

Good Chemistry

The Life and Legacy of
Valium Inventor Leo Sternbach

Alex Baenninger
Jorge Alberto Costa e Silva
Ian Hindmarch
Hans-Juergen Moeller
Karl Rickels

McGraw-Hill

New York Chicago San Francisco Lisbon London Madrid
Mexico City Milan New Delhi San Juan Seoul
Singapore Sydney Toronto

Library of Congress Cataloging-in-Publication Data

Baenninger, Alex.

Good chemistry : the life and legacy of valium inventor Leo Sternbach /
by Alex Baenninger.

p. cm.

ISBN 0-07-142617-5 (alk. paper)

1. Sternbach, L. H. (Leo H.) 2. Benzodiazepines—History. 3. Diazepam—History.
4. Chemists—New Jersey—Biography. I. Title.

RM666.B42S743 2004

615'.7882—dc21

2003013224

Copyright © 2004 by F. Hoffmann-La Roche. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

2 3 4 5 6 7 8 9 0 DOC/DOC 0 9 8 7 6 5 4 3

ISBN 0-07-142617-5

McGraw-Hill books are available at special quantity discounts to use as premiums and sales promotions, or for use in corporate training programs. For more information, please write to the Director of Special Sales, Professional Publishing, McGraw-Hill, Two Penn Plaza, New York, NY 10121-2298. Or contact your local bookstore.



This book is printed on recycled, acid-free paper containing a minimum of 50% recycled de-inked fiber.

Thoughts and Reflections on Dr. Sternbach and His Work

Dr. Armin Walser, chemist and Sternbach associate and inventor of the injectable sedative Versed

The well-being of his subordinates was always a concern and high priority for Sternbach. While working under his direction, I got to appreciate his many admirable qualities, such as his sense of humor, his contagious optimism and good mood, his modesty and openness. I was particularly impressed by his skill in solving chemistry problems without the now-standard spectroscopic tools. For managers of pharmaceutical research, it is also interesting to emphasize that Sternbach made his big discovery by working on his pet project without the approval of his boss. He knew that Lady Luck had been extremely good to him, not only with the discovery of the benzodiazepines. Nobody seemed to envy him, because he was so well liked and such a nice guy. He liked to share his success with his friends and co-workers. He loved parties and enjoyed food and drink, giving little thought to the calories or the cholesterol content. If I recall correctly, a vodka martini and olive was his favored cocktail and the meat had to be laced with fat. He enjoyed playing Santa at Christmas parties and getting hugged by female admirers. And bridge was his favorite game, beside the stock market.

Dr. Milan Uskokovic, chemist and Sternbach associate, inventor of the vitamin D metabolite Rocaltrol (used by patients with chronic renal failure), and fellow member of the New Jersey Inventors Hall of Fame

By the early 1940s there was a significant migration of European organic medicinal chemists to America in search of opportunities in the rapidly growing field of pharmaceutical research. Leo Sternbach was an outstanding example in this newborn age. In a matter of a year or two after his coming to Roche in Nutley, he accomplished the monumental task of achieving the first total synthesis of the vitamin biotin. His synthesis is still practiced today, almost 60 years later, and is frequently cited as one of the most significant events of natural products synthesis. But that was just the beginning of his growth as a medicinal chemist. He decided to reexamine the chemistry of his student period in Poland and resurrected the benzodiazepines into the most significant series of drugs to combat anxiety, at that time a newly defined mental disorder. He became a grand master of modern medicinal chemistry. He also became a lasting example to all scientists at Roche up to the present time.

Dr. Pius Wehrli, chemist and Sternbach associate, and holder of 17 U.S. patents

Leo Sternbach was an extremely well-trained organic synthesis chemist with a keen ability to observe reactions and draw conclusions based on them. One of his outstanding qualities was his persistence. "Try until you succeed" must have been one of his fundamentals. A truly scientific achievement was his total synthesis of the vitamin biotin. The fact that after over 50 years his process is still commercially used and has not been replaced by a different approach speaks for itself. This is virtually unheard of in synthetic organic chemistry. Dr. Sternbach was well aware that you cannot whip up success at will. It will come at its own pace and often at unexpected moments. The road is full of surprises and predictions are often difficult. Chemistry, and science in general, needs in a certain sense a nonpush atmosphere. That is not to say that chemistry is not pushed, but the push of the true chemist comes from within, and that is what Dr. Sternbach personified.

Acknowledgment

Medical writer Bill Breckon worked closely with the four distinguished experts to compile the sections of the book covering the medical and social impact of the benzodiazepines.

Contents

Acknowledgments vii

Part I The Biography of Leo Henryk Sternbach

Chapter 1 A Cure for Troubled Souls 3

Chapter 2 Pearl of the Adriatic 9

Chapter 3 First Blossoming 25

Chapter 4 A Chemist of World Renown 35

Chapter 5 Upholding Success 53

Part II The Drug That Changed the World

Chapter 6 The Benzodiazepine Story 65

Chapter 7 The Crippling Cost of Anxiety, and the
Benzodiazepine Revolution 79

Chapter 8 A Social History: Putting Benzodiazepines
into Perspective 103

Chapter 9 The Scientific Impact of the
Benzodiazepines 131

Chapter 10 The Present—and the Future 149

Index 163

Part I

The Biography of Leo Henryk Sternbach

Chapter 1

A Cure for Troubled Souls

Librium is famous, and Valium even more so. Their discovery 40 years ago opened up undreamed-of opportunities for the medical and pharmaceutical worlds. Both medications exhibit the characteristic effects of the benzodiazepines: They are anxiolytics, anticonvulsants, muscle relaxants, and tranquilizers. No previous drugs treated such a range of indications.

The man who discovered the benzodiazepine group of active substances is Leo Henryk Sternbach. His work heralded the start of a new era in research and therapeutics.

The list of Sternbach's extraordinary achievements includes 125 publications, 230 U.S. patents, the Carl Mannich Medal of the German Pharmaceutical Society, the Chemical Pioneer Award of the American Institute of Chemists, induction into the New Jersey Inventors Hall of Fame, and honorary doctorates from the Johann Wolfgang Goethe University, Frankfurt am Main, the University of Vienna, and Centenary College, Hackettstown, New Jersey. *US News & World Report* numbers Sternbach among the 25 most important people of the 20th century, along with Louis Armstrong, Levi Strauss (the inventor of blue jeans), Frank McNamara, (the creator of credit cards), and Charles Houston (the brilliant lawyer who wanted justice for all).

Librium has an international reputation, and Valium is even more widely known. Sternbach, in contrast, has lived his life in the shadow of anonymity. It is a life that should have piqued the curiosity of poten-

tial biographers long ago; anyone who rises to the challenge of exploring that life will be rewarded with a tale of suspense and excitement. Sternbach pushed open doors, only to reveal new obstacles. On the heels of recognition came contempt. Periods of a secure and sheltered existence gave way to periods of menace and fear. Scientific breakthroughs triggered political attacks.

At each triumphant step, wisdom dictated modesty. And even in the darkest days of distress, his strength of body and mind bolstered his confidence and optimism.

Sternbach's story is exemplary and simple, shocking and encouraging, fascinating and moving.

Inner Strength

Every day for more than 60 years, Leo Henryk Sternbach, born in 1908, went to work at Roche, the company at which he began his pharmaceutical career in 1940. Even when he stopped driving in the early 1980s, his wife, Herta Sternbach, born 1920, drove her husband to his office daily. It was a 10-minute drive from their single-family home in Upper Montclair, through Bloomfield, to Roche headquarters in Nutley, New Jersey; then she drove him back home again in the early afternoon.

The 10-minute drive through suburban northern New Jersey, 12 miles west of New York, with the skyline of Manhattan in the distance, passed quickly. At intersections the white Chevrolet did not hesitate to claim the right of way; at the security check the car simply slowed to a crawl as it passed the uniformed guards. It stopped in a "No Stopping" zone to let Sternbach out, walking stick first—to the nods and waves of passing people, greetings that linked several generations.

This ritual tells in a nutshell a story of love, success, and happiness, and also the story of the Sternbachs' ability to awaken admiration and affection among friends and acquaintances of all ages.

Sternbach has not been to his office since autumn 2002. He finds it difficult to walk; the stick no longer gives him proper support. What had troubled his wife for a long time now began to worry Sternbach too: the fear of falling and injuring himself. With the sensibility that the couple have always been able to rely on, Sternbach restricted his radius to their house and its immediate surroundings. Forever? For the time being! For with the sensibility comes hope that one will soon be able to do what one wants.

With characteristic intellectual strength and philosophical cheerfulness, Sternbach fashioned his lot in life into a program for living. The late 1950s is a particularly dramatic instance of this. Sternbach had gone his own route in the tranquilizer project in his research laboratory in Nutley, New Jersey, home of the U.S. affiliate of Roche, the Swiss-based healthcare company. As a result he lost his position in the official research group. Ignoring colleagues' condescension for the rebel who was on the wrong track, he doggedly pursued his ideas, developing the insights gained during research for his doctoral dissertation, to discover—at the moment that his patient manager finally reached the end of his tether—the first of the “minor tranquilizers.” It was marketed in 1960 as Librium. Valium followed in 1963, sealing the phenomenal breakthrough in benzodiazepine research, and bringing Roche incredible financial success—billions of dollars over a period of many years.

Librium and Valium symbolize the achievements of a lifetime. As scientific answers, though, they do not mark the culmination of a life's work, but raise new questions that keep this field of research topical. Sternbach himself views his discovery not as a conclusion, but as a part of a continuation of the scientific exploration to be pursued by scientists of subsequent generations.

Esteem and Fame

In 1973, Sternbach retired from Roche with a pension that ensured his financial security. Since then he has worked as a consultant with his for-

mer company. His office is crammed full of books and files; Post-Its everywhere give some idea of the legendary chaos of his laboratory. Until well into his 94th year he sat down at his desk every day from Monday to Friday, pushed aside the piles of paper with his forearms, and edited his autobiographical notes. He read for a while in the library and ate lunch in the staff canteen. These are privileges—expressions of esteem, and a source of quiet pleasure—starting with the perfunctory security check and his stopping in a no-stopping zone. Even the young employees knew Dr. Sternbach, greet and stop to chat with him.

Fame embraced Sternbach warmly. Accolades gain special importance in the autumn of life—as irreplaceable as the “love and drive” from Monday to Friday for years beyond the diamond wedding anniversary.

Why did Sternbach become a discoverer, and why did he remain one? Why did he fight for his discoveries, working night after night in their cause? And why did he continue, despite the danger that the drugs that resulted from his research could be abused?

“To help the sick,” says Sternbach, “not everybody, just those that suffer.” He adds, “I was successful because I loved my work and was completely dedicated, like any true artist.”

Sternbach has finally received the recognition he has always deserved. He knows it and appreciates it, with a modesty that far exceeds his pride. Even today he accepts any praise for his achievements as unwarranted: he, a great chemist prevented from studying chemistry through malice, hate, and inhuman madness.

Surmounting Suffering

Anti-Semitism in Poland colored Sternbach’s experience and presented obstacles in his path. A realist, he accepted that Jewish students were effectively barred from the study of pharmacy or medicine. However, this acceptance in no way diminished his desire to succeed in the one subject he really loved—chemistry. With a mixture of prudence and

conviction-driven stubbornness, he forged his own roundabout route; despite being Jewish, he was permitted to study pharmacy only because his father was a pharmacist, having established his profession in that field before it was denied to Jews. Then, with a pharmacy degree added to his name, Sternbach obtained permission to study chemistry.

Although fate and circumstance dictated hardship, he bore the difficulty with character—during the 1920s as a student in Krakow, in the years preceding his studies, as well as afterward. The scientific and private sections of Sternbach's biography—to the extent that one can separate them—play out along circuitous routes, detours, and narrow paths along the edge of a precipice.

Transcendent Lightness of Being

Hearing of such harassment and the need to repeatedly defend oneself in most unfavorable circumstances makes listeners angry. Yet, the Sternbachs' account of these experiences is free of accusation. They talk about their most bitter hours with matter-of-factness, even a laconic smile. This is when their philosophical cheerfulness comes into play. There are two sides to it. On the one hand, it is the cheerfulness and transcendent lightness that masters afflictions, prejudices, and existential difficulties supremely well; on the other hand it is the cheerfulness and transcendent lightness of refusing to let potential concerns about the future restrict their immediate freedom. Today is today and tomorrow is tomorrow.

It all began in Abbazia, in the twilight of the Austro-Hungarian empire, before World War I. It all began a long time ago, in another age, in a remote corner of Europe.

Chapter 2

Pearl of the Adriatic

Leo Henryk Sternbach, the elder child of a Polish Jew and his Hungarian Jewish wife, was born in Abbazia on the Istrian Peninsula on May 7, 1908. His brother Gyuszi, born 3 years later, died young of scarlet fever. The town, the Nice of the East and one of the most fashionable spas on the Adriatic coast, was part of the Austro-Hungarian Empire until after World War I. In 1920, it passed to Italy, and in 1947, as a result of World War II, to Yugoslavia. Now part of the independent republic of Croatia, which gained international recognition in 1992 and established its authority over the whole peninsula 6 years later, the “Pearl of the Adriatic,” with its restored Art Nouveau hotels, has experienced a renaissance as the tourist center Opatija.

The communist dictatorship put an end to the former splendor that had been the reality for the Sternbachs. Once emperors and kings came to Abbazia for rest and recuperation, followed by fashionable society and the demimonde. James Joyce stayed there, as did the world boxing champion Primo Carnera, the tenor Beniamino Gigli, and the composers Gustav Mahler and Giacomo Puccini.

“Abbazia,” wrote Henryk Sienkiewicz, a Polish Nobel prize winner and author of *Quo Vadis*, in a letter, “has everything: mountains, good air, it is well protected, and is on the sea with its healthy breezes.” The Russian writer and playwright Anton Chekhov, however, complained that the hotels and their ugly petit bourgeois architecture destroyed the view of the bay.

Isadora Duncan, the American dancer, on the other hand, found the place inspiring, and recorded in her memoirs:

A palm growing below the window of our villa drew complete attention; it was the first time that I had seen a palm growing outdoors. Every day I observed how its beautiful leaves fluttered in the morning breeze, and from it I got that light quivering in the hands and fingers.

Thus, Abbazia appeared on stage, artistically sublimated in the gentlest of movements.

Father Sternbach's Business Sense

By moving from Krakow to the spa and bathing resort where cultured living was a way of life, the elder Sternbach revealed his view of personal happiness and good sense for business.

Sternbach wrote in his autobiographical notes:

My father was apparently not a very good student. Therefore, his parents had him study pharmacy, a study which at that time took only 3 years and needed only 6 years of high school. Thus, he began studying pharmacy in Lemberg (Lwow) at the age of 16. At the age of 19 he finished his studies and apparently became a master of pharmacy (magister pharmaciae) but had to practice a few years until he achieved the right to manage a pharmacy.

He worked for a few years in a pharmacy in Krakow (Magister Rosenberg's), which was then Austrian. He decided afterward to open a pharmacy in Abbazia, which was a flourishing spa on the Adriatic Sea, the only Austrian sea resort.

My mother's grandmother, who lived in Hungary, owned a villa in Abbazia. My mother spent her summer vacations with her parents in

that villa and met my father. After a very short time they fell in love and my father proposed. My mother was 17 and my father was 35.

My father came to Orosháza (a town near Szeged in Hungary) to be introduced to the family, who were very upset that a member of their clan would marry a Polish Jew, a member of the lowest class of Jews. My father, however, must have succeeded in convincing them that he was not so bad, and they got married in 1907.

As a result of this, I, Leo Henryk Sternbach, was born on May 7, 1908, to Michael Abraham Sternbach and Piroška "Piri" Sternbach-Cohn in Abbazia.

Medical Center

The natural beauty, the healthy climate, and the rapid growth in tourism following the opening of the Southern Railway Company (Südbahn-Gesellschaft) also attracted the sick and ailing to Abbazia, and with them physicians. Theodor Billroth (1829–1894), a German surgeon, enhanced the town's reputation as a health resort. Julius Glax (1846–1922), a Viennese scientist of bathing, organized a world congress on thalassotherapy and treated prominent patients. By 1912 there were 12 clinics in the town, specializing in the treatment of bronchitis, asthma, and heart disease. This environment also offered interesting business prospects for pharmacists. The elder Sternbach acquired the Kromir & Poriz pharmacy in the Mandria Bazar on the main street. He ran a very successful enterprise, as inventor of ovolecithin-based Oval lozenges and Laurol, a dermatological treatment for rheumatism made from laurel leaves.

It is quite possible that the older Sternbach passed on his talent for invention to his son, in whom it blossomed into genius. At any rate, as a child Leo Sternbach spent a lot of time in the pharmacy, helping his father where he could—and unable to resist the temptation to help himself to fruit gums, licorice, and sweet-tasting pills.

Ethnic Mix and Anti-Semitism

The immediate environs, too, had the feel of a paradise. Neighbors of the pharmacy included the souvenir shop of a Palestinian, Abu-Khalil, Kadish's musical instruments and sheet music, Köraus's glazier's shop, the Jewish butcher Hus, Tauber and Barbini's Italian restaurant, and the post office.

The city was an ethnic mix. The local Croatians, mostly farmers, fishermen, or hotel workers, were poor. Aside from Croatian Abbazia, there was a Polish, Hungarian, Czech, Slovak, Italian, and Jewish Abbazia as well. Since the end of the 19th century, Jewish businessmen, hoteliers, and doctors had played a leading role in the town. Jews built the first sanitariums. Initially, Jewish religious services were held in the Pension Breiner and later in the Pension Stern. The Jewish cemetery was laid out in 1912, and construction of the synagogue began in 1926.

The arrival of Jewish immigrants triggered a latent anti-Semitism that became overt in the 1930s, with Mussolini's proclamation of his "provisions to defend the Italian race." Leo Sternbach can recall Christian classmates in primary school calling him "dirt."

Family and Religion

The Sternbach family moved in upper middle class circles. They made no secret that they were Jewish, but were not very observant, although they did celebrate the High Holidays: Rosh Hashanah, the Jewish New Year, and Yom Kippur, the Day of Atonement. Leo's mother observed the rules of fasting, but his father did not. "People who work do not have to fast," explained his mother with a mixture of seriousness and ironic reproof. Leo Sternbach has never tried to hide the fact that he is a Jew, because "I was born a Jew," but he refuses to take part in any religious activity on the grounds that all religion is "senseless and negative"; nor does he believe in God. He married a Christian and his sons were brought up as Christians. But there was never any question of