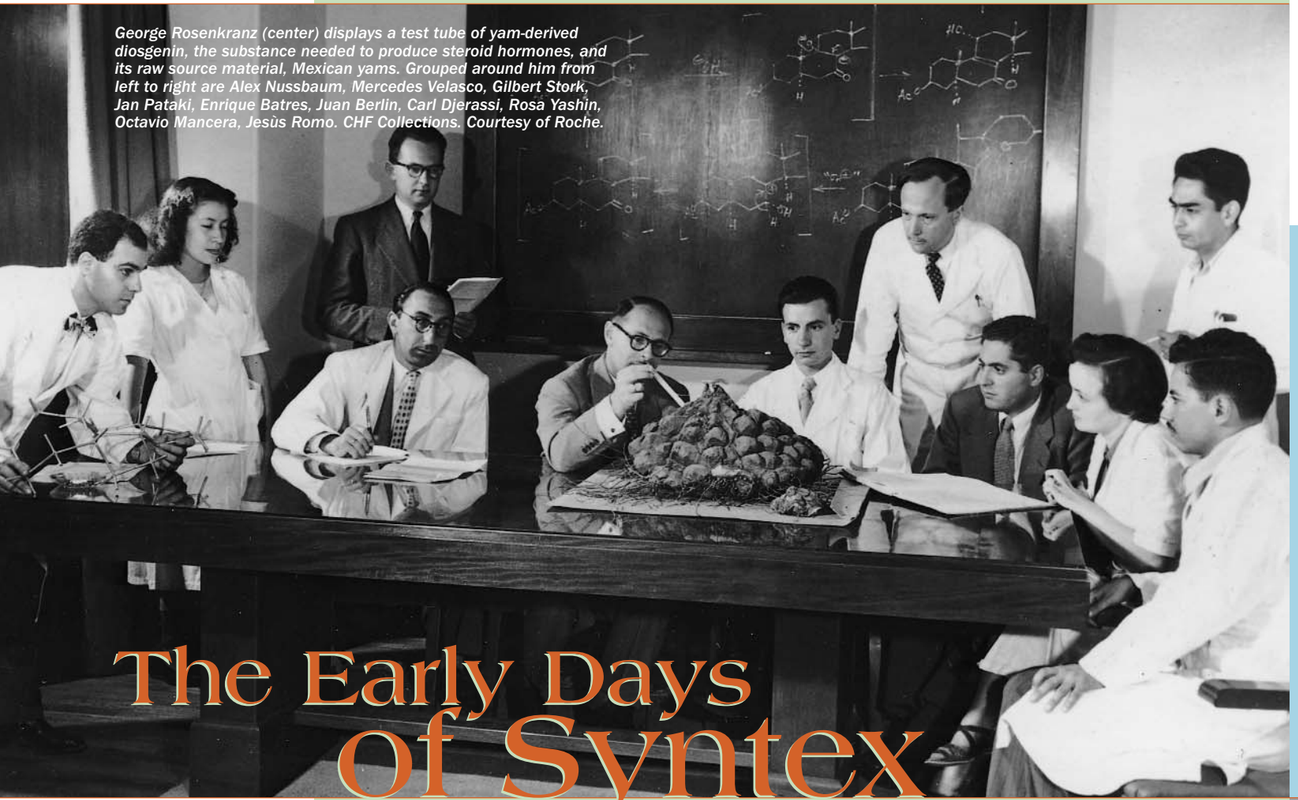

George Rosenkranz (center) displays a test tube of yam-derived diosgenin, the substance needed to produce steroid hormones, and its raw source material, Mexican yams. Grouped around him from left to right are Alex Nussbaum, Mercedes Velasco, Gilbert Stork, Jan Pataki, Enrique Batres, Juan Berlin, Carl Djerassi, Rosa Yashin, Octavio Mancera, Jesùs Romo. CHF Collections. Courtesy of Roche.

The Early Days of Syntex

George Rosenkranz at CHF in 2004. Photo by Steven Begleiter.

By George Rosenkranz

Flashbacks from My Life

If I examine my early youth, I can detect hardly any signs of entrepreneurship. Sure, critical decisions had to be made: first, to leave Hungary to study in Switzerland over the strong objections of my parents; later, to abandon my academic career, my wonderful mentor, Leopold Ruzicka, and the old continent for an essentially unknown future. In retrospect, I consider the causes of these events, speaking in chemical terms, more the push-pull effect of the grave political circumstances of that time than entrepreneurship.

When Pearl Harbor was attacked, I was in Havana waiting for a boat to Ecuador, where I had been offered a chair in organic chemistry at the University of Quito. After a futile wait, I decided to take advantage of President Fulgencio Batista's decree allowing refugees to settle in Cuba. And when the national university showed no interest in me, I tried to get a job at the largest local pharmaceutical firm—Laboratorios Vieta-Plascencia.

The reaction of the owner, Angel Vieta, dean of the University of Havana medical school, was negative. To quote: "In the 18 successful years at my firm, I never had a chemist. Why should I hire you now?" My answer was short and bold: "Give me a chance and I'll show you."

Apparently impressed, he offered me the glorious salary of $20 a week. I did not fail him. A dozen products later, I was making $1,000 a month and 15% on those products' sales. The university offered me a professorship. I declined but eventually agreed to direct a research program for Ph.D. candidates in my laboratories. The most famous of my two dozen students of those days was Ernest Eliel, who became a president of the American Chemical Society.

My Zurich-born interest in steroids led me to look for domestic sources of steroidal sapogenins suitable for hormone synthesis. Finding none, I imported sarsaparilla root from Mexico and made small quantities of progesterone and testosterone. Rumors of these activities led to an invitation to visit a start-up firm in Mexico named Syntex.

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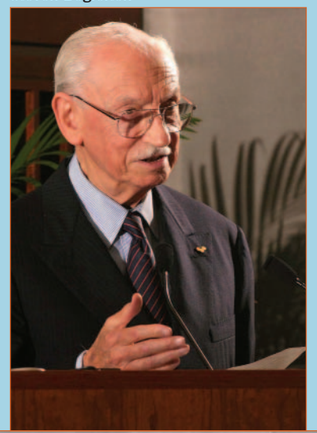
Life after Syntex

By Alejandro Zaffaroni

Alejandro Zaffaroni at CHF in 2004. Photo by Steven Begleiter.



Early Years

My life started in Montevideo, Uruguay, many years ago. Uruguay is a small country; today it has three million people. Back then life in Uruguay was wonderful. It was a great place to live—safe and peaceful—and the standard of living was high. For many years, Uruguay was known as the Switzerland of South America. The social and political organizations were very progressive: women were allowed to vote; it had the highest rates of literacy; it was the first social democracy on the continent; primary, secondary, and university education was (and still is) free.

The population was and still is mainly of European descent, mostly Italians and Spaniards. My grandfather emigrated from Italy and arrived in Uruguay when he was 16 years of age. My father was in the banking business, and our family enjoyed a good standard of living.

Early in my life, I lost both my parents. My mother passed away when I was 12 years of age, and my father when I was 18. Now, when I look back, I think that loss forced me to learn to be on my own. I was also lucky enough to have an uncle and an older sister who supported and encouraged me to continue my education.

After earning a B.Sc. at the University of Montevideo in 1941, I began studying at the school of medicine. I soon realized, however, that anatomy was not one of my favorite courses. I had taken some chemistry and biochemistry courses while in premed, and I decided to study biochemistry instead. Since there was no biochemistry degree in Uruguay or South America, I started to inquire about studying abroad.

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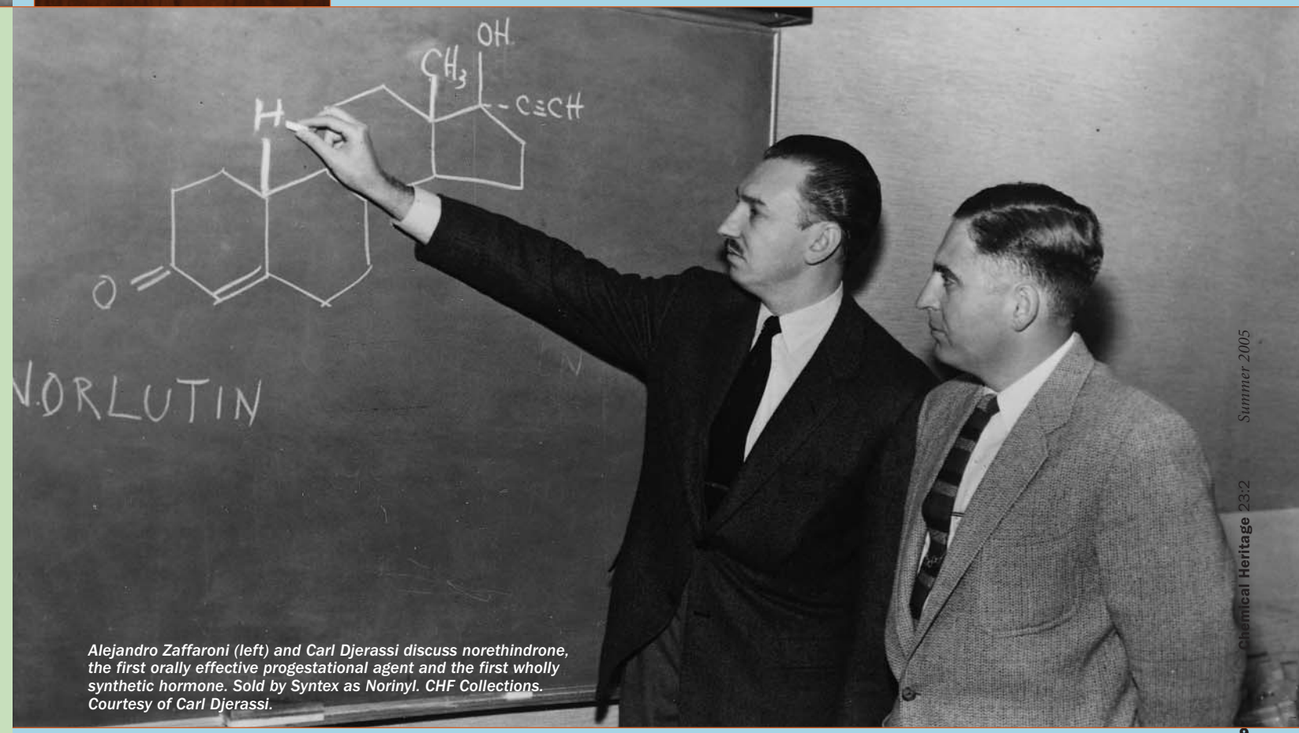

Alejandro Zaffaroni (left) and Carl Djerassi discuss norethindrone, the first orally effective progestational agent and the first wholly synthetic hormone. Sold by Syntex as Norinyl. CHF Collections. Courtesy of Carl Djerassi.

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Russell Marker with his Syntex lab assistants, 1945. CHF Collections. Courtesy of Roche.

Syntex

On my arrival in Mexico I found a small family enterprise dedicated to the manufacture of progesterone based on methods of a brilliant but temperamental chemist, Russell E. Marker (see *CH*, Summer 1987, pp 3–6). However, the owners had had a bitter falling-out with Marker, who left and shortly thereafter set up a competitive venture.

In a burst of true entrepreneurial spirit, I accepted the offer to take over the technical part of direction. My compensation was roughly equivalent to the one in Havana but included the option of buying 15% of Syntex stock at book value. No big deal, since the company was $330,000 in the red and practically broke. For years to come, my darling wife, Edith, and I faced the dilemma of whether to buy a new household item or invest in company stock.

There were no manuals, no process descriptions, and reagents and intermediates bore coded labels. My staff consisted of nine female laboratory assistants, three workers for moving the heavy stuff, and one chemist.

As chemical archaeology was not my area of expertise, I started from square one, developing my own processes. Soon we were back in production. The high price of progesterone —$18 a gram, though way down from the original price of $180 a gram— produced handsome profits and allowed me to expand my staff. With the help of a few newly hired Mexican and foreign chemists, we soon developed novel, patentable, kilogram-scale syntheses of all the sex hormones with the exception of estrone.

While tackling this last problem, my attention was drawn to a young chemist, Carl Djerassi. Following a hunch, I invited him to Mexico. He was charmed and accepted my offer to come to work with us. Soon we solved the last remaining problem, the aromatization of androstadiendione, and were producing estrone. During this time, a former president of Mexico visited us and on observing our process remarked wittily: "So, in goes Adam, out comes Eve!"

Since profits selling hormones and steroid intermediates were significant, nobody questioned my budget. I invested in research, bringing the most talented scientists available to Mexico. Interestingly, organic chemists, in contrast to biologists, were more ready to assume risks.

The big exception was an outstanding biochemist: Alejandro Zaffaroni. We met at the 1951 Laurentian Hormone Conference in New Hampton, New Hampshire, after a long correspondence involving steroid samples for Alex's paper chromatography. This encounter turned out to be one of the most significant events in our lives; the empathy and friendship we built has carried through all these years.

I will not describe in detail the two monumental events in Syntex's history: the cortisone race and the pill. These are well known. For a short time, they focused the attention of the world on our company, our achievements, and Mexico.

At this stage we had an outstanding team of scientists and consultants, an astounding number of patent applications and publications, and an impressive number of new compounds that resulted from what I used to call "molecular acrobatics." Our scientific reputation allowed us to attract the best talent. But all this was not in line with the operation of a small-sized chemical producer of steroid intermediates. Prices fell and other steroid manufacturers became competitive.

Going Public

The stage was set for the next big step in Syntex's history: the change of ownership. This occurred when the legendary Wall Street entrepreneur Charles Allen decided to acquire the promising Mexican upstart and eventually take it public.

This group acquired 100% of the Syntex stock for $2 million in cash and $2 million in notes payable from future profits. I became president and CEO, and Alex was executive vice president. Allen's words to us were: "Boys, you have all my support, all my help; just don't ask for money, because you won't get any." During the following decades he became a cherished friend and invaluable adviser, sharing our problems and enjoying with keen interest our successes.

We were on our own—our dreams had come true! It is impossible to describe our joy, elation, and enthusiasm. Our first big decision was to become a pharmaceutical company built on research. I brought back Carl, who had moved to Wayne State University, together with eight of his best postdocs.

The collaboration between Alex, Carl, and me became an incredibly creative driving force. We got so close to each other that anyone could finish a sentence started or sum up a grandiose idea. At the end, no one remembered who the originator was. Yet the discussions were so forceful, the decibel level so high, that on occasions with our children watching, Edith came running down the staircase in our home, looking

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Going to the United States

I managed to get a scholarship to come to the United States thanks to the Institute of International Education. My two options were Harvard University or the University of Rochester.

I boarded a Liberty ship in Montevideo while World War II was still going on and arrived in the United States at the port of New York on 16 August 1945, two days after the Japanese had surrendered. For me, arriving in New York at that time was an unforgettable experience. It was like a big party: people were celebrating in the streets; there was music; it was incredible. After a couple of weeks I went on to Harvard. There I met a young professor who explained my options. I would be part of a group of six students following a research program under the guidance of the professor.

I then went to visit the University of Rochester. During those times, the entire medical school was working on the Manhattan Project. As a foreign student I could not participate in that project, so the chairman of the chemistry department, Walter R. Bloor, told me they would give me a lab, and that the research for my Ph.D. had to relate to the field of lipids. Having my own lab and the freedom to choose what I wanted to work on sounded great: it convinced me to decide on the University of Rochester.

After I had lived in Rochester for one year, I decided to invite my fiancée, Lida, to join me. We got married via proxy, and she arrived in the United States after a three-day trip by airplane. Having Lida with me in Rochester was one of the important factors that influenced my success.

At Rochester I became interested in better analytical methods for finding corticosteroids produced and secreted by the adrenal cortex. I had read about a new technology invented by two English scientists, A. J. P. Martin and R. L. M. Synge, called *paper chromatography,* which was used for the analysis of amino acids. My question was, could I modify this technology for the field of steroids, which are not water soluble?

Soon after I had started my studies at Rochester, Walter Bloor decided to retire. The new head of our department, Elmer Stotz, formerly of Harvard, told us at one of our first meetings that he was working on cytochrome C and wanted all of us to work on his project. This created a problem for me because I had already started working on my paper chromatography idea and was convinced it would work out. I asked Stotz if I could still work on my own project on my own time at night, and he agreed. After a few months he reviewed my own work, saw that I was onto something, and told me to forget about his project and to continue with my own work. I have always appreciated the opportunity he gave me.

I finished my Ph.D. in 1949 and stayed at Rochester while I continued my postdoctoral work. I developed a paper chromatography technique that became very useful in the synthesis of steroids; it allowed for much cheaper and faster analyses than the methods developed by others at about the same time. Unexpectedly, the technique had a great impact in steroid chemistry, which at the time was focused on what later became known as the "race for cortisone." All the big pharmaceutical companies were trying to win the cortisone race. In 1948 scientists at the Mayo Clinic had used cortisone to heal severely arthritic patients. In 1950 the Nobel Prize in medicine was awarded to the three who had discovered the hormones of the adrenal cortex: Philip S. Hench, Edward C. Kendall, and Tadeus Reichstein. It was a very hot area to be working in.

During my postdoc years I attended the Laurentian Hormone Conference in New Hampton, New Hampshire, in 1951 to present my paper chromatography technique, and I met George Rosenkranz. George and I clicked right away: it was the beginning of a wonderful friendship. To make the story short, a few months after that conference I was working with George for Syntex in Mexico.

Syntex won the cortisone race. One reason for the firm's success was its ability to produce very large quantities of raw materials at very low cost. Upjohn, in collaboration with Syntex, then utilized my paper chromatography technique to produce cortisone at the lowest cost and in the shortest time and thus was able to upstage all other "pharmas."

To Mexico—and Back

The early years of Syntex in Mexico were a great experience for me. We were doing transformative science and had an incredible group of very smart and talented scientists. The progress we made in the area of steroids made us realize that Syntex could become an important company at the edge of new technology. Once we realized this potential, George and I started to transform Syntex from a chemical company into a pharmaceutical company.

At one point, we realized that to become a top-tier pharmaceutical company we needed to move to the United States. Carl Djerassi, one of our distinguished Syntex scientists, had recently started teaching at Stanford University in Palo Alto, California. Carl encouraged us to settle in Palo Alto. The next decision was who should establish the company. I took the step to leave Mexico and moved back to the United States. We started Syntex Laboratories in 1958, and from then on there was no looking back.

ALZA—and After

After about 10 years of being with Syntex in Palo Alto, I started to think about ways to optimize the delivery of medications to and within the body. I had the belief that a novel drug-delivery technology could overcome the body's natural barriers and thereby improve existing medicines, creating a whole range of new therapies. When I presented my concept to the Syntex board, however, the investor group decided not to participate in this new technology. I felt so passionate about these novel concepts that I decided to branch out from Syntex and start my own company.

I decided to call the company ALZA, after my name. I wanted to show my full commitment to this new controlled-release concept. I founded ALZA Corporation in 1968. Syntex retained a 25% ownership in ALZA,

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for survivors, only to find us roaring with laughter.

We were the brilliant amateurs with a "can do anything" attitude. We were like stem cells (though then none of us really knew the concept). We could differentiate into anything we desired. Production, finance, sales, marketing—all held no fear for us.

The source of all these activities had to be our chemists. We rapidly turned the risk-taking volunteers into executives. This movement resulted in a healthy effect on our research. Talented youngsters moved up rapidly, allowing new ideas to blossom and preventing our research from becoming stale.

Expansion

Profits from sales of our bulk steroid products, now on a much larger scale, still provided our basic income. Yet in 1958 we started a pharmaceutical company in Mexico based on novel topical and systemic steroids. Our first big hit was Synalar. This topical corticoid for treatment of psoriasis later became the first product of our U.S. venture. Innovative research collaborations with large pharmaceutical firms provided another source of income. Apart from becoming eventual providers of the so-called active ingredients, we showed great foresight in retaining the right to market under our own label. Nobody thought of us as becoming a competitor in the pharmaceutical market.

Alex and I were traveling the world, writing new collaboration and license agreements. Our biggest coup was to create a worldwide distribution of our new compounds practically overnight and without a cent of investment. This novel approach consisted of selecting as a partner one of the top five drug firms in a European country. We proposed to provide them with the active ingredients, not for a fixed price and royalty, but for 30% of the net sales price. We would have no say in the pricing. The label would bear the Syntex name jointly with theirs. They would have right of first refusal for our future products. But again, we retained our right for marketing under our own label. This arrangement was unheard of in those days, but our research productivity proved to be convincing. Eventually among others, Syntex-ICI, Syntex-Recordati, and Syntex-Astra products were launched.

The year 1961 marked the start of the inevitable changes Syntex was to undergo.

It began with the decision to begin moving the company to the United States to become an important factor in the domestic and world market. We all accepted Djerassi's idea of Palo Alto as a desirable site because of its closeness to Stanford University and other major academic centers, and also because no major pharmaceutical company was located on the West Coast. After painful soul-searching, Alex accepted the challenge of launching the start-up (Carl was already at Stanford), excited by the possibility of laying the foundations of a new major, international pharmaceutical company. I remained in Mexico, but was in daily phone contact with Palo Alto, and every month went for a week to the West Coast.

Slowly the era of gifted amateurs yielded to outstanding professionals. A host of new talent entered the picture. In all activities, scientific or business, the motto was *excellence*.

The Mature Company

One of the early important decisions we had to face was whether we should stick to steroids or expand additionally into the field of organic medicinal chemistry. After heated discussions my point of view prevailed, and we opted for an ambitious plan: to enter the vast and for us new world of nonsteroidal drug research. The consequences were monumental, as we had to deal with fundamental aspects of biology, pharmacology, and toxicology—all areas where we lacked experience.

This decision ultimately led to the discovery, development, and commercialization of our first blockbuster, the nonsteroid anti-inflammatory drug naproxen.

A few years later, important organizational changes were made. Institutes were created along disciplinary lines. In fact one of the first institutes established in Palo Alto was that for molecular biology, under the leadership of Joshua Lederberg and Carl Djerassi, and represented what would become the driving force behind the future biotechnology boom in Silicon Valley. This discipline-based, rather than therapeutically structured, organizational model led to a wide-ranging approach to identifying target drugs.

In 1968, Alex came to us with the idea of a new venture dedicated to his novel concepts on drug delivery, and eventually the decision was made to launch such a company outside of Syntex. Thus, to the regret of his many friends, after 17 years he ended his brilliant career with us to take up new challenges.

The growth of our business was meteoric, ever expanding domestically and internationally.

Retirement—and Thoughts on Management

In 1982, strictly adhering to the rules I established, I relinquished my executive positions, but continued on the board of directors with the title of founding chairman.

I also became chairman of the newly created board of science. This move sent a forceful message to employees and the outside world about the importance of research for our company. The board enabled brilliant scientists, such as E. J. Corey and Michael Bishop, not only to provide their invaluable scientific input into Syntex's search for new medicines but also to pursue their love of science within a pharmaceutical industry.

Over the years, my management philosophy began to jell, a corporate culture to develop. To quote one of my own speeches, I observed that "people tend to be most productive, creative, and innovative when they work in an atmosphere of joy, mutual trust, and respect. Intellectual honesty, quality, and striving for excellence are the key."

Our research philosophy was "patent and publish," as we understood the profound need of scientists for peer recognition and provided them with a collegial, quasi-academic atmosphere. This was in stark contrast to the prevailing emphasis on secrecy of our competitors. To foster entrepreneurship, we encouraged reasonable risk taking. Another distinguishing characteristic, perhaps unique at that time, of the Syntex organizational model was that researchers could spend up to 20% of their time on personal projects (a forerunner of today's Google concept!). This enabled creative scientists to pursue projects outside of the mainstream research dictated by senior management.

Offering job security was high on our list. In the eyes of the business community, Syntex was perceived as a "nice" company, and we consistently made the list of best companies to work for. I am often approached by former employees of Syntex who speak fondly of the good old times at our company and the caring family spirit characteristic of our corporate culture. I feel particularly gratified that even today many of my former coworkers and colleagues, who found their way into new business ventures, embraced many of these ideas—and my management philosophy lives on.

The value of our company rose astronomically. After a large number of stock splits, at its maximum an original investment of $2 per share was worth $16,750. In 1994, Syntex was acquired by Roche Holdings for $5.3 billion.

In closing, I want to share with you my favorite quote by Anatole France, which has always inspired me: "To accomplish great things, we must not only act, but also dream, not only plan, but also believe."

George Rosenkranz and Alejandro Zaffaroni with their awards. Photo by Steven Begleiter.

For their lifetime achievements in Syntex and elsewhere, George Rosenkranz and Alejandro Zaffaroni were both awarded the Chemists' Club Winthrop-Sears Award at CHF in 2004. These articles are based on their speeches of acceptance for the awards.

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which became the pioneer in controlled drug delivery, and in fact I am proud to say that I was the inventor of the controlled-release technology.

After many years of hard work, ALZA became profitable in 1981. It was acquired by Johnson & Johnson in 2000 and contributed $700 million in sales to Johnson & Johnson that same year.

Looking back, the stories of ALZA and Syntex are so different. At Syntex everything went on smoothly, we had products the market needed, the company had sales, and financing was not a problem. At ALZA it was the opposite. The concept of controlled drug delivery was very hard to sell, our first two products did not make the numbers we had planned, and at one point the financial situation of ALZA was seriously compromised. It took a lot of effort and hard work to perfect the technology and to demonstrate the benefits of the drug-delivery concept.

Among the many technologies we developed at ALZA were the transdermal patch, oral osmotic delivery (Oros), and liposomal delivery (Stealth). Our pharmaceutical products include Procardia XL, Duragesic, Nicoderm, Glucotrol XL, and Ditropan XL. The company currently has more than 900 active patents and about 1,200 patents pending.

The success of the controlled drug-delivery technology can be seen by the size of the market and the number of companies and products that use the wide range of drug-delivery technologies. Looking back to the early days of this technology, I am amazed at how large the current size of the market is and how much it promises to grow, and also at how many drug-delivery technologies and patents now exist. Even today, controlled-release technologies are being used in new fields such as consumer products and agriculture.

Since ALZA, I have been blessed with the opportunity to start many other companies. Some of these technologies stemmed from my own ideas, but in large part they resulted from the collaboration of a large number of very capable scientists with whom I have had the fortune to be associated. The companies are too numerous to list them all, but we have developed many novel technologies, for example, computational chemistry and combinatorial chemistry; gene shuffling; biomarkers, including nano bar codes, and much more. I am also proud that many ALZA alumni have branched out as I did and created their own companies.

My most recent endeavor, Alexza MDC, is worth special mention. During the late 1990s, I did some research on addiction and became very interested in the cigarette as a potential drug-delivery device. After further research I learned that after a single puff nicotine gets into the brain in approximately 15 seconds. The question I had was, can existing drugs be delivered via a similar device? We know now the answer is yes.

I founded Alexza in 2000 to explore the idea of delivering existing drugs via a rapid-onset-of-action device. We began with a short list of existing medications and soon discovered that a large percentage of these can be volatilized. We now have a large library of existing drugs and an ever-increasing number of patents. Alexza has developed very interesting technologies and is well advanced in developing new medications.

Thus both the first company I started on my own and my latest company are in the drug-delivery field.