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Father and Son

In Two Generations, Drug Research Sees a Big Shift

Valium's Inventor, Now 95, Relied on His Instincts; Markets, Machines Today

Ban on 'Two-Legged Rats'

By Julia Flynn

As a drug-industry researcher more than half a century ago, Leo Sternbach stirred up a new concoction in a kettle with a big wooden paddle—taking care not to breathe in too many of the potentially poisonous fumes. In the 1950s and 1960s, when tinkering with new drugs, he tested them on himself. After trying one particularly potent medicine, he had so much trouble walking that he asked colleagues to call his wife to pick him up.

Leo Sternbach

"I got very disoriented and was half-conscious," he recalls. "For two days, I was not at all well."

One of the drugs he tested on himself became Valium, the most-prescribed medicine in the U.S. between 1969 and 1992. Dr. Sternbach, now 95 years old, helped develop 12 drugs for Roche Holding AG which have generated total sales of about $10 billion over four decades.

His son, Daniel, 54, is also a successful drug researcher. His work is tested by machines, strictly regulated and dictated in part by the marketing department. After 17 years with GlaxoSmithKline PLC, he's still waiting for one of his inventions to hit pharmacy shelves; the earliest one might be submitted for government approval is 2008. While his father has 241 patents, Daniel Sternbach has seven. Even so, Glaxo considers him a very productive chemist.

The different careers of the father and son point to seismic shifts in the pharmaceutical industry. A business that once had hundreds of companies has consolidated into one dominated by a few giants. The younger Dr. Sternbach has seen his research bounce through a series of new colleagues and restructurings as Glaxo swallowed up one company after another.

Overall, the industry is turning out more drugs now than it did 40 years ago. At the same time, drug discovery has become a technology-intensive, market-driven process that makes it much harder for an individual scientist to hit a home run.

Glaxo spent $4.3 billion on drug research in 2002. The cost of clearing a single drug past today's legal, regulatory and marketplace hurdles has risen to $1.7 billion, according to a recent study by consultants Bain & Co. In short, says the elder Dr. Sternbach, with a German accent barely diluted after 62 years in the U.S., it's "a lot harder now than it was in my day."

Daniel Sternbach

Leo Sternbach grew up in a seaside town, then part of the Austro-Hungarian empire. With his father running a pharmacy, he developed an interest in chemistry, scavenging gunpowder from unexploded World War I shells and making homemade fireworks.

He earned a master's degree in pharmacy in Poland, but was advised by a mentor he wouldn't advance at Krakow University. "I had no chance as a Jew," he recalls being told. Instead, he joined the labs at Zurich's Federal Institute of Technology. He married his Swiss landlady's daughter, Herta Mia Kreuzer; the couple recently celebrated their 63rd anniversary.

As anti-Semitism mounted, Dr. Sternbach's colleagues urged him to move to

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A Son Follows His Father Into Drug Research

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private industry, where he might be safer. He joined Roche in 1940 as a medicinal chemist, one year after the outbreak of World War II.

Roche was alone among the four major Swiss chemical companies to resist pressure by the Nazis to "Aryanize" the work force of its German units before the war. In Switzerland, by retaining its Jewish and foreign employees, Roche protected them from being deported. Some of those people risked being sent to Germany or occupied Poland as forced laborers, according to a 2001 study commissioned by the Swiss government to examine the nation's wartime past. Roche was more sensitive to the dangers facing employees because its chairman at the time was married to a Jewish woman, the study contends.

Soon after Dr. Sternbach joined the company, it transferred him and other Jewish scientists to its new research facility in Nutley, N.J.—where he worked until his retirement in 1973, and still maintains a spacious office. "Roche saved my life," he says.

His first big discovery in New Jersey was a new way to make biotin, a B complex vitamin. To test the mixture, Dr. Sternbach says he walked into a confined space in the lab and stirred the chemicals by hand in an enamel kettle. He had to be careful: One of the chemicals involved, phosgene, becomes a poisonous gas at room temperature.

His Valium breakthrough came after he followed a hunch about compounds he had tested years earlier in Poland as dyes. He wondered if they might have some effect on humans; he knew that certain anesthetics, such as novocaine, had similar molecular structures. He tested that hypothesis, but after hitting a dead end, his boss told him to move on to other projects in 1955.

Dr. Sternbach pursued his research anyway. "I always did what I wanted to do," he says.

Two years later, when clearing space in their cluttered lab, Dr. Sternbach's colleague, Earl Reeder, found two bottles containing the contents of old experiments with the compounds. Dr. Sternbach tinkered with the molecular structure, adding a chain of chemicals to a molecule. He sent off the new version for pharmacological testing at Roche. The compounds seemed to tranquilize mice, cats and even monkeys, with the unusual effect that the animals remained alert.

Intrigued, Dr. Sternbach tried the experimental drugs on himself, a practice unheard of today. Roche says it didn't condone the practice but was aware some scientists tested drugs on themselves. One industry executive, recalling the practice, refers to such researchers as "two-legged rats." Today, Roche says it has a strict policy prohibiting researchers from self-testing their work.

Dr. Sternbach's experiments led to the creation of benzodiazepines, a new class of drugs—with Librium hitting the market in 1960 and Valium in 1963.

Widely dispensed for calming anxiety and nerves, Valium also became a cultural icon—it was the "Mother's Little Helper" of the 1966 Rolling Stones song. Roche declines to provide full sales data but says that in 1973, its peak year, Valium produced $230 million in U.S. sales, or about $1 billion in current dollars when adjusted for inflation.

By the time Dr. Sternbach's son, Daniel, was ready to enter the lab, things had changed dramatically. As a boy, he would tag along with his dad to the lab on weekends. "Nowadays, you're not allowed to bring your children," says Daniel, the father of two teenage girls and a grown stepson. Glaxo even requests employees to put lids on their coffee cups if they carry them through the labs, so the drinks don't get contaminated.

His father was delighted when Daniel spent the summer after high school at Roche's New Jersey campus, tending dogs and feeding rats. During college, he worked for a summer at Roche's headquarters in Basel, Switzerland.

Daniel did a post-doctorate research fellowship at the Swiss Federal Institute of Technology, the same place his father had. He worked with chemist Albert Eschenmoser, who remembers him as "a marvellous experimentalist, with a distinctively original side in his chemical thinking." He went on to do a second post-doctorate at Harvard.

After seven years in Duke University's chemistry department, he got an offer to join Glaxo in 1986 as its first medicinal chemist—one who focuses on finding new medicines. The London-based drug maker was setting up its U.S. research operation in North Carolina's Research Triangle Park. "At a very young age, he was a serious and accomplished chemist," recalls Pedro Cuatrecasas, a former Glaxo research head, who hired Dr. Sternbach.

Daniel worked as a Glaxo "bench chemist"—literally working on a bench, experimenting with molecules. But by the mid-1990s, much of the work was automated. Through a technique called "combinatorial chemistry," labs were using computers to generate many molecules at once, instead of having researchers create them in small batches. Robotic systems scanned the compounds to see if any might have an effect in humans—a process called "high-throughput screening"—rather than having a researcher test them one by one.

Such modernization has helped pharmaceutical companies become more productive. Forty years ago, when the elder Dr. Sternbach was hitting his prime as a researcher, the U.S. drug industry produced 13.7 new medicines a year, according to the Tufts Center for the Study of Drug Development. In the 1990s, as the biotech revolution took off, the industry was spinning out an average of 27.5 new drugs a year. In recent years, that has dropped, to 20.8.

Advances in molecular biology and understanding the human genome during the last decade turned the traditional method of looking for drugs upside-down. Instead of tinkering with compounds and then testing to see if they might be effective, drug companies now begin by identifying molecular targets in the body that lead to disease—a process known as "rational drug design." Once targets are identified, researchers set out to try to find drugs that work against them.

The result was that medicinal chemists such as Daniel Sternbach—who had once been at the very heart of drug discovery—found their influence waning. Business and marketing units increasingly set the researcher's agenda. Dr. Sternbach's job is to create compounds that might be active against biological targets. His objectives are set by Glaxo's biologists, in conjunction with its marketers.

Consider the discovery of an experimental drug called 501516. It began in 2001 with the first of two papers that Daniel Sternbach and several colleagues published on a small molecule which interacts with other compounds to help control fats and cholesterol. Glaxo hoped this could lead to a treatment for dyslipedemia, a condition of abnormal levels of fat in the bloodstream, which often accompanies diabetes. Glaxo's marketers played a big role in choosing diabetes as an area for its chemists to explore because it is a chronic illness that isn't well treated by current medicines.

After identifying the molecule, the team of chemists created a group of 11,000 compounds. These were screened by machines to determine which might have an effect on humans. Scientists took the most potent ones, and using molecular modeling—which helped them peer inside the crystal structure of the compounds—designed a number of new drugs, including 501516.

Daniel spent a summer at Roche's New Jersey campus, tending dogs and feeding rats.

Then began the long process of testing, another big difference in drug development today. First, the drug was fed to rats. Most experimental compounds fail to get beyond this stage, but 501516 went on. It was given to obese, pre-diabetic Rhesus monkeys. Now it's in what the Food and Drug Administration calls Phase II clinical trials, where a drug is tested in a small number of people.

A recent study in the journal Nature Medicine found that 501516 caused an increase in polyps in specially-bred mice. Glaxo says its own studies in test-tubes and animals don't reveal any safety problems and that it will continue to develop the drug. The company hopes to file for approval with the FDA by 2008. That would be on the quick end of the 10 to 15 years it typically takes to get a drug to market these days.

Drugs came to market much faster before 1963, when a law requiring more rigorous testing took effect. Before that, the clinical phase of testing took an average of 2.8 years, according to Tufts. Now, it takes six or more years, and far more drugs drop out during trials.

If 501516 wins FDA approval, it would be Daniel Sternbach's first drug on the market—a success in an industry where chemists can toil a lifetime without making a marketable drug. He and the eight others named on the patent may receive raises or bonuses if the drug becomes a hit, but they won't receive royalties. Glaxo says it is industry practice for company scientists to assign patents to their employers. Leo Sternbach sold his patents for Librium and Valium to Roche for $1.

Daniel Sternbach has another drug in testing, which has been shown to reduce glucose and insulin levels in diabetic rhesus monkeys. "Dan is a very productive chemist," says Ken Batchelor, the Glaxo senior vice president in charge of Daniel's unit. Someday, he may "look back on his career and say he had a significant role in producing medicines that are helping a countless number of people."

The younger Dr. Sternbach says his working conditions are "very controlled," compared with those of his father. "In a modern chem-lab, we have almost no contact with chemicals." He says he'd be reluctant to work on a speculative project, as his father did, mainly because he faces tight deadlines to meet a number of performance targets. While he appreciates the chance to work with more advanced technology, he has less freedom to experiment than his father did.

"At one level, you can say he just got lucky," the son says of his father. "But as I've grown older and have come to realize more about the things he was involved with, I realize luck doesn't happen over and over again, as it did with him. There's a saying: Chance happens to the prepared mind."