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15th Edition

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*"We have been reviewing the literature now every year for the last 29 years, and that's over 3000 references every year. There are around 100,000 references in the Annuals, and about 40,000 references in the new encyclopedia. And it's not just that the references are there; all the authors comment critically on the nature of the evidence and its relevance to clinical practice so it's a commentary as well as a source book."*

### What inspired you to study medicine?

I always wanted to do it. I can't recall a time when I did not want to be a doctor.

### Are there doctors in your family?

Not in the immediate family with whom I grew up. My mother's twin brother and his wife were both doctors, but in another city, and I only saw them occasionally. I didn't get to know them well until I was in my teens, and I had long wanted to be a doctor by that time, so I don't think they were influences.

### You don't remember having something specific spark your interest?

I don't recall a moment on the road to Damascus or anything like that.

### How did you start off?

I went to medical school in Glasgow University, which offered a six-year course in pre-clinical and clinical medicine. Then my first internships were at two local hospitals in Glasgow. One was with a physician whom I much respected, a man called Sam Lazarus. He had been a professor of medicine and had gone back into the NHS to be a consultant physician. He gave me my first job in general internal medicine. His eclectic style, informed by a deep interest in both medicine and the humanities influenced me greatly.

### How long did you do that?

It was a six-month internship. You had to do six months in general medicine and six months in general surgery. I did my surgery job at another local hospital and then I looked around for jobs in clinical pharmacology. I already knew at that stage that I wanted to be a clinical pharmacologist.

### How did you decide to be a clinical pharmacologist?

I came home from the university one afternoon, just after the results of our final examinations had been announced. I met a neighbor, Jake Davidson, who was a radiologist. He congratulated me and asked what I was going to do after my internships. I said I hadn't really thought about it. He asked what my best subject had been at medical school and I told him it was materia medica, which was what we called drug therapy in Scotland. He said if I was good at materia medica, I ought to be a clinical pharmacologist. I asked him, "What's that?"

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**You hadn't heard that term before?**

No, it was new in those days. This was 1970, and the clinical section of the British Pharmacological Society had only just been established, so it was a very new subject. Dr Davidson suggested that I go and read about clinical pharmacology. So I went and looked up the journals, and sure enough there were articles about it. The Royal College of Physicians in London had published a report in 1969 and the World Health Organization had published a report in 1970, and they were all saying that this was an up-and-coming specialty that was going to be important for general medical practice. I went to see people in the field and said I would like to be trained. Abe Goldberg, who at that time was Professor of Materia Medica in Glasgow, called back and gave me a job after my internships. Then after I had done my basic training I came to Oxford to specialize.

**I read that you currently working are in the Department of Clinical Pharmacology at Radcliffe Infirmary.**

Yes, that's one of the main hospitals in Oxford.

**Is that part of Oxford University?**

Yes.

**Can you tell me about your position?**

I'm one of the senior physicians here and I hold a senior post in clinical pharmacology at the University.

**Do you conduct research at the hospital?**

I'm a consultant (attending) physician doing general internal medicine, I teach the medical students and others about drug therapy and clinical pharmacology, and I do research into drug therapy. I also have a variety of positions on national committees advising about drug therapy.

**What have been the biggest developments in clinical pharmacology during your career?**

Many things have happened in the field. I suppose a major development in drug therapy was the introduction of highly selective drugs for specific targets in the body. The so-called "magic bullet" of Paul Ehrlich has been a dream of pharmacology for over 100 years. At the beginning of the 20<sup>th</sup> century, John Newport Langley suggested the idea of receptors. He said that there were proteins on cells in the body that were receptive substances for drugs, and that drugs would attach to these receptors and in some way produce effects that would stimulate the body in particular ways to do things. When I started to do research in clinical pharmacology, this idea of receptors had just come of age. It had taken a long time, because the tools were not there to study receptors. When I started, the tools, radioactively labeled drugs and techniques for studying their binding to tissue receptors, had just become available, and since then there has been a big proliferation of compounds that have relative specificity for individual receptors in the body. The identification of pharmacological targets in the form of receptors, and enzymes as well, that can be targeted very specifically by drugs that can be synthesized for that purpose has been a major development. Our ability to study receptors and the mechanisms of action of drugs was a major event in the second half of the 20<sup>th</sup> century, just as the first half of the 21<sup>st</sup> century will be dominated by genetics and genomics. The discovery of the human genome will probably have a major impact on clinical practice in general and drug therapy in particular.

**Have you been the Editor-in-Chief of the last two editions of *Meyler's Side Effects of Drugs*?**

I was co-Editor-in-Chief of the 14<sup>th</sup> edition with Graham Dukes. Now I'm the Editor-in-Chief of the 15<sup>th</sup> edition.

**How long ago was the 14<sup>th</sup> edition published?**

It was published in 2000.

**How is this edition different?**

It's hugely different. It's a complete overhaul.

### **Can you give me some specifics?**

To tell you about this I ought to tell you a little about the history of the book. Leopold Meyler was a Dutch physician, who developed tuberculosis during the late 1940s. In 1948 streptomycin was discovered, the first effective treatment for tuberculosis, and during the next few years other drugs became available. Meyler was treated for tuberculosis in around 1950, and he got side effects from the drugs that he was given. He wanted to find out more about this and he looked for literature on it but couldn't find a textbook that described adverse effects of drugs. So he decided to write one. From his hospital bed, so the story goes, he got his research assistants and students to scour the literature for papers on side effects of drugs. In 1951 he published a book in Dutch in which he described all of these adverse effects. It was 192 pages long and was published by a local publisher. It was so successful that he managed to persuade Elsevier to publish an English translation in 1952. That was the same book essentially, but it ran to 268 pages, and it was the first comprehensive 20th century textbook on the adverse effects of drugs. The only previous one was written in the late 19th century by a toxicologist called Louis Lewin in Germany. Meyler then persuaded Elsevier to publish updates roughly every four years. In 1957 he published volume two, in 1960 volume three, and so on. He died in 1975, and Elsevier asked Graham Dukes if he would edit volume eight, which was published in 1976. Volume eight was about twice as thick as volume seven.

### **Is that because there were so many more drugs?**

Yes, more drugs and many more reports.

### **When did this book become more than one volume?**

In 1976 Graham Dukes told Elsevier that the book was getting too big to be published in a single volume, and was getting bigger and bigger. He suggested that instead of publishing update volumes every four years they should publish an update volume every year, because there was enough literature for that. In addition, he suggested publishing an encyclopedic version, summarizing it all in a single volume. Elsevier agreed to do that. The first update volume was published in 1977 and they called it *Side Effects of Drugs Annual*. We've published one of those every year since.

### **Are you the current editor of that annual?**

Yes, I've been editor since the 15th volume and I'm currently editing the 29th volume. I've been associated with it pretty much since the start, first as an author and then as editor. The first encyclopedic edition was published in 1980 and was called the 9th edition, and an encyclopedic version has appeared every four years since then, based on the previous encyclopedia plus the four most recent annual updates.

### **So everything is brought together.**

Yes. When it came to looking at this whole text again for the 15th edition, I thought there were two things that needed to be done. First, it needed to be put into a format that could be put on the web, so that people could access it electronically. Secondly, it needed to be cleaned out and reorganized. Because the text had been repeatedly modified cumulatively over the years, it had become rather messy. The whole text needed to be reorganized. Furthermore, increasingly over the years reliance had been placed on the Annuals for cross referencing, and a lot of primary references had disappeared. They were still available in the Annuals but they weren't in the encyclopedic version, and not everyone has access to the Annuals. So what you were looking at was a reference text that you had to trust, and it is a trustworthy text, but in these days of evidence-based medicine people like to see the original evidence. Meyler had rather taken that for granted over the years. I decided this had to be rectified and that the original references had to be put back into the encyclopedia, so that people could actually look up the original material if they wanted. I also added back some treatments that had disappeared from later editions, such as smallpox vaccine and thalidomide. Because of this major revamping, the book has taken an extra two years to complete.

**In reorganizing the text, did you change the format?**

I have reorganized it completely into monographs dealing with individual drugs. The previous structure was based on chapters on drugs affecting the gut, the heart, and so on. Of course, there are some drugs that affect more than one system. For example, lidocaine was included in the chapter on local anesthetics and in the chapter on antiarrhythmic drugs, so information was scattered here and there. All of that needed to be rationalized for the 15th edition. I decided to do it drug by drug instead of topic by topic.

**How do you choose what drugs to include? I can't image that you could include all drugs.**

The new edition will contain 1500 monographs; most deal with a single drug but some deal with groups of drugs, so about 1800 drugs are covered. If you look in the British National Formulary you'll find there are about 1200 drugs listed there. So every drug that is in the British National Formulary is in Meyler, plus some that aren't.

**So it's very thorough.**

Yes, *very* thorough. Every year I'm looking out for drugs to add to the text that haven't been reviewed before. The other thing I didn't mention before is that the new edition is much, much bigger. The previous edition was one volume; this one is six volumes. Overall, it's about three times as big as the previous edition.

**You know, I was surprised to find out that *Meyler's Side Effects of Drugs* was the first comprehensive book to bring together side effects of drugs since Louis Lewin published his book in the 1800s.**

I wrote an essay about this in one of the Side Effects of Drugs Annuals (Annual 27, 2004). It tells you the history of Lewin's contribution to side effects of drugs. He published his book in German, and although an English translation was published in 1883, it was never properly brought up-to-date and was forgotten after the last German edition was published in 1909. I suspect that Meyler didn't know about it himself. It was almost 70 years after Lewin's book was first published that Meyler came on the scene, so in effect, he was creating the field.

**I imagine in by 1950 there was already a growing problem with adverse effects of drugs. I know it is a big problem today.**

Yes. The most recent British data, published two years ago in an issue of the British Medical Journal that I edited (July 3, 2004), showed that something like 6-7% of all admissions to hospitals are associated with adverse effects. It's a big problem.

**Is that why you feel this is such an important work?**

Yes. Meyler is *the* source of information on this. It's the one source that really tells you what is going on; there isn't another book like it. We have been reviewing the literature now every year for the last 29 years, and that's over 3000 references every year. There are around 100,000 references in the Annuals, and about 40,000 references in the new encyclopedia. And it's not just that the references are there; all the authors comment critically on the nature of the evidence and its relevance to clinical practice so it's a commentary as well as a source book.

**What would you like librarians to know about this book?**

It's the most comprehensive source of information on the adverse effects of just about any drug they will ever hear about.

**Who is the intended audience of this book?**

Anyone who has any dealings with medicines of any sort should have access to this information. That includes pharmacologists, pharmacists, prescribing doctors, nurses, dentists, and other individuals in health care who prescribe, supply, or administer medicines of any sort. They should all be interested in having this information.

**I've read that factors that alter patient's response to drugs are things like age, sex,**

**weight, but I've read that the most important factors are genetic factors.**

That has been overstated in my view. Genetic factors are important, but other factors are equally important. A whole host of environmental factors are important and should not be discounted.

**Can you give me an example of an environmental factor?**

The use of other drugs, causing drug interactions, is an example. If you take two drugs, an adverse effect is more likely than if you take one, because they may interact with each other. Your diet can also affect your response to a drug and so can other diseases besides the one you're treating. For example, if you get an infection it can change your response to a drug. If you get kidney or liver disease it can affect your response. If you are exposed to a drug that makes you allergic in some way, it will be determined partly by genetics and partly by environmental factors. Antibiotic resistance is an important adverse effect of drugs that is partly determined by environmental exposure. For instance, a drug was introduced into the veterinary market to treat animals and it caused resistance to antimicrobial drugs, among a population of bacteria that are important to man. Consequently, because that drug was introduced into animals, the bacterium that it affected, which can infect people, is now resistant to antibiotics. That drug therapy, which was never intended for us, has had an adverse effect on an organism that may infect us and may therefore be more difficult to treat. So you can see there are all kinds of effects that medicines can have in ways that are totally unrelated to any genetic factors. I'm not saying that genetic factors are not important, I'm just saying that there are other factors that are equally important and should not be neglected.

**What do you think about DNA Drug Reaction Testing? Is it an effective way to find out whether or not a drug will affect you negatively?**

I think there has been a lot of hype about this, and it hasn't yet fulfilled its potential. One or two tests are available for this kind of thing. The oldest one of these is an enzyme that you measure in red blood cells that tells you whether the patient will be more or less susceptible to the adverse effect of a particular type drug. It was first described over 30 years ago and it's still not widely used or well understood. There is now a huge amount of work going on because of the sequencing of the human genome. People are looking for polymorphisms, in other words, differences between you and me in our genetic structure that make you susceptible to an effect and me not, or vice versa. So if you have the polymorphism and your doctor can detect it, then you wouldn't be given a drug that might give you an adverse reaction. On the other hand, if I don't have the polymorphism it would be safe to give me that drug. That's the idea. There are two major problems with that. The first, as I said, is that there are many environmental factors that determine responses. So unless you have a response that is very largely genetic it's not going to help to know only the genetics, you need to know other things too. The second problem is that most effects of drugs, even if they are largely genetic, are not attributable to a single gene, but often two or three or more genes. To put it very simply, if you take a drug it has to be handled by the body; the body absorbs it, distributes it to the tissues, metabolizes it, and eliminates it. The response to the drug depends in part on how well the body handles the drug. On the other hand, the drug has to do something in the body as well. It has to get to a receptor and act on it. The effect will depend on how well it does that. It's more complex than a single test can necessarily tell you. You may be able to test for some of the genetic factors, but if there are more than two or three of them it becomes too complicated, and you can't always test for the environmental factors.

**How can you determine the causes of side effects when there are so many factors and limited documentation?**

Well, we used the *Side Effects of Drugs Annual* to study that question, because it contains references to all the important world literature. What I did was to collate all the references that were published in one annual, in one year, and I analyzed their sources. What I found was that 30% of all reports on adverse effects of drugs are stories. They are single anecdotes.

**Stories by doctors?**

Stories reported in journals, usually by doctors. That's 30% of all the information we have, coming from single case reports or short reports about handfuls of cases. As a result, a major part

of our primary information on adverse drug reactions comes simply from narratives of single case reports. On the whole, such reports do not constitute evidence of high quality, because there is no control for them. An event happens, and it's associated with the drug, but it might not be cause and effect. Anecdotes may be more or less convincing, depending on how much work the doctor did to try and establish the cause. But except in a few cases it's not the kind of hard evidence that people now like to see from big randomized controlled trials. So determining cause and effect can be difficult.

**And where does the other evidence come from?**

30% comes from good quality trials, and the rest comes mostly from major review articles, small clinical studies, and statements by regulatory bodies like the FDA or the WHO.

**What about evidence during human drug trials when they are trying to establish the effectiveness?**

There is some of that, but not as much as we need. There are several reasons. First, it is much more difficult to discover adverse effects than beneficial effects. Beneficial effects are easier to determine because we know the result we are looking for, and we can measure that result. We don't know what the unwanted effects are going to be. We can't necessarily predict them and we may just have to wait and see what happens. Also, the beneficial effects are usually single, but there may be a dozen adverse effects and it takes a bigger number of patients to find them out. But relatively few patients are studied during drug development. Generally, a pharmaceutical company won't do a major trial or continue with a major trial once they've showed that the drug works; they stop there. Getting information about all the unwanted effects is a much bigger task, so it's actually quite difficult to get that information from trials that are conducted during drug development.

**I'm sure side effects must be monitored by pharmaceutical companies after a drug is marketed.**

Yes, it's called post-marketing surveillance. And of course prescribers are also on the lookout for adverse effects and are encouraged to report them.

**Is there one central place for this information to be held?**

Yes, there is. Many countries in the world have repositories of such information.

**Is this a requirement?**

No, nowhere in the world is it an absolute requirement.

**It just makes a pharmaceutical company look better if they are reporting adverse effects?**

The pharmaceutical companies do it and they report adverse effects, but there is no requirement for doctors to report adverse effects. In fact, we studied this some years ago in Oxford and we found that only 10% of all the adverse effects that could have been reported were actually reported.

**I think I may have read an article that you wrote about that. Doctors don't always have the time to make a report.**

Yes, it is a problem. If a prescriber sees an adverse event, whether or not it may be due to a drug that the patient is taking, it should be reported to their national organization, like the FDA in the United States, using a system called Med Watch, or to the MHRA in the UK using a system known as Yellow Cards. Many countries around the world have different systems and they gather information of this sort. Then they report what they have found to the Drug Monitoring Centre in Uppsala, Sweden.

**I wondered how all this information comes together.**

The database in Uppsala is huge and really high-class. It is the best database of reports on adverse reactions that you could possibly get. They do a lot of analysis of reports of adverse

reactions.

**By the way, what is the standard length of a drug trial during a licensing phase?**

The whole drug development process takes about ten to fifteen years. The length of an individual trial depends on what the end point is. If you are looking for death as an end point it can take several years. If you are looking for a reduction in blood pressure, for example, you can do that in six months. People are often interested in preventing or delaying death, and it takes years and years to accumulate enough information about that, and very large trials are required.

**Aren't more side effects detected after the licensing phase because the drug is marketed and used by a much bigger quantity of people?**

Yes, that's right, because before licensing very few patients are studied. The figures that are quoted are usually up to about two thousand, and of course after marketing it may be hundreds of thousands or even millions of people exposed, and so information comes out more readily. Even so, most of the information is anecdotal rather than from trials. One thing we've been interested in doing is what we call systematic review. If you've got ten trials, each with a hundred patients then you can pool all of that information, and it's known as a systematic review. When I counted up all the references to adverse effects in the world literature, I found that only about 2% of all papers in the field are systematic reviews. There isn't enough of that going on.

**I'm sure over the years technology has helped.**

Computerized technology is able to bring data together and do big number crunching studies. This is known as data mining. There is a huge effort going on at the moment into data mining, looking for information about adverse drug reactions from large databases, such as the Uppsala database and using sophisticated statistical methods.

**What has been your biggest contribution to your field?**

The encyclopedia and the Annuals have been a major contribution, in terms of getting information and organizing it. The other contribution that I feel should be influential is my work on the classification of adverse drug reactions with my colleague Robin Ferner (BMJ 2003 Nov 22; 327: 1222-5). We invented a system called DoTS, which describes the several features that characterize adverse drug reactions, based on the dose of the drug, the time-course of the reaction, and the factors that make individuals susceptible. It has many potential applications.

**Do you plan to continue to edit?**

I enjoy editing, and I'm keen on continuing to be involved with Meyler's encyclopedia as it develops further. Keeping the electronic version continually updated will be another big challenge.

**When will the encyclopedia be published?**

We've had a lot of enquiries from people all over the world, asking when the next edition is due. I've just finished correcting the proofs, and the book is scheduled to be published in June 2006 and the electronic version in August.

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