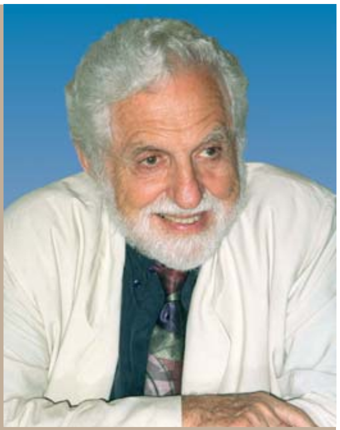
interview

Carl Djerassi discusses pills, plays and prizes

Interviewed by Samantha Barton and Jayne Carey

Carl Djerassi

Playwright and emeritus professor of chemistry



Carl Djerassi, emeritus professor of chemistry at Stanford University, is one of the few US scientists to have been awarded both the National Medal of Science (for the first synthesis of a steroid oral contraceptive) and the National Medal of Technology (for promoting new approaches to insect control). A member of the National Academy of Sciences, the Leopoldina and the Swedish and other foreign academies, he is also the recipient of 20 honorary doctorates and numerous awards. Recent ones include the Österreichische Ehrenkreuz für Wissenschaft und Kunst (1999), the Preis der Gesellschaft Deutscher Chemiker für Schriftsteller (2001), the Grosse Verdienstkreuz der Bundesrepublik Deutschland, as well as the Erasmus Medal of the Academia Europeae (2003) and the Gold Medal of the American Institute of Chemists (2004). He founded the Djerassi Resident Artists Program near San Francisco, which has provided residencies and studio space for over 1400 artists in the visual arts, literature, choreography and music. His literary writing (short stories, poems, five novels and five plays, as well as an autobiography and a memoir) focuses mostly on themes related to science. Djerassi's fiction and plays have been translated into over a dozen languages; several of his plays were also broadcast by the BBC World Service and the West German Rundfunk (WDR).

During your career, you've been instrumental in the development of several life-changing drugs, including norethisterone, the active ingredient in the birth-control pill, which is based on a natural product. What first interested you in the area of natural product research?

My interest in this area really started with steroid chemistry, which is what I was interested in as a graduate student. My PhD thesis dealt with the then difficult problem, which even now is not an easy one, of the chemical conversion of male sex hormones to female sex hormones. In other words, testosterone to estradiol. Now, it turns out that a lot of interesting natural products are steroids. My interest initially was as a synthetic chemist. While living in Mexico, where I was working as associate director of chemical research at Syntex, I became interested, as a tourist, in the archaeology and the flora and fauna of Mexico, particularly in giant cacti. In 1952, I started my academic research at Wayne State University (MI, USA), where I remained for seven years before going to Stanford University (CA, USA), with a major research project on the chemistry of natural products from giant cacti, and that led to an interest in triterpenes and alkaloids and from there to other natural products. So, I really gradually became a natural product chemist from my interest in steroids rather than the other way around.

'…the more significant one in terms of general utility, is the development of physical methods…'

The other major area of my chemical career, and probably the one that I think organic chemists in general would consider the more significant one in terms of general utility, is the development of physical methods and their application to organic chemistry, particularly, optical rotatory dispersion (ORD), optical circular dichroism (CD), mass spectrometry (MS) and, finally, computer artificial intelligence techniques. And the reason again for that is that, as a natural product chemist, one is interested in any help one can get to elucidate structures. Thus, you become interested in using these techniques – much more so than synthetic chemists! Not only did I become a user of them, but my research group was a pioneer in introducing them to organic chemistry and that turned out to be, I think, a longer lasting and much broader effect of my work than just the structure elucidation of natural products.

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You have had a great impact on the development of methodologies for the elucidation of the structure of complex organic molecules. If the technologies of today had been available to you in the early 1950s, and the regulatory procedures had been in place, how do you think your research would have differed?

First of all, I would say, if all these physical methods had then been available, I think natural product chemistry, and not just in particular for us, would have been very different. Natural product chemistry, and I emphasize the word chemistry, was really the most interesting area, I would say, of organic chemistry for a period of well over 100 years, because it involved a lot of actual chemistry. This has been essentially destroyed by the use of physical methods – I use the word 'destroyed' as a very pejorative one because in a way it's a pity from an aesthetic intellectual standpoint, although not from a practical standpoint, and I contributed greatly to this destruction. But, it is a pity because in the process one learned an awful lot of organic chemistry and a lot of organic chemistry was developed through hard chemical work in structure elucidation. Nowadays, structure elucidation is exclusively the utilization of sophisticated physical methods – there is practically no laboratory chemistry being done.

'…I contributed greatly to this destruction.'

Your other question was about regulatory climate. Well, that's a completely different question that I need to answer as a professional bigamist. I was always an academic as well as an industrialist. As an academic, regulatory affairs would not have affected me at all as a professor. It would have affected me greatly as an industrialist, no question whatsoever. I don't think, to disappoint or deflect you even more, that I would have become a chemist if everything had occurred 50 years later.

What do you think you would have done?

I think I would have become, one way or another, a biologist. Let me say right away, I wouldn't go butterfly collecting or put beetles in museum cases or be a taxonomist. I would be very much a chemical biologist. I would have probably studied for a PhD in organic chemistry, as so many biochemists or molecular biologists and protein people do. But, I think the work would have been primarily in the area of what are now the hot areas of biology, in the broadest context.

'…research does not have to be as expensive as many of the large pharmaceutical companies make it out to be.'

How effectively do you think academia and industry collaborate?

Well, it was rather different when I did this in the USA. I was probably one of the very first ones who was able to work concurrently in both areas, primarily through a great deal of luck by being hired as a full professor at Stanford University rather than starting up the academic ladder. Stanford's Provost at that time, Fred Terman, who many considered the 'Father of Silicon Valley', was a great believer in collaboration between industry and academia. And no question that is why the Stanford Industrial Park was the focus of this type of integration, which we now have in many different places. Although it has its pros and cons, at that time, because it was so unusual, it worked very well. I drew a firewall between my academic and industrial work – the academic work I did had nothing to do with my industrial and my industrial nothing with my academic. So, I didn't file a single patent for any of my academic research – it was all published and I published well over 1000 papers, which is probably too much for many people. On the other hand, I performed or directed serious industrial research, but I was very careful not to have that overlap. That is a luxury that most people who now work in industry and academia cannot afford. Academics are hired by industrial firms as consultants for exactly what they are doing in academia. The potential conflict of interest, let's say, with people who establish small biotech companies and are also in academia is complicated. I'm not against it. I just think there has to be utter transparency and the thing one has to be extremely careful about is not to exploit graduate students and post-docs.

Your early research on the precursor to the pill was conducted at Syntex, which was based in Mexico. Do you think that 'big Pharma' should invest more money in research in developing countries?

Well, yes and no. Considering the matter of humanity and goodwill and long-term vision, the answer would be a categorical 'yes'. It depends what place you are talking about, what you call a 'developing' country – for instance, Burkina Faso or Brazil. People still call Mexico, Brazil and India, and China perhaps, 'developing' countries. With China, we all know the writing is on the wall, Brazil is, in many areas, very sophisticated, and India is certainly progressing very rapidly. Furthermore, Indian generic manufacturers have had quite an impact on cheap drugs, notably for AIDS. Mexico is a good example of a country that became, in the 1950s, a hotbed for steroid chemistry. But, on the whole, it's easier to do advanced research in highly developed countries. The advantage in the lesser-developed countries also involves the cheaper labour cost. But I think that the answer that I would give is that the enormous changes in the pharmaceutical industry, such as the mega-mergers that occurred in the past 15 years and their emphasis on blockbuster billion-dollar drugs that didn't exist before the late 1970s (Tagamet was the first one), also resulted in greatly escalating costs of research. These costs were, in some respects, self-generated – research does not have to be as expensive as many of the large pharmaceutical companies make it out to be. I think they are paying the price of ungainly and inefficient size and, at the same time, you had the explosion of emerging small biotech companies during the last 20–25 years that at one stage were discounted by the large companies. I am both a great proponent of the pharmaceutical industry and also a great critic. I think that the manner in which drugs are promoted via drug 'detail' men is one of the most preposterous and inefficient ways to accomplish that. I also think that the 'me-too' type of research, which is enormous, is just completely absurd and therefore leads to a form of escalation of drug costs which are societally unwarranted.

I would say that research funds should be spent on other and as yet unavailable drugs –

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say developing a male pill. But, of course, I can also give you good economic reasons why, if I ran a pharmaceutical company for profit, I would not spend it on a male pill. If I did not have philanthropic or worldwide views, but parochial company views, I would focus on Viagra substitutes and oncology and anti-inflammatory drugs, and of course Alzheimer's disease and other health problems of a geriatric population. I would not spend it on malaria or any tropical diseases of the 'paediatric' world. But I have the luxury now of being able to criticize such an attitude as a bystander who has nothing to do with a pharmaceutical company. So I can make such statements, but I do not make them in an accusatory way. I think the changes, quite frankly, will not be instituted by the pharmaceutical industry. And it's unrealistic to assume that they should carry the entire burden. The burden also has to be carried by the public, it has to be carried by governments, and they have to provide incentives to do research in different, less popular areas. They should have a form of price control for me-too drugs, to make it as difficult as possible to market new me-too drugs because most are just created to maintain or establish a proprietary position with relatively little incremental medical benefits. It has to be a 'carrot and a stick' proposition, but right now there are plenty of 'sticks' but few 'carrots'.

> 'It has to be a 'carrot and a stick' proposition…right now there are plenty of 'sticks' but few 'carrots'.'

You mentioned the male contraceptive pill. Do you think that a male contraceptive pill would ever be successful?

If we'd had one 10–20 years ago, the answer might have been 'yes'. But I'll answer it a different way. If no oral contraceptives for women had been discovered in the 1950s and early 1960s, there wouldn't be any oral contraceptive now. The climate now is such that you couldn't develop, in my opinion, the first oral contraceptive for women. Because now the question would be asked – 'well, what if the woman takes it for 20 years?' You would never get it in any sort of economic way through regulatory trials. Also, women are postponing childbearing until they are older because most of them are working or have other priorities. I can see a future scenario where people will get sterilized when they are very young (rather than in middle age, as they do now) after cryopreserving their gametes and then have only one or two children by means of *in vitro* fertilization (IVF). From that standpoint, putting the onus on the male is very simple, because the long-term storage of sperm is well perfected and the success rate of IVF in fertile people as high as in natural intercourse. Thus, I think that in 20–30 years, people in Europe and other highly developed areas won't need birth control anymore at all. You will have to worry about conception and infection of sexually transmitted diseases rather than about contraception. And so that is one other reason why I think pharmaceutical companies don't pay much attention to the field of contraception anymore. And I can understand that from a hard-nosed commercial standpoint.

> 'The climate now is such that you couldn't develop…the first oral contraceptive for women.'

You are also well-known for your literary exploits, with your first 'science-in-theatre' play,* An Immaculate Misconception*, premiering in 1998. What do you think is the role of the theatre in the promotion of science?

Well I think this is a good example that you picked. *An Immaculate Misconception* was my first play, and of course I learned a lot about play writing, because in the process I wrote 24 versions. In my earlier life, and since then, I've never written 24 versions of anything! Although this play was by an unknown playwright and was his very first play, it was nevertheless broadcast by the BBC World Service and other radio stations, and within four years was translated into eleven languages – this is not common for any play. Not that it was a sensational success commercially, but it has had an important impact and continues to be performed in theatres in many countries.

I believe that when one deals with things that address science, and I don't mean just scientific topics, but especially the behaviour of scientists and the societal implications of science, these topics are always presented in monologist forms. Nothing in science is ever published in dialogic form. No scientific journal ever appears in dialogic form. Everything is monologist, it's preaching, it's pontificating. This brings me to a wider use of science plays, beyond just theatrical performances, which, of course, are entirely dialogic. So why not read on occasion books that are entirely dialogic, in other words plays? People are not accustomed to reading plays except by canonical authors like Shakespeare and so on. Otherwise, most of the plays being published, at least contemporary plays, are being published in theatre editions for actors and theatres and theatre goers, rather than for a book-reading public. I'm interested in my plays also appearing in that broader 'book' way. Fortunately, that has been the case with my first four plays, which have already appeared in eight languages in book form. To go even further, *Calculus*, the third one, which was performed wonderfully well in London in August 2004, has now been converted into a chamber opera, which will have its premiere in May 2005 at the Zurich Opera House. That's going to be very exciting. Again, how many operas, or chamber operas – ones that you know – deal with a scientific topic? Very few. That is why I am currently focusing on playwriting. It is a way of gradually bridging the gulf between the scientific culture, on the one hand, and the scientifically ignorant or even scientifically antagonistic public on the other.

> 'If you want to be interested in the ethics of research, then you also ought to be interested in what drives us as a scientist…'

With regard to your plays, do you think there are any particular aspects of science that have not been dealt with in a theatrical medium?

Well, I think assisted reproduction is a particular example, which was used in my first play. There had been essentially nothing in this area, nothing in the context in which I do it, done in a realistic way. You have an audiovisual where you see a real intracytoplasmic sperm injection. It was done at the University of California and we filmed it. It's done in the play as if it were done right in front of you.

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The woman actually hunches over a microscope connected to a video monitor as they do it in real life. So, you really think you are seeing the real thing. Or take the second play, *Oxygen*, which has a lot about the Nobel Prize. It was written in a very realistic way for the centenary of the Nobel Prize. My collaborator, Roald Hoffmann, incidentally, has won the Nobel Prize. We are both foreign members of the Swedish Academy, and can therefore nominate people for the Nobel Prize every year and we are very familiar with the manner in which Nobel winners are picked. Initially, we thought that staging the play in Stockholm at the centenary of the Nobel Prize would be exactly what the Swedes would do, because the BBC broadcast the play on that day over the World Service, and so did the West German radio. At the last minute, the Swedes rejected it because they really felt, well I can't say that they felt we demeaned it, because we didn't, that we were perhaps too realistic. My third play, *Calculus*, is about Newton. And it's really about Newton the man, not Newton the genius, but Newton in terms of being really a terrible person. He was a fantastic scientist, a genius. But as a person, he was terrible. And the question was – is it appropriate to talk about this? Write a critical rather than hagiographic play about him? It's called *Calculus* and deals with the 30-year long bitter struggle between Newton and Leibniz as to who first invented calculus. Actually, in the *Times Literary Supplement* review of the book, a historian says, 'Well, what does a moral calculus have to do with the mathematical calculus?' I was sort of surprised that a historian would ask that. Usually, it's the scientist who would say that. But, of course, in my opinion, it does indeed have a great deal to do with it. If you want to be interested in the ethics of research, then you also ought to be interested in what drives us as a scientist both in a positive and a negative way. So it is not a derogatory view of Newton at all – it is a historically very well documented, but revisionist review of Newton as a person, not, of course, as a scientist.

Moving on to the general public, do you think the general public has a sufficiently developed awareness of the issues in science?
Especially not about the culture of science. They have zero knowledge – or I would say 0.5% knowledge – but the trouble is that even most scientists are not very knowledgeable about that since we are not a very self-reflective tribe or society. We learn our behaviour and cultural practices not through lectures and courses and books, but through intellectual osmosis from our mentors and colleagues and thus gradually acquire these very tribal customs without realizing what they are. Basically, we analyse the world around ourselves and analyse ourselves very little.

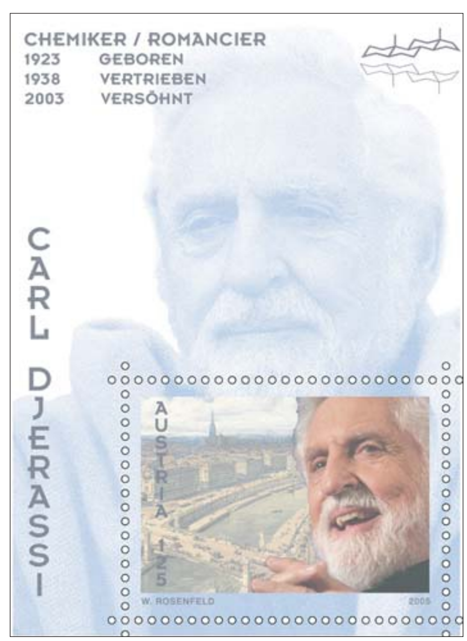
> ***'…we analyse the world around ourselves and analyse ourselves very little.'***

I particularly attempted to do this in my first two 'science-in-fiction' novels – not to be confused with science fiction. These first two novels deal primarily with the behavioural practices of academics. In the first one (*Cantor's Dilemma*), I have the entire age range from undergraduate to graduate to post-docs to professors. In the second one (*The Bourbaki Gambit*), I have mostly older scientific types to reflect our rapidly ageing society. It turned out that these two books that I've written for the general public are still being reprinted all the time. The first one has been reprinted, I think so far seventeen times, including three times last year, only because it has been used as a textbook in many colleges and universities, which is not at all the reason for which I wrote it initially. It's now a completely different readership, hardly anymore the general public. Now it is mostly the graduate students and undergraduates who are going into science and the novels tell them something realistic about what it's really like in the scientific tribal culture.

> ***'Ambition is both a nourishment and a poison of a successful person.'***

Who would you say has been the greatest influence on your career? Is there anyone in particular?
You are not the first person who has asked that and I've often asked that of myself. It is strange that I cannot point to anyone. I've not had a real mentor. I was always an outsider. So, I would say that I didn't have any real influence. My motivation was always ambition. I'm an extremely ambitious person. I'm not bragging. On the contrary, it's undoubtedly a character fault, but it's also an advantage. Ambition is both a nourishment and a poison of a successful person.

During your career, you've been the recipient of countless awards. Is there any in particular that you are most proud of?
Well, I tell you, the Austrian post office is coming out with a stamp of me and usually you have to be dead before you can see yourself on a stamp! It is a rather nice one because it has a steroid chemical structure on it and it also describes me both as a chemist and as a fiction writer. Of course, one usually talks about awards one hasn't gotten, but that one would like to get. The answer is, I think, it's things like this stamp, the ones that you do not expect. You know, most awards are standard ones. If you don't expect them, at least you lust for them. But I'm talking about something like a stamp that I didn't expect at all. I didn't have the foggiest idea. I was both amused and pleased by it, especially when I learned that my face consists of microscopic chemical structures! No wonder I grabbed my magnifying glass!



Stamp issued by the Austrian postal service honouring Carl Pjerassi. Image kindly supplied by Carl Djerassi.

business trends

When you were given the National Medal of Science, you had made Nixon's White House 'Enemies' list. What did you do to get onto this list?

That was discovered in 1973 about two weeks after I got the National Medal of Science, which was hilarious. The newspapers, particularly the big newspaper in San Francisco, *The San Francisco Chronicle*, had this wonderful headline: 'Nixon gives medal to enemy'. Somehow, I'd gotten on the list of people who were opposed to Nixon and opposed to the Vietnam War. Nixon and I are shown in a photograph, where we shook hands and beamed at each other. When I hung it up in my office, my students prepared a lovely counterpart in calligraphy saying: 'Support your local enemy'. Those two were always hanging side by side in my office.

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Carl Djerassi's latest play *Phallacy* is running from 5 April–14 May 2005 at the New End Theatre in Hampstead, London, UK. For more information, go to: http://www.djerassi.com.

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Cannabinoid therapeutics: high hopes for the future

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The psychoactive properties of *Cannabis sativa* (cannabis) were first recognized 4000 years ago by the Chinese. However, it is the illicit properties of cannabis that are rendering it increasingly popular worldwide, with the number of recreational cannabis users rising considerably [according to a United Nations (UN) report] compared with other abused narcotics. At low doses, the effects are euphoria, feelings of relaxation, altered sensations, reduced pain and increased laughter, talkativeness and hunger. In addition, users experience decreased problem-solving ability, short-term memory and psychomotor performance. At higher doses, effects include personality changes and hallucinations. In addition to its recreational use, cannabis has been used in medicine for thousands of years for the treatment of diseases, such as malaria, constipation and rheumatism, in countries including China and India, as well as the Middle East. However, in the Western World, the medicinal benefits of cannabis were not appreciated until the middle of the 19th century.

Research into cannabinoids and their receptors

The active compounds of cannabis are cannabinoids. Interest in the potential medicinal value of these compounds led to the identification of over 60 separate cannabinoids and, of these, δ-9-tetrahydrocannabinol (THC) and cannabidiol have been extensively characterized. The resultant understanding of their interactions at the molecular level has enabled major advances over the past two decades in realizing the therapeutic potential of cannabinoids. THC is largely responsible for the psychoactive properties of cannabis and has demonstrated analgesic, antispasmodic, antitremor, anti-inflammatory, appetite stimulant and antiemetic properties. Cannabidiol has had anti-inflammatory, anticonvulsant, antipsychotic, antioxidant, neuroprotective and immunomodulatory effects.

The endogenous cannabinoid system was identified in the late 1980s, and, in 1992, anandamide, the first endogenous cannabinoid, was discovered. Anandamide, the name of which comes from the Sanskrit word for bliss, can be found in numerous areas of the brain, including the hippocampus, striatum, thalamus and cerebellum. Other endogenous cannabinoids, such as arachidonyl glycerol, have also been identified.

These compounds act via two distinct G-protein-coupled receptors – the cannabinoid (CB) receptors CB_1 and CB_2. Recreationally and medically, the biological effects of cannabis and other exogenous cannabinoids on CB_1 and CB_2 receptors have been extensively investigated. CB_1 is abundantly expressed in the brain, particularly in regions where anandamide is found, and those areas concerned with movement, postural control, pain and sensory perception, memory, cognition, emotion and autonomic and

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