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IN MEMORIAM

Remembering Carl Djerassi: a centennial

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Carl Djerassi (1923−2015, Fig. 1) was first and foremost a structural chemist in the heroic, pioneering age of this field of research. He was also a pharmaceutical chemist, a novelist and playwright, and a generous supporter of the arts. Today, the elucidation of the structural formula of a newly synthesized or a newly isolated compound is more the task of analytical chemistry than structural chemistry. In the popular notion though this is not at all clear. This is manifested in the frequent submissions to our journal in which the identification of a hitherto unknown substance is reported by physical and computational techniques without hardly anything more. This is not what *Structural Chemistry* is about as it is described in its Aims and Scope. However, when the principal physical techniques of such analyses were being developed, such tasks were in the forefront of relevant research. Carl Djerrassi was one of the principal architects of the transition making structure elucidation into applied spectroscopy and then routine analysis.

In 1996, I recorded a long conversation with him [1] about his life and career and we kept in touch during the remaining two decades of his life [2]. He considered himself to be a degradative chemist rather than a synthetic chemist exactly because of his interest in structure elucidation. He worked in organic chemistry, primarily with steroids. First, he used ultraviolet spectroscopy and next came infrared spectroscopy. Just to give a feeling of the changes, prior to that it was the determination of melting points chemists used for the identification of substances. The next spectroscopy that appeared in the organic chemistry laboratory was NMR, followed soon by mass spectrometry. Chiroptical methods, ESR and other techniques enriched the tools, especially for solving special problems. Djerassi was different from most of his organic chemistry colleagues in that he became interested in the physical methods themselves. He ascribed his tremendous success in steroid chemistry to his mastery of those techniques.

Another designation he liked for describing his interests was as a natural products chemist. This also signaled his care for the science and scientists in the so-called third-world countries. The availability of plant products and sometimes even animal products meant some advantage of chemists working in the third world over their colleagues working under much better conditions in the more advanced countries. It was of course not only the availability of such resources but also the knowledge that made their utilization possible. Djerassi was a dedicated student of Chinese and Indian as well as Mexican and Latin American medicine. He worked a great deal in Mexico and Brazil. Eventually, he developed a deep interest in marine natural products.

Djerassi was a celebrated professor of chemistry at Stanford University, but his road to academia was harder than for most. He was born in Vienna to a Bulgarian dermatologist father, Samuel Djerassi, and a Viennese dentist mother, Alice Friedmann, both Jewish – he, Sephardic; she, Ashkenazi. The Austrian and Bulgarian connections were lately manifested with postage stamps by the two respective countries (Figs. 2 and 3). After Djerassi's birth, the family moved to Sofia, Bulgaria. When his parents divorced, Djerassi and his mother moved back to Vienna and he attended a Viennese high school, a gymnasium and spent his summers with his father in Bulgaria. After Germany's annexation of Austria, the *Anschluss*, in 1938, Djerassi and his mother escaped to Bulgaria. There, he attended the American College and learned to speak fluent English. He and his mother arrived in the United States in 1939. His father emigrated to America in 1949.

Djerassi attended a two-year community college in Newark, New Jersey, where he was exposed to chemistry for the first time, and it was by an excellent teacher, Nathan Washton. Djerassi then spent one semester at Tarkio College in Missouri (it no longer exists). For the completion of his studies, he went to Kenyon College in Ohio. There, he learned from excellent chemistry professors; organic chemistry from Walter Coolidge and physical chemistry from Bayes Norton. Djerassi's college education

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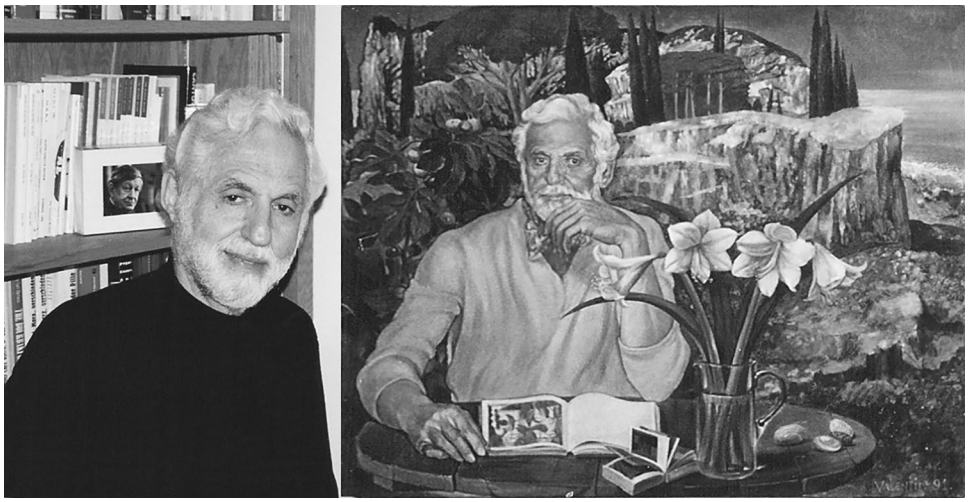

Fig. 1 Photographic (1996) and painted portraits of Carl Djerassi in his former San Francisco home (photograph by I. Hargittai)

was made possible by an American scholarship covering room and board as well as tuition. Lacking financial resources (initially, his mother could work only as a physician's assistant), Djerassi worked for one year for CIBA as a junior chemist. He then attended graduate school at the University of Wisconsin-Madison and earned his PhD in 1945 – he was still only 22 years old.

As a fresh PhD, first, he wanted to gain experience in industry. Then, in 1949, he joined the company Syntex in Mexico. This was more than unusual; many considered this absurd, if for nothing else for the lack of possibilities for communication that are so easily available today but were not yet existent then. He considered his time in Mexico the most productive of his scientific life. The first synthesis of cortisone from plant products, the first oral contraceptive, and a lot of steroids signaled his success. He helped Mexico to become the center of worldwide production and even research in the field of steroid hormones. His achievements in Mexico landed him his first academic job at Wayne State University where he had become full professor before he moved to Stanford.

The Stanford professorship was a great recognition, one among many he was recognized with during his long career. He was a member of the National Academy of Sciences of

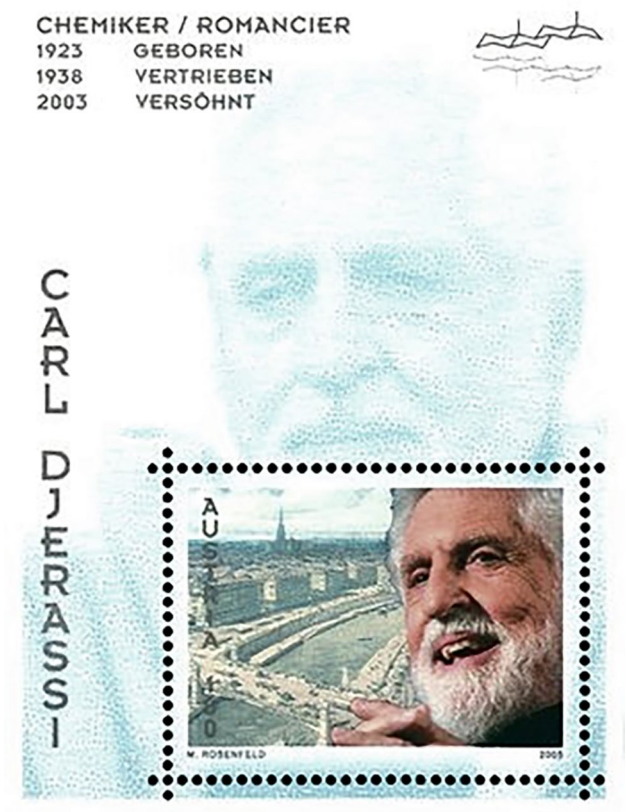

Fig. 2 Austrian postage stamp 2005. In the upper left corner, the English translation of the text: Chemist/Novelist, 1923 born, 1938 expelled, 2003 reconciled. In the upper right corner, a steroid frame with its mirror image. There is a second, larger background image of Djerassi's faintly visible face, constructed from microscopic steroid structures [3]

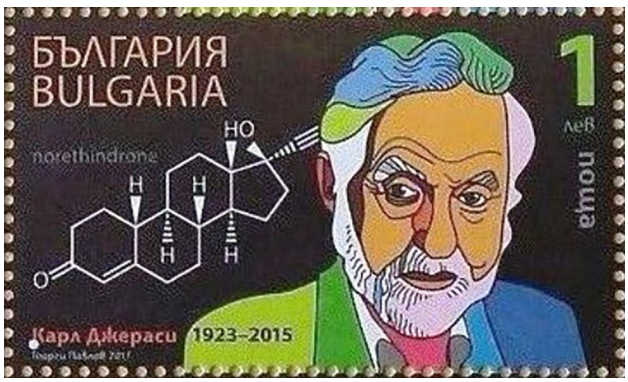

Fig. 3 Bulgarian postage stamp, 2017. In addition to displaying Djerassi's colorful portrait, it shows the structural formula of norethindrone, partially hidden by the portrait

the U.S.A. He had the unique distinction of having received both the National Medal of Science in 1973 and the National Medal of Technology in 1991. This demonstrated his excellence both in fundamental science and its applications. He was the first recipient of the Wolf Prize in Chemistry in 1978. He was also a Foreign Member of the Royal Society and of the Royal Swedish Academy of Sciences. Thanks to the latter, on one occasion, he participated in the discussion of the chemistry Nobel Prize.

He never won the Nobel Prize though he might have, and the prize was on his mind as witnessed by his writings. There was a long and gradual transition for him from science to producing novels and plays. His first novel was *Cantor's Dilemma* [4] in which he described the Nobel ceremonies in detail, including the festive dinner. In his narrative, peas are being served as a side dish, and he provides an enjoyable discussion of how people of different backgrounds eat it. A few years after the publication of the novel, when Djerassi gave a lecture at the Royal Swedish Academy of Sciences, he was presented a can of peas wrapped in a Swedish flag. To Djerassi, who might have received a real Nobel Prize, receiving this Peas Prize, might have appeared as a cruel joke. However, with good humor, he considered it as a recognition of his literary acumen by his Swedish colleagues.

To the broader world, Djerassi's name is better known as the father of the Pill, the highly successful oral contraceptive. This was the achievement of the work by him and his team at Sytex in Mexico. They set out to synthesize a progestational hormone that would retain the biological activity of the natural female sex hormone progesterone and could be administered orally. There were important therapeutic applications of progesterone already at that time, among them against menstrual disorders. Another application was for the treatment of infertility of women who became pregnant but could not maintain the embryo for the inability of producing enough progesterone. Then, a potential application was for treatment against cervical cancer. Progesterone was applied in the form of injection in all its applications. Djerassi and his team wanted to develop a progesterone modification that would be orally consumable. At the time the general view was that any modification would destroy or diminish the biological activity of progesterone. In the field of the other female sex hormone, estrogen, it was known that many similar compounds had estrogenic properties and all kinds of modifications could be produced with retaining them.

When Djerassi and his team produced a powerful analog of the progestational hormone, this achievement had a great impact. They sent their sample for bioassay to many testing laboratories. One of them was at the Worcester Foundation where Gregory Pincus was interested in studying the ovulation inhibiting properties of progesterone. Pincus became considered the biological father of the Pill. Djerassi's product, called "Norethindrone," first earned FDA approval in 1957 for menstrual disorders. By then, the group of Pincus and another group in Los Angeles had shown that Norethindrone had ovulation inhibiting properties, and by 1960, Djerassi and his colleagues had recognized that the oral contraceptive properties would be *the* important thing. Both the scientists and the pharmaceutical companies as well as the physicians were astonished by the speed with which the market skyrocketed for the Pill.

Despite a most successful career and an avalanche of recognitions, Djerassi considered himself an outsider at a multiple of levels and areas. He felt this in academia, in the community of organic chemists, even in the American Chemical Society. He mentioned his having been the first Jewish Professor of Chemistry at Stanford University when he joined it. This was not because Stanford was anti-Semitic, he stressed, but because it was just not yet done. He thought that it took him thirty years to overcome his Jewish refugee paranoia; I wonder if he ever did and whether it was entirely paranoia.

During the two last decades of his life, we had quite some interactions. They included our seeing his plays: *Oxygen* (co-authored by Roald Hoffmann) in London, with both authors present, and *Phallacy* in New York, together with Djerassi. As a playwright he was also an outsider. He was a scientist rather than a writer; furthermore, he protested being considered engaged in science fiction; rather, he wrote *science in fiction*. His literary activities could be considered the best kind of science popularization. He generously produced a Foreword to my book *Drive and Curiosity* and defined the special genre of

Fig. 4 Carl Djerassi with the author, 2013, in front of the Holocaust Memorial, resembling a weeping willow, by Imre Varga, in the Wallenberg Park, on Wesselényi Street, on the north side of the Dohány Street Great Synagogue in Budapest (photograph by Magdolna Hargittai)

Fig. 5 Carl Djerassi, 2013, in front of Baruch Benedictus Spinoza's memorial plaque by Antal Czinder on the wall of "Spinoza House," 15 Dob Street, Budapest. The English version of the Spinoza quote on the plaque is: "Minds are conquered not by arms, but by love and nobility." [Baruch Spinoza Quotes (Author of Ethics) (page 2 of 8) (goodreads.com)]

this book, which was applicable to much of my writings, viz., description of the nature of *Homo scientificus* [5].

My wife and I met him for the last time when he visited us in Budapest in 2013, a year and a half before his demise. He knew the end was close but was as curious as ever. We did a lot of sightseeing and he was willing to go everywhere despite his limited mobility. He had three items that he was especially keen to see: Arthur Koestler's statue, the Holocaust Memorial in the Wallenberg Park (Fig. 4), and the Spinoza memorial plaque (Fig. 5). The highlight of this visit was his meeting with a group of leading intellectuals in our home. He left a memorable and inspiring impression in all of us as he did in many others with whom he had been in contact throughout his long, creative life.

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