is the catch-22. It does go on to say that processing may be carried out where there is manifestly no infringement of the patient's privacy or freedom. At least one department of health in the European Community has taken legal advice on this point and understands that it means still that one can use it only for the care of the patient and for the immediate administrative purposes of the health-care provider. According to the Directive, "personal data" means any information related to an identifiable person — one who can be identified directly or indirectly by one or more factors; this raises the problem of what I call the red-headed dwarf, the case where indirect identification can be achieved by successive subdivision of the data and the patient finally identified. There is no indication of the level of subdivision which is considered unacceptable. A previous draft had a guideline that said where this could only be done at unreasonable cost. That has been dropped from the present text and now the case remains to be tested in the courts.

Data control

I use the UK National Health Service (NHS) as an example of data control. There is a general situation here, where the NHS is a data provider. The same case may arise in regard to health maintenance organizations, insurance companies, medical cooperatives, and anyone who employs doctors to provide medical services. In the NHS the legal view is that general practitioners owe a duty of confidence not only to the patient but also to the NHS itself. The NHS records are held by NHS doctors on behalf of the NHS rather than for their own or their patients' purposes. Doctors who provide information to parties outside the NHS are in breach of duty to the NHS. Anonymization does not justify disclosure of data, and anonymized disclosure for commercial purposes is a breach of duty of confidentiality owed to the NHS. These are all extremely tough and restrictive provisions, which if implemented after consultation will cut a swathe through the use of data for many significant worthwhile purposes. In particular, with economic pressures driving to fragment health care provision, we must be concerned about other health-care providers and funders taking a similar view to that of the NHS. I believe this threat to data freedom is likely to grow, and that all those who believe that the balance on data availability threatens to move against the public interest should make their voices heard whenever the case presents in their environment. There is the risk of a shadow of data regulation falling across health-care research. The price of research freedom is eternal vigilance.

DRUG SAFETY MEASURES AND PUBLIC RELEASE OF DRUG-PRODUCT INFORMATION IN JAPAN

Osamu Doi*

Introduction

It is said that the usefulness of a drug product should be judged on the basis of the balance between its risks and benefits. For the maximum efficacy of drug therapy, the efficacy of drugs should be maximized and their adverse reactions minimized. To do so medical institutions must be supplied with highly effective and safe drugs, and at the same time drugs must be appropriately employed in medical practice on the basis of sufficient information. In Japan, to assure the efficacy and safety of drugs from the research and developmental stage through the stage of actual use and application, the Pharmaceutical Affairs Law enforces a number of regulations.

Dissemination of drug information to medical institutions, patients and the general public

Information on the efficacy and safety of a drug is obtained during each of the various stages of its development and life, from the phase of research and development through the stage of the examination of the new drug for approval, re-examination, re-evaluation and post-marketing surveillance. To promote the appropriate use of drugs in Japan, this information is made available to the greatest extent possible to medical experts, and the Ministry of Health and Welfare (MHW) is striving to make this information available to patients and general consumers.

Public release of information at stage of approval

It is required that the principal contents of the application for approval of the new drug be published in scientific journals, and efforts are being made to achieve public release and transparency of drug information.

In addition, from 1994, with regard to newly approved drugs, the MHW will prepare a *Summary Basis of Approval* of the information on their efficacy and safety obtained at the time of the examination for approval, and will quickly distribute it to medical institutions. As this information will be accessible to both medical institutions and general consumers, it is expected to improve the transparency of the system for examination and approval of new drugs as well as promote the appropriate use of drugs in Japan.

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The *Summary Basis of Approval* is expected to include the following items:

Name of the product, name of the manufacturer
Name and content of active ingredient(s)
Dosage forms, route of administration, dosage
Indications or effects
Precautions for use
Information on manufacturing process
Data from the results of non-clinical studies in animals (toxicity, pharmacological action, absorption, distribution, metabolism and excretion)
Data from the results of clinical studies (efficacy, safety)
Processes and conclusions from discussions of the Central Pharmaceutical Affairs Council

Public release of information at stage of re-examination

In Japan the Pharmaceutical Affairs Law stipulates that the manufacturer is responsible for compiling data on the clinical cases of actual use of a drug in the medical institutions for a period of, in principle, six years after approval of a new drug, and submit an annual report of those data to the MHW. Moreover, after six years, the MHW re-examines the efficacy, safety and quality of the new drug on the basis of the data received during the re-examination period.

During the re-examination periods, the MHW carries out an evaluation of the adverse-reaction reports submitted to it each year. In addition to devising safety measures such as revision of *Warnings and Precautions for Use*, the MHW prepares reports entitled *Information on Adverse Reactions* every two months, and distributes them to the medical institutions. They are released also to the public.

Moreover, at present, only the results of the re-examination carried out six years after approval of a new drug are being publicly released. However, from 1994 the information regarding the examination for approval of a new drug will be released in the form of a *Summary Basis of Approval* and the MHW is conducting studies to determine whether, as the next step, similar public release of information about the re-examination — in the form of a *Summary Basis of Re-examination* — in the near future would result in the more appropriate use of drugs.

Public release of information at stage of re-evaluation

The Pharmaceutical Affairs Law stipulates that all prescription drugs must be re-evaluated for efficacy and safety, in principle, every five years. Drugs are selected for this re-evaluation by screening on the basis of information published in Japan and overseas, adverse-reaction information, and materials submitted by the pharmaceutical industry

relating to their efficacy and safety. Only a summary of the re-evaluation and its results is being publicly released.

At present, the MHW is not planning to compile a summary basis of re-evaluation for public release, because (1) the materials used for the re-evaluation are not systematically prepared, and (2) most of the materials for the re-evaluation are based on papers already published in Japan or in other countries.

Public release of information on adverse drug reactions

The Pharmaceutical Affairs Law stipulates that pharmaceutical manufacturers compile and report to the MHW information from the medical institutions on the efficacy and safety of their drug products. The MHW thus — via the pharmaceutical manufacturers — compiles information on adverse drug reactions.

Moreover, the MHW has established an adverse-drug-reaction monitoring system through the cooperation of medical institutions and pharmacies, which transmit information on adverse drug reactions direct to the Ministry. This information is then evaluated from the medical and pharmacological viewpoints in the Ministry's Central Affairs Council. Safety measures are devised, such as revision of *Warnings and Precautions for Use*, distribution of *Doctor Letters*, and revision of *Dosage and Administration* and of *Indications*.

In particular, with regard to the revision of *Warnings and Precautions for Use*, including the *Doctor Letters*, the manufacturer must inform medical institutions, etc. throughout Japan of the nature of those changes within 30 days of making them. In addition, the Federation of Pharmaceutical Manufacturers Association of Japan also prepares a monthly leaflet which thoroughly summarizes the information and mails it to approximately 200 000 medical institutions and pharmacies.

Moreover, the MHW prepares the most important information in the form of *Information on Adverse Reactions* and distributes it to the main medical institutions throughout Japan every two months. Any interested person can access this information by means of a nation-wide facsimile network, and it is also reported in medical and pharmacological journals. In addition, English translations are prepared and distributed to countries participating in the WHO International Drug Monitoring Programme.

Problems to be solved regarding provision of information to patients and the general public

From the standpoint of patients and general consumers, access to information about drugs is still considered inadequate, for the following reasons:

(1) Progress has been slow in separating dispensing of drugs from medical practice; physicians commonly hand drugs directly to patients, with no explanation of the nature of the drugs.
(2) The concept of informed consent is still not well understood or applied by medical-care practitioners and therefore they often do not explain to patients the nature of the drug, its expected efficacy, or its possible adverse reactions.
(3) Because the medical experts are very busy they often do not have the time to give patients adequate directions on how to take the drugs or to respond adequately to patients' questions.
(4) The system in Japan's hospitals, etc., does not easily permit patients or the public to receive consultation about drug products.

The MHW believes that, for the appropriate use of drugs, patients must be able to obtain adequate information about drugs and then to take them on the basis of a good understanding of their nature and appropriate use. Accordingly, to improve the access of patients and the public to drug information, the following measures are being implemented from 1994.

(1) The MHW will prepare a data-base including as much information as possible about drugs, including adverse reactions, and will create a nation-wide drug-information network that will be accessible to medical institutions as well as to patients and the public.
(2) The MHW will, in cooperation with the Japan Pharmaceutical Association, establish a drug emergency-call service nation-wide so that patients and the public can easily receive consultations about drug products.
(3) So that medical experts can accurately instruct patients on how to take drugs, the MHW will prepare for patients and others a drug-ingestion instruction manual for each active ingredient.
(4) To make the best use of the professional skills of physicians and pharmacists, and to inform patients of the contents of prescriptions and instruct them thoroughly about taking a drug, the MHW will continue its effort to separate the dispensing of drugs from medical practice.

The MHW is committed to continuous cooperation with drug manufacturers, medical experts, patients and the general public to maximize the benefits of drugs to patients, and, since improved health care is a goal that transcends national borders, to further increase cooperation with other countries through such international organizations as WHO and CIOMS.

THE FRENCH INFORMATION PROGRAMME

René-Jean Royer*

"Increasingly patients are seeking and getting more information about the medications they receive. Concern about proper use and controlling side-effects is evident... But experience suggests that only a small portion of patients receive and comprehend the information that is required to make good decisions about drug therapy and drug use..."[1].

The mass media are the primary providers of background information on which potential patients form their beliefs about drugs. Prescribers are the primary contact for specific information. In France, without neglecting the drug consumers, we bring our efforts to bear on prescribers. Data-sheets, the *Dictionnaire Vidal* (similar to *PDR, Rote Buch, Compendium suisse*, etc.) are the controlled sources of information for prescribers. Some academic or scientific books are available. Training at a medical school is essential.

Two particular features are the provision of information by regional centres, and the training of medical representatives.

1. Information provided by the regional centres

The telephone answering service. The French pharmacovigilance network links 30 regional centres dispersed throughout the country. They have the duty to collect and analyse ADR reports but also to spread information about drugs.[2]

The most frequent type of information service is telephone answering. Physicians often telephone for information about a suspected case of ADR; more and more, they call preventively, to avoid ADR. The answers to their questions are provided by standard textbooks (*Dictionnaire Vidal*, Martindale, Meyler's side-effects of drugs, Drugs, X Reactions, etc.) These are complemented by reports of side-effects — recently published or not — compiled in the above volumes. Finally, the national data bank and the WHO data can help in giving answers on unpublished side-effects. In some specialized fields such as hepatology, pancreatic diseases, or haematology, we use ADRs national data-bank such as Hepatox, Pancreatox and Hematox.

The answers consist of pharmacological advice in respect of a patient (interactions, teratology, help in diagnosis, etc); general information about a drug or family of drugs; and literature references.

In 1992 the number of questions asked of the regional centres was about 25,000. They are more numerous than ADR reports, though some of the subjects of questions are notified later. The telephone call is systematically used to remind the health professionals they have to report. A report form is sent with a systematic mail reply.

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Other ways of disseminating information. Members of the team participate in postgraduate or continuing medical education. Some centres publish a local information bulletin on recent advances and matters of general interest in ADR management. It is sent to physicians in hospitals and to private practitioners who wish to receive it. The Association of Regional Centres organizes an annual national convention on ADRs, generally with selected themes, and the major lectures are published in *Therapie*. The Association has contributed to the foundation of the European Society of Pharmacovigilance. The centres do experimental, clinical or epidemiological research into the various aspects of ADRs. More than 500 publications have been published in national and international journals.

The educational activity of the pharmacovigilance centres is often bound to the training in clinical pharmacology of physicians, nurses, dentists, pharmacists, and graduate and post-graduate students.

2. The training of medical representatives

In France the pharmaceutical industry employs medical representatives to visit prescribers to inform them about brand-name products. For some time the aim was only to persuade doctors to prescribe a brand-named drug. Now more information is given but it is not sufficiently objective, and under the pressure of health authorities, consumers, academics, doctors, and pharmacists, a collective agreement has been reached between the professional bodies and the Pharmaceutical Industry Federation.

The terms and conditions of the training of medical representatives have been defined. A trade committee has been charged with approving agreements with the teaching partners and keeping the system under supervision. The teaching partners can be universities, medical schools or private teaching groups. Training consists of 250 to 500 hours of academic courses, working groups and professional exercises, including basic practical training.

Only fully qualified persons may work as medical representatives. A partnership between five universities and five pharmaceutical laboratories, called *Partenariat Emeraude,* has been created to help fully qualified people find employment. Others are expected.

References

1. McGallum, D.B., and Yenney S. *Communicating the benefits and risks of prescription drugs* 1988; 1 vol.: 58 pp. Institute for health policies analysis, Georgetown University Medical Center.
2. Lagier G. and Royer R.J. Information to the physician: Role of French regional pharmacovigilance centres. *Drug Information Journal* 1990; **24**: 203-206.

CLOSING OF THE CONFERENCE

John H. Bryant*

This conference, I believe, has provided a systematic coverage of the various aspects of drug surveillance. But it had other dimensions, which rose largely out of the unusual diversity of the subject matter and the participants. It was not a monodisciplinary conference, and this brought even some discomfort, but it also brought a richness — in the exchange of ideas and experience, and the participation of people from different cultures, backgrounds, and disciplines, and with different responsibilities. The field is young and growing; we have had a good exposition of where it has come from, where it is, but also where it is going. This sense of the future is a strong part of what has happened here. We recognize that there is going to be a further strengthening of the administrative systems, of managerial systems of surveillance. The methodologies are advancing even as we sit here. New technologies, particularly the management of large data sets, will play a very important role. These ideas will be included in the education of health personnel. There will be wider participation in the processes involved — doctors, nurses, pharmacists, community people.

One subject we have agreed requires early and intense attention: the needs of developing countries in this field. We know that they have a very limited capacity for surveillance of adverse drug reactions, but this is only a part of their deep weaknesses in the entire field of the availability and safety of drugs. The surveillance of adverse drug reactions should not be considered in isolation from the rest of the context of development. Therefore, we think it would be inadequate, even naive, to suggest that we limit our attention to this field, and I suppose even more so to consider simply transferring the best of this evolving field to developing countries; that would be a mistake. Rather we believe that the best approach would be a consultative process with a prominent role for people from developing countries, as well as for the relevant disciplines, to examine the wider problems of the availability and safety of drugs in the developing world. WHO is doing a great deal already in this regard, and is in a position to take a wider analytical look and on that basis to develop strategies to meet the needs of developing countries.

Such strategies would include surveillance of adverse drug reactions.

The comparable problems of Eastern Europe countries have been mentioned but not discussed. No doubt their needs will be taken into account in the continual international harmonization of drug-safety surveillance.

Now let me ask Dr Vilardell, Immediate-Past President of CIOMS, if he would formally close the conference.

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* Council for International Organizations of Medical Sciences (CIOMS), Moscow, Vermont, USA

Fancisco Vilardell

Dr Bryant, Dr Antezana, Dr Bankowski, Members of CIOMS, and Distinguished Guests: Dr Bryant has been kind enough to let me close this conference, this, I think, excellent conference, on the monitoring of drug safety. It was kind of him, for he had every right, himself, to close these proceedings.

If you have enjoyed this meeting, you can imagine how much I have enjoyed being at meetings of this sort during six years as President of CIOMS. Dr Bankowski always manages to amass an impressive amount of brain-power at CIOMS conferences. Obviously, this is what results in the very high quality of meetings such as this one.

For this conference, CIOMS had considerable help from WHO's Division of Drug Management and Policies, especially from its Director, Dr John Dunne, who has also contributed substantially to the conduct of the meeting and as a member of the Programme Committee. We are most grateful to him and to Dr Martin ten Ham. I thank all the speakers for their contributions, and I thank particularly the Programme Committee for its efforts in bringing about such an interesting and successful conference. Finally, I am sure you all join me in expressing my appreciation of the efforts of Dr Bankowski and his staff, Mrs Kathryn Chalaby-Amsler and Mrs Christine Dübendorfer, greatly assisted for this conference by Mrs Christine Encrenaz of the Division of Drug Management and Policies.

It has been for me a great privilege to collaborate with CIOMS all these years. You have seen what our new president, Dr Bryant, is able to do, but these are only part of his considerable skills. He has vast experience in medicine and public health, both in the West and in the developing world. CIOMS could not be in better hands. So, with this feeling, and my hope of attending further CIOMS meetings, I declare the conference closed.

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