Gordon L. Amidon: Very Sustained Drug Absorption

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This special edition of the Journal of Pharmaceutical Sciences is dedicated to Professor Gordon L. Amidon and honors his many contributions to the pharmaceutical sciences, particularly in oral drug absorption. This biographical summary of Professors Amidon's career refers to work that was actually carried out by the many graduate students, postdoctoral students, visiting and collaborating scientists over the years. We apologize to the readers for not being able to recognize all of his many students and colleagues.

THE EARLY YEARS: SENECA FALLS AND BUFFALO, NEW YORK

Gordon L. Amidon was born in Seneca Falls, New York in 1944 and grew up in the central New York farming communities. He worked on farms as a young boy; he loved driving a tractor, plowing fields, and bailing hay. Ten years old at the time, he told his mom he wanted to be a farmer when he grew up. Although she was not discouraging, he could tell that a farming career was not what his mother had in mind. In 1954, the family separated and Gordon, the oldest, was put largely in charge of managing his little brother, Greg, along with their middle brother, Thomas. Somehow Gordon never lost Greg in those very early years and eventually (today) they are faculty colleagues at the University of Michigan College of Pharmacy. The family, single mom and three boys, moved to a new school district in 1959, to obtain, in his mother's view, a better education. One of Gordon's distinct memories as a young boy was his mother's desire for him to get a college education. This motherly goal was no doubt passed down to his younger brothers Tom and Greg as well. As an aside, Gordon and Greg's middle brother, Thomas, is a faculty member at Syracuse University in the Paper and Bioprocessing Department, serving as department chair for 10 years. Gordon is, of course, quite proud to have two successful academic brothers.

Gordon, after the family relocation, attended high school at Mynderse Academy, a public school in Seneca Falls, New York. Although he tried sports in high school, he was not particularly successful nor in love with them, especially the contact sport of football. After getting "kicked-off" the football team (to save face), he found a job as a stock boy in his uncle's pharmacy. Such is the nature of serendipity and fate! Chemistry, math, and history were the most interesting subjects to Gordon in high school, whereas English was just of passing interest. However, he found study of the French language moderately interesting.

The science component of the pharmacy curriculum attracted Gordon and he matriculated into the Pharmacy program at the State University of New York at Buffalo (his uncle was an alumnus of UB Pharmacy School). The University of Buffalo (a private school) had just become a state school (SUNY at Buffalo) in 1962 and tuition was quite reasonable. That plus his scholarships made a college education affordable for Gordon. His teachers at SUNY Buffalo, including Dr. Gary Levy and Dr. Milo Gibaldi in pharmacokinetics, Dr. Michael Schwartz in physical pharmacy and Dr. Howard Schaefer in Medicinal Chemistry, introduced him to very modern, at the time, pharmaceutical sciences, including pharmacokinetics, physical pharmacy, and medicinal chemistry. Gordon remembers a course in Pharmacy Calculations (Pharmacy "Math") and the math symbols and methods of compounding pharmacy, taught by Professor Eino Nelson, an early leader

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in the science of physical pharmacy, biopharmaceutics, and pharmacokinetics.[1–5] What surprised him in this course was that Professor Nelson supplemented the course with teaching calculus. Math was becoming important for pharmacokinetics in 1965 and Professor Eino Nelson along with Professor Gary Levy were the early leaders in this field in the United States. This had the direct effect on Gordon of stimulation (rekindling) of his interest in the mathematical field. For the first time, he realized that math could be useful in pharmacy. Gordon subsequently began taking applied math courses in order to more deeply understand physical chemistry, and, as a secondary interest pharmacokinetics. He ultimately obtained a MS in Mathematics at the University of Michigan during his graduate studies in physical pharmacy. Math was to become one of Gordon's unique strengths in the physical and biopharmaceutical sciences and continues to this day to be a field of special interest to him. During his many international travels, teaching, and lecturing on the biopharmaceutical sciences and the drug regulatory science of oral pharmaceutical products, he reads almost exclusively in the area of math history, particularly the historical development of crucial mathematical concepts, for example, imaginary numbers, nonlinear differential equations, chaos theory, fundamental concepts in number theory, and Fermat's Last Theorem.

GRADUATE SCHOOL: THE UNIVERSITY OF MICHIGAN

Choosing Physical Pharmacy as his best career option, he entered graduate school at the University of Michigan, receiving a MS in Mathematics (1970) and a PhD in Pharmaceutical Chemistry (1971), working under Professor William Higuchi. He managed to secure a NSF fellowship for graduate studies pursuing a computational research program, writing a nonbonded force field program, with the ultimate goal of computationally determining drug–receptor interactions. His general early scientific interest focused on physical chemistry and the rapidly developing field of computational quantum mechanics, because of the advances in computer technologies, and subsequently nonbonded molecular force field calculations for large molecules such as proteins, enzymes as model drug receptors. This appealed to his mathematical interest, as Gordon was simultaneously pursuing a MS in Mathematics as a Pharmacy graduate student. His research goal was to use α-chymotrypsin (α-CT) as a model receptor. α-CT was the first (second after lysozyme) interesting enzyme whose three-dimensional structure was determined in the mid-1960s and α-CT served as his model of a receptor "active-site." His interest at that time, with a background in the pharmacology training of the "new" pharmacy curriculum (pharmacognosy replaced by pharmacology), focused on drug–receptor interactions and the medicinal chemistry of drug design. α-CT, a gastrointestinal pancreatic protein digestive enzyme, secreted as an inactive zymogen into the gastrointestinal tract, leading to tangential study of gastrointestinal protein and peptide digestion and the absorption of peptides from the gastrointestinal tract. At this same time (late 1960s and 1970s), peptide drug discovery and the medicinal chemistry of small peptide synthesis was advancing significantly because of improvements in solid phase peptide synthesis and synthetic protection strategies.[6–10] With these advances in drug discovery, he developed an interest in oral peptide absorption.

THE UNIVERSITY OF WISCONSIN: BEGINNING AN ACADEMIC CAREER

By the mid-1970s, Gordon had concluded that theoretical drug–receptor interactions were a long way off in the scientific future, because of the complexity and subtlety of tertiary protein structure and ligand binding. Further, and perhaps more importantly, pharmacy was not an ideal place to pursue advanced "theoretical" (computational physical chemical) drug–receptor interactions. From his background in proteolytic enzymes, gastrointestinal physiology, and oral nutrient absorption, he saw that mechanistic oral drug absorption was a scientific area that would be fruitful to pursue, especially oral absorption of small peptides and amino acids. In parallel to his interest in drug–receptor interactions, his background training in pharmacokinetics and interest in computer programming, and the parallel advances in computer and analytical technologies of the 1970s, lead to collaboration with Professor Peter Welling, a pharmacokinetic colleague at the University of Wisconsin. Gordon worked mainly on the computational aspects of pharmacokinetic plasma level analysis, wrote a pharmacokinetic nonlinear regression program for data analysis, and did much "curve fitting" to pharmacokinetic models of the time; simple compartmental models, very simple models by today's standards. The simplicity of the pharmacokinetics oral absorption model and the "first-order" absorption rate constant, "k_a," almost never, "'fit" very well in the models of the time, whereas the intravenous (i.v.) plasma data could, almost always, be fit quite well to the models. This "mystery" of poor fitting of oral pharmacokinetic data and his knowledge of gastrointestinal physiology yielded the key scientific question of "why?" Even today the "fitting" or analysis of the early absorption profiles based on plasma level results is usually a backward analysis, for example, by deconvolution rather than a "forward" mechanistic analysis. Thus, he "saw" a scientific field that he could pursue and that could be a base for a pharmaceutical research program whose home was in a School of Pharmacy. His thinking at the time was that, because of the time scales of the processes, oral absorption of drugs and nutrients typically occurs in about 1–4 h, whereas changes in drug plasma profiles typically occur over 1–12 or more hours; thus, the usual plasma sampling designs missed much of the complexity of the oral absorption process.

In the mid-1970s, Gordon realized chemical engineers, particularly at Wisconsin, had really set the science of transport phenomena on a solid, physical science basis. Although he had studied transport, including Fick's First Law and diffusion, as a graduate student and was well aware of the work on dissolution and membrane transport of Higuchi and coworkers,[1,11–14] he was never very satisfied with the "stagnant film" approach to dissolution or membrane transport, as the fluid was obviously not stagnant. He began to attend the Chemical Engineering lectures at Wisconsin and studied from the all-time classic textbook "BSL," Bird, Stewart, and Lightfoot "Transport Phenomena."[15] Professor Amidon (he was still going to "school") studied from the 30th printing, and Figure 1 is an image of his personal, somewhat tattered copy, from which many of his graduate students have also had the opportunity to learn. He eventually developed an extremely influential collaboration with one of the authors, Professor Edwin Lightfoot, and attended many of Professor Lightfoot's graduate lectures at the University of Wisconsin. In collaboration with Edwin