

Dr. Louis Sherwood on the Past, Present and Future of the Clinical Research Enterprise

By Norman M. Goldfarb

Louis M. Sherwood, MD, MACP, passed away Thursday, January 25, 2007, at his home in Florida. This interview has been published with the kind permission of Judy Sherwood, his wife of 41 years.

Dr. Sherwood "retired" in 2002 after an extraordinary 40-year career in medical research. To mention just a few highlights of his 38-page C.V., he was Merck & Co.'s Executive Vice President, Worldwide Drug Development and then Senior Vice President, Medical & Scientific Affairs, U.S. Human Health Division, over a 14-year period, including the seven years when Merck was rated the most-admired company in the United States. Prior to joining Merck & Co., Dr. Sherwood's distinguished academic career included appointments as Baumritter Professor and Chairman of the Department of Medicine, Albert Einstein College of Medicine; Physician-in-Chief, Montefiore Medical Center; Chairman of Medicine, Michael Reese Medical Center; Professor of Medicine, University of Chicago; Associate Professor of Medicine, Harvard Medical School; and Chief of Endocrinology, Beth Israel Hospital in Boston.

Dr. Sherwood was, most recently, President of MEDSA, LLC, an independent consulting firm, but spent much of his time as President and Chairman of the Board of the Academy of Pharmaceutical Physicians and Investigators (APPI), his fourth presidency of a national medical society. As president-elect of its predecessor organization, the American Academy of Pharmaceutical Physicians (AAPP), Dr. Sherwood played a key role in the development of APPI and its affiliation with the Association of Clinical Research Professionals (ACRP). APPI is a physician organization dedicated to improving the science, practice and ethics of developing safe and effective drugs, vaccines, diagnostics and medical devices by providing educational programs, certification programs, and tools and services to meet its members' needs. The organization currently has more than 1,400 members.

Dr. Sherwood's experience as clinician, researcher, teacher and leader in academia, industry and professional associations gives him unique insights into the clinical research enterprise.

The Interview

Lou, how would you compare your experiences in academia and industry?

I had a superb intellectual experience in academia and very much enjoyed the opportunities to do research, teach and run large clinical departments. At the same time, the academic system, although very democratic, is somewhat inefficient. Within months after I arrived at Merck, I was very impressed with the quality and rigor of the science and the data-driven nature of the company. The research was as good, or better, than I had seen at NIH or in academia. I also was very impressed with the strong ethical base of the company; if there was ever a question about safety, the patient came first. When I went to Merck, I had considered myself a sophisticated scientist, having been supported by NIH grants for more than 20 years. When I was placed, after a year, in charge of Worldwide Drug Development, I realized that there was a whole dimension beyond basic and clinical research skills that led to the successful discovery, development and registration of new drugs. I found myself learning a great deal.

I was also impressed with the teamwork in industry and the resulting ability to get things accomplished. Research these days requires a collaborative effort and teamwork. That is true not only in industry, but also in academia. An individual scientist can do a lot. But, with the complexity of scientific projects that exist today, very quickly after an individual scientist makes an initial discovery, others who may have more resources and larger teams and more collaborators may pick up on that concept and carry it much, much further.

The key thing in industry is getting the job done. To get registration of a safe and effective drug, there are many hurdles along the way. It is an intellectually challenging and also a long, complex, expensive process that depends on a number of high-quality individuals working together. I found that the communications, teamwork, discipline and rigor, as well as the complex problem-solving, were conducted at a high level. I also found the support personnel to be very helpful and usually of high quality.

Medical schools are not schools of management. Does that pose any issues in the team environment you describe?

Physicians are trained to be independent thinkers. That is fine and good, but you would not want eleven independent thinkers on a football team. To be effective leaders, physicians also have to understand teamwork. I probably recruited more than 80 physicians to industry. When they ran into trouble, it was usually not because they didn't have the skills or the intellectual ability, but because they focused too much attention on their own needs rather than on the team effort. If someone exceeded their objectives, but in the process bumped everybody around them with large elbows, they weren't highly regarded because they did not show leadership qualities. At the present time, with the many challenges facing physicians both in science and healthcare, it is important for them to be trained better to be effective leaders.

What has changed in the clinical research enterprise during your career?

You have to go back to the major advances in basic science that have occurred over the last 50, 60 years, largely spurred by federal investment into research. Through the National Institutes of Health, the National Science Foundation, Department of Defense, and the Department of Veterans' Affairs, there has been a huge investment in basic science, leading to spectacular advances in fundamental scientific knowledge. There is then the need to translate those advances in basic science into new clinical knowledge and new drugs, devices, therapies, diagnostics, etc., that will both facilitate our understanding of disease and help us deal with either preventing or treating human clinical problems. The full cycle involves going from the bench to the bedside. That involves taking the advances in basic science, figuring out how to relate them to clinical problems, and completing technology transfer by discovering and developing new drugs and devices and novel approaches to dealing with disease.

When I entered the pharmaceutical industry in 1987, it was going full force. Lots of scientific information was being translated into new discoveries and new drugs. It was a booming period. During the '80s and '90s, there was the successful development of a large number of new drugs that have had a major effect on preventing and treating human disease.

During this time period, we picked off some of the "low-hanging fruit" with drugs that blocked key enzymes or receptors and had a significant impact on disease. Now, we continue to make tremendous advances in the scientific base and identifying many new potential therapeutic targets, but finding drugs that have a significant impact on disease is getting more challenging and there have been fewer New Drug Applications to FDA and other regulatory bodies.

As a result of the doubling of the NIH budget and the growth in the size and sophistication of the pharmaceutical industry, the whole clinical research enterprise grew. As with all rapid growth, some problems have emerged. Not every clinical investigator is optimally qualified. Occasional blatant examples of poor function have emerged at clinical practice sites, but also in academia and government. These problems have been an inevitable part of the growth and we need to deal with them. It is our collective responsibility to enhance the system and raise the standards. I strongly believe in the synergy of academia, government and industry in dealing with these challenges and continuing to improve human health.

Another change in the research enterprise occurred over the years. Initially, clinical trials were done almost exclusively at academic sites. As trials expanded and the need for broader patient populations developed, the expansion outside the academic centers to clinical and practice sites and clinical research networks occurred. Indeed, many of our APPI members are physician investigators in excellent clinics and practice sites. In the last couple of years, there has been a tendency to outsource some trials to other countries because of lower costs and faster enrollment. Every country has the right to participate in clinical research, but it is essential that global standards be maintained. It is also essential that we preserve the clinical research enterprise in the U.S., with investigators that are well-trained and credentialed, efficient and cost-effective, and focused on high standards and patient safety. We have to find ways for investigators in the U.S. to operate in an economically viable manner without sacrificing high standards.

From 2000 to 2004, I was a member of the Clinical Research Round Table at the Institute of Medicine. Among the four major challenges and roadblocks we identified were, first, the lack of a large enough and well-trained enough clinical research workforce and, second, some gaps in engaging the public in clinical research. The Roundtable spent four years developing a very good problem list, but not implementing solutions. As President and Chairman of APPI, I want to work on solutions. I believe APPI and ACRP can make a significant difference in addressing at least these two challenges.

APPI is focused on the physicians, both the pharmaceutical physicians and the physician investigators. We want to make sure that people are adequately trained and fully knowledgeable about the things they do and the regulations, whether they are working in a company or as an investigator in academia or in clinical practice. We also want to make sure that they have the appropriate credentials by encouraging certification. This is an important part of restoring the confidence of the public. So we are making a very vigorous effort not only to encourage our members to get educated and become certified, but also working with other organizations, such as the Association of American Medical Colleges, PhRMA, and the leadership in individual pharmaceutical companies to place value on the credentialing of physicians and other personnel. If the companies place that value, then the investigators will become certified.

The message to physicians is that, whether they are caring for the patient or doing clinical research, they still have to "care for the patient." The Hippocratic Oath, which involves in part, "first do no harm," has to be an integral part of their work. If physicians stand up to that challenge, take a leadership role, weed out the people who are not able to do research effectively, credential the people who are, and insist on standards, we can make major advances in the clinical research process.

Do sponsors care about investigator certification?

First of all, certification of investigators is relatively new; it has only occurred over the past five years. Only about 800 individuals have been certified. That is in striking contrast to the certification of over 20,000 CRAs and CRCs over the past 15 years.

The critical issue is for the sponsors to place value on certification. The evidence suggests that certified personnel operate with lower costs, more rapid turnaround, fewer errors, and greater safety. We have to inform sponsors of the availability and value of certification and obtain their support.

Investigators who have gone out and gotten certified are making a statement. They are saying that "I, as a physician involved in clinical research, want to be sure that I have the training I need and the credentials I need to be recognized as a well-qualified investigator." Certification will translate into more and better trials for investigators that make the commitment. It won't happen overnight, but the process is coming together.

The good news is that the decision to get certified has become much simpler. In the past, ACRP, AAPP and DIA all certified investigators. Now, these separate programs have been consolidated under APPI.

Maintaining certification will also become easier. We are developing alternative ways for people to obtain continuing medical education credits by writing papers, attending CME programs, getting online information, etc.

APPI is an organization for "physician investigators" and "pharmaceutical physicians." What is the difference?

APPI defines a pharmaceutical physician as one who spends significant time devoted to the discovery, research, development and/or support of ethical promotion and safe use of pharmaceuticals, biotechnology products, vaccines, devices or diagnostics. A physician investigator is one who serves as a clinical investigator or designs, monitors or supervises clinical studies and trials and accepts responsibility for the safe and ethical conduct of research involving human participants. In general, pharmaceutical physicians work full-time or part-time for a pharmaceutical, biotechnology or device company, or a CRO. They can also work in academia or NIH or FDA. Physician investigators conduct clinical trials at both academic and non-academic clinical sites. There can be overlaps. For example, a lead investigator may contribute to the design of a clinical trial and also participate in the trial.

Historically, AAPP members were mostly pharmaceutical physicians and ACRP physician members were mostly physician investigators. Now, APPI combines both constituencies. It is a real benefit to both groups. A lot of dialogue needs to take place, not just at a leadership level, but also at the grass roots level between physicians in companies designing studies and physicians who conduct those studies. APPI provides an organized forum for that interaction.

AAPP's affiliation with ACRP gives our members access to much broader educational programs and a larger organization with more diverse expertise. There are much larger meetings, with more cross-pollination, more exhibitors, and more areas of mutual interest. At the same time, APPI is able to implement its own scientific program within the Global Conference. Working together with ACRP, our ability to impact public policy related to clinical research is substantial. We represent the full spectrum of the clinical research workforce. So, I really look to the combined impact of the two organizations in Washington and in leading alliances with other organizations related to clinical research issues.

In addition to training, certification and public outreach, what issues can ACRP/APPI address?

There are obviously a lot of issues that have come up about various industry practices. The media have highlighted some incidents of poor practice, real or potential conflicts of interest, and failure of some investigators to always put safety first. By raising the bar, insisting on higher standards and ethics, emphasizing leadership by physicians in "caring for

the patient" and focusing on improvements in the process, there is much that APPI and ACRP can do. At the same time, if standards are raised, fewer regulations and less bureaucracy will be needed. There has also been a lot of concern about conflict of interest, and some academic institutions have gone overboard in being too restrictive on their faculty; we don't want to lose the synergies. Some of the unfortunate stories about trials in developing countries may also bring back earlier images of unfortunate events in the history of clinical research in the United States. Different countries are different in their cultures, but ethics are ethics and should be global.

APPI has a unique capacity to encourage doctors to take a leadership role with the public. Although the medical profession has suffered some decline in its image in recent years, the relationship between physician and patient is still central. I have called on physicians to take a leadership role not only through organizations but individually, one-on-one. That is an extraordinary way to reach out to the public. We want to be sure the public understands that physicians who are involved in clinical research are well-trained and, ideally, have the CPI designation as certified investigators.

Lou, given the challenges pharma and the clinical research enterprise are now facing, how optimistic are you about the future?

The future is bright, but there certainly are challenges. There is much scientific information available now about genetics – so-called pharmacogenomics – that has not fully made its way into clinical trials. For example, in the past, when one had a new anti-hypertensive drug, one would have tested it or had it approved for use in a broad spectrum of patients with hypertension. Some would be responders and some would be non-responders. As we have learned over the years, there are different responses in different populations, some better than others. That may also translate into safety issues, that certain drugs may be safer in certain populations than they are in others.

There's now a much greater focus on safety, both during the clinical research process and during the post-marketing period. The availability of databases, information systems, and electronic medical records in health plans and large medical groups helps one develop a broader information base about the experience in those settings.

However, one has to be cautious about epidemiologic studies. They are not randomized, controlled trials (RCTs) and the results can be misleading. For example, from the epidemiologic data on estrogen, it was believed that estrogen was beneficial for cardiovascular health in post-menopausal women. The Women's Health Initiative and other RCTs did not show this benefit, and in some instances showed increased risk. Epidemiologic studies raise important questions that need to be tested in RCTs. The perspectives are different.

There is more sensitivity now about some of the problems, the conflicts of interest, the qualifications of investigators. In the past, companies might have recruited investigators based almost entirely on who could just enroll quickly. Now, we want to be sure we have the right mix of subjects in a study, that the sites are appropriate, that they will do their best to minimize problems, and not have to go through FDA audits because of compliance problems. With the growth of the clinical research enterprise, there is a lot more general knowledge and common sense, and that will translate into better science. Better science and higher standards and ethics mean safer, more effective, drugs and devices.

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