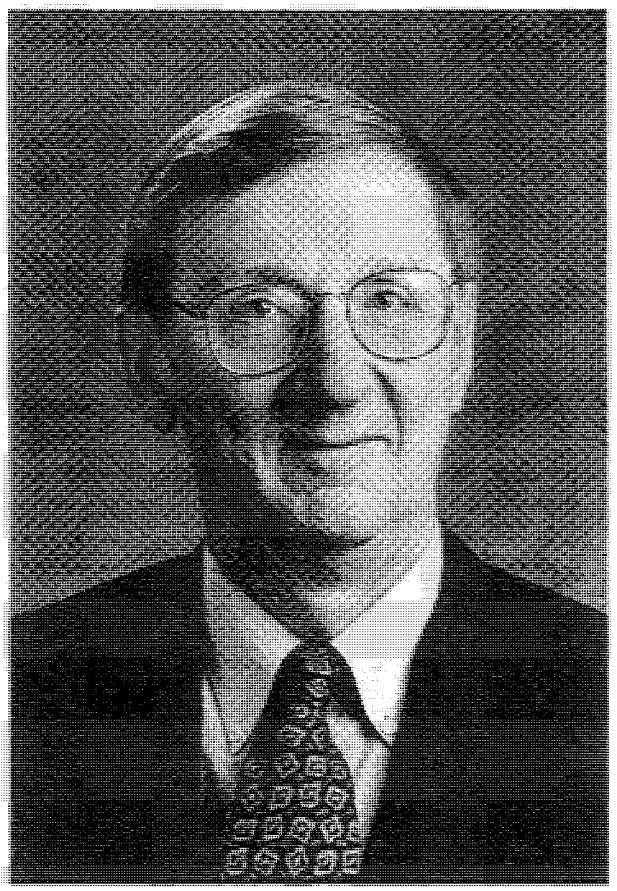
Interview with a Distinguished Pharmaceutical Scientist

Ronald T. Borchardt, Ph.D., Recipient of the 1997 AAPS Distinguished Pharmaceutical Scientist Award



Ronald T. Borchardt is the Solon E. Summerfield Distinguished Professor and Chairman of the Department of Pharmaceutical Chemistry at The University of Kansas-Lawrence. Professor Borchardt received his undergraduate education (B.S. in Pharmacy, 1967) from the University of Wisconsin-Madison and his graduate education (Ph.D. in Medicinal Chemistry, 1970) from The University of Kansas-Lawrence. After serving as a Postdoctoral Fellow at the National Institutes of Health (Bethesda, Maryland) from 1969–1971, Professor Borchardt returned to The University of Kansas as an Assistant Professor in the Department of Biochemistry in the College of Liberal Arts and Sciences. In the 1970's Professor Borchardt was promoted through the academic ranks to his current position as Solon E. Summerfield Distinguished Professor. In 1983, Professor Borchardt became the Chairman of the Department of Pharmaceutical Chemistry in the School of Pharmacy. During his academic career Professor Borchardt has received numerous awards and honors for his teaching and research accomplishments including: Established Investigatorship from the American Heart Association (1974–1979); Mortar Board Outstanding Educator (1980), Solon E. Summerfield Distinguished Professor (1983), Dolph C. Simons, Sr. Research Award in the Biomedical Sciences (1983), and Louise Byrd Graduate Educator Award (1997) from The University of Kansas; Sato Memorial International Award from the Pharmaceutical Society of Japan (1981); Fellow of the American Association for the Advancement of Science (1995); Citation of Merit from the University of Wisconsin (1989); Fellow (1988), Meritorious Manuscript Award (1991), Research Achievement Awards in Biotechnology (1993) and Medicinal Chemistry (1994), and Distinguished Pharmaceutical Scientist Award (1997) from the American Association of Pharmaceutical Scientists; the Takeru and Aya Higuchi Memorial Lectureship Award from the Academy of Pharmaceutical Sciences and Technology of Japan (1993); and the Paul Dawson Biotechnology Award from the American Association of Colleges of Pharmacy (1997) Professor Borchardt is the author or co-author of approximately 400 scientific publications and 350 abstracts. Professor Borchardt is also the Editor of six books and the Series Editor of "Pharmaceutical Biotechnology." His research interests are focused in the areas of drug design and drug delivery.

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

Response: I think that the success I have achieved as a pharmaceutical scientist can be attributed to four key factors: 1) the excellent undergraduate and graduate education that I received at The University of Wisconsin and The University of Kansas, respectively; 2) the stimulating and supportive environment that I have enjoyed during my tenure as a faculty member at The University of Kansas; 3) the many outstanding undergraduate, graduate and postdoctoral students who have worked in my laboratory at The University of Kansas; and 4) the support and understanding that I have enjoyed from my wife (Pamela) and our three children (Scott, Paul and Kelly).

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

Response: From a professional perspective, I am particularly proud of the many undergraduate, graduate and postgraduate students who have worked with me as my collaborators over the past 26 years. It is with tremendous pride and pleasure that I now watch these individuals become productive scientists and/or educators in the pharmaceutical sciences. From a research perspective, I am most proud of our accomplishments in biopharmaceutics, particularly in the area of cell culture systems and their use to study drug transport. I have had the good fortune in recent years to see cell culture systems that we

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helped to develop in the late 1980s being used routinely in the pharmaceutical industry to design safer and more efficacious drugs.

WHAT WAS THE TURNING POINT IN YOUR DISTINGUISHED CAREER?

Response: It is difficult for me to identify a *single* turning point. Instead, I would say there were four turning points in my career. The first was when I decided to attend graduate school at The University of Kansas, where I was mentored by the late Professor Edward E. Smissman. The second turning point was my decision to postdoc at the National Institutes of Health, where I became "street smart" with respect to what one needed to do to succeed as an academic researcher. The third turning point was my return to The University of Kansas as a faculty member in the Department of Biochemistry, where I was able to develop my research interests in biochemistry and cell biology. Finally, the fourth and perhaps most significant turning point occurred when I moved from the Department of Biochemistry to become Chairman of the Department of Pharmaceutical Chemistry at The University of Kansas in 1983. This was truly a turning point because it meant that, at the age of 40, I had to change my research interests from medicinal chemistry/biochemistry to pharmaceutics/biopharmaceutics. This was a very stimulating time in my life.

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

Response: Perhaps first and foremost was the late Professor Edward E. Smissman, who was my Ph.D. advisor at The University of Kansas in the late 1960s and my "unofficial mentor" when I returned to the faculty at Kansas in the early 1970s. I learned many things from Ed, but, most importantly, I learned that you could be a successful scientist and also be a caring and kind person. Another person who was very influential in my life was the late Professor Takeru Higuchi. While I never worked directly with Tak, I had the opportunity to observe him during the early stages of my academic career. To this day I am still amazed by his vision and foresight. I only hope that I can accomplish in my career a fraction of what these two "giants" contributed to the pharmaceutical sciences.

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 SCIENCES VENUES. DOES IT MEAN THAT CUTTING EDGE SCIENCE WILL NOT LIKELY BE FEATURED IN THE PHARMACEUTICAL SCIENCES FORUM?

Response: In the pharmaceutical sciences, one can find scientists doing both basic and applied work. Therefore, it is only natural that some of the research results forthcoming from pharmaceutical scientists should be published in basic science journals and some in more applied science journals. I think this is very healthy situation! Hopefully, publication of our results in basic science journals will create more opportunities for interdisciplinary research and help to stimulate the interests of chemists, cell biologists, molecular biologists and engineers in the pharmaceutical sciences. I feel that this is a particularly exciting time to be working in the pharmaceutical sciences. I find it interesting that scientists in other disciplines (e.g., organic chemists) think that pharmaceutical scientists are, in fact, doing "cutting edge research". Why are we having difficulties recognizing the importance of our own work?

ALTHOUGH YOU WERE TRAINED IN "MEDICINAL CHEMISTRY", WHY DID YOU INCLUDE A BIOLOGICAL COMPONENT IN YOUR RESEARCH? IN PARTICULAR, WHY DID YOU FOCUS RECENTLY ON DRUG TRANSPORT?

Response: My interests in biology started when I entered Pharmacy School at The University of Wisconsin as an undergraduate. Since I could not decide between a major in chemistry and biology as an undergraduate, I decided that the undergraduate curriculum in pharmacy could give me the opportunity to learn more about both disciplines. With respect to my Ph.D. training in medicinal chemistry, it should be noted that the program at Kansas provided me with strong training in organic synthetic chemistry, as well as excellent exposure to biology. It was at this point in my career that I decided to use my talents as a synthetic organic chemist to address interesting problems in biology. Early in my academic career in the Department of Biochemistry, I was able to develop this dual research interest. When I was presented with the opportunity to move into the Department of Pharmaceutical Chemistry in 1983, I realized that one of the major challenges in medicinal chemistry was how to get a drug to its site of action. Therefore, it was only natural for me to focus some of my research efforts in the area of drug delivery. What was perhaps different about my approach to drug delivery compared to that of other pharmaceutical scientists working in the field in the 1980s, was that I looked at drug delivery as a medicinal chemist/biochemist, and I tried to reduce the problems to the cellular and molecular level.

WHAT IS YOUR VIEW ON THE CURRENT STATE OF CACO-2 CELL CULTURE AS A RESEARCH AND DRUG DEVELOPMENT TOOL? HOW HAS THIS TOOL BEEN MISUSED?

Response: My opinions about the Caco-2 cell culture system as a research and drug development tool were recently articulated in an Editorial in the *Journal of Drug Targeting* (*3*:179–182, 1995). To summarize my thoughts here, I think Caco-2 cells have proven to be a *very* useful tool for estimating the ability of a molecule to permeate across the intestinal mucosa, and for elucidating pathways of drug transport and the physicochemical factors that influence it. My only disappointment is that pharmaceutical scientists have not devoted more time and energy to further refinement of the Caco-2 cell model or the development of other cell culture models of the intestinal mucosa. Perhaps this is a good example of where our field is putting too much emphasis on applied science rather than basic science.

WHAT ARE THE FUTURE CHALLENGES IN DRUG DELIVERY?

Response: Let me respond to that question by addressing separately the problem of delivering organic-based drugs and drugs

developed from biotechnology. With respect to the delivery of small organic-based drugs, I think the major challenge is to learn how to design optimal pharmaceutical characteristics (e.g., high intestinal permeability, low liver clearance) into drug candidates while retaining their abilities to bind to their pharmacological targets. Medicinal chemists have become very effective at designing "high affinity ligands". Now, with the help of pharmaceutical scientists who have expertise in drug delivery, medicinal chemists need to learn how to design "good drugs" that have optimal pharmaceutical as well as pharmacological characteristics. With respect to molecules derived from biotechnology (e.g., protein, genes), I think the major challenge will be to deliver them to their site of action and, in the case of genes, to obtain efficient expression of the therapeutic proteins. To achieve these objectives, pharmaceutical scientists will need to exploit scientific advances in the basic fields of molecular biology, immunology, cell biology, biochemistry and biophysical chemistry. If we simply try to apply existing technologies that were developed for small organic-based drugs to the delivery of biotechnology products, it is highly probable that we will fail to achieve optimal therapeutic efficacy. I think the solution to this problem is to learn from "Mother Nature", who has the ability to deliver these types of molecules very efficiently.

YOU ARE ONE OF THE PIONEERS WHO ELUCIDATED THE BIOCHEMICAL BARRIERS TO DRUG ABSORPTION. WHAT PROMPTED YOU TO INVESTIGATE THIS AREA OF GROWING SCIENTIFIC, THERAPEUTIC, AND REGULATORY IMPORTANCE? WHAT ARE YOUR KEY FINDINGS? WHERE WOULD THESE FINDINGS LEAD TO?

Response: As mentioned earlier in this interview, our interest in drug absorption arose from my experience in medicinal chemistry. In the mid-to-late 1980s, I saw many very promising drug candidates fail because they exhibited poor pharmaceutical properties (i.e., low oral bioavailability). I felt that medicinal chemists did not have available the type of data that would allow them to develop structure-transport relationships. For this reason, we initiated our research on the development of cell culture models of the intestinal mucosa and the blood-brain barrier. Once these models had been developed and validated, we realized that we did not understand the "rules" concerning the relationship between the chemical structure of a molecule and its ability to permeate a biological barrier (e.g., intestinal mucosa). For that reason, we initiated our most recent research aimed at elucidating the physicochemical characteristics of peptides and peptidomimetics that influence their permeability characteristics. Because of the rapid advances being made in this field, in the near future we will be able to predict with a high degree of accuracy, based on the chemical structure of a molecule, whether it is a substrate for the peptide transporter, whether it permeates a cell monolayer by passive diffusion via the paracellular and/or transcellular pathway, and whether it is a substrate for apically polarized efflux systems that might limit its permeation. To me these are very exciting possibilities that, when reduced to practice, will have a significant effect on how medicinal chemists design drug candidates.

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

Response: I prefer to look at this issue more broadly. I think we all have an obligation to provide some type of service to our profession. This service could take many different forms. For example, one might serve as a reviewer of manuscripts for scientific journals or of grant applications for funding agencies (e.g., NIH), as a member of a committee for a professional organization, and/or as an elected official in a professional organization. While I think it is important to provide this type of service to your profession, I also think it is important to carefully balance this type of activity with your other responsibilities, which for academic people include research and teaching.

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

Response: This is a very open-ended question, which is difficult to answer in a concise manner. Therefore, I am only going to give two pieces of advice. First, during your predoctoral and postdoctoral training, strive to achieve depth in a particular field since this is what will make you competitive for your first job. But also strive to gain breadth in your scientific background, since this breadth in your background will help you sustain a long and productive career. Second, remain flexible during your scientific career because I guarantee that you will experience significant change during your career. The best way to deal with this change is to fall back on the breadth in your training. As you can tell from my career at The University of Kansas, I have gone through several changes. The decision to make these changes was in each case very difficult but, in hindsight, these changes probably lead in part to my success. I had the confidence to initiate these changes because I had excellent depth in my undergraduate and graduate experience.

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

Response: In my opinion, it does not matter whether we are talking about industry or academia, senior pharmaceutical scientists have a responsibility to *mentor* junior scientists. In my opinion, it generally takes a person 5–7 years post-Ph.D. to truly become an independent scientist. During this time, young scientists benefit tremendously from the advice and consultation of more senior scientists. However, as a senior scientist, you walk a fine line, because you truly need to be an advisor and not exploit the interaction with the young scientist to your own advantage. In other words, a true mentor gives freely of his/her self with the only return being the satisfaction of seeing the young scientist succeed. In many respects, it is no different than raising your own children.

WHAT ARE THE FUTURE CHALLENGES TO THE PHARMACEUTICAL SCIENCES?

Response: I think our most significant challenge in the pharmaceutical sciences is to learn how to utilize basic knowledge

from other disciplines (e.g., molecular biology, cell biology, immunology, organic chemistry, engineering) to solve pharmaceutically relevant problems (i.e., cell specific delivery of genes). We have to avoid the tendency to "reinvent the wheel". We cannot be afraid to collaborate with scientists in other disciplines, to read journals in other disciplines, or to attend meetings, workshops, and conferences in other disciplines. The most exciting and the most significant advances are often made at the interface between disciplines.

WHAT IS THE PLACE FOR ENTREPRENEURSHIP IN ACADEMIA?

Response: I think it is important for some academic scientists to find a way to transfer proprietary technology developed in their university laboratories to the private sector. However, this transfer process *should not* be done at the expense of that individual continuing to do peer-reviewed research, continuing to train graduate and undergraduate students, and continuing to serve the profession. If academic scientists want to actually be intimately involved in transferring their technology, then they should elect to leave the university and join the private sector. I think we cannot lose sight of the perspective that the mission of the university is to do scholarly research and to educate students.

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

Response: My philosophy of educating graduate students was recently articulated in an Editorial in *Pharmaceutical Research* (*14*:554–555, 1997). To summarize my thoughts here, I have always strived to train graduate students to have depth in a particular area of science, but I also tried to give them the opportunity to get breadth in their education. I also have tried to teach them the following five general principles of doing good research: (i) how to identify important and interesting scientific problems; (ii) how to design key experiments to address these scientific problems; (iii) how to run the right control experiments; (iv) how to properly analyze their data; and (v) how to put their data in the context of the rest of the scientific literature. In addition, however, I try to help students refine their written and verbal communication skills, their computer skills, their ability to perform as part of a team, and their appreciation for issues in scientific ethics. Refinement of all of these skills will be crucial for their future success in the new, highly integrated and globalized pharmaceutical industry.

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

Response: My philosophy of mentoring junior faculty has always been the same. It is based on what I observed Ed Smissman and Tak Higuchi doing for their young faculty in the Departments of Medicinal Chemistry and Pharmaceutical Chemistry, respectively, at The University of Kansas in the 1960s and 1970s. As a Chairman of a department, you find the resources that young faculty will need to properly initiate their research programs. However, the key is that the resources *cannot* have any strings attached. You then serve as a mentor to that faculty member by being available to give advice *when asked*. On occasion, you may find it necessary to give advice even if you are not asked, but this should be done sparingly. Finally, in spite of the administrative load of being a Chairman, you try to serve as a role model by maintaining an active and productive research program and continuing to be an effective classroom teacher.