Carl Djerassi: Chemist and entrepreneur

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Much has been said about the scientific entrepreneur. Although the term ordinarily is applied to the person who has been successful in business—one thinks of Thomas Edison or Edwin Land, among others—there also are scientific entrepreneurs in the academic community. It is not often that one finds a scientist who can fit both descriptions. To maintain a credible academic existence one needs enormous dedication and energy; to function in a scientifically oriented business these qualities as well as significant managerial competence are needed. That rare combination of qualities is found in my friend Carl Djerassi.

I recently had the honor of speaking informally at an unusual event. The numerous friends and collaborators of Djerassi attended a party celebrating the publication of his thousandth 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 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 elucidating the structures of complex organic molecules and in applying these discoveries to the synthesis of pharmaceutically important compounds. He also is 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 used widely.

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 U.S. with $80 in his pocket. He spent two semesters at a now-defunct junior college in Newark, N.J., before accepting a scholarship from Tarkio College, a small school in Tarkio, Mo. In 1948, Carl enrolled in the graduate program at the University of Wisconsin, where he earned a Ph.D. in organic chemistry before his twenty-second birthday. After four years of industrial experience at Ciba, he grew restless and eager for a position in academe, but could not find one.

In the spring of 1949, Djerassi received a call from chemist George Rosenkranz--who was director of a small Mexican company called Syntex--inviting Djerassi to head a research team there (1). 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. Steroid chemistry had been the subject of Djerassi's doctoral dissertation, but at Ciba most steroid research was done in the laboratories at Ciba's Swiss headquarters.

It is of interest to mention that during this period work on steroid chemistry was almost frantic. In fact, the backlog of applications at the U.S. Patent Office eventually was so large that the Pharmaceutical Manufacturers Association financed a steroid literature coding project. Eugene Garfield Associates, predecessor of the Institute for Scientific Information (ISI), received the contract to do this work in 1958. We encoded more than 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 on the discovery that cortisone could alleviate arthritis symptoms. The chemical was derived from animal bile, but initially in amounts too small for treating this chronic, widespread disease. Scientists around the world were racing to find a more practical method of synthesis. In 1951, Djerassi and his team at Syntex won the race; they found a relatively simple way to make cortisone using a readily available raw material, the Mexican yam (2).

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 they could change the structure of progesterone to increase its potency eightfold. This progesterone analogue was strong enough to work when injected, but lost its potency when administered orally. The Syntex group needed a chemical that could be absorbed orally. A breakthrough came when they rediscovered a compound that, although synthesized more than a decade earlier, had largely been ignored because of its apparent lack of medicinal value (1). 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 made the same chemical modification in ethisterone that they had earlier made in progesterone. The result was synthetic norethisterone, which prevented ovulation, was orally active, and could be incorporated into a pill (1).

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. Natural products can be used as models for synthetic compounds. However, many natural products consist of molecules so large, complex, and delicate that relationships between their structures and functions—and in some cases, the structures themselves—are often obscure. At the time that Djerassi was beginning his career, it was still not uncommon for a natural-products chemist using traditional analytical methods to spend a lifetime analyzing the structure of a single substance (8).

New tools

It was to the inadequacy of physical methods available for assessing organic structures that Djerassi now turned his attention. In 1952, he was offered a professorship at Wayne State University in Detroit. 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 the principle of the Cotton effect; wherein polarized light changes as it passes through certain substances (4). Djerassi transformed this phenomenon into a practical tool for analyzing molecular structures. He found that many organic substances, notably those containing carbonyl groups,

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 by using them as fingerprints of molecules, made comparisons between molecules that never before were possible. The stereochemistry of unknown structures could be deduced from known structures and subtle differences between similar molecules discerned (5).

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 (5). 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.

Moreover, unlike the analytical techniques previously in use, Djerassi's inventions made it possible for chemists to establish the absolute configuration of molecules. Thus, chemists may effectively distinguish among enantiomorphs, crucial because mirror-image molecules often have entirely different biological properties.

Although optical rotatory dispersion and circular dichroism quickly became part of the standard vocabulary of organic chemistry, some of the most important discoveries involving these techniques have been made in Djerassi's laboratorv. During the 1950s, much of his work involved the elucidation of the structures of terpenoids *(6-14).* Djerassi provided information that had long been sought concerning the biosynthesis of terpenoids by determining the structure of iresin, a key biosynthetic "missing link" between the lower and higher terpenes *(14).*

During the 1950s, Djerassi also grew interested in other classes of chemicals, particularly alkaloids and macrolide antibiotics. In 1956, he and J. A. Zderic became the first investigators to identify the structure of a macrolide antibiotic. The size and complexity of macrolides 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. One special feature of the macrolides is that they include the only antibiotics effective against fungal disorders (5).

During the 1950s and 1960s, much of Djerassi's work involved novel alkaloids found in tropical plants. In this field, Djerassi saw promise in a new analytical technique called mass spectrometry (MS). Until the 1960s, MS had not been a useful tool for organic chemists because under electron bombardment, molecules would merely "shatter into a confusing array of pieces" *(15).* Without detailed knowledge of how these molecules were likely to split apart, it was hard to identify fragments just based on mass and charge.

In 1961, Djerassi, who had been on the Stanford faculty for tx~o years, began to develop MS as a tool for structural elucidation. This involved looking for rules that 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 them ~ ith electrons. In this way, they determined how different groups of atoms, which normally make up segments of organic molecules, respond to electron bombardment (16). They compared these results with fragmentation patterns of more complex molecules and were eventually able to produce a comprehensive set of theories that could be used to interpret the mass spectra of organic molecules. I remember the early days of Carl's interest in mass spectrometry because we considered creating a new molecular weight index for *Index Chemicus,* derived automatically from the molecular formula. Since then, some of Carl's most important discoveries and influential publications have been buih on that earlier research, making it possible for him to use and interpret mass spectral data *(16-24).*

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During the past 10 years, Djerassi has continued his efforts to develop and refine the tools used for structural elucidation. Together with Joshua Lederberg and Edward Feigenbaum, Djerassi undertook a major collaborative program on the use of computer "artificial intelligence" techniques in organic chemistry (25, 26). The group developed a series of computer programs to analyze raw data from MS and other techniques. For instance, given the mass and charge of a particular fragment, a computer could create a list of possible identities for that 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" (4). The MetaDENDRAL program 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 MS *(26).*

In the past decade, Djerassi has employed the new analytical methods he helped develop to examine a group of exotic sterols found only in marine sponges and soft corals. While terrestrial organisms produce only cholesterol and a few simple variations, a single marine organism may produce 70 different sterols *(27).* "The question," Djerassi muses, "is what are these things doing in the ocean, and why are they not in plants and animals on earth?" (4).

One intriguing possibility is that these sterols represent missing links that will tell us something about the evolution of cell membranes *(28).* It was discovered recently that sterols help to maintain the integrity of cell membranes, and are involved with regulating their permeability. Primitive single-celled organisms like bacteria and blue-green algae cannot manufacture sterols; the ability to do so was probably a prerequisite for the evolution of multicellular forms of life. The sterols in primitive aquatic animals may reveal the first step in the evolution of higher life forms and offer further insight into the physiology of cell membranes *(28).*

Until 197'2, in addition to the research Djerassi did at Wayne State and Stanford, he maintained his affiliation with Syntex. He continued to serve as a vice-president of Syntex until 1959, when he accepted a 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, when he resigned to devote his nonacademic time to Zoecon Corporation, a small offshoot of Syntex that he helped to found. Zoecon is engaged in developing "'biorational" insecticides. It receives much of his attention: he is president and chairman of the board.

Crop protection

The insect control agents being developed at Zoecon are analogues of naturally occurring insect hormones. For instance, by modifying the chemical structure of insect "'juvenile" hormone, Zoecon workers have derived substances that can retard insect development. The result is either the death of the insect, or its ineffectiveness as a pest. Further, because hormone analogues, 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 *(29).* Thus, they appear to be remarkably free from adverse ecological effects.

In addition to hormone analogues that stunt insect growth, others can cause "mental retardation," interfere with molting, or cause insects to develop in miniature. The Zoecon group has also initiated studies of pheromones, chemicals that can send false signals to insects, confusing them enough to cause them to emerge prematurely from hibernation and freeze, or "run like crazy or drop off the leaf" they may be eating *(29).*

Djerassi believes these new pesticides can help reduce the "chemical load" in the environment. "Although we cannot eliminate the chemicals in our environment, we can have both fewer chemicals and more exquisitely designed ones," he says. "I can think of no area where we can do this more effectively than with pest control." Insect-borne diseases kill more people worldwide than cancer or heart disease. In addition, much of the world's food supply is destroyed each year by insects (4).

Djerassi feels that his most significant contributions have been made in basic research.

In areas such as pest control and birth control, Djerassi has argued that the problems of the less-developed countries should 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 *(30).* In his most recent book, "The Politics of Contraception," Djerassi examines the web of economic and political factors affecting the fate of new technologies (1). In her review of the book, Elizabeth B. Connel writes, "Only an individual with Djerassi's diverse background--scientist, politician, writer, and keen observer of the social and bureaucratic scenei have produced a volume so vitally important and eminently readable" *(31).*

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 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" (1).

In addition to gearing investigations more toward the needs of the less-developed countries, Djerassi feels that the international scientific community should provide more aid to researchers in these countries. He has sponsored a number of measures to increase the level of scientific exchange between industrialized and nonindustrialized countries. For several years he chaired the National Academv, 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 (32). 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 in Nairobi, Kenya. It is a fine 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. The number of papers Djerassi has published that can be regarded as classics is remarkable. Formerly, his most-cited paper was "The Direct Conversion of Steroidal A5-3“ to A5- and A4-3-Ketones" *(33).* Several years ago we invited Carl to write this up as a "Citation Classic" for *Current Contents* but he declined because he felt that his 1961 article, "Structure and tile Optical Rotatory Dispersion of Saturated Ketones" (8), was far more influential. The citation data now agree with Djerassi's assessment. The paper's coauthor is Nobel chemist Robert B. Woodward, and is based on Djerassi's initial work with optical rotatory dispersion. It disclosed the correlation between the optical and structural characteristics of sterols.

Another "Citation (;lassie" *(34)* by Djerassi is a book written with his postdoctoral fellows Herbert Budzikiewicz and Dudley Williams, entitled "'Mass Spectrometry of Organic Compounds."

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 U.S. National Academy of Sciences, the American Academy of Arts and Sciences, and several foreign academies. The American Chemical Society has honored him with the Award in Pure Chemistry (1959), the Baekeland Medal (1959), the Fritzsche Award (1960), the Award for Creative, Invention (1973), and most recently the American Chemical Society's Award in the Chemistry of Contemporary Technological Problems (1982). He also has received the Freedman Foundation Patent Award (1971), 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, President Richard M. Nixon presented Djerassi with the National Medal of Science; he was inducted into the National Inventors Hall of Fame in

1978. That same year he was the first recipient of the World Foundation Prize, one of the most remunerative and prestigious awards in science.

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 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 education, developing a series of policy courses as part of Stanford's innovative human biology program.

Carl's penchant for inventing things has carried over into his private life. 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 that enables him to continue his taw)rite sport. His other avocations include collecting 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 to altitudes of 16 000 ft.

1 look forward to following Carl's work in the future. Maybe, he jokes, he will change his name and begin publishing another 1000 papers. That would be an impressive feat. There is actually a record of one scientist, entomologist Theodore Dru Alison Cockerell (1865-19481, who published more than ,3900 items. On the other hand, 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. Within a field, however, according to Derek J. de Solla Price, there generally is 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" (,35).

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.

For a unique list

I 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, U.K., recently brought to my attention the fact that the bibliography of the late Nikolai Vassilevich Belov, Institute of Crystallography, Moscow, U.S.S.R., includes about 1500 publications. If any readers know of other authors who have published, or are about to publish, their one-thousandth paper, please let me know. When we have completed publication of the *Science Citation Index* for 1955-64 we will obtain a list of the most prolific authors in the past 25 years.

References

(1) Djerassi, C. "'The Politics of Contraception": W H. Freeman; San Francisco, Calif., 1981.
(2) Rosenkranz, G.; Pataki, J.; Djerassi, *C. J. Am. Chem. Soc.* 1951, 73, 4055 56.
(3) Djerassi, C. *Pure Appl. Chem.* 1975, *4I.* 113 44.
(4) Djerassi, C., personal communication, 1982.
(5) Djerassi. C. "Modern Scientists and Engineers"; Parker. S. P.. Ed.: McGrawi Hill: New York, 1980; Vol. 1, pp 294 96.
(61 Djerassi, C.; Riniker, R.; Riniker, *B. J. Am. Chem. Soc.* 1956, 78, 6362 77.
(7) Djerassi, C.; Halpern, O.: Halpern, V.; Riniker, B. J. Am. *Chem. Soc.* 1958, 80, 4001 15.
(8) Moffitt. W.: Woodward, R. B.: Moscowitz, A.; Klyne, W.: Djerassi. C *J. Am. Chem. Soc.* 1961,83, 40113 IS.
(9) Djerassi. C.: Records, It.: Bunnenberg, E.; Mislow. K: Moscowitz, A. *J. Am. Chem. So(:.* 1962, *84,* 87(1 72.
(101 Moscowitz.A.: Mislow, K.; Glass, M. A. W.; Djerassi, C *J. Am. Chem. Soc.* 1962, 84, 1945 55.
(111 Djerassi, C.; Klyne, *W. J. Chem. Soc. Chem. Commun.* 1962, 4929 50.
(121 Wellman, K. M.; Djerassi, *C. J. Am. Chem. Soc.* 1975, 87, 60 66.
(13) Barth, G.; Djerassi, C. *Tetrahedron* 1981, *37,* 4123 42.
(14) Djerassi, C.; Rittel, W.; Nussbaum, A. L.; Donovan. F. W.; Herran, *J. J. Am. Chem. Soc.* 1954, 76, 6410 11.
(151 Peterson, I. *Sci. News* 1981, *120,264* 67.
(161 Budzikiewicz, H.; Djerassi, C.; Williams, D. H. "Interpretation of Mass Spectra of Organic Cnmpounds"; Holdeni Day: San Francisco. Calif., 1964.
(171 Budzikiewicz, H e t al. "Structure Elucidation of Natural Products by Mass Spectrometry": Holdeni Day: San Francisco. Calif.. 1964; Vols. 1 and 2.
(181 Shapiro, B. H; Djerassi, *C. J. Am. Chem. Soc.* 1964, 86. 2825-:32.
(191 Budzikiewicz, It.; Wilson, J. M.; Djerassi. *C. J. Am. Chem. Soc.* 1963, 85, :3688-99.
(20) Brown, P.; Djerassi, (2. *Angew. Chem. Int. Ed.* 1967, 6. 477-96.
(21) T¦233 L.; Jones, G.: Djerassi. C. J. Am. *Chem.* Soc. 1968, *90.* 5465-76.
(22) Dixon, J. S.; Midgley, I.; Djerassi, C. *J. Am Chem.* Soc. 1977, *99.* :34:32-41.
(2:3) Partridge, L. G.; Midgley, I.; Djerassi, C. J. Am. *Chem. Soc.* 1977, *99,* 7686 95.
(24) Massey, 1. J.; Djerassi, *C. J. Org. Chem.* 1979, *44,* 2448 56.
(25) Djerassi, C; Smith, D. It.; Varkony, T. H. *Naturwissenschaften* 1979, *66.9* 21.
(26) Lindsay, t1. K.; Buchanan, B. G.; Feigenbaum, E. A.; Lederberg, J. "Applications of Artificial Intelligence for Organic Chemistry. The DENDRAL Project"; McGrawi Hill: New York, 1980.
(27) Djerassi, C. *Pure Appl. Chem.* 1981, 53, 875i 911.
(28) Carlson, R. M. K.; Tarchini, C.; Djerassi. C. In "Frontiers of Biorganic Chemistry and Molecular Biology"; Ananchenko, S. N.. Ed: Pergamon Press: New York, 1980; pp. 211-24.
(29) Bylinsky, G. *Fortune* 1973, 88(12), 94-103.
(30) Djerassi, C. *Chem. Ind. London* 1975, 14, 59:3 95(Perkin Medal Award address).
(311 Connell, E. B. *Bull. Atom. Sci.* 1981,,'37(:31.46
(:32) Garfield. E. "'The Pugwash Conferenceson Scienceand World Affairs: Twenty-Two Years in Search of Peace,"' in "Essays of an Information Scientist": ISI Press: Philadelphia. 1981; Vol. 4. pp. 2IX) 207 ireprinted from *Current Contents* 1979, 26 (June 25), 5 12.
(33) Djerassi, C.; Engle, it. 11.: Bowers. A. J. Org. *Cherm.* 1956, *2l.* 1547 49.
(34) Budzikiewicz, H.; Djerassi. C.; Williams. D It. "'Mass Spectrometry of Organic Compounds"; Holden-Day: San Francisco. Calif., 1967; *Current Contents/Phys. Chem. Earth* Sci. 1982, 22(:34). 18.
(35) Price, DJ. D "Britannica 1975 Yearbook of Science and the Future": Encyclopaedia Britannica, Inc.: Chicago, 1974: pp. 409-21: s.v. productivity of research scientists.

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