School of Chemical Sciences

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University of Illinois
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INSIDE

Seemon Pines of Merck Led the Team That Developed Primaxin

The Directors' Scientific Award, displayed on his office wall, demonstrates that Merck recognizes the outstanding achievement of Seemon H. Pines, chemistry Ph.D. of 1951. As Vice President for Process Research and Development, he brought the development of Primaxin, the broadest spectrum antibiotic ever produced, to a successful conclusion. Also adorning his office, Pines' exquisite photographs of scenery in the U.S. and in Europe, show that he has other interests and talents which he will have occasion to enjoy after his retirement in January, 1991.

Seemon H. Pines

Dr. Pines has devoted his entire career to Merck, beginning in 1951 as a bench chemist on the team that introduced the process for cortisone. While his interests have broadened to include other fields, along with other responsibilities, he has remained aligned to developmental research throughout.

Early Days

Pines has vivid memories of hardships during the depression of the 30s when he lived in the anthracite coal region of Pennsylvania. Although his own family did not actually suffer hunger, many of the miners in the surrounding area lived on a diet of bread and potatoes. That recollection was in part responsible for his seeking out the practical rather than the theoretical applications of science. As he states it, the job at Merck has meant 40 years of "getting paid for having fun, for doing what I have always wanted to do."

Although his work on Primaxin was the crowning achievement of his career, Pines has been involved in a wide variety of projects. He contributed to manufacturing processes on niacin, glutamic acid, penicillin, and other antibiotics and holds about 30 patents. He also worked on other key Merck products, including methyldopa, indomethacin, carbidopa, and sulindac.

Pines' first projects were in synthetic organic chemistry, but he switched to natural product isolation chemistry for eight years at the urging of his superiors, with the understanding that he could return to synthetic organic chemistry if he really liked it better. When he ultimately returned to synthetic chemistry, he found that the field had become even more exciting because of the variety of new techniques that had been developed in the interim, such as NMR, which opened up new vistas in chemical research.

Beginnings of Primaxin Development

During the years that Primaxin was under development at Merck, Pines led the team as Executive Director of Process Research. According to company literature, Primaxin has been one of the "most difficult, most costly, most frustrating, and most rewarding programs in the history of Merck research. (It is also) the culmination thus far in the pharmaceutical industry's 40-year search for wider spectrum, more potent antibiotics."

Part of the problem was the complexity of the total chemical synthesis that required stringent stereochemical control. Ten of the 16 reactions used in the process

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of synthesizing the natural product thienamycin were unknown when the process was first undertaken. Secondly, the thienamycin molecule was so unstable that it was difficult to design in appropriate scale-up methods for a robust, efficient route of manufacture. The time frame was also a significant constraint in that clinical and toxicological studies demanded continuing supplies throughout the program.

Complexity Went Beyond Chemistry

Economics was an extreme challenge, especially since the antibiotic was to be coadministered with cilastatin sodium to prevent deactivation of the drug in the urinary tract. Both entities were produced optically pure, leaving no isomers to compromise safety. As Pines said, "Probably no other company than Merck would have undertaken this project and there were times when I wondered whether we should do it." But they did, and today Primaxin is still the drug of choice in the case of serious infection, especially where the harmful microorganism(s) cannot be identified.

As leader of the total process project, Pines had to forgo the satisfaction of being in the laboratory where the chemical development was taking place. He left the laboratory in 1978 when his administrative responsibilities became more than a sideline. He now gets his satisfaction vicariously through a team that is not only successful but also world renown.

Team Management

Pines credits the U. of I. with teaching him chemistry but he learned management by observation. By watching his bosses, he learned how to manage and how not to manage. Perhaps the most important lesson was that people do not need to be treated equally but equitably. He finds it a real challenge to bring out the best in all members of his team, remembering that people have different aptitudes that determine their accomplishments. As for communications, the toughest element of managing, he notes, "Every time you open your mouth you give three messages: what you said, what you thought you said, and what the other person heard. The art of management is to minimize the discrepancies."

The U. of I. Post WWII

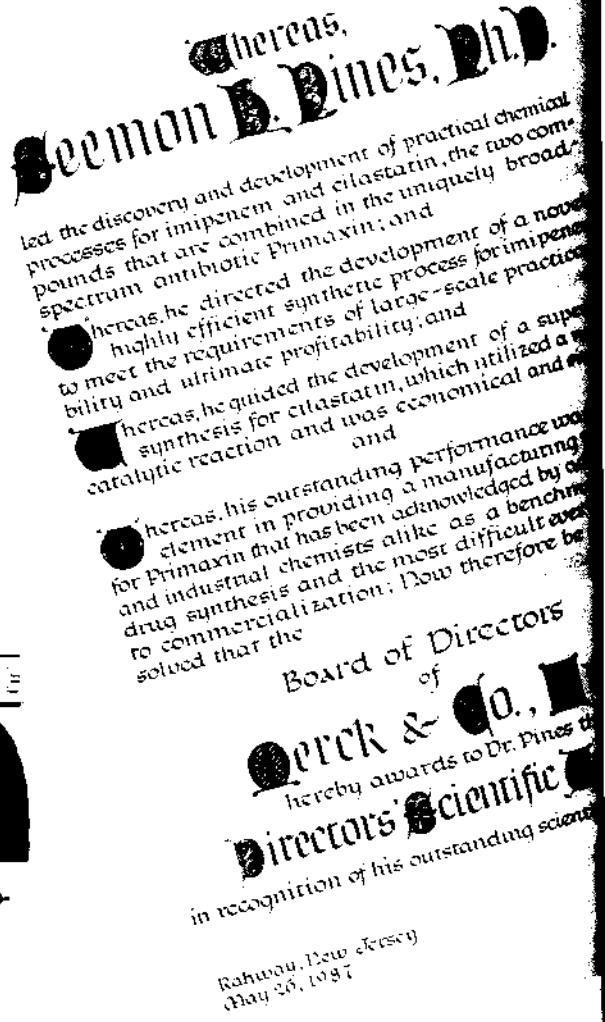
Through all the years since his graduation in 1951, Pines has made many trips back to the U. of I. and remains a staunch supporter of our chemistry program, which he considers one of the very best. Pines first arrived at the U. of I. in 1948. Having had his education interrupted with service in the navy during WWII, he was in a hurry to get through. Housing was tight and he spent his first year in an attic. After his marriage in the summer of 1949, he returned to the campus to find that the house on Church Street, containing the apartment he had rented, had been sold by the landlord.

After further search they found a little house. One room was a combined kitchen-livingroom, one a bedroom, and the last one was a combination closet-bathroom. In the autumn, a "pet" cricket frequently came into the bedroom from the closet and walked out the front door. Because the apartment was directly on a cement slab, it was so cold in winter that they left the water running to keep it from freezing, but it froze anyway.

Nevertheless, they both loved their years in Champaign-Urbana. The faculty was marvelous, "the best in the world." The senior faculty taught classes, something that was not true of many other schools. Pines finished his work in just three years due to his fellowship and the kindness of his excellent advisor, Professor Nelson Leonard.

The two most important places around town were Farwells and Katsinas where you went for special occasions. He remembered having dinner at the Urbana-Lincoln Hotel for his first wedding anniversary and hearing Marian Anderson sing, soon after she had been refused permission to perform in Washington DC because she was black.

The Directors' Scientific Award ►


Whereas,
Seemon B. Pines, Ph.D.
led the discovery and development of practical chemical
processes for imipenem and cilastatin, the two com-
pounds that are combined in the uniquely broad-
spectrum antibiotic Primaxin; and
Whereas, he directed the development of a novel
highly efficient synthetic process for imipenem
to meet the requirements of large-scale practice
bility and ultimate profitability; and
Whereas, he guided the development of a super
synthesis for cilastatin, which utilized a
catalytic reaction and was economical and
and
Whereas, his outstanding performance was
element in providing a manufacturing
for Primaxin that has been acknowledged by
and industrial chemists alike as a benchm
drug synthesis and the most difficult ever
to commercialization; Now therefore be
solved that the
Board of Directors
of
Merck & Co.,
hereby awards to Dr. Pines the
Directors' Scientific
in recognition of his outstanding scient
Rahway, New Jersey
May 26, 1987

Seemon Pines showing one of his photographs from Italy

The Seemon Pines/Merck Allerton Conferences

Pines has watched the changes in Urbana and at the U. of I. with frequent returns to his alma mater. In 1987 he designated the organic chemistry program at the U. of I. as recipient of the money portion of the Directors' Award. This grant instituted the annual Seemon Pines/Merck Allerton conferences, which Pines usually attends.

Pines has noted a subtle shift in the career patterns of top chemistry graduates. In days past, the best students went to academia, but due to financial stringencies in research support, an increasing number of top students now come to industry. This shift has been a boon to companies like Merck that can afford the costs of bringing new drugs to market only if they can attract excellent researchers who can produce the products and processes. Pines estimated the current cost of bringing a successful drug to market at about $130 million and rising rapidly. This astronomical price tag does not include the many leads that fail or are abandoned.

"A truly remarkable achievement even for Merck..."

Without access to first class scientists, Merck could not have undertaken the enormous task of bringing Primaxin to commercialization. The total chemical synthesis that led to the development of imipenem, the basis of Primaxin, was, according to Professor of Chemistry, David Paisley, "a truly remarkable achievement even for Merck, which has a unique reputation for achievements in total syntheses." After the drug came on the market, Professor Paisley was quoted by the *Wall Street Journal* as saying, "In my opinion, it was the best piece of developmental science in the pharmaceutical industry."

This is high praise indeed from an expert who has followed developments in the pharmaceutical industry for about twenty years. Seemon Pines has made an extraordinary, unique contribution to the pharmaceutical industry. The U. of I. shares the pride of Merck's directors in having helped to make this possible.

By The Way . . .

Where Did "Speed" Marvel Get His Name?

To date, three versions have come to light. According to one account Marvel always took an overload of courses and got to bed very late. In the morning, he slept till the last possible moment and then made a dash for the dining room, getting in to breakfast just before the doors closed.

In the most recent newsletter, **Karl Heumann, Ph.D. '51,** provides an alternative version. According to him, the name may have emerged from the "Marvel Rule." Evidently, the students taking his organic chemistry course believed that if you dropped your pencil you would flunk the course by missing 30 seconds of facts.

In response to the latter, **Dr. George (Doc) Symons, Ph.D.'32,** offers a third version. In his letter to the editor, he said,

> *The story told on campus (1926-33) was: Dr. Marvel earned the nickname when taking an organic chemical analysis lab course as a grad student. He had a keen nose which could identify chemicals by their odor. He finished the course in 6 weeks – hence "Speed."*

Are there any other versions out there? Maybe, we will ask his son, Jack, or his daughter, Molly, to serve as final arbiters.

What was the shortest final oral?

I read the article about Dr. Lester Coleman in the SCS Alumni Newsletter with interest. However, I feel I must comment on the reference to his final oral exam being completed in "record time," namely 45 minutes.

I obtained my Ph.D. under Speed Marvel in 1950 and will always recall his comments to me on the day of my final oral exam. The exam was scheduled at 2 p.m. in May 1950. Upon his return from lunch at 1 p.m., Speed stopped by my lab and said that he had some instructions for my exam. My immediate reaction was to wonder why he waited until only one hour before the exam to issue instructions. When I asked what his advise was, he replied, "For C_____'s sake keep it short because it is as hot as H_____ today." I immediately relaxed and took the advice to heart. Thus, my final oral exam lasted only 8 minutes and that included the questions. Then we adjourned to Farwell's where the beer was readily available in the afternoon.

I also enjoyed the contribution by Karl Heumann which reflected on the organic activities following WWII. That was certainly an interesting and inspiring time in the Illinois Chemistry Department.

Keep up the good reporting through the SCS Newsletter.

Sincerely,

H. Wayne Hill
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Alumni:
Your letters to the editor are welcome and if space permits they will be included.