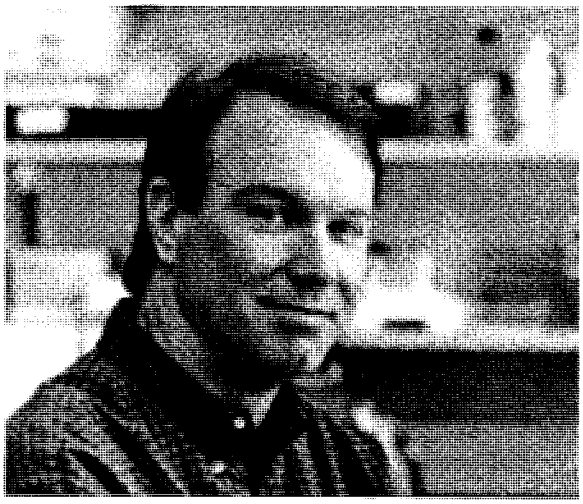
An Interview with a Distinguished Pharmaceutical Scientist

William E. Evans[1]

Dr. Evans is currently Deputy Director of St. Jude Children's Research Hospital, Chair of the Pharmaceutical Department at St. Jude and First Tennessee Bank Professor of Clinical Pharmacy, Pharmaceutics and Pediatrics at the University of Tennessee Colleges of Pharmacy and Medicine. He also serves as Co-Director of the UT Center for Pediatric Pharmacokinetics and Therapeutics, and Co-Leader of the Hematological Malignancies Program at St. Jude. He received his B.Sc. and Pharm. D. degrees from the University of Tennessee in 1973 and 1974, after which he joined the faculty at UT and subsequently St. Jude. He spent a sabbatical year in Professor Urs Meyer's laboratory at the University of Basel, Switzerland, in 1987–88. For the past 25 years, Dr. Evans' research has focused on the pharmacokinetics and pharmacodynamics of anticancer drugs in children, exploring the mechanisms for interindividual differences in drug disposition and the biological and pharmacological basis for heterogeneity in response to antileukemic therapy. He has received two MERIT Awards from the NIH, for his studies of hepatic drug clearance in children (1987–1995) and drug metabolism in childhood cancer (1995–2005). He received the Leon Goldberg Award from ASCPT in 1991, the ACCP Therapeutic Frontiers Lecture Award in 1989, the ACCP Russell Miller Research Award in 1992, the Volwiler Research Award from AACP in 1994, the APhA Research Achievement Award in 1996, and the Charles Pippenger Award from the International Society for Therapeutic Drug Monitoring and Clinical Toxicology in 1997. He has been elected a Fellow in AAAS, AAPS, and ACCP, and was held elected offices as President of the American College of Clinical Pharmacy (1982), President of APhA's Academy of Pharmaceutical Research and Science (1988), and Chair of the AAAS Pharmaceutical Sciences Section (1998–1999). He was a member of the FIP Board of Pharmaceutical Sciences from 1995–1999, and currently serves on the ASCPT Board of Directors, the AFPE Clinical Sciences Advisory Committee, the ASCO Program Committee, and the Editorial Boards of six scientific and professional journals. He is an Editor of the textbook *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*, currently in its third edition, and Associate Editor of *Pharmaceutical Research*. Dr. Evans has written over 200 research articles, and has been an invited speaker at over 200 universities, research institutes and international symposia.



WHAT DO YOU THINK HOLDS THE KEY TO YOUR SUCCESS AS A PHARMACEUTICAL SCIENTIST?

Response: Whatever success I may have enjoyed can be attributed to several factors, including: (1) an incredibly strong environment provided by St. Jude Children's Research Hospital and the University of Tennessee, where my research program has been based for the past 25 years, (2) the fact that my research has remained focused on the pharmacodynamics of cancer therapy in children, but has evolved over time to incorporate new strategies and methods that have emerged from biomedical advances over the past two decades, and (3) my good fortune of having worked with many bright and dedicated colleagues, post-doctoral fellows and students over the years.

WHAT ARE THE 2–3 ACHIEVEMENTS THAT YOU ARE MOST PROUD OF? WHY?

Response: This is a difficult question, as I consider my achievements to have been rather modest when viewed as single events. When viewed as a whole, it is probably the evolution of methotrexate (MTX) and mercaptopurine (MP) therapy for childhood acute lymphoblastic leukemia (ALL) that is the most gratifying. Methotrexate therapy is now based on a more complete understanding of its pharmacokinetic and pharmacodynamic characteristics in children and in their leukemia cells, with recognition that both patient and disease differences in drug disposition govern ultimate response to treatment. I would single out the identification of a pharmacodynamic relationship for MTX in childhood ALL, originally published in the *NEJM* in 1986, and confirmed in a prospective randomized study published 12 years later in the same journal, as a highlight. The lag time between publication of these two papers was created by the fact that it took over a year to design and open the randomized study, three-plus years to accrue patients, five years of follow-up to

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assess outcome, a year to analyze the data and another year to get it published in a good journal, exemplifying some of the challenges in conducting prospective, randomized clinical trials. Not all environments will tolerate such a delayed return on investments, but this is what may be required for definitive "outcomes research." Our discovery of the genetic basis for the inherited polymorphism of thiopurine S-methyltransferase is a more recent highlight that emerged from the incorporation of molecular biology into our pharmacokinetic studies of anticancer drugs. Seeing the cure rate for childhood ALL steadily improve over the past two decades, from about 50% in 1975 to above 80% in 1999, motivates all of us to continue our pursuit of better therapeutics for this and other childhood cancers.

WHAT WAS THE TURNING POINT IN YOUR DISTINGUISHED CAREER?

Response: There is no doubt that joining the faculty of St. Jude Children's Research Hospital in 1975 was a major turning point in my career, although this was not obvious to me at the time, and many of my colleagues questioned my decision to join such a small and relatively unknown institution. However, I sensed that the institution aspired to become great, and I knew that it had a laudable mission. Importantly, St. Jude welcomed new ideas from all disciplines, encouraged innovation and multidisciplinary collaboration and facilitated translational research at a time when the term had not yet been coined. Yes, there were many subsequent events that helped shape my career, including my first NIH grant, awarded in large part because members of the study section saw the *potential* of what we proposed to do, and certainly not because the proposal was perfect. To this day, I remain grateful to those who gave me advice on how to revise my first NIH grant application, one that had failed miserably I would add, but one that was ultimately funded. Finally, I would mention a sabbatical year at the University of Basel in 1987–88, which gave me a fresh view of how to structure and manage a research program and gave my nascent interests in molecular biology an air of legitimacy.

CAN YOU NAME THE TWO OR THREE INDIVIDUALS WHO HAVE MADE A DIFFERENCE IN YOUR CAREER? HOW SO?

Response: There have been many more than two or three individuals who have had an important influence on my career. It began with Larry Barker, who was the faculty sponsor for my Pharm.D. research project (a requirement in those days) and subsequently the person who encouraged me to return to St. Jude to establish my research program. He instilled in me the importance of developing a research program on par with the best medical and scientific research programs in the field, and not simply the best pharmacy research in the field. I must also mention the late Dick Feurt, and Gary Cripps and Bill Miller, my first Dean and Department Chairs at the University of Tennessee, who guided my early days and taught me the importance of primary research as the foundation for clinical practice. They convinced me that clinical pharmacy would not flourish without a critical mass of investigators helping to generate the scientific basis for rational therapeutics. There was another group of individuals who had a profound effect on my career, including Gary Levy, Bill Jusko, Les Benet and Milo Gibaldi. While I never had the opportunity to study directly with these icons of pharmacokinetics, their lectures, writings and advice were instrumental in establishing my personal definitions of rigor and quality in research. And of course there is Mary, and the energy and creativity she has instilled in my life, both inside and outside the laboratory.

WHAT DO YOU FIND ATTRACTIVE BEING IN THE ENVIRONMENT OF A RESEARCH HOSPITAL AS COMPARED WITH AN ACADEMIC INSTITUTION?

Response: This is simple, a research hospital like St. Jude, which is rare if not unique, provides the perfect environment for conducting laboratory-based clinical research, and translating fundamental discoveries to clinical therapeutics. This is what I enjoy trying to do, and thus it is no surprise that I have remained at SJCRH for the past 23 years. I would also note that St. Jude *is* an academic institution in my mind, it just does not award degrees.

PHARMACEUTICAL SCIENTISTS ARE FACED WITH THE DILEMMA OF HAVING TO PUBLISH IN BIOMEDICAL OR BASIC SCIENCE JOURNALS AND HAVING TO PRESENT IN THEIR SPECIALTY MEETINGS IN ADDITION TO THE PHARMACEUTICAL SCIENCE VENUES. DOES IT MEAN THAT CUTTING EDGE SCIENCE WILL NOT LIKELY BE FEATURED IN THE PHARMACEUTICAL SCIENCES FORUM?

Response: This is a difficult question. I understand the need to present and publish data in both forums, but I have no easy answer to the dilemma you have identified. I have tried to do both, yet my strategy has always been to publish my research in the most rigorous multidisciplinary journals that will publish it. For some of our papers, that has been multidisciplinary journals like *NEJM* or *PNAS*, and for others it has been journals within our own discipline. While I have complete confidence in all the work we have published, regardless of where it was published, there is no doubt that the immediate impact has been greater for those papers published in the higher-impact journals. In the end, it depends on the extent to which one's findings capture the attention of the reviewers and fit within the scope of the journals. Ultimately, our discipline will benefit more from papers published by pharmaceutical scientists in high-impact multidisciplinary journals, despite the short-term loss of these papers from our own journals.

WHAT IS YOUR VIEW ON THE CURRENT STATE OF RESEARCH IN CANCER DRUG PHARMACOKINETICS AND PHARMACODYNAMICS?

Response: This is a healthy and exciting area of investigation, but you might guess I would have this view. Pharmacokinetic and pharmacodynamic characterization of cytotoxic anticancer agents must be conducted in cancer patients, and not healthy volunteers, placing additional challenges on these studies. Our post-doctoral fellows are finding excellent career opportunities to conduct these studies in cancer centers in the US and abroad. The NCI requires pharmacokinetic studies to be conducted in

early clinical trials, providing the opportunity to do human pharmacodynamic studies when these medications are given as single agents. Finally, the integration of molecular biology and genetics has provided important new tools to embellish these studies and elucidate mechanisms underlying inter-individual differences in drug response. The rapid evolution of pharmacogenomics holds great promise to provide important new mechanistic insights, making all of us excited about the future of translational research in the pharmaceutical sciences.

WHAT ARE FUTURE CHALLENGES TO THE PHARMACEUTICAL SCIENCES?

Response: I think one of our biggest challenges may be articulating the unique contributions we make to the research enterprise. For some, such as those developing unique methods for drug delivery, it may be rather straightforward, but for others like me, the distinction between what I do and what is done by a pharmacologist, or a geneticist, or a physician may be more challenging to articulate. I am not too worried about this, however, as the same problem exists within the basic sciences; it is now hard to distinguish a pharmacologist from a physiologist from a biochemist, but who really cares? In addition, I have long been inspired by accomplished people like Gertrude Elion, who won the Nobel Prize in Physiology and Medicine even though few could articulate the discipline of her formal education and training.

WHAT ARE FUTURE CHALLENGES IN CANCER DRUG PHARMACOKINETICS AND PHARMACODYNAMICS?

Response: There are many. One is to further elucidate the pharmacodynamics of classic cytotoxic chemotherapy, and identify those drugs and diseases where individualizing therapy based on pharmacokinetic principles will enhance treatment outcome. Ultimately, comprehensive pharmacogenomic studies hold promise to elucidate the network of genes that determine an individual's response to chemotherapy (e.g., genes for drug metabolizing enzymes and transporters, genes for drug targets and genes for molecular oncogenesis). The combination of pharmacodynamics, functional genomics, high throughput screening and bioinformatics provide the tools needed to attack these questions in a comprehensive and definitive fashion. Another challenge will be to elucidate the pharmacodynamics of the new generation of anticancer therapy that will evolve from a more complete understanding of molecular oncogenesis. Many of the same pharmaceutical issues will pertain (drug delivery, pharmacokinetics, etc), but the therapeutic endpoints may differ (cell differentiation versus cytotoxicity).

YOU ARE ONE OF THE LEADERS IN TRANSLATIONAL RESEARCH. WHAT IS TRANSLATIONAL RESEARCH AND HOW CAN ONE BE TRAINED FOR IT?

Response: To me, translational research is any form of research that translates laboratory-based discoveries to the clinic, or vice versa. While this is nothing new to the pharmaceutical sciences, the concept has gained notoriety as fundamental disciplines like molecular genetics, pharmacology, immunology and biochemistry begin to see their basic research have an impact on how patients are evaluated or treated in the clinic. Good training programs appear to be those that put a properly motivated clinician into a basic science laboratory to conduct laboratory research addressing clinically relevant questions, or programs that place a basic scientist in an environment where clinical research is also a priority. St. Jude provides both of these options, yet recognizes that not all research programs should be translational in nature, as fundamental discovery-oriented research remains an essential component of any thriving biomedical research enterprise.

AS YOUR RESEARCH IS TAKING ON AN INCREASINGLY MOLECULAR AND CELLULAR THRUST, ARE YOU CONCERNED THAT OVER TIME, THERE WILL BE NO ONE TRAINED IN THE TENETS OF CLASSICAL PHARMACOKINETICS AND PHARMACODYNAMICS?

Response: I hope that I never migrate so far away from pharmacokinetics and pharmacodynamics, that I lose the foundation to my research, and an important characteristic that differentiates me from other types of biomedical investigators. I tell my Pharm. D. post-docs that they are not in my program to become molecular biologists, because there are other young scientists who are better prepared as molecular biologists. I try to emphasize that they are in my program to hone their PK/PD skills, while embellishing them with tools from biochemical pharmacology, molecular biology, genetics and other basic sciences. If they leave with expertise in the former and insights into the latter, they are well prepared to fill an important void in many biomedical research programs.

YOU ARE EXTREMELY WELL FUNDED. WHAT HAS CONTRIBUTED TO YOUR SUCCESS IN THIS ARENA?

Response: Focusing on problems that I am well positioned to address, because of my training and the environment in which I work. I also spend a lot of time developing my grant applications, to ensure that they are definitive yet easy to comprehend. I seek to identify important and novel specific aims that are difficult or impossible for others to address, but that are well suited for the environment where I work. I should also note that I am in awe of those who can develop an NIH grant in a few weeks, because I typically spend several months writing dozens of drafts and getting abundant feedback from numerous colleagues.

YOU ARE ONE OF THE FEW PHARM.D.'S WHO ARE VERY ACCOMPLISHED IN BASIC RESEARCH. WHAT WOULD IT TAKE FOR MORE PHARM.D.'S TO TAKE ON A MORE VISIBLE RESEARCH PROFILE AT THE CUTTING EDGE OF BIOMEDICAL SCIENCES?

Response: First, we need to attract a few more research-oriented people into our entry-level Pharm.D. programs. Twenty years ago, only a few people tracked into the post-BS Pharm.D. programs, and these were students who discovered that they

were interested in more than the routine practice of pharmacy. Today, almost all students enter Pharm.D. programs to become clinical practitioners, as is the case for students entering medical school. Few M.D.'s or Pharm. D.'s become researchers, in part because that is not what they were seeking when they entered the professional degree programs, and in part because most have little opportunity during their professional curriculum to discover whether they would enjoy or be good at research. If we were to do a better job of "selling" pharmacy school as an avenue to a clinical, translational or basic science research career, we might attract more substrate for PharmD/PhD programs or post-PharmD research fellowships. I am referring to undergraduate biology, chemistry or mathematics majors who would otherwise never consider pharmacy school. If we continue to wait until students are already in pharmacy school, it is going to be too late to find very many who are interested in research careers. Today, I have as many PhDs in my post-doctoral training program as I do PharmDs, in part because there are not enough of the latter to sustain my research, and in part because my program is enhanced by attracting bright young minds from other disciplines.

YOU HAVE BEEN AN ASSOCIATE EDITOR OF *PHARMACEUTICAL RESEARCH* SINCE 1995, WHAT ARE THE EMERGING TRENDS YOU HAVE NOTICED? WHAT DO YOU THINK IS THE REALISTIC NICHE FOR THE JOURNAL IN THE COMMUNITY OF ELITE SCIENTIFIC JOURNALS?

Response: I suppose that the nature of our research has become increasingly biological, which I think is terrific. It is hard for me to pinpoint the niche for *Pharmaceutical Research*, and it seems as though I am not alone in this regard. We are a diverse journal that aspires to be to the pharmaceutical sciences what *Science* is to research at large. This is a tall challenge, especially when we encourage our colleagues to publish in major multi-disciplinary journals whenever possible. However, there is an abundance of outstanding pharmaceutical research after subtracting those papers published in *Cell, Science, Nature*, and *NEJM*, we just have to ensure that *Pharmaceutical Research* gets its share of those papers.

HOW HAS YOUR PHILOSOPHY OF EDUCATING GRADUATE STUDENTS/POSTDOCTORAL FELLOWS BEEN CHANGED OVER THE YEARS?

Response: I am not sure it has. I try to find post-docs who are smarter than me, who are interested in the type of research we do, who want to work as hard as I do, and who are willing to pay the price that it takes to tackle difficult problems in a comprehensive fashion. I am open to people of all educational backgrounds who met these criteria, and I can always find a slot for top-notch applicants. I realize that even those who are not pharmaceutical scientists on day one, may leave as pharmaceutical scientists at the end of their fellowship.

HOW HAS YOUR PHILOSOPHY OF MENTORING JUNIOR COLLEAGUES CHANGED OVER THE YEARS?

Response: I do not think I am necessarily very good at this, although I really want to be. I am not very good at casual or unsolicited mentoring, but I am delighted to help a colleague who has a problem or who needs advice on their grant application or manuscript. I probably read one or two grants a month, sometimes more; our group is very good about having each other provide feedback on grant applications and manuscripts. Mentoring is a bit like golf, in that it is an easy game to talk about, but difficult to master. However, mentoring is a very important responsibility of senior faculty, and we must make our best effort even if we have not mastered the art. Some people are born good mentors, but for others it is a learned trait, yet it is a skill that can be acquired with the appropriate commitment.

WHAT WOULD BE YOUR ADVICE TO OUR JUNIOR PHARMACEUTICAL SCIENTISTS WHO ARE ABOUT TO EMBARK ON THEIR CAREERS?

Response: Think big but focused, work hard but smart, become independent but stay interactive. And then there is money. "Get your own money" was advice given to me 20 years ago, when I asked what I needed to do to establish a truly independent research program. Of course, seek to support what you want to do scientifically, and not simply what some drug company wants you to do for them. Obviously, there is more to it than money, good ideas, solid strategies and consistent productivity are *sine qui non's* of a thriving research program. However, in addition to fueling the program, grant funding is an external imprimatur indicating that your peers agree that your ideas and plans are sound, and that will probably make your dean and department chair more interested in supporting your program and career.

WHAT WOULD BE YOUR ADVICE TO OUR SENIOR PHARMACEUTICAL SCIENTISTS IN THEIR RELATIONSHIP TO THEIR JUNIOR COLLEAGUES?

Response: Help them, and you help your discipline and yourself.

DO YOU FEEL THAT WE ALL HAVE AN OBLIGATION TO BE A VOLUNTEER IN SCIENTIFIC ORGANIZATIONS? IF SO, WHY?

Response: Yes, I think that is more or less correct, but few organizations have enough important opportunities for all the talented and interested members. So, when a member must fight to be given the opportunity to volunteer, he or she is likely to channel their energies elsewhere. Could AAPS accommodate 10,000 volunteers? There is no doubt that many talented and willing people do not have the chance to contribute, in part because they are not well connected. I realize that it is difficult for organizations to identify and seek out talented members who should be invited to help, but developing tomorrow's leaders is a vital responsibility of those in charge today. It is just another form of mentoring.

WHAT IS THE PLACE FOR ENTREPRENEURSHIP IN ACADEMIA?

Response: Most accomplished scientists are entrepreneurial, it is just channeled toward their research and not toward making money, as the stereotypical definition would expect of an entrepreneur. Creating new knowledge can be as entrepreneurial as creating new wealth, and a lot more meaningful in the long run. Unfortunately, there are more than a few administrators who find it easier to measure new money than to measure new knowledge, and that espouses the wrong standards for measuring academic productivity.