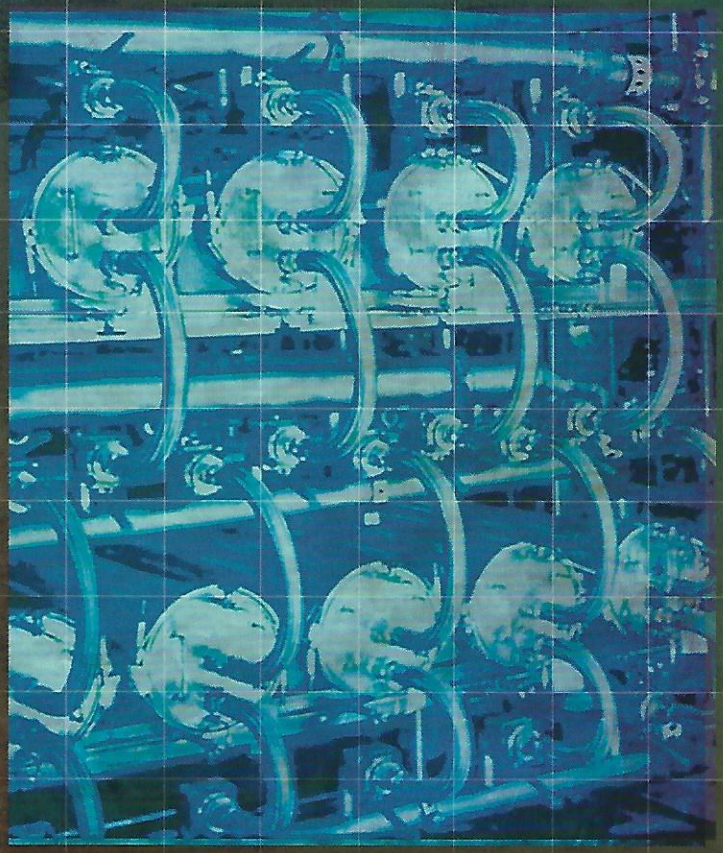
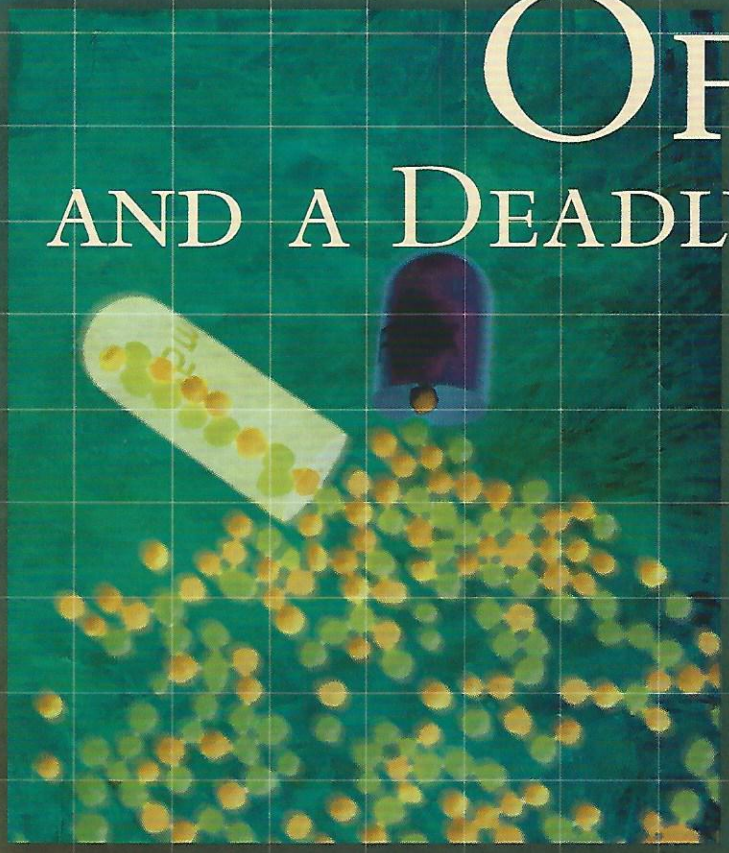
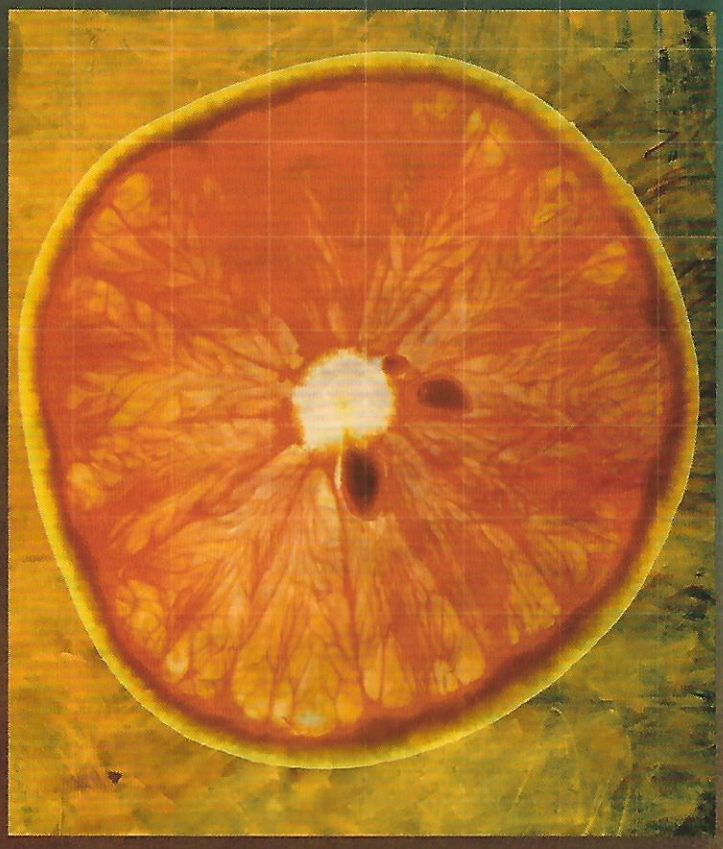


Penn Engineers at the Frontiers of Drug Discovery





Doppelgangers
Glass of Grapefruit Juice—

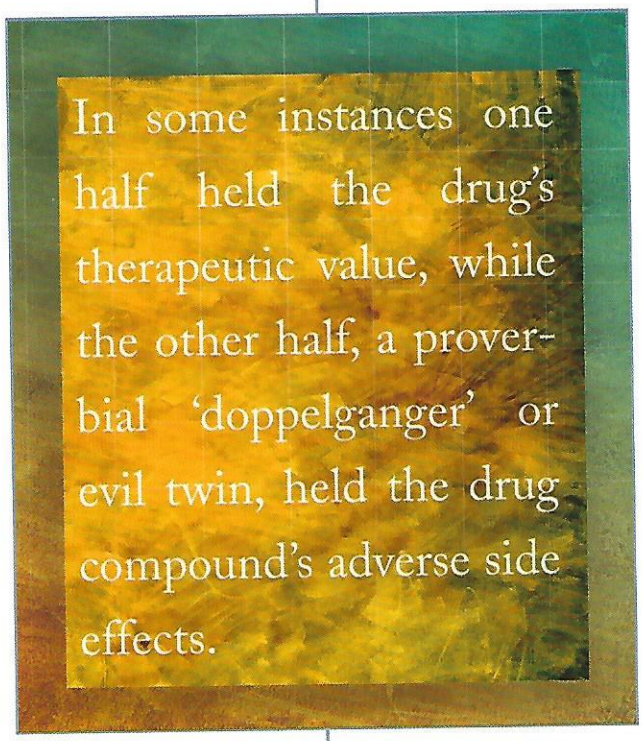
BY JESSICA STEIN DIAMOND

No one had imagined it could be lethal to have a runny nose until one day in December 1989. A young woman, complaining of dizziness, was admitted to the emergency room of Bethesda Naval Hospital. After she fainted in the emergency room, physicians discovered that she had a potentially fatal, abnormal heart rhythm.

The patient survived. But the fallout from what turned out to be a near-overdose on Seldane—curiously at the prescribed amount—resulted in a significant safety and cost improvement in the Food and Drug Administration's drug approval process. The case eventually led to the withdrawal of Seldane, a seasonal allergy medication, then one of the most popular drugs in the nation. It was found to be unusually prone to drug-to-drug interactions, in this case with a common anti-fungal medication taken for a yeast infection. The outcome also accelerated the growth trajectory of Sepracor Inc., a small start-up firm that at the time was on the verge of launching a successor drug to Seldane that avoided this dangerous side effect.

In a tale that illustrates the growing relevance of chemical engineering training to the pharmaceutical industry and also Penn's leadership role in this realm, key scientists at the FDA and at the start-up company were 1970s era graduates of Penn's Chemical Engineering program. Both were also advised by Professor John A. Quinn, now the Robert D. Bent Professor Emeritus of Penn's department of Chemical and Biomolecular Engineering.

"Seldane was a turning point that changed the way the FDA and the drug development industry look at metabolism-based drug-to-drug interactions," says Jerry M. Collins, Director of the Laboratory of Clinical Pharmacology at the FDA, who completed his Ph.D. at Penn under Quinn in 1976. "This was one of the safest drugs ever marketed, as long as somebody wasn't taking a drug that interfered with its metabolism in the liver."



The lessons learned improved the FDA approval process for drugs that are metabolized in the liver with a new requirement: bench-top studies on human livers from organ donors that were unsuitable for transplantation. These studies identify the pathways or molecular 'highways' on which a particular drug prospect is metabolized—allowing scientists to identify possible collisions with other drugs metabolized along the same pathways that would result in an under-dose or over-dose.

"It's not like we hadn't seen drug-to-drug interactions before, but this just opened up the possibility of understanding and preventing them prior to approval at a relatively low cost through new testing strategies and new screening tools," says Collins. "Now, when a clinical study is done, it's tailored to what you've already learned in the lab with liver studies. And the cost of this bench-top study is 10% the cost of doing a clinical study."

"Like anything good in science, these liver tests became converted into everyday, routine lab assays that are very rewarding," says Collins. "People reviewing the data for the FDA have a lot of confidence that this prevents future problems; and people generating the data for drug companies realize it has a specific impact on their product and patient safety."

The parallel story, which eventually led to the market introduction of Allegra® as a successor drug to Seldane, began when Stephen L. Matson decided to take a leave from his position at GE's Research and Development Center after a one-hour conversation with Professor Quinn, a consultant at the time to GE. They discussed a mutually intriguing challenge: how to create a synthetic 'membrane reactor' capable of performing the type of powerful reactive separations that in the body are conducted by enzymes embedded in cell membranes.

"I said to heck with my job and joined him at Penn," recalls Matson, who then developed a membrane reactor for optical isomer separation and completed his Ph.D. under Quinn in 1979. Matson, who once turned down a job offer to engineer a dark ring around the edge of a stackable potato chip, says, "I decided there had to be more to life as a chemical engineer. For me, the value added wasn't in chemical engineering's traditional fields of chemical manufacturing and the oil industry. I was more interested in seeing what I could do at the interface between chemical engineering and the new biological sciences that were emerging."

After a few years back at GE and then at a contract engineering research firm, Matson says, "I had entrepreneurial fever and wanted to get out of contract R&D so that I could commercialize membrane reactors." Again, Professor Quinn altered Matson's life, this time with a simple invitation to dinner with a valuable contact, Timothy J. Barberich, who was looking to invest in new technologies. "I had the technology, and he saw the value where pure isomers were concerned," says Matson, who launched Sepracor Inc. in 1984 with Barberich.

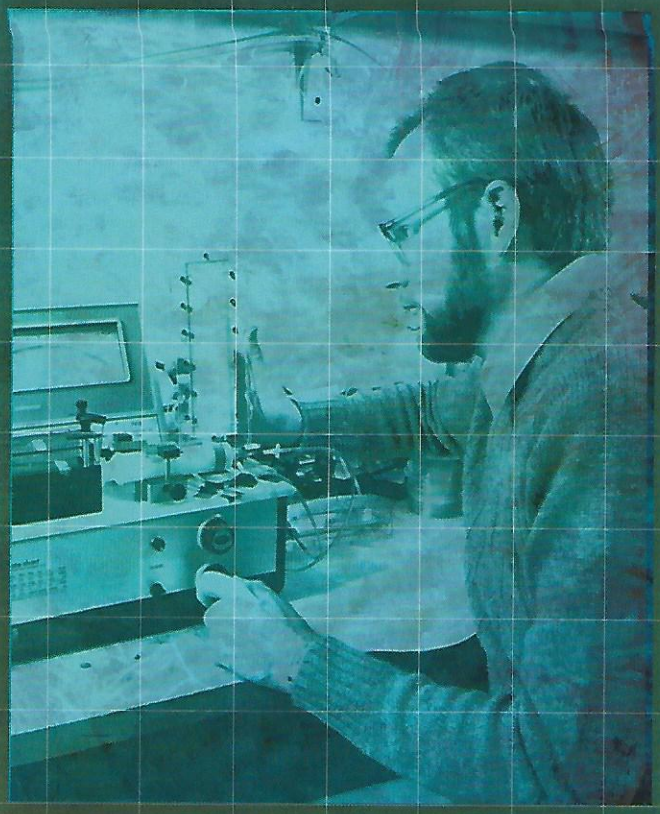
At the time, many of the FDA-approved drugs on the market were composed of 'racemic' mixtures comprised of two chemically identical but mirror-image matching halves or 'optical isomers' that historically had been difficult to separate.

In some instances one half held the drug's therapeutic value, while the other half, a proverbial 'doppelganger' or evil twin, held the drug compound's adverse side effects. Drug companies didn't have the technology to do these separations easily at the time; Sepracor did.

"We were not universally loved because we were messing with billion dollar drugs owned by big pharma," says Matson, of their early efforts. "We knew which marketed drugs existed as 'chiral compounds,'" meaning that they could, in principal, be separated into the form of optically pure isomers. Sepracor began evaluating drug compounds that might have greater therapeutic value in their separated isomers. Seldane, then owned by Merion Merrill Dow, emerged as a promising candidate.

But Sepracor made a puzzling discovery: it turned out that the Seldane compound wasn't active at all as an antihistamine. Rather, its therapeutic value occurred only after the drug was metabolized or broken down by enzymes in the liver.

"We were sitting on this discovery—quite unexpected, at least to us—that the anti-allergy activity wasn't associated with the Seldane molecule itself," says Matson. "I recall



Steve Matson during his grad years at Penn

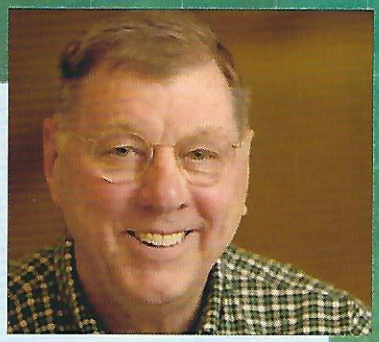
Former Students Sponsor Quinn Lecture Series

When former graduate students of Penn Professor John A. Quinn organized themselves to endow a lecture series in his name, they had an ulterior motive.

"We wanted to formalize an opportunity for John and his students to get together," says Stephen L. Matson, one of the co-founders of Sepracor Inc. "The connections he has maintained with his graduate students are extraordinary. We work to keep that connection and sense of being part of his extended family. Mentorship and guidance is the professional aspect of it. He has always been critically important to my career. But he's also just fun, always challenging and can usually be counted on to have a thought-provoking perspective and a unique anecdote to go with it."

Quinn shares that sense of connection. "To interact with very talented people at a crucial time in their formative years, and to remove barriers for them and get them to produce as you know they're capable, then you really have something to be proud of," Quinn says. "If it gels, then you have friends for life who know you're interested in promoting their careers, and also they reflect back favorably on you."

The John A. Quinn Lecture Series was launched in January of 2003 with a symposium in his honor. His former student Jerry M. Collins remembers a long, thoughtful snowy drive home to Washington, D.C. that night, pondering what he had learned from Quinn's other former students who also attended. Collins, the director of the FDA's Laboratory of Clinical Pharmacology, and author and co-author of more than 180 papers on the topic, remembers, "What kept me awake was the realization that the experience each of us had with John was replicated many times over. Not just the absolute number of people who were there, but the kinds of activities they've engaged in since leaving Penn really defines his influence in training a generation or two of people."



John A. Quinn

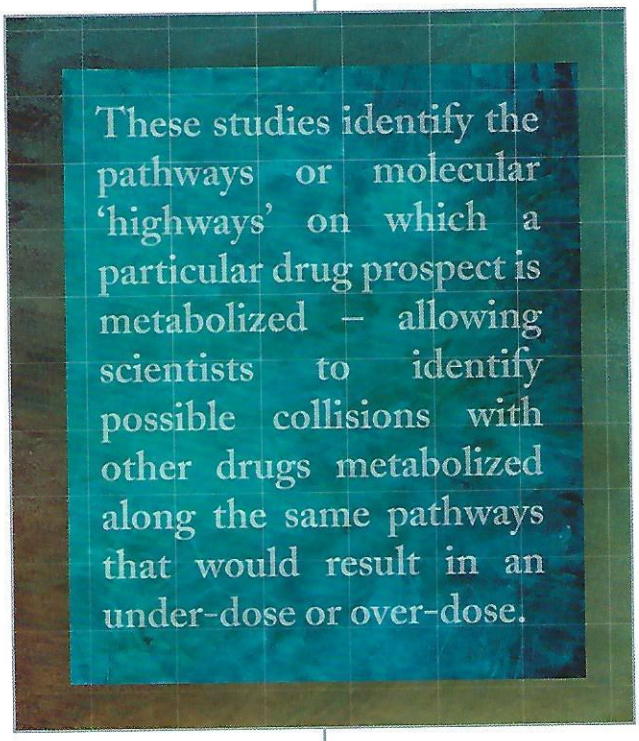
In 2004, the inaugural Quinn lecture, "Diversity of Electrokinetics: Nonuniformly Charged Surfaces," was presented by John L. Anderson, then Dean of the College of Engineering and Chemical Engineering Professor at Carnegie Mellon University. Dr. Anderson, a member of the National Academy of Engineering, conducted his Ph.D. research with Quinn.

In 2005, the Quinn lecture topic was "Adventures in Micro-Fabrication: Patterning of Thin Polymer Films via Electrostatic and Elastic Instabilities," a talk by William B. Russel, the A.W. Marks '19 Professor of Chemical Engineering and Dean of the Graduate School of Princeton University.

The lecture series honors the pioneering contributions that Quinn has made in bringing chemical engineering science to problems in human health, pharmaceutical production and nanotechnology.

feeling 'shucks, there's no way to use the membrane reactor here.' Seldane was not the active drug. Instead, it was a 'pro-drug' of an active metabolite that differed from Seldane at only one of 32 carbon atoms. This is a little difference, but it matters."

"At the time, a mess of things were happening around Seldane with more than a dozen unfortunate people even dying when all they were trying to do was make their nose dry. Weird anecdotes were emerging, including stories of people who would drink grapefruit juice or treat toenail fungus while taking Seldane who would then have heart problems," says Matson, noting that a pharmacology consultant and co-inventor on Sepracor's patent helped sort this all out. "The liver serves as the body's garbage disposal where compounds like drugs that are strange to the body get chewed up and spit out. Some chemical compounds—for instance those in anti-fungal medications and grapefruit juice—can inhibit certain liver enzymes. As a result, the liver loses the ability to rapidly and completely metabolize certain foreign compounds such as Seldane, leading to cardiac arrhythmias."



As Matson aggressively pursued Sepracor's patent position on the active metabolite, his activities fortuitously coincided with the FDA's decision to place a severe 'black box' warning on Seldane and ultimately withdraw it from the market. By that time, Sepracor had already licensed its metabolite formulation of Seldane, Allegra®, to a company that would eventually become Sanofi-Aventis. The drug was immediately rolled out to the lucrative market for non-drowsy seasonal allergy or 'allergic rhinitis' medications.

"That was a big hit for us that continues to generate revenues," says Matson, who increasingly became involved in guiding the firm's legal efforts to achieve patent protection for pure-isomer and active-metabolite drugs, a fruitful strategy for discovering new drugs that were potential improvements over existing therapies.

"That was the way forward for Sepracor, and it's been the company's business model ever since," says Matson, who eventually became a consultant to the firm, and now works on a new venture, ConTechs Associates Inc. He envisions this as a sort of Peace Corps for senior engineers working as volunteers on web-based projects in partnership with engineering professors and their students in third world countries. Currently, Sepracor is a publicly-held firm with a market capitalization of $6 billion. It is working toward profitability with a lucrative portfolio of drugs and drug candidates for respiratory and central nervous system disorders.

Matson attributes his fortuitous path in large part to the chemical engineering education he received at Penn. "By virtue of my training at Penn—a bit of biology, a lot of chemical engineering, and the exposure to the broad vision of my Ph.D. advisor—it was easy to imagine using biology in a process context. It has not been a straight line from my Ph.D. to Sepracor, but I was set on the right track at Penn, where I learned to sniff out those scientific frontiers that were going to need some chemical engineering."

Similarly, Collins notes, "The kinds of research projects at the university then and now aren't just symbols of random variations in the field. They're manifestations that the seeds of change were planted 30 years ago. Professor Quinn had a major influence in the early unfurling of the potential of this department. He and his engineering colleagues opened the door into biomedical applications at a time when this was just a small slice of the graduating pie, but it was clear that this was a direction that was emerging."

"Our engineering training at Penn was based on a quantitative model of breaking down a complicated system into pieces, understanding the individual pieces, and then assembling them back together," says Collins. "That training, in the scale-up from the bench to the plant, has also been good for the scale-up from the bench to the bedside. We have the tools to interconnect drug metabolism with the rest of the body."

As for Professor Quinn, who trained more than 40 Ph.D.'s over the course of his career, "he's good at bringing together an explosive mix of people and ideas that stand a pretty good chance of being productive," says Matson.