COMMENTARY

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The ISoP Bengt-Erik Wiholm Memorial Lecture

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The International Society of Pharmacovigilance (ISoP) decided to create an annual Bengt-Erik Wiholm Memorial Lecture with the broad theme of pluralistic approaches to pharmacovigilance. The following is an adaptation of the first Memorial Lecture remembering Bengt-Erik Wiholm –'Beje' to his many friends – and outlining a few examples of the work he did that justifies the theme.

1. The Person

Beje was a physician, clinical pharmacologist and pharmacoepidemiologist. He was Head of Pharmacovigilance in the Swedish Medical Products Agency (MPA), before moving to Hoechst-Marion-Roussel, and finally to Merck. In all his posts he contributed much, and he was one of the founders of the International Society of Pharmacoepidemiology (ISPE). The following is taken from my 'in memoriam' in the Uppsala Reports[1] after he had been killed whilst racing his Porsche:

''To say that Beje will be sorely missed, for me and his many friends and associates, is both a truth and a failure to describe the loss of a complex and delightful, caring, friend and professional.''

Memories of Beje whisper insistently in many areas of life and thought. Everything he did was modest and unassuming. Little escaped his notice, evaluation and comment and to miss his quietly spoken, precise observations was to lose his wisdom, so valuable in many situations. He would often stop you mid-conversation, and say, 'Look at that!' or 'I know! What do you think of this?' He was often frustrated by his failure to be heard when he wanted, particularly in meetings, but even in anger he kept restraint and objectivity: and he usually found a way of impressing people anyway!

We all know he was superb professionally. He was a careful, progressive and clever pharmacoepidemiologist, one of the leaders in drug safety and in ISPE, of which he was a past President. He had a flare and imaginative skill for designing studies to fit practical issues, and for general planning to enable better monitoring of drug safety. His handling of zimeldine and Guillain-Barré Syndrome cases was an early example of the first skill, and his creation of the devolved Swedish pharmacovigilance system, and the use of nurses to create a rolling control group for case-control studies were amongst many other far-sighted developments in Sweden. He was also quick to incorporate others' good ideas and unfailingly to give credit for them. In an area where disputes over ideas and data seem common, it was always a pleasure to trust his integrity. He was also an epidemiologist who did not show the usual disdain for anecdotes and spontaneous reports of drug concerns. He was able to balance all information available and propose pragmatic solutions to safety problems, based on his extensive experience. His professional work has always been focussed towards individual patient care, as much as to public health. It was this humanity that shone through everything he did,

and motivated him. The combination of his tireless hard work, idealism and a genuine care for people meant that those close to him would always give of their utmost to support him, in spite of the irritations. Why was he always 10 minutes late for any meeting?

He could never say, 'No'. His family and those who worked with him had to cope with this trait; not easy when his quiet but insistent expectation was always to do the best. He never stopped trying to do more. It is a great shame that more professional and academic acclaim has not been forthcoming for all Beje's efforts and involvement in key areas of national and international drug safety. I know he was very disappointed by this, but he was generous with his thoughts and ideas, and did not always get credit when it was due. Most of his ideas are in multi-authored publications. He certainly deserved better, but I was delighted that the Royal College of Physicians of London recognised his work by an honorary Fellowship, a clear mark of international distinction.

It was Beje who gently persuaded me to move to Sweden. It was he who helped smooth the passage for me to enter life in a new country and to become useful. Even with my linguistic limitations, he made it possible for me to work. It was so enjoyable to sit with someone whose knowledge was broad, whose gentle wit was always there to lighten the tougher times, and whose imagination and idealism was a continuing inspiration. Tackling problems was a pleasant task with such a person. We already had common ground concerning the need to be able to move from reported suspicions of drug safety to harder data, and Beje was very interested in the New Zealand Intensive Medicines Monitoring Programme, and the ways we developed and utilized cohorts. It was also Beje who proposed that he in Sweden, and I from New Zealand, should join forces to persuade the Council for International Organizations of Medical Sciences (CIOMS) to work on what was to later become Periodic Safety Update Reporting by industry (several others have taken credit for that development!).

The following are a selection for Beje's work in summary and based on those matters that interested him most.

2. The 'Puzzle Method'

Zimeldine was a new and different antidepressant introduced into Sweden in 1982 and in the first 18 months three Guillain-Barré syndrome cases were reported to the Swedish MPA. Beje liked to call the analysis of this problem the 'puzzle method', not because he thought he had discovered a new approach, but because he thought it was a neat example of competent pharmacovigilance, where the question is always, ''Does the association of this clinical event relate to a drug and how frequent is the association?''. The puzzle may be solved by looking at what the individual case details tell, what differences the group has compared with some control group, and which alternative explanations are tenable. A major challenge here was to decide whether these cases, which all had influenza-like symptoms at some point, were 'ordinary' Guillain-Barré cases. The painstaking and methodical way in which Beje and some of his co-workers approached this task is described in Fagius et al.[2] The main lesson is that no single approach/tool would have given a complete answer to this problem; only the assembled totality of the positive and negative information and argument, the pieces of the puzzle, is convincing.

3. What's a Signal?

Beje and I had many conversations with colleagues about what evidence constitutes a signal. This led to four of us writing a 'thought paper' for *The Lancet*.[3] The basic approach to cases used in the 'puzzle method' was the basis for our thinking. The heart of the matter in considering a signal is the variability of the data and the quantity of the reports related to the use of the drug, and we decided on a way which would categorize data in a transparent way. The paper produced little discussion other than from Bernard Bégaud who produced elegant support for the idea that three strong 'index' cases constituted a signal, and the approach we published is still referred to today, for example in the joint ISPE/ISoP guidelines for case report publication, previously published in this journal.[4] The debate still goes on, and Beje's

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interest in definition and transparency is so important when controversial ideas – signals – are introduced.

4. Periodic Safety Update Reports

When the CIOMS first considered international pharmacovigilance in the late 1980s,[5] it was to propose an international reporting form, and the US FDA made it mandatory for US companies to report any adverse drug reactions (ADRs) to their drugs, wherever they occurred in the world. Most countries had used the WHO database as their sole international information source before. This was adequate for most countries since their reports went direct to a government-recognized national centre, unlike the US situation, where most reports were collected via the pharmaceutical industry.

A consequence of this development was that the international industry asked global regulatory authorities to accept their international ADR reports as a fulfilment of their safety obligations. Beje approached me about this because he was experiencing a huge multiplication of reported ADRs, and much duplication: so was I, and we agreed that the load was too much for small countries, and not very useful, particularly considering the duplications with the WHO data we already had. His very good idea was to ask industry to review and summarize their safety data, and comment upon it. Since CIOMS had started the process, he thought it right that they should consider the idea, and the Periodic Safety Update Report (PSUR) was born.[6]

Beje's initial vision was that the process would be helpful to industry, to give them a methodology and timelines for examining safety of all products. He also envisaged that the commentary made by the company would be a legal commitment by them to the safety status of their product at the time of the 'data lock'. This, we thought, meant that little time needed to be spent looking at the individual reports: the conclusions by the industry would be binding on them. Now it seems that many regard the bureaucratic quality assurance of all the data evaluated in a PSUR is more important than the inferences drawn from it.

I know that Beje was concerned that the PSUR should be a work saver for the regulatory national authority, and that the company should be very thoughtful about the statements made on their products in the PSUR, so enhancing their reputation for good stewardship.

5. Benefit and Risk

Beje was involved in most of the CIOMS work. CIOMS IV[7] was an attempt to tackle a new topic as opposed to the aim of the previous work, which had a normative goal for work already being done. The work started well enough with the group able to delineate what evidence was available for 'benefit' and what for 'risk'. Unfortunately, as Beje said, there was no clear definition of those two terms and I was also bothered about what we could say in respect of how one could balance risk and benefit objectively, and, therefore, how one might be able to compare the merits of two drugs for the same indication.

In the end, three of us got together and wrote a 'thought paper', which was also the basis of a section in CIOMS IV. We thought that the three dimensions of seriousness, duration and frequency were measurable, or at least assessable, for the treated disease, the effect of the drug on that disease and for each adverse effect, so providing a basis for comparing like parameters for both efficacy/effectiveness and risk. CIOMS IV had several worked examples of how the principles could be used: those principles are still used today.

Beje was very concerned that safety should always be seen in context with effectiveness, but much remains to be achieved in this area. He was brave enough to use scientifically valid benefit/risk information to reinstate the analgesic dipyrone in Sweden. Dipyrone had first been banned in Sweden in the 1970s because of the risk of agranulocytosis, but an international agranulocytosis/aplasia study[8] had produced evidence that seemed clear on the frequency of this type of ADR with this drug. The risk of morbidity and

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mortality seemed no greater, or even less, than respective risks for gastrointestinal (GI) bleeding with NSAIDs. An expert committee, on this evidence of comparative risk, reinstated the drug as a useful analgesic for limited use and in clinical situations where the risk of GI bleeding was particularly high. It was found that there were many reports of agranulocytosis in patients on dipyrone within a few months of its reinstatement. There is no clear explanation as to why this was so.

6. Chemical Predictors

Beje asked for the Uppsala Monitoring Centre's collaboration in a novel project to compare rofecoxib, a methyl sulphone, and celecoxib, a sulphonamide, before rofecoxib was withdrawn from the market because of cardiovascular risks. His idea was to find the typical reporting pattern of 'sulfonamides' from the WHO database by pattern recognition, and then to compare the ADR profiles of the two drugs for a fit to that sulfonamide profile. For the 19 selected sulfonamide parameters in the pattern, the relative risk for celecoxib was greater than for rofecoxib for all, and statistically significantly so for rash, urticaria, Stevens-Johnson syndrome and photosensitivity, as well as for the overall average relative risk of 1.8.[9,10]

This was a very thoughtful study using the strength of a large body of data and modern pattern recognition for a risk prediction.

7. Controls for Observational Studies

Like all observational epidemiologists, Beje was very concerned about the issues surrounding the choices of controls. He was as much concerned about over-matching as about inappropriate matching or lack of matching. His view was that most often one wanted to have a large group of societal (non-inpatient) controls to call upon immediately, to help resolve drug safety signals.

He had in his vision that for each observational study performed, there was a huge investment in getting controls, and that a major part of that investment was in training healthcare staff in how to find suitable controls. He proposed that it would be more effective all round to have trained healthcare professionals to work continuously on a rolling panel of controls that would therefore remain contemporary for any societal changes including the uses of drugs.

As an alternative he thought that the pharmaceutical industry might be willing to pool their controls for general use.

It is tempting to think that longitudinal healthcare datasets may make the finding of controls easier. This is so, but the need for certain detailed information, such as the use of over-the-counter drugs and herbal preparations, may be relevant, but unavailable in such datasets. Beje and his colleagues were able to show that inter-interviewer variability and quality assurance is an important consideration in the selection of both subjects and controls in case-control studies, and that erroneous coding for diagnoses and medication was more frequent for controls.[11]

8. Conclusions

The examples given are taken from a much greater body of work accomplished by Beje Wiholm. The examples are selected because of my close personal knowledge with some of the work he was involved in, and guided by my memories of how he felt about some issues. Others will have different memories, but the main point related to the Memorial Lecture is to demonstrate the eclectic nature of his approach to pharmacovigilance, and his broad interest in how one can best conceptualize the complexities of drug safety problems and how to solve them. This broad interest is essential to the practice of pharmacovigilance, and I hope this summary will stimulate future presenters of the Memorial Lecture to demonstrate how they have solved difficult problems around the safety of medicines, and to show how several tools can be used together to produce information that will further the practice of clinical therapeutics.

Finally, an anecdote: after the discontinuation in Sweden of the anti-urinary incontinence drug

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terodiline, which had serious pro-arrhythmic adverse effects, Beje had a phone call from a 90-year-old woman asking why it was no longer available. On being told that it may sometimes cause fatal arrhythmias, she responded, ''Young man, I would rather die dry than live in a wet hell.'' Beje often told this story as a caution on individuals' needs and risk perception.

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