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ISPE COMMENTARY

ISPE as a balanced forum. Summary of the President's address at the International Conference of Pharmacoepidemiology, Toronto, 2001

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One of the most attractive features of the International Society of Pharmacoepidemiology (ISPE) is that it represents a balanced forum where topical issues on drug effectiveness, safety, outcomes and other aspects of prescription drugs and their effects can be discussed and reflected upon. The greatest asset of ISPE lies in the qualities of its diverse membership, including representation from the health professions, industry, academia, and government. This diversity was also reflected by the participants of the latest International Conference of Pharmacoepidemiology (ICPE). All the relevant stakeholders are represented, have sent in abstracts, and present their scientific work at the various symposia, workshops and poster sessions. ISPE is constantly focused on the exchange of scientific information and the quest for scientific quality. The annual ICPE is the main 'product' of those endeavours. ISPE is a typical 'one annual meeting' society, and with other such societies shares features of a membership size between 500 and 1000, a complex system of committees and councils providing a network for policy making and 'flocking', a central office and a budget of limited size. On the other hand, there is a fascinating commitment of individuals who volunteer to support the society in numerous ways, many of them in a rather plain and simple fashion, though important nonetheless. Such humble features are in sharp contrast to the level of ambition and the mission needed to produce science that matters, science that makes a difference in how we judge issues on drug safety and risk, in how we approach the gap between efficacy and effectiveness, or how we handle the question of efficient resource allocation in the pharmaceutical marketplace.

ICPE is abstract-driven, which means that the programme is built mainly upon the contents and the quality of the abstracts submitted early each year. Since the mid-1990s we have seen a steady rise in the number of abstracts from around 200 to more than 300 at this time. One out of five is selected for an oral presentation and almost all others of acceptable quality are assigned to one of the poster sessions. This makes ICPE very much 'bottom-up', and I believe this system has many good features. It is the membership that shapes the conference both in content and in participation. As ICPE is the most visible activity of the Society and thus the most visible manifestation of the balanced forum, we should address the question whether ICPE is able to provide adequate coverage of the relevant topical areas in the field. I believe that ICPE is providing this coverage. In particular, I am very positive about the coverage of the debates on controversies dealing with safety of individual drugs or drug classes. At past conferences, we had very successful sessions on the risks of calcium channel blockers, on sildenafil, on cisapride, on the oral contraceptives, and others. ICPE has been a good sensor of 'what's cooking' at the safety side. The hot topic sessions on these issues have always been the 'main course' at the conferences in the past: a sign of the balanced forum we are and want to continue to be!

There are two issues about which I am more concerned. First of all, I believe that looking at the trend

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in ICPE presentations over the last few years, we are increasingly losing our connection to clinical pharmacology and other more drug mechanism-oriented life sciences. When we look at recent drug withdrawals, such as Baycol or Rezulin, we realize that a full understanding of these topics requires in-depth knowledge of the molecular concepts, e.g. drug metabolism, toxicogenomics, physiology and the like. I would call for the use of more pharmacological approaches to the analysis of data on effectiveness and safety while remaining statistically and epidemiologically rigorous. This means, in my view, that the ties between clinical pharmacology and pharmacoepidemiology need to become closer again, as they were for many years. There is an increasing need for integration between the 'numbers' of epidemiology and the subject matter of drug actions.

ISPE is fortunate in that it includes many members with backgrounds in clinical pharmacology. Yet the Programme Committee was not able to compile a full session on an emerging topic such as pharmacogenetics this year due to a lack of abstract submissions on this subject. A strong signal I believe! The obvious lack of a strong link between epidemiology and the molecular sciences may be a real threat to the Society and I believe that should be changed. Pharmacoepidemiology is in an excellent position to bridge drug exposure and molecular parameters with patient outcomes.

The other concern I would like to share with you is the observation that not all papers presented at ICPE eventually appear in the international peer-reviewed literature. Stolk, Egberts and I recently evaluated the fate of the papers presented at ICPE in the period 1995–1999, a full account of which will be submitted to this Journal. We learned that by 3 to 4 years after the ICPE presentation a maximum of around one out of three presentations had been published in the peer-reviewed literature. Oral presentations were twice as likely to get published, and also tend to appear in journals with a higher impact, but the overall picture warrants an answer to the question: what happened to the other papers presented at our annual conference? These findings need further evaluation to determine what they mean for programme committees planning future conferences.

GOOD POLICY NEEDS GOOD SCIENCE AND CONTROVERSIES ARE IMPORTANT FOR LEARNING

As addressed in one of my columns in *Scribe*, the science policy orientation of ISPE is the subject of a lively debate within the various bodies of the Society. ISPE is of course, dedicated to both science and policy making. The bridging of science with policy issues makes ISPE a very special forum. It creates a challenging environment where scientists, regulators, policymakers and industry meet, try to understand each others problems, and to solve emerging problems on drug responses in various patient populations. Again, I would like to underscore the great importance of rigorous science in resolving important policy questions. Good policy needs good science. A sound scientific understanding of design, conduct, and results of epidemiological research is crucial to the assessment of drug responses in clinical practice.

While we attempt to be involved in decision and policy making, we also can and do anticipate controversies on how to interpret research results, on how we should handle conflicting results on the same topic which may occur even when the same database is used, and, of course, how we weigh safety data in a society that demands 'zero risk' drugs. Last year we were confronted with a landmark event, namely the editorial in the *British Medical Journal* (BMJ) on the conflicting results of studies on the risk of venous thromboembolism in women using third generation oral contraceptives.[1]

One of the most challenging research areas in pharmacoepidemiology is to understand why individuals respond differently to drug therapy once a drug has been approved for marketing, thus *after* clinical pharmacologists have done their premarketing work. Successful effectiveness research must integrate both fields to allow a full understanding of the individual variability in drug therapy. Instead of looking only at controversies as a problem or threat, one also may see them as an opportunity for what Lewis Sheiner has called 'learning' in the 'learn–confirm cycle in drug development'.[2] Controversies and variability in research results should be seen as useful learning vehicles, if applied with an open and constructive mind, and with a clear focus of the evolution of the quality of the studies. This makes ISPE an attractive platform for further thinking, debate and research on how the learning cycle in the proof of principle (classical pharmacology), proof of efficacy (placebo-controlled RCTs), and the proofs of effectiveness and safety may rotate. Observational epidemiological studies can be used to investigate drug outcomes hypotheses. The learning-cycle never stops and therefore we need proactive research strategies to complement experimental research with observational 'learning' studies.

The story is well known. When a drug is newly marketed, there is limited effectiveness and safety

information. Fewer than 5000 (sometimes a much smaller number) humans may have been exposed to the drug, making it impossible to be sure of long-term effectiveness in 'real life' populations and detecting serious adverse reactions occurring less frequently than 1/1000. For sure, the roots of pharmacoepidemiology lie in the attraction to bad news, i.e. the hazards of drug therapy. From its inception, the field has been devoted to the elucidation and quantification of potential adverse effects of medicines. Our field is 'risk'-driven and many of us spend large proportions of our time finding ways to protect patients from adverse effects, or health professionals from hazardous decisions, or manufacturers from economic loss, or regulators from unproven action and loss of face. The last decade has seen a surge in the use of computerized health care data for pharmacoepidemiology, making the design and conduct of, e.g. quick case–control studies easily achievable. The field of pharmacoepidemiology, however, is not waiting for quick and easy studies, but depends on rigorous data linked to thoughtful reflection on mechanisms, a etiologic pathways and the like. Postmarketing safety still relies very often on spontaneous reporting of adverse reactions. Such reporting, though, is usually incomplete and little use is made of drug exposure, clinical chemistry and clinical data in analysing for benefit versus risk and the mechanisms behind that assessment. This work must be done in collaboration with experts in both medicine, molecular pharmacology, and clinical epidemiology.

In my presidential column in *Scribe*, summer 2001, I have linked the issue of patient variability to the topic of 'class effects'. Prescribers have many choices in the drug treatment of most diseases. Although individual members of a 'drug class' share main features, they may have clinically important differences. Herein lie both the benefits and the problems of the concept of drug 'classes'. While the advantages of the class rubric are evident, it has an unfortunate tendency to hypnotize clinicians and researchers into overlooking aspects of individual drug's actions that transcend the characteristics expected of drugs in the 'class'. In drug development, drug 'class' can be an important point of reference. Pharmaceutical innovation is sometimes targeted to bring a new drug to the market with at least the same risk–benefit ratio as other 'class' members. More often, new drugs are designed to show superiority over existing compounds that populate the 'class', in which case inclusion of the new agent in the same class with the 'old stuff' is not a premium option. Industry attempts to show evidence for the uniqueness of their newborn, and very often considers drug 'class' as an unwanted strait-jacket.

Individual differences in drug effects are not easy to interpret. Selective prescribing of certain drugs, drug channelling, and variability of duration of use are all factors influencing outcomes of therapy. Interchangeability is not only a question of the drug as such, but a function of both the molecule's action and the way it is used. Therefore, it is clear that the question of whether drugs within a class are fully interchangeable is dynamic. Numerous important examples in our field (e.g. NSAIDs and GI risk, safety of inhalational beta-2 agonists, CCBs and coronary risk, psychotropics and car accidents) highlight both the positive and negative aspects of 'drug class'. We anticipate more questions on safety in patients who have already a high baseline risk before they start drug treatment. Obvious examples are the evaluation of cardiovascular safety in patients using BPH drugs or sildenafil. Epidemiological research shows that two out of five, or more, of such patients already have cardiovascular morbidity and risk factors before they are exposed to the drugs of interest. Questions regarding confounding and bias are on the table. This feature of patient selection highlights one of the basic, often difficult-to-answer questions in pharmacoepidemiology: 'Did the drug bring the problems to the patient, or did the patient bring the problems to the drug?'[3] Comparisons are the essence of research in pharmacoepidemiology, but they depend on comparing like with like. The practice of medicine ought to be based on solid data on 'class' effects, but assessment of individual drug actions should not be fettered by preconceptions stemming from overemphasis on the 'class' construct. The research agenda of pharmacoepidemiology should address this topic in a more extensive way.

A POSTSCRIPT

Many of us find the experience of contributing to ISPE pleasant and satisfying. Since the ISPE office has been established in Bethesda, and Mark Epstein appointed as General Secretary, the Society has achieved stability and strength. I would like to acknowledge past presidents of ISPE Elizabeth Andrews and Keith Beard, both of whom did a great job in making this happen. I must admit that the hard work was already done when I took over the presidency of the Society. I was able to pay more attention to the contents of the field, to the science, to how we can improve our methods to assess drug exposure–outcome associations. Of course, further improvements are possible, and in some cases warranted, but generally speaking ISPE

is in good shape. The full potential of this richly balanced forum has yet to come. This notion should serve to encourage others to contribute to the Society and to ICPE programmes. Thanks to many of you, in particular the chairs of the meeting, Drs Tom Einarson and Paul Stang, the conference this year was a great success. We will continue to have controversies on benefits and risks of drug treatment. Whether science fails here, or whether other factors contribute, remains unclear. Probably, there is no single answer here. But at the end of the day, for sure, science matters. I was very pleased when Ralph Edwards and colleagues classified ISPE in their *Lancet* paper as an organization 'which is specifically interested in the SCIENCE of pharmacovigilance'.[4] This statement echoes precisely the profile of an organization of which I was very pleased to serve as President. Thank you.

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EDITOR'S NOTE

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