EDITORIAL

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Wonder Vigilance

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The *British Medical Journal's* 'ethics man', Daniel K. Sokol, has recently penned an article called 'Wonder in Medicine';[1] I found it very refreshing.

Sokol argues the case for seeing the medical world with something different than clinical detachment and research objectivity. Doubtless, dispassion can stop us making errors due to subjective influences and involvement, but those same attitudes do bring with them the possibility of the opposite – cool indifference. Sokol mentions the legendary neurosurgeon, Harvey Cushing, and how he appeared to view the pituitary gland and its function with an awe that was evident from his writing and the drawings he made.

More than that, Sokol tells us that Plato had a high regard for wonder and bewilderment, and that they were ''the mark of the philosopher''. Certainly, without the curiousness that is bred of keen interest and observation we would not examine the richness of our existence.

Unusual in a philosopher is Sokol's skill as a practising magician. He performs to a variety of audiences and uses the art to illuminate not only this but other writings on medical ethics. Visual illusion and competence in the rhetoric of persuasion are the hallmark of the magician. I certainly wonder at my inability to see through such trickery, but it is salutary to remember that I, in company with many other clinicians and scientists, are tricked or delude ourselves into seeing the obvious and not maintaining a wondering scepticism about what we see and do.

So what does all this have to do with pharmacovigilance? Of all the branches of healthcare I have witnessed over the years, pharmacovigilance is the one that has the greatest wonder rating in both meanings of the word. There are very many reasons why.

1. Variety in People

We think we know so much about disease, but we still don't know why Mr X or Ms Y will get any particular disease. I have often wondered at the number of patients whose medical records bear voluminous evidence to multiple clinical problems that seem to be uncorrelated, whereas there are others who have no significant medical history before they die suddenly in old age. 'It's the genes', we argue, and we are perhaps just on the edge of an in principle understanding of the wondrous complexity of the genome and its interactions with the environment.

In pharmacovigilance we have the privilege of being able to meet, help and research people who have unusual responses to medicines. We have one of the most controlled disease areas there is for our contemplation. In iatrogenic illness we know much better than for other illnesses when the cause was introduced, at what dose and what the nature of the causative agent was. (That is once we determine causality! But diagnosis is a challenge for all diseases and we do have the possibility to stop the use of a drug and even rechallenge!) We also have much more information about how the medicine that caused the disease interacts with the body because it has been tested under controlled conditions.

All this information is the baseline for those of us in pharmacovigilance to wonder at and ask why does this particular person behave differently with this drug? Being perverse, from my first exposure to epidemiology in medical school I

have thought that the really interesting people were those who were more than two standard deviations from the norm!

2. How Safe Medicines Are

Given the apparent variety between people – their genomic, environmental and psychological differences – it seems amazing that their response to medicines is so predictable as to allow for a 'normal' dose, and the mostly unsupervised use of medicinal products. Go to the doctor; get pills from the pharmacy; get better!

Take statins (many of us do!). They competitively reduce the activity of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. Cholesterol is essential in cell membranes and in the synthesis of steroid hormones. The result of using statins is not death but life enhancement for many, and the pharmacological potential for the statins seems not to be exhausted.[2] The body's ability to cope with pharmacological interference in critical biochemical processes is vast and we seem to end up with our bodies somehow sorting it all out. What about the selective serotonin reuptake inhibitors, antipsychotic drugs and anti-parkinsonian drugs? Their pharmacological actions in the brain are really imprecise: the whole brain is soaked in them, not just the target areas where we wish to modify the transmitters, but seemingly we can mostly respond to the drugs favourably, although adverse effects do occur.

Selective toxicity is also wonderful. For antibacterials it is amazing: I can take amoxicillin (if I am not allergic) and not notice anything while it disposes of millions of bacterial cells lurking around. The selection is not so good for cancer, but it is amazing that we can find drugs that will take advantage of small but critical differences in our tumours as distinct from us. My first experience in the use of fluorouracil was in an old, frail lady with a fungating rectal cancer that was prolapsed out of the anus and visible. We watched the horrible thing shrivel and disappear due to fluorouracil, and the lady had some happy, comfortable months.

3. The Precautionary Principle: Do No Harm

Having said the above, perhaps I should not be surprised at the naive view that drugs are completely safe, a view that seems to be held by many from both the health profession and the general public. How can anyone think that anything other than the mythological, perfectly selective, perfectly targeted magic bullet will be totally without adverse effects sometimes?

Some years ago, during a CIOMS working group, one of the group decided to test our understanding of the terms 'rare', 'common', 'frequent', etc., in terms of adverse drug reactions as ratios. The astonishing result of a blinded questionnaire was that there was a difference of at least two orders of magnitude in our responses, thus 'common' could be anything between 1/10 and 1/1000. Since then I have never doubted the huge challenge of risk perception and what we think of as acceptable and commonplace. Books have been written on this topic and confirm that rationality does not play the major role in comparison of risks. What a challenge we have in arguing for the undoubted benefit over risk of vaccines for the large majority, so much so that we dare not talk about any risk of vaccines in case we destroy a valuable public health exercise.

I do wonder at our relentless search for perfect safety. That is what the public wants, and we work globally, and in different professional disciplines, to move forward in safety towards that distant goal. But I am overwhelmed when I consider the complexity of the drug safety issues we confront. We need to look at all drugs, not just at single substances but combination products and polytherapy; we need to analyse a multiplicity of possible adverse drug reactions; we need to quantify and consider background incidence; compare effectiveness and risk across products; consider special subgroups of patients at risk; we need to make decisions on availability of products and give information and warnings to avoid medical error; and we need to determine our own effectiveness in improving patient care. Can we, should we, aim for the star of perfect safety or should we settle for an honest

understanding of our limitations – at least we should be honest about where we are now.

4. Methods to Improve Safety

I am amazed how much we can get to know about the actions of drugs in the body for good and ill. Nanotechnology and accumulated data on billions of test results have allowed us to screen thousands and thousands of candidate chemicals for medicinal potential and to investigate them cautiously in animals, and then in humans as well, mostly safely.

Genomics and proteomics are aspiring areas with great potential, but the awesome aspect is the possibility to change human biological processes permanently, perhaps for harm as well as good. There is huge knowledge now put into safe drug development but this will not alter the need to follow the effectiveness and risks of a drug in the kaleidoscope of patients who will use the drugs.

Pharmacovigilance also changes; the development of information technology allowing us to store and transfer data and information should give us pause for wonder. The WHO has 5 million patient records and, in my daily work, I can see any selection within seconds and in a format that is useful for the task in hand. This is so commonplace now we take it for granted. When there is a glitch in a data search I recommend considering how it would be to do the search with dusty, hard copy files – that is how it was at the start of my professional life. One step further, knowledge finding with neural networks is even more amazing. Just look how Google not only remembers the kinds of things you are interested in but prompts you with stuff you might be!

This is all wonderful for pharmacovigilance, and perhaps we will be able to fully predict problems with new products and signal emerging problems with only computer algorithms, which link different datasets. Already many of us are working on that, but it is not so easy to measure how good these new methods really are since we have little information on our current performance.

The relentless logic of statistics and epidemiology is at the heart of much of our pharmacovigilance work. It is wonderful how casual conjecture can wither under the gaze of confounding and bias. On the other hand, I am surprised how often the hypothetico-deductive model results in confirmation of early signals by epidemiology. I still find the arguments between the different epidemiological factions fascinating. How can it be that experts argue about whether controlled clinical trials are 'better' than case-control studies? Is it really so that we cannot yet understand the strengths and weaknesses of our tools for different purposes and in differing contexts?[3]

5. Safety and Benefit in Clinical Practice

There are astonishingly good clinicians who use knowledge, intellect and apparently magical intuition (almost as good as Sokol) to make diagnoses and to select just the right treatments for their patients. We tend to concentrate on the failures, and forget about the successes of therapeutics day-in and day-out. I am impressed by my colleagues who bother to spend the time finding out about patients' cold feet before prescribing an antihypertensive, do not use a β-blocker and include some vasodilator in the regimen, taking advantage of a side effect. One of my gastroenterological colleagues used amitriptyline for patients who had miserable bouts of diarrhoea from intractable irritable bowel syndrome and who were also depressed. He reasoned that the anticholinergic effects would help the bowel, and at the same time as their depression was also helped! I am not at all sure about the *post hoc ergo propter hoc* arguments around this treatment, but it seemed to work.

The use of side effects positively has been widespread in some situations amongst good clinicians. Euphoria from corticosteroids and the peaceful distance from discomfort from opiates have aided so many patients in their terminal diseases, even though their use was not strictly indicated. These side effects can be used by doctors effectively to pursue ethical, humanitarian ends, and I hope that we will continue to have thoughtful health professionals who have a solid grounding in clinical pharmacology and the time

with their patients to decide together on the best treatments for individuals.

Patients, particularly older patients taking multiple drugs, also amaze me. Perhaps this is because we hear so much about failure of adherence or compliance to treatment, that I find it fascinating to see how often patients use what a colleague of mine called 'intelligent non-compliance' very effectively. I think the numbers of patients who diagnose their upper gastrointestinal discomfort as being caused by NSAIDs and stop using them must have saved huge amounts of money, as well as their doctors' reputations, although perhaps not so much saving on the drugs since it is also a source of surprise at how patients will continue to get supplies of the same or similar medicine simply because they do not want to upset the doctor!

The gratitude of patients to clinicians whose reputations rest on the appropriate use of medicines is disconcerting as well as heart-warming. Patients do not like to blame nice doctors with whom they have personal contact. It is a cliché that doctors sometimes get away with murder. I wish that patients knew the extent of work, knowledge and dedication that goes into the pill that may save or change their lives. It is clinicians who take the credit and blame often goes to the more anonymous industry or regulators. This is not always so, and I also wonder at the ability of patients and relatives to forgive serious and even fatal errors in medication. There is a literally awful moment, which is a lifetime, as a health professional injects a fatally high dose, or a wrong or contraindicated medicine. Once the act is done there is a hollow pause in eternity to wait for the inevitable. I have witnessed this on two occasions, but mercifully never been responsible. One was an intramuscular penicillin injection to a patient with known allergy with an immediately fatal anaphylaxis; the other occasion was in a cardiac emergency when a doctor injected a dose of potassium chloride. The patient was potassium deficient, but the dose should not have been a bolus. The doctor was relatively senior and the dreadful thing was that some of us anticipated the error as the doctor picked up the syringe and started to inject into an intravenous line. We moved, but the fatal moment came and went – a dead straight line on the electrocardiograph monitor. Such experiences are not, and should not be, ever forgotten by those of us in pharmacovigilance.

The dreadful awe of the end of a life by another's hand, unwittingly, is something that should take us beyond mere regulation, to seek technical solutions and safety systems that will never let our errors be repeated, or to catch them before they can do harm.

The beginning of a new year (for some of us) seems a good time to be in wonder and be fascinated about the mysteries and benefits brought to us through pharmacovigilance, and to wonder how to solve our challenges of the future.

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References

1. Sokol DK. Wonder in medicine. BMJ 2009; 339: b4976
2. Constable S, Pirmohamed M. Statin therapy: pharmacology, current uses and widening potential [online]. Available from URL: http://behindthemedicalheadlines.com/articles/statin-therapy-pharmacology-current-uses-and-widening-potential [Accessed 2009 Dec 7]
3. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med 2008; 5 (3): e67

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