Essays of an Information Scientist, Vol:5, p.721-730, 1981-82 Current Contents, #42, p.5-14, October 18, 1982

Current Comments

A Tribute to Carl Djerassi: Reflections on a Remarkable Scientific Entrepreneur

Number 42 October 18, 1982

There has been much said about the scientific entrepreneur. Ordinarily the term is applied to the scientist who has been successful in business. One thinks of Thomas Edison or Edwin Land, founder of Polaroid, among others. But there are also scientific entrepreneurs in the academic community. Many *Current Contents*® (*CC*®) readers fall into this category so I will not belabor the point. My reason for mentioning these two meanings of scientific entrepreneur is to emphasize that we rarely find both kinds in one person. To maintain a credible academic existence one needs enormous dedication and energy. To function in a scientifically oriented business you need these qualities as well as significant managerial competence. That rare combination of qualities is found in my friend Carl Djerassi.

I recently had the honor of speaking informally at a very unusual event. The numerous friends and collaborators of Djerassi attended a party celebrating the publication of his 1,000th paper. My ad-lib comments on that occasion left me somewhat frustrated. In the euphoria of the moment I failed to state so many of the more relevant facts about his many accomplishments that I wished I had come prepared with an appropriate oration, which I now belatedly provide. Perhaps only Carl and his closest friends will understand the special sympathies we share, not the least of which is his appreciation of art and humanistic studies.

Djerassi is best known to the public for his contribution to the development of the birth control pill. But research in contraception is only one aspect of his multifaceted career. He is one of the giants of modern organic chemistry. Carl has been a leader in analyzing or "elucidating" the structures of complex organic molecules and in applying these discoveries to the synthesis of pharmaceutically important compounds. He is also responsible for major advances in the methodologies used by organic chemists. Analytical techniques which he helped develop, such as optical rotatory dispersion, circular dichroism, and mass spectrometry, are now among the most widely used tools in organic chemistry.

I first met Djerassi back in 1959. We were introduced by Joshua Lederberg, who refers to Carl as one of the "wonders of nature."[1] In 1960, when ISI® began publishing *Index Chemicus*® (*IC*®), now *Current Abstracts of Chemistry and Index Chemicus*® (*CAC&IC*®), Carl served on the editorial advisory board. He also lent his enthusiastic support to our next project, *Science Citation Index*® (*SCI*®). Carl became one of the first members of the editorial advisory board of *CC/Space, Electronic & Physical Sciences,* a predecessor of *CC/Physical, Chemical & Earth Sciences* (*CC/PC&ES*). In addition to his professional advice and encouragement, Carl has shared with me his friendship and *joie de vivre.*

Carl Djerassi

Djerassi was born in Vienna in 1923. His Bulgarian-born father and Austrian mother were both physicians. After the outbreak of World War II, he emigrated to the US with only $30 in his pocket. He spent two semesters at a now defunct junior college in Newark, New Jersey, before accepting a scholarship from Tarkio College, a small school in Tarkio, Missouri. He later transferred to Kenyon College, Ohio, and graduated *summa cum laude* before his nineteenth birthday. Our foreign readers should realize that most Americans graduate at the age of 22.

At this point, he joined a research team at the Ciba Pharmaceutical Company, Summit, New Jersey. Within a year, he and his co-workers developed one of the first successful antihistamines, tripelannamine. This compound, marketed by the Ciba-Geigy Corporation as Pyribenzamine, is still used to treat a variety of allergy symptoms.

In 1943, Carl enrolled in the graduate program at the University of Wisconsin. He earned a PhD in organic chemistry before his twenty-second birthday and returned to Ciba. After four more years of industrial experience he grew restless and eager for a position in academe, but he could not find one. Then, in the spring of 1949, Djerassi received a call from chemist George Rosenkranz. Rosenkranz was the director of a small Mexican company called Syntex, and he invited Djerassi to head a research team there.[2] The job was appealing in that it would allow Carl to continue his investigation into the chemistry of steroids.

Steroids were of interest to Djerassi and others because of their complicated structures and their prominent role in regulating such physiological processes as reproduction, digestion, and calcium metabolism. As more and more was understood about the function of steroids in the body, their importance as pharmaceutical agents increased dramatically. Steroid chemistry had been the subject of Djerassi's PhD thesis, but at Ciba it was difficult to keep working in this area. Company policy confined most steroid research to the laboratories at Ciba's Swiss headquarters.

It is of interest to mention that during this period the work on steroid chemistry was almost frantic. In fact, the backlog of applications at the US Patent Office was eventually so large that the Pharmaceutical Manufacturers Association financed a steroid literature coding project. Eugene Garfield Associates, predecessor of ISI, received the contract to do this work in 1958. We encoded over 20,000 steroid compounds and established a precedent for the widely used fragment coding system employed in the *Index Chemicus Registry System*® (*ICRS*®) and other systems.

At the end of the 1940s, much of the excitement centered around the discovery that a steroid hormone, cortisone, could alleviate arthritis symptoms. The chemical could be derived from animal bile, but initially not in amounts large enough to be of use in treating this chronic, widespread disease. Scientists around the world were racing to find a more practical method for synthesizing

cortisone. The team Djerassi was invited to head at Syntex was in fact attempting to develop a new synthesis. Djerassi accepted the job, and in 1951, his team won the race. They found a way to make cortisone relatively simply, using a readily available raw material, the Mexican yam.[3]

That same year, Djerassi's team synthesized another compound which received much less attention at the time. They named it "norethisterone," and it was to become the active ingredient in the birth control pill. Today it is known as norethindrone.

The work began with the female hormone progesterone. Among other things, progesterone prevents women from ovulating during pregnancy, thus acting as a natural contraceptive. Djerassi's team found that by making a very specific change in progesterone's chemical structure, they could increase its potency eightfold. This "analog" or synthetic version of progesterone was strong enough to work when injected, but it lost its potency when administered orally. The Syntex group needed a chemical which would be absorbed by the oral route. A breakthrough came when they "rediscovered" a compound synthesized more than a decade earlier but largely ignored because of its apparent lack of medicinal value.[2] It was called ethisterone and its activity in the body was not unlike that of progesterone. Moreover, its activity persisted even when taken orally. Djerassi's group devised a way to make the same chemical modification in ethisterone which they had earlier made in progesterone. The result was synthetic norethisterone, which prevented ovulation, was orally active, and could be incorporated into a pill.[2]

It is, of course, more efficient to methodically rearrange molecules, enhancing or creating desirable chemical properties, than it is to randomly synthesize compounds for biological testing. But until recently, specific manipulations of the kind described earlier were rarely performed. "Natural products," or naturally occurring organic substances, can be used as models for synthetic compounds. However, many natural products consist of molecules so large, complex, and delicate that relationships between their structure and function—and in some cases, the structures themselves—are often obscure. At the time when Djerassi was beginning his career, it was still not uncommon for a natural products chemist using traditional analytical methods to spend a lifetime elucidating the structure of a single substance.[4]

It was to a persistent problem, the inadequacy of physical methods available for assessing organic structures, that Djerassi now turned his attention. He was offered a professorship at Wayne State University, Detroit, in 1952. The following year he and his colleagues began to investigate optical rotatory dispersion.

Optical rotatory dispersion and optical circular dichroism, which Djerassi and others developed a decade later, use polarized light to take an "impression" of a molecule's three-dimensional shape. Both techniques operate on a principle known as the "Cotton effect," named for a nineteenth-century French physicist, François Cotton.[5] Cotton observed that polarized light can undergo changes when it passes through certain substances. Djerassi was able to transform this phenomenon into a practical tool for analyzing molecular structures. He found that many organic substances, notably those containing a carbonyl group, produced the Cotton effect, and that the intensity of the effect varied with the wavelength of the light. He graphed these changes as "Cotton effect curves," and determined that many molecular structures produced their own distinctive curves. By using these curves as "fingerprints" of molecules, he could make comparisons between molecules never before possible. The "stereochem-

istry" or three-dimensionality of unknown structures could be deduced from known structures and subtle differences between similar molecules discerned.[6]

Optical rotatory dispersion and circular dichroism measure two different components of the Cotton effect. The former detects a rotation in the light waves. The latter measures a change in the way the waves oscillate, a transition from a strictly "back-and-forth" to an elliptical motion. Both techniques have opened new fields in organic chemistry.[6] In addition to enormously speeding up the process of stereochemical elucidation, they have made it possible for chemists to work with minute quantities of compounds they are examining. This is important because many naturally occurring organic chemicals are scarce.

Moreover, unlike the analytical techniques previously in use, Djerassi's inventions made it possible for chemists to "see" how atoms are positioned in space—or, in other words, establish their "absolute configuration." Thus, chemists may effectively distinguish between molecules which are mirror images of one another. Such distinctions are crucial, Djerassi explains, because mirror-image molecules may have entirely different biological properties. For example, the important hormones or amino acids are biologically active in one mirror-image form, but totally inactive in the other.[5]

Although optical rotatory dispersion and circular dichroism quickly became part of the standard vocabulary of organic chemistry, some of the most important discoveries involving them have been made in Djerassi's laboratory.[7-14] During the 1950s much of this work involved the elucidation of the structures of terpenoids. Terpenoids are a large class of chemicals which include the body's essential oils, vitamins A, E, and K, most perfumes, natural rubber, and the chemicals which are the precursors of cholesterol, to name only a few examples. Djerassi provided information which had long been sought concerning the biosynthesis of terpenoids. He did this by determining the structure of iresin, a key biosynthetic "missing link" between the lower and higher terpenes.[15]

Djerassi also grew interested, during the 1950s, in other classes of chemicals, particularly the alkaloids and the macrolide antibiotics. In 1956, he and J.A. Zderic became the first investigators to elucidate the structure of a macrolide antibiotic.[6] As the prefix "macro" suggests, the macrolides are large ring compounds. Their size and complexity had impeded prior efforts to elucidate them. Djerassi and his team established the structures of methymycin and neomethymycin and helped to elucidate the clinically important macrolide, erythromycin.[6] One special feature of the macrolides is that they include the only antibiotics effective against fungal disorders.

During the 1950s and 1960s, much of Djerassi's work involved novel alkaloids found in tropical plants. Alkaloids are a class of chemicals with a long history as hallucinogens, narcotics, poisons, and medicines. Their name comes from the fact that they are generally basic, or "alkaline." In this field, Djerassi saw promise in a new analytical technique called mass spectrometry.

A mass spectrometer is essentially a "sophisticated weighing machine."[16] The substance under study, in gaseous form, enters a chamber where its molecules are broken into a variety of fragments through electron bombardment. Some of these fragments carry a charge and thus can be deflected and focused by electric and magnetic fields. Heavy particles will be deflected less than light ones with the same charge. Depending on their masses and charges, fragments will fall in predictable locations on a photographic or electronic detector.[16]

Up until the 1960s, mass spectrometry had not been a very useful tool for chem-

ists elucidating organic structures. The reason was that under electron bombardment, organic molecules would merely "shatter into a confusing array of pieces." As was recently noted in *Science News*, it was a bit like "dissecting a watch with a sledge hammer."[16] Without a detailed knowledge of how these molecules were likely to split apart, it was difficult to identify fragments just on the basis of their mass and charge.

In 1961, Djerassi, who had been on the faculty of Stanford University for two years, began to develop mass spectrometry as a tool for structural elucidation. This involved looking for rules which could be used to understand the fragmentation behavior of organic molecules. He and his associates began by synthesizing hundreds of small "model" compounds, and bombarding these with electrons. In this way, they determined how different groups of atoms, which normally make up segments of organic molecules, responded to electron bombardment.[17] They compared these results with the fragmentation patterns of more complex molecules and were eventually able to produce a comprehensive set of theories which could be used to interpret the mass spectra of organic molecules. Their work was crucial in making available a technique which is now one of the two most widely used physical methods in organic chemistry.[6] I remember the early days of Carl's interest in mass spectrometry because we considered the possibility of creating a new molecular weight index for *IC*, to be derived automatically from the molecular formula. Since that time, some of Carl's most important discoveries and influential publications[17-25] have been built on the earlier research, which made it possible for him to use and interpret mass spectral data.

During the past ten years, Djerassi has continued his efforts to develop and refine the tools used for structural elucidation. Together with Lederberg and Edward Feigenbaum, Djerassi undertook "a major collaborative program on the use of computer 'artificial intelligence' techniques in organic chemistry."[26,27] Their group developed a series of computer programs which take raw data from mass spectrometry and other physical or chemical data and process it in ways which make it easier to analyze. For instance, given the mass and charge of a particular fragment, a computer could create a list of possible identities for the fragment. Different programs could produce similar lists on the basis of other criteria. Computers, as Djerassi points out, allow chemists to examine alternative structures in an "absolutely rigorous way."[5] One program, the Meta-DENDRAL program,[27] can even search for new rules concerning the fragmentation behavior of complex molecules by working "backward," or generalizing from patterns found in specific data, thus further refining the technique of mass spectrometry.

In the past decade, Djerassi has employed the new analytical methods he helped develop to examine a group of exotic sterols found only in such marine animals as sponges and soft corals. The sterols produced by terrestrial organisms include only cholesterol and a few simple variations. But a single marine organism may produce as many as 70 different sterols.[28] "The question," Djerassi muses, "is what are these things doing in the ocean, and why are they not in plants and animals on earth?"[5]

One intriguing possibility is that these sterols represent "missing links" which will tell us something about the evolution of cell membranes.[29] It has recently been discovered that sterols help to maintain the integrity of cell membranes, and are involved with regulating their permeability. Prokaryotes, primitive single-celled organisms like bacteria and blue-green algae, cannot manufacture sterols as do eukaryotes. The ability to do so was probably a prerequisite for the evolution of multicellular forms of life.[29] The presence of a host of novel

sterols in primitive aquatic animals may reveal how the first step in the evolution of higher life forms took place. It may also offer further insight into the physiology of cell membranes.[29]

Up until 1972, in addition to the research which Djerassi did at Wayne State and Stanford, he also maintained his affiliation with Syntex. He traveled to Mexico when he was on sabbatical leave from Wayne State, and continued to serve as a vice-president of Syntex until 1959, when he accepted his professorship at Stanford. A few years later, Syntex moved its research headquarters to the Stanford Industrial Park and Djerassi served as its president until 1972. That year he resigned from Syntex in order to devote his time outside the university to Zoecon Corporation, a small offshoot of Syntex which he helped to found. Zoecon, a company engaged in developing "biorational" insecticides, continues to receive much of Djerassi's attention, as he is both the president and chairman of the board.

The insect control agents being developed at Zoecon are analogs, or near duplicates, of naturally occurring insect hormones. For instance, by modifying the chemical structure of insect "juvenile" hormone, Zoecon workers have derived substances which can retard an insect's development. The result is either the death of the insect, or its ineffectiveness as a pest. Hormone analogs, unlike other pesticides, can be made quite specific in their action. They do not kill the targeted insects' natural predators, nor do they persist in the environment.[30] Thus it appears that they are remarkably free from adverse ecological effects.

In addition to hormone analogs which stunt insects' growth, there are others which can cause "insect mental retardation." A treated moth, for instance, might continue to behave like a larva.[30] Other analogs interfere with molting, and still others cause insects to develop in miniature. The Zoecon group has also initiated studies of pheromones, chemicals which insects secrete in order to communicate with one another. Pheromones can attract insects to traps, which they mistake for females; can convince them to emerge prematurely from hibernation and freeze; or can alarm them, causing them to "run like crazy or drop off the leaf" or whatever they may be eating.[30]

Djerassi believes these new pesticides can help reduce the "chemical load" in the environment.[5] "Although we cannot eliminate the chemicals in our environment, we can have both fewer chemicals and more exquisitely designed ones," says Djerassi. "I can think of no area where we can do this more effectively than with pest control." Insect-borne diseases, he points out, kill more people worldwide "than cancer, heart disease, or anything else we are worried about here."[5] Much of the world's food supply is also destroyed each year by insects and other pests.

In areas like pest control and birth control, Djerassi has argued that the problems of the less-developed countries ought to be given more priority in the scientific community. He feels that safer and more effective technologies are needed but are not being developed for a number of reasons.[31] In his most recent book, *The Politics of Contraception*,[2] reviewed in *CC*,[32] Djerassi examines the web of economic and political factors affecting the fate of new technologies. In her review of the book, Elizabeth B. Connell, Northwestern University, Chicago, Illinois, writes, "Only an individual with Djerassi's diverse background—scientist, politician, writer, and keen observer of the social and bureaucratic scene—could have produced a volume so vitally important and eminently readable."[33]

One issue Djerassi confronts is that of government regulation. Our regulatory apparatus, as he points out, is geared

toward preventing risks, rather than encouraging needed kinds of research. There is no mechanism for taking account of the price that society might have to pay for letting certain technologies go undeveloped. Since birth control is an urgent problem for the populations of the less-developed countries, the price of our failure to innovate is paid most heavily by them. It is interesting to ponder Djerassi's suggestion that if the regulatory climate had been the same in the 1950s as it is today, the birth control pill might still be a "laboratory curiosity."[2] (p. 85)

In addition to gearing investigations more toward the needs of the less-developed countries, Djerassi feels that the international scientific community ought to provide more aid to researchers in these countries. He has sponsored a number of measures to increase the level of scientific exchange between the industrialized and the nonindustrialized countries. He served on, and for several years chaired, the National Academy of Sciences Board on Science and Technology for International Development. The board has organized bilateral workshops in many countries of Latin America, Asia, and Africa.

Djerassi has also been a longtime participant in the Pugwash Conferences on Science and World Affairs.[34] His proposal for a scientific exchange program, presented to a Pugwash Conference in 1967, resulted in the establishment of the International Center for Insect Physiology and Ecology (ICIPE) in Nairobi, Kenya. This center is an outstanding example of effective international collaboration.

Despite the attention he has received for his role in the development of the birth control pill, and for his efforts to lessen the technological and economic gap between developed and less-developed countries, Djerassi feels that his most significant contributions have been in basic research. Indeed, the impact of Djerassi's work on the methodology and direction of research in organic chemistry has been enormous. This is consistently reflected in our citation studies. In our most recent study of the 1,000 most-cited authors publishing between 1965 and 1978,[35] he appeared as the 49th most-cited author, having received over 7,700 citations during these years. When we did our 1976 study of the top 300 scientists cited between 1961 and 1976, we discovered that Djerassi's citation count for this period was over 11,000,[36] higher than that of any other organic chemist. As a senior researcher, Djerassi usually is named last when coauthoring a paper. Nonetheless, his first author papers alone have been cited over 10,000 times since 1961. When we publish the 1955-1964 *SCI* we will have more data on the crucial 1950s.

The number of papers Djerassi has published which can be regarded as classics is remarkable in itself. Formerly, his most-cited paper was "The direct conversion of steroidal Δ^5-3β-alcohols to Δ^5- and Δ^4-3-ketones."[37] Several years ago we invited Carl to write this up as a *Citation Classic*, but he declined because he felt that his 1961 article, "Structure and the optical rotatory dispersion of saturated ketones,"[9] was far more influential. The citation data now agree with Djerassi's assessment and this is currently his most-cited paper. We are pleased that his personal report on that milestone work appears on page 22 of this week's issue of *CC/PC&ES*.[38] The paper is coauthored with Nobel chemist Robert B. Woodward, and is based on Djerassi's initial work with optical rotatory dispersion. It discloses the correlation between the optical and structural characteristics of sterols.

Another *Citation Classic*[39] by Djerassi is a book he coauthored with his postdoctoral fellows Herbert Budzikiewicz and Dudley Williams, entitled *Mass Spectrometry of Organic Compounds*.[40] Since its appearance in 1967, it has been

explicitly cited over 2,750 times. The book is based largely on conclusions which emerged from Djerassi's experimental work with mass spectrometry. It outlines the theoretical basis of fragmentation behavior of organic molecules. Djerassi also wrote a book entitled *Optical Rotatory Dispersion: Applications to Organic Chemistry*,[41] which has been cited over 1,200 times since its publication in 1960.

Djerassi's achievements have been recognized with a long list of honors and awards. In addition to being awarded nine honorary doctorates, he is a member of the US National Academy of Sciences, the American Academy of Arts and Sciences, and several foreign academies.

The American Chemical Society has honored him with many different awards, among them the Award in Pure Chemistry (1959), the Baekeland Medal (1959), the Fritzsche Award (1960), the Award for Creative Invention (1973), and most recently (1982) the American Chemical Society's Award in the Chemistry of Contemporary Technological Problems. He also received the Freedman Foundation Patent Award (1971) and the Chemical Pioneer Award (1973) of the American Institute of Chemists, and the Perkin Medal of the Society for Chemical Industry (1975). At a ceremony at the White House in 1973, then President Richard M. Nixon presented Djerassi with the National Medal of Science. Djerassi was inducted into the National Inventors Hall of Fame in 1978. That same year he was the first recipient of the Wolf Foundation Prize. As we will explain in a future essay, this is one of the most remunerative and prestigious awards in science today.

In addition to his duties directing projects at Zoecon, Djerassi has a full schedule as a Stanford faculty member. Even though formally on a half-time appointment, he supervises the research work of approximately 20 graduate students and postdoctoral fellows, and carries a moderate teaching load. During the past few years he has been particularly active in undergraduate teaching by developing a series of policy courses taught as part of Stanford's innovative human biology program.

Carl's penchant for inventing things has carried over into his private life. Unfortunately, as the result of a skiing accident, Carl has a fused knee. But, with the help of a student, he designed a special ski boot which has enabled him to continue his favorite sport. In addition to skiing, Carl's avocations include collecting both primitive and modern art (notably the works of Paul Klee), and attending every performance of the San Francisco opera. His love for travel and outdoor sports culminated last year in a three-week trek through the Himalayas in Bhutan, where his fused knee did not prevent him from climbing up to altitudes of 15,000-16,000 feet.

It is a privilege to know and write about someone with Djerassi's range of interests and humanitarian concerns. His efforts to develop new technical methods for organic chemists, and his desire to unstop administrative and regulatory bottlenecks, reflect two different sides of his fierce commitment to productive science. Generations of chemists as well as the world's population at large will benefit from his tireless intellect and from his capacity to share his discoveries and perspectives with others.

I look forward to following Carl's work in the future. Maybe, he jokes, he will change his name and begin publishing another 1,000 papers. This would be an impressive feat. There is actually a record of one scientist, entomologist Theodore Dru Alison Cockerell (1865-1948), who published over 3,904 items. On the other hand, the eminent researcher Lord Kelvin published "only" about 650 papers. Of course, it is difficult to measure the quality and import in the fields involved. The ability to publish large numbers of papers varies from field

to field. In modern astronomy it is not feasible to publish a paper every week for 20 years or more. Perhaps in ancient times it was. Today, even prolific mathematicians do not produce as many papers as do, say, life scientists. Within a field, however, according to Derek J. de Solla Price, there is generally a good correlation between "the quantity and quality" of a researcher's publications. The most widely accepted explanation for this phenomenon is that successful publication leads to further publication and lack of success tends to discourage publication. The best researchers tend to be prolific publishers as well, and only rarely will their papers be "trivial and uncited."[42] There is a tendency to denigrate prolific scientists and lump them all together as though there were not considerable variation in the reasons why they are so prolific.

We hope that this essay will be the first in a series of tributes to prolific scientists like Djerassi. For instance, my friend Alan L. Mackay, Birbeck College, University of London, UK, recently brought to my attention the fact that the bibliography of the late Nikolai Vassilevich Belov, Institute of Crystallography, Moscow, USSR, includes approximately 1,500 publications.[43] If any *CC* readers know of other authors who have published, or are about to publish, their 1,000th paper, please let us know. When we have completed publication of *SCI* for 1955-1964 we will obtain a list of the most prolific authors for the past 25 years.

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My thanks to Patricia Heller and Kathleen Nell Schalch for their help in the preparation of this essay.

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