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PERSPECTIVE

The advent and evolution of QSAR at Pomona College

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Setting a new idea (QSAR) in the context of five dimensional space

We are pushed willy-nilly into this incredibly complex universe at a particular point in time, in n-dimensional space, for an almost instantaneous blick around and then pass into oblivion.

First, consider the usual three dimensions. A single human is about 1,000,000,000,000,000,000,000,000 times smaller than the earth it momentarily inhabits, but the earth is so insignificant. It is a speck circling the sun that is 2,000,000 times larger. However, the sun is an ordinary star embedded with 100,000,000,000 stars in our galaxy. But our galaxy is only one of around 50,000,000,000 galaxies. Only very slowly during the past 500 years have people begun to develop some feeling for the fact that they and the earth are not the center of the universe. Fifty years ago, there were astronomers who thought that the earth, with man, was possibly unique in the universe. Today most have little doubt that life something like ours occurs elsewhere. However, even communicating with a very near star, say 20 light years away, would be virtually impossible. An exchange of messages would require 40 years! It is about 10–15 billion light years to the edge of the universe. Almost everything is beyond our reach for the foreseeable future, but that does not mean it is of no importance (a light year is about 5,000,000,000,000 miles).

Now considering a fourth dimension, time, we shrink still further in significance. Life on earth has been evolving for over a billion years, but only in the last few 1,000 years have we begun to leave some kind of written record. It is highly likely that the earth will survive another billion or more years. What will the history of the last (primitive) few 1,000 years mean in 500,000 years, or 10,000,000 years! The accumulation of data in the form of history (even at the present very slow rate) will be gargantuan.

This leads to a fifth dimension that is overwhelming. Already we are adrift in a huge cloud of information from the past brief moment of recorded history. For example, the Library of Congress acquired its 100,000,000th item in 1992. The collection at that time contained about 15,000,000 books, 39,000,000 manuscripts, 13,000,000 photographs, 4,000,000 maps, 3,500,000 pieces of music and 500,000 motion pictures. How many of these books can a person consider in say, 50 years? One might read 5,000 books, but which ones? What the many older libraries of Europe and Asia contain is incredible. Of course much of our reading is squandered on escape literature, such as mysteries, light headed novels, cheap newspapers, etc. From my own point of view, I am aghast at what is happening in the single area of chemistry. With *most* of the world not yet participating, the abstracts of over 2,000 articles and patents appear daily! If you miss 10 days, you fall behind over 20,000 reports. Libraries are finally beginning to realize that they cannot continue to collect such huge volumes of work on paper. Just in time, the Internet, on which anyone or everyone can have one or more web sites and on which unlimited information can be stored, has arrived. People are now publishing their own novels and scientific papers on the Web. It has been said that within a few years, a billion computers around the world will be connected via the Internet and the Web. The distillation of honest and relevant information out of this babble remains a work in progress. How much of it has already been lost or buried?

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If, in the next 1,000,000 years we accumulate information (newspapers, magazines, books, scientific journals, web sites, movies, and music) at an ever-increasing rate, what will it all mean? We are already lost in 4-D space. Will we, in a few 100 or 1,000 years, through advances in chemistry and biology mastermind our own evolution and become an unrecognizable species by today's standards? We have now worked out the structure of the human genome. With the cloning of people and the ability to modify DNA, some "studies without boundaries" will be undertaken. We are already beginning to tinker with the human mind with specialty antidepressants such as Prozac. The book *Listening to Prozac* reveals cases where a number of previously reclusive women after taking Prozac lost their inhibitions and ventured out onto the social scene. The author time and again asks: "would it have been right to give Emily Dickinson Prozac?" She might have then become the life of the party and not written a single line of her beautiful poetry! Tinkering with the human mind will no doubt have its downside, but it may be the only way to temper the meanness of man. For some time sperm banks have capitalized on the desire of women wanting to produce geniuses or handsome offspring by selling sperm of desirable and attractive men. Recently women have gotten into the act by offering to sell their eggs (for as high as $150,000 each). It is now possible to buy both reproductive items in order to produce "wonder kids" (*maybe*). Will the consilience of the sciences allow man to totally re-design himself? Or will nuclear bombs and biological warfare send us back to the beginning?

The above is one way of looking at mankind that leaves one with the feeling that life is meaningless. Obviously few people appear at present to act on such information. There is some sense that the history of the past few years is very important (do people in Rwanda act this way?). Personal relationships between family members, friends and countrymen seem important. How can all of this be reconciled? We are left with Niel Bohr's Principle of Complementarity that addresses wave-particle and space–time duality. Bohr suggested that the two complementary ways of describing an electron were analogous to that used in describing life.

We are left today with our various forms of amusement such as drugs, sex, politics, science, sports, etc. awaiting heaven or oblivion, while lost as insignificant specks in a constantly expanding n-dimensional set of coordinates. Maybe the only unifying idea is that the meaning of life is the search for meaning. This is of course, most evident in religion and science. Both of these themes were evident in the very earliest records of the Egyptians 6,000 years ago. There is a general feeling that scientists are atheists, but this is not true. Many are solid church-going people. If scientists *really* believed that life is meaningless, why would they work so hard? I well remember a series of Robbins lectures at Pomona College by the famous Nobel laureate Monod out of which came his book, *Chance and Necessity*, recently selected by the *American Scientist* as one of the 100 most important books on science of the 20th century. It was eventually translated into twenty languages. These lectures were indirectly devoted to showing the meaninglessness nature of life. Still, Monod got up each day eager and content to work like mad to understand the biochemistry behind life. He had the relaxed standards of his fellow Frenchmen. He gave the honorarium for the lecture series to his wife who then went on a trip to Nepal while he was accompanied by an attractive, young lady who sat in the middle of the auditorium near the front row. However, he showed consideration for American sensibilities by not having her stay with him in the faculty house, but in a different hotel off campus.

Life-sustaining meaning can be found in an uncountable number of ways, such as music, art, literature, science, sports, accumulating wealth etc. A question that has always been worrisome is how much, if any, free will does a person have? It used to be said that nature and nurture determined one's life pattern. Monod termed it chance and necessity. Today one might say environment and DNA. An eminent founder of psychology, William James, brother of Henry James, wondered most of his life if man had any free will. What we accomplish in life, be it a scientific discovery or a championship football record, clearly depends on the environment we grew up in and our DNA.

What were the roles of chance and necessity? A malfunctioning mind (perhaps at the molecular level) like Hitler's or Stalin's usurps the free will of countless millions, as have many other crazy leaders of religious cults. The field of science is not immune to misconceived ideas and notions. The incredible slaughter of countless wars has been one result. As yet, we cannot define a 'normal mind' with 'free will' but undoubtedly this has to do with molecular biology and chemistry.

Arthur Koestler in his offbeat book, *Call Girls*, wonders how the inherent meanness can be taken out of man. He concludes that the only possibility is by injecting some kind of super drug in the world's drinking water. Religions have failed completely. I remember as a child hearing the frightening biblical story of being 'possessed by the devil' and of Christ casting the devils out. Years later I concluded that such a problem could well have been an epileptic fit. From the beginning of history this was not unusual. Now it is rare because of simple drugs. Nevertheless, it is easy to understand how the concept of the devil seems necessary to explain man's incredible inhumanity to man.

Manic-Depressive disorder can disrupt families or even whole organizations. Today, a very simple mood-stabilizing chemical, valproic acid, enables such a person to lead a somewhat normal life. Some of the recent new drugs for schizophrenia have profoundly affected patients and allows a significant number of them to return to the work-force. Do these drugs restore free will?

Most people are slowly beginning to understand that homosexuality is not a matter of choice. Who would choose to be gay in a society such as ours? Where is free will? What one achieves in life is a matter of chance and necessity. Nobel laureate Steven Weinberg's famous euphemism "the more the universe seems comprehensible, the more it seems pointless" is hard to forget. As to a miniscule perspective of our position in n-dimensional space, we can go along with Scarlett O'Hara's comment in the novel *Gone With the Wind*, "Oh fiddle dee dee, I'll think about that tomorrow."

With this horrendously large and complex backdrop, we now turn to the putterings of a few minds in a miniscule slice of 5-D space.

Chance prepares the favored mind

The development of QSAR

Pasteur said that chance *favors* the prepared mind, but what constitutes a prepared mind? A better way of viewing the enigma of explaining significant discoveries that people make, is that chance *prepares* the favored mind. For example, if Einstein had been born and raised in the Congo, it is highly unlikely that he would be remembered today. The chance meeting of Crick and Watson at the same time as Rosalind Franklin was examining the X-ray crystallography of DNA gave rise to their elucidation of the structure of DNA. Crick's understanding of X-ray crystallography and Watson's passionate interest in DNA coupled with the essential data of Rosalind Franklin, delivered the Nobel Prize to Crick and Watson instead of another group (Pauling's?) at a later date. Of course, minds capable of stringing together strands of information to form a new and meaningful concept are essential. Such a mind is prepared by years of the right kind of experience and then being in the right place at the right time in n-dimensional space. Simple brilliance and hard work alone are not enough. As teachers, we all know of many examples of brilliant students who made no significant discoveries. We also know of many seemingly mediocre students who do outstanding work, years later.

Now that I am in my eighties, I am compelled to look back at the development of Quantitative Structure-Activities Relationships (QSAR) as it slowly evolved at Pomona College over the past 50 years. To do so demonstrates how chance prepared my mind. It was a hard struggle at a small liberal arts college with no graduate students to lend a hand. From the beginning, most thought that it was a hopeless quest. Embarrassingly, many who thought that QSAR was wonderful, clearly did not understand it. I remember one research director at a major drug company telling me that if what I was saying was right, I deserved the Nobel Prize. Clearly, he believed that an unknown scientist, working at a small liberal arts college with a heavy teaching load, had no such chance. Another research director at a major pesticide company introduced me to my audience by saying, "today we have Corwin Hansch as our guest speaker. We don't believe that his work is the answer to a maiden's prayer, but we thought that we would have him speak anyway." Such graciousness! Most surprising is that almost nothing negative is published about our work! I had expected many such articles. Clearly, there was no brilliance on my part in the development of QSAR, it was chance and necessity as we shall now see.

Much to the concern and chagrin of my mother, I was a terrible student in school. After the third grade in Central School in Lincoln, Illinois, my mother decided that I simply was not up to the competition in Central School which was in no way an exceptional school. Still, she convinced those with the authority to allow me to transfer to Jefferson Elementary School in a seedier part of town. I don't recall that I made a better showing at Jefferson. Our family then moved to Colorado, where I attended school for one semester before the family moved to San Antonio, Texas. Again, my grades were mediocre. I simply had no interest in any of the subjects presented to me. My real interest was in hunting and fishing that also happened to be the sole interest of my father. I remember flunking algebra in High School and feeling that it was pointless to do better than "C" work, since that was all that was necessary for passing. I had obviously miscalculated in this instance. The family moved outside of the city and for 2 years I became interested in trapping small animals and selling the skins for money to buy ammunition for hunting. I remember hearing my father say that he would much rather see me become a good shot than go to College. It was exactly what I wanted to hear. I loved trap shooting as well as all forms of hunting and was fascinated by magazines on hunting and fishing. I began to think of becoming a professional trap shooter and finding a job representing an ammunition manufacturer or becoming a professional trapper in Canada or Mexico. At the time of my second year of High School, my parents separated and then divorced. My mother returned to Lincoln, Illinois (her place of birth) with her three children and I was forced to go along. It was a great disappointment for me because of the lack of hunting and trapping possibilities. After a semester of school, I

persuaded a friend, Walter Dengler, to run away with me to San Antonio. My father used to say to me: "now for Christ's sake, don't run off half-cocked." This was certainly the most half-cocked thing that I ever did! That trip was the most awful experience of my entire life. We had less than two dollars between us and the trip required 7 days. We soon began to learn from the hobos how to survive and where to get handouts. At this time, the mid-1930's, it was estimated that around 4,000,000 men and boys and a very few women were riding the rails for lack of anything better to do.

Facing the shock of sleeping in railroad yards and trying to determine which was the appropriate, next train to hop was a frightful experience. I remember being chased around an oil tanker by a cop pointing his gun at us until we had to jump from a rather fast moving train. Finally, we arrived in San Antonio and then, very tired, walked 14 miles to our house in the country that was still held in my mother's name. Looking back on the experience, I believe that it did much to help me "grow up". Troubles are good for you *if* you can overcome them.

It was an *enormous* pleasure to reach our home and our horses, traps and guns. However, my mother sold the house and we were forced to return to Illinois after one semester. Walter took the bus, but I decided to drive home in a 1918 model T Ford that I had been tinkering with. Unfortunately, when it stalled, it had to be pushed to start as it had no battery operated starter; I decided to drive without stopping to Central Illinois. Somewhere in the middle of the first night I fell asleep and ran into a ditch. Amazingly, a local garage towed me in and repaired the slight damage without charge! There really are kind people in this world, despite what one reads in the daily newspapers. I had essentially no money. The next day I reached a point about 100 miles south of St. Louis and hilly country. Now real trouble began! The old Ford could not make it up the hills in high gear and the low gear failed to work. It was necessary to back up the hills. At this point, I gave up and wired my mother for a bus ticket. The car was left to a family that allowed me to spend a night sleeping on their porch. Arriving back in Lincoln, I was shocked to find that they had stolen my two guns out of my sleeping bag. The overall experience must have had a *profound* effect on me. Suddenly, my grades improved to the point where I was excused from final exams, although I don't remember trying any harder.

After I graduated from Lincoln High School, my mother finally dissuaded me from the trapper's life in the Carmen Mountains of northern Mexico. Having enjoyed working on my old model T Ford, I decided engineering would be a good subject to study. Hence, my first year's study at Lincoln Junior College involved Chemistry. This seemed interesting, but more importantly it led to my meeting a superb second-year student named Fred Uhle. In 4 years of College, his record was straight A's except for one B in a semester of Economics. Fred had worked his way through a textbook of organic chemistry in high school! We decided to set up a chemistry lab in the basement of my house to do organic synthesis. Somehow, we found that we could buy chemicals directly from the chemical storeroom at the University of Illinois—a short drive from Lincoln. Such a thing would be impossible today. Meeting Uhle profoundly changed my life. Organic chemistry became my passion, but beyond this, Fred was of immense help to me; he taught me how to study. This chance event began to prepare my mind. Still, I flunked English at Lincoln College, even though I dated the girl who graded the English homework and who constantly raised my grades (unbeknownst to me until later)! Looking back I doubt that Mrs. Baloff, my English teacher, gave me the benefit of the doubt. Her husband, who taught Math, was a grumpy, unpleasant man and a most unusual teacher. Each day he sent his few students (5 or 6—the College had only 69) to the blackboard assigning each a problem. Then leaning back with his feet on his desk, he read the newspaper. Now and then he lowered the paper to make snide remarks to those having trouble or to assign a new problem to those who had made the grade.

I decided to drum up interest among my friends to petition the College to fire him. No luck. Students in those far off days (1936) knew their place. The Sixties were a long way in the future. We decided to harass him a bit. Putting a car bomb on his car was the first move. Next, I put a whiskey bottle on the lectern he used for his weekly chapel address. That did it. I was expelled from College for 3 days. This must have had *some* influence on Mrs. Baloff, in deciding my English grade. I might well have deserved a D-. However, I must admit that the next year at the University of Illinois, I discovered that Math was the only subject I was well prepared for.

There are many ways to teach. Max Mason who was a Physics professor at the University of Chicago, before he became President of the University, told me of another unusual example. Almost every year his department got one or two exceptional students for graduate work from a small college in Michigan. Finally, he simply had to learn its secret for teaching and made an appointment to meet the exceptional physics teacher while on a trip to that region. The teacher said, right out, that he knew nothing about physics. Each year he picked one or two students who seemed the brightest and had them give the lectures! They obviously profited greatly, but I wish I knew how the rest of the class fared. At least they had no problem talking to their teachers.

The next year Uhle graduated from the 2-year college and planned to go to the University of Illinois. My mother

was easily persuaded to provide the money for me to go with him. I spent 2 years rooming with Fred before he went on to Columbia for a Ph.D., eventually becoming a Professor at Harvard Medical School. I must confess that I would never have made it through the University of Illinois without his help. Indeed, I thoroughly hated college except for organic chemistry and ice hockey. I tried to quit school and enter the Naval Academy, but (fortunately) I failed to get the necessary appointment. Of course, I think I would have been *really* unhappy if I had gotten into Annapolis.

The next crucial event occurred in my senior year at the U. of I. The Chemistry Department watched over its majors carefully. The senior year students who were considered 'suitable' were guided to 'appropriate' graduate schools by helping them obtain graduate assistantships. At this time, Illinois was so strong in Chemistry that they could locate their graduates more or less wherever they deemed appropriate. Because of my low grades (4.3 average out of 5), thanks to 8 h of D in German and 6 h of C in English, I was not included on the list. On hearing this, a friend of mine, Art Anderson, went around to Professor Marvel and pointed out that I really was much better than my record would indicate. Since Anderson was an excellent student, Professor Marvel called me in for a justification of my weak record. He decided that they could overlook the results in German and one poor semester when I had a relapse of malaria during final exams. I had caught malaria the previous summer when my brother Paul and I used the family car to make an excursion to Acapulco, Mexico. Here we found a guide to help us hunt deer at night in a nearby swamp but all we got out of that adventure was a strong bout of malaria. When we reached San Antonio Texas, we both had fevers of 106*F! Fortunately an old family friend took us in and promptly called a doctor.

Art Anderson's unusual move was absolutely essential for my growth. It got me to New York University where I met Warren Garrison who enabled me to meet R. Nelson Smith who got me to Pomona College where I got to work with Robert Muir, learned physical organic chemistry and had a computer dumped in my lap with someone (Donald McIntyre) to show me how to use it.

After hearing my unusual story, Professor Marvel said that he could arrange an assistantship for me at New York University's School of Engineering in the Bronx, where I met Warren Garrison. This is also where I had the amazing good luck to meet my wife Gloria, on a blind date when we went ice-skating. We have been married for 58 years. Although the Chemistry Department was second rate I jumped at the chance, this being 1939 a depression year, when money was scarce. As we shall see getting to this Chemistry Department was crucial in the chain of events that eventually led me to Pomona College, where Robert Muir and I commenced the experiments that 15 years later led to QSAR. I completed my thesis under Harry Lindwall at NYU and defended my thesis on the morning of January 8, 1944. That afternoon I married Gloria Tomasulo and in the evening we started a slow drive back to the University of Illinois, where I had lined up work as a postdoctoral fellow for Harold Snyder on a project to develop new drugs for malaria (a project naturally of great interest to me).

It has been said that behind most successful men stand devoted, hard-working women (now this may be changing), Gloria was all of that and more. She has always managed all of the housework and much of the yardwork, taken care of our two children (Clifford and Carol), managed our finances, paid the bills and arranged the details of our many, many trips to all parts of the world. Moreover, her very stoic character has enabled her to survive two bouts with melanoma, a most serious ovarian cancer and an uncounted number of skin cancers with nary a word of complaint. In a small college with no graduate student "slave labor" and a heavy teaching load, her hard working, non-complaining character was extremely important for me. Probably the time I had for research was double that of others in my position. This is another example of exceptionally good luck in my unending succession of lucky events. Now to continue the set of events that got me to Pomona College in 1946.

My closest friend at New York University was Warren Garrison, a physical chemistry student. On graduating from NYU, Warren took a job on the Manhattan project (atomic bomb project) at the University of Chicago. After 3 months, the Army discontinued the anti-malarial project I was working on, so I needed another war related job. Garrison persuaded me to apply for a position on the Manhattan project, but said that I could be told nothing about the nature of the project except that they needed an analytical chemist. He assured me that the project was intensely interesting. Since there was such an acute shortage of chemists, I was offered a position in analytical chemistry under the distinguished Paul Kirk, a professor from U.C. Berkeley, even though my knowledge of analytical chemistry was weak, to say the most.

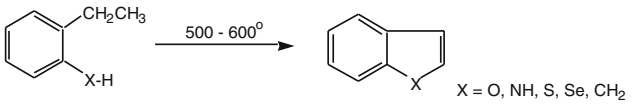
The horrible potential of the atomic bomb was explained to me on my first day at work. It was a shocking experience since it had never occurred to me that such a thing was possible. I'll never forget being told on that first day that if such a bomb was dropped on London, for example, the place would be uninhabitable for 200 years because of the radioactivity. Although it did not turn out to be *that* bad, it was the most awful contribution of science to society. However, on the good side, the theoretical knowledge gained has been of great importance in developing our understanding of how the universe works and *maybe* inhibiting wars between major countries.

During my 3 months at the University of Chicago, Warren and I bought a sailboat and we had many pleasant evenings sailing on Lake Michigan. In Chicago I met Nelson Smith, the next person to have a profound effect on my life. In the fall of 1944, Nelson and I were both transferred to Richland, Washington where plutonium production was soon to start. Here my job was to develop a procedure to analyze the plutonium content of shipments to be made to Los Alamos where the bombs were to be assembled. The method had to be simple enough for housewives to run, since there was such a shortage of chemists. I had the 'pleasure' of analyzing the first shipment of plutonium sent to Los Alamos. However, plutonium is one of the most carcinogenic substances and it was a great relief to leave Richland after a year's work.

In the fall of 1945 a big reduction in staff was started, since the necessary research was mostly over. I went out to Wilmington, Delaware for a job interview with the DuPont company that managed our portion of the Manhattan project. On the train coming home, I learned about the first explosion. I took a job at DuPont and Nelson Smith took one at Pomona College, his alma mater. I told Smith that he was making an awful mistake to go to such a small institution with essentially no research facilities. But, I was the one who made the mistake! The group I elected to join (out of six possibilities) in Wilmington was directed by a man who believed in applying enormous pressure for results. We were required to write *daily* reports about our research. These were circulated to the eight other members of the group who were supposed to add critical comments. Then we wrote weekly reports and finally, monthly reports. On finishing a project, another report had to be submitted (I finished three in my 3+ months). In addition, our director stopped by once or twice a day to see how things were going and to show his interest in our work. Looking back now, I see that it was a godsend to work for "Wild Bill Gresham". If I had been working for a reasonable man, I might still be at DuPont. My good luck continued.

At this point, I heard from Nelson Smith that Pomona needed an Organic Chemist and that the new post-war chairman of the department, Conway Pierce, was going to be near Wilmington so that I could talk to him about the job. I jumped at the chance! Pierce had had a distinguished career at the University of Chicago in Analytical Chemistry. He was the author of the most popular book on analytical chemistry with one of his students named Hanisch. I took the job at Pomona as an escape from the high pressure at DuPont, with the thought in mind that I would use Pomona as a base to look for a more suitable teaching/research position.

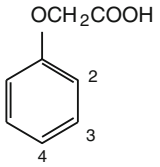
If I had not gone to Pomona, I would never have been involved in the development of QSAR. Chance in the form of Robert Muir prepared my mind. Here I met Muir, a plant physiologist with an office in the chemistry building, as there was not room for him in the small biology building. It soon became clear that he had an excellent background in the area of plant growth regulators. His experience in quantitatively testing them on sections of oat sprouts (a seemingly crazy way to start QSAR) got us going, but of course we had no idea of what we were doing or where we were headed. One of the pleasant things about Pomona at that time, was that no one really cared much about whether or not you were doing research. Thus no one looked over your shoulder to see if what you were doing was "world-class". Getting our first QSAR was not to happen for the next 15 years! No research university would have tolerated my "fooling around" for 14 years making the simplest kind of chemicals and trying to make sense about how they affected sections of oat seedlings. I would have had to turn out something in synthetic, organic chemistry. I would have been isolated from biologists, the vast majority of whom had no interest in tedious testing to get quantitative data. Even worse, I would have had no opportunity to teach (and learn) about mechanistic organic chemistry. At this point in time, 2,4-D (2,4-dichlorophenoxyacetic acid, a common commercial weed killer) was known to cause cell elongation at low concentrations. At high concentrations, it was a weed killer. We soon decided that I would start making simple X-phenoxyacetic acids and Muir and his students would test them, the idea being to decipher the molecular features important to growth promoting activity. This was a side project for me, as my primary interest at that time was in the high temperature (500–600 °C.) dehydrocyclization reaction I had learned about at DuPont:



I slowly lost interest in this work since our publications sparked no interest in the academic community.

Little did I realize in 1947 that studying how chemicals influence living systems would become a major preoccupation of science in the last half of the century. Linus Pauling was far ahead of his time. He was bringing biologists into the chemistry department at Cal Tech in the mid 1930's, much to the consternation of his colleagues. At that time chemists often viewed biologists as a much lower form of life. Our tentative ideas about the mechanism of action of the plant hormones did excite interest among very few biologists, but chemists were not attracted to the very fuzzy and difficult interface between chemistry and biology. We put forth the hypothesis that for biological activity, one needed an open ortho-position and an electron

attracting substituent in the 3-position of the phenoxyacetic acid.



About 1948, another chance event had a *very* crucial effect on my professional development. Pierce, the chairman of our three-man department, thought that I should give a one-semester advanced course in organic chemistry. He suggested advanced synthesis. Being by trade a synthetic chemist, I look back now with amazement that I did not follow his suggestion, the reason being that I had stumbled across a book in our very small chemistry library on "Electronic Interpretations of Organic Chemistry" by Remick. He was trying to organize and clarify the so-called English School of reaction mechanisms (later to be the heart of our QSAR) surrounding the work of Ingold and Hughes at the University of London. For some strange reason, I was strongly attracted to what eventually came to be known as physical or mechanistic organic chemistry. I decided to pursue it by making it the subject of my advanced course. This, despite the fact that the short course I had had on the subject during graduate school seemed boring! Looking back now, I can't understand why the subject seemed so difficult, but of course this was long before computers. It was several years before I began to feel some security in teaching this, even to undergraduates. In fact, it was not until 1961 when we obtained our first computer that I began to get a firm grasp of the subject and to really appreciate how Hammett transformed the qualitative ideas of Ingold and his followers into quantitative terms. Hammett said that the German chemist Hantzsch influenced him most. So for QSAR, it was Hantzsch to Hammett to Hansch!

From 1947 to 1961, Muir and I worked to develop what came to be known as the two-point reaction hypothesis. The two essential features were the OCH_2COOH side chain and an unsubstituted ortho-position with a low electron density. We were quite surprised that the Japanese scientist, Fukui, destined to win the Nobel Prize for his work in quantum chemistry, published a paper in the late 1950's saying that his calculations validated our idea of the importance of a low electron density in the ortho-position. Our spirits were buoyed by his support even though I did not understand the details of his thinking. If one cannot understand something highly mathematical, it must be of great importance.

For my first Guggenheim-funded sabbatical in Prelog's laboratory at the famous ETH in Zurich, I tried without success to isolate some reaction product with something in the oat cells at the 2-position. I had been astonished to win a Guggenheim fellowship for this project. Many years later I came to understand that my interest in the interface between chemistry and biology had won me the fellowship. At that time, Pauling was the key person in awarding fellowships for chemistry and he was intensely interested in bringing chemistry to bear on biology. He had heard a seminar I gave at Cal Tech on our plant hormone work of which I had considerable doubt that we really knew what we were talking about. It is *highly* unlikely that a committee of standard chemists would have even considered selecting me. More unending good luck.

During the 1950's, Muir and I were competing with Veldstra (a professor in Holland) for a theory to describe the varying activity of the many X-phenoxyacetic acids. He argued that electron density had nothing to do with activity. In his view, the way chemicals distributed themselves between fatty and aqueous phases of a biological system could directly account for the different activities. Things moved slowly in those days and teaching loads were heavy. By the time of my second sabbatical in Huisgen's laboratory at the University of Munich, we had not progressed beyond the simple idea of the essential side chain and a low electron density at an open ortho-position. I spent much of the year in Germany reading and thinking about all of the research that had been published on plant growth regulators. The most important event was Gloria's talking me into trying skiing in Austria. Soon we were both hooked on skiing and many vacations and side trips on lecture tours were spent skiing in California, Colorado, Utah, Austria, France, Switzerland, Chile, New Zealand and Japan. How lucky I was to have met Gloria.

At the turn of the century Meyer and Overton, independently, had shown qualitatively that the toxicity of organic chemicals to tadpoles was related to their partition coefficients between olive oil and water. Olive oil seemed like a poor choice to me. Meyer's son indicated that his father was wrong to use olive oil and recommended using an 18-carbon alcohol. He suggested olyel alcohol, but this interested no one. It was viscous (hard to work with) and very difficult to obtain in pure form. I decided to use octanol, a simpler, cheaper alcohol that could readily be obtained in pure form. This was the first solvent selected and despite many efforts by us and many others to find a better solvent, octanol is still the gold standard. This led to the famous bumper sticker that a chemist spotted on a freeway near New York City that read "Hansch walks on Octanol".

The initial work using octanol and water as a model to estimate the way chemicals distributed themselves between fatty tissues and water was started in our laboratory by Peyton Maloney, but was soon put into high gear by Toshio

Fujita, who arrived from Kyoto University to join our group. His results soon showed that Veldstra had been partially right. However, we found that in general, the relationship was not linear and that electronic effects were also important. Later on we developed ways for dealing with the shape of molecules and nonlinearity.

The concept of mathematically handling the nonlinear character of log P *and* an electronic term was mind boggling in that distant time. Least squares regression analysis was totally foreign to chemists and in fact, to most other scientists. At about this time, as chance would have it, Mr. Clarey, one of Pomona College's trustees, provided the chemistry department with an incredibly small computer (by today's standards). I had no idea how to use it, but Donald McIntyre in the Pomona Geology Department had already purchased a Clarey and learned how to program it. It was a complicated process in which three "boards" full of holes were wired to carry out three steps. One first entered the data using board one, then the second board was utilized to invert the data matrix and the third board was used to print out the results. As chance would have it, McIntyre's help in writing our first program was crucial, as I had had no thought of ever needing a computer or how to use it. The three-term limit of the Clarey was all that we needed at that time.

Earlier, I had received a grant from the NIH with sufficient funds to hire a postdoctoral associate although I had no idea how to attract such an individual to a small liberal arts college. The best hope seemed to be to find a foreign person wanting to visit the US. Remembering Fukui's endorsement of our idea about the mechanism of plant hormone action, I wrote to him for help. As usual, chance was on my side. Fukui knew Toshio Fujita at Kyoto University who had been working with plant growth regulators for several years. Before long, Toshio was busy measuring partition coefficients at Pomona. Still, I was fuzzy about formulating a mathematical model. Toshio suggested that we follow the lead of Robert Taft who had used a linear combination of two parameters (steric and electronic) to correlate reaction rates of organic reactions without worrying about the *justification* for such a step that had been holding us back.

Today, it appears that one makes linear combinations of dozens of parameters without a second thought. If it works, use it and try to justify it later. Still a combination of σ and log P was not enough. We had already observed that activity was not linearly dependent on log P. I finally decided that we would simply use a "squared" hydrophobic term (log P^2 or π^2) term and worry about it later.

$$\log 1/C = a \cdot \sigma + b \cdot \pi - c \cdot \pi^2 + d$$

C is the molar concentration of hormone needed to cause a 10% increase in elongation of oat sections (over controls) in 24 h, σ is the Hammett parameter that accounts for the lower electron density in the ortho-position produced by electron-attracting substituents in the 3-position. Substituents in the 4-position destroyed activity, something that we still do not understand. The parameter π? is a measure of the hydrophobic character of 3-substituents derived from log P for the whole molecule. We were so fortunate that the small Clarey computer could deal with equations up to 3 terms!

The encounter with Toshio Fujita changed both of our lives. On going back to his professorship in the Agricultural Chemistry Department at Kyoto University, he commenced to work on QSAR with a passion that almost no one outside of Pomona has since shown. Eventually he began to turn out many Ph.D.'s who went on to carry the gospel to the Japanese pesticide industry from where it spread around the world. I clearly realize now that I could not possibly have found a postdoctoral associate in the US, or anywhere else for that matter, who could even begin to do what Toshio accomplished (what luck!). The formidable problem of dealing with our 'complex' equation put off the biologists. The chemists of that time were also uninterested in computers and had no knowledge of the use of regression analysis to build mathematical models. I remember one research director at a major drug company asking me, where did a, b, and c, in the above equation, come from? In addition, problems in biology were simply too messy to worry about. The enormous success in the drug industry soon began to change all of that.

The chance event of Toshio's strong interest in this area was crucial to the development of QSAR and no doubt the main reason that it has been applied so successfully to develop new agrochemicals. There is still little published work by drug companies that compares with that of agrochemical successes.

Again, we were amazingly lucky that Donald Bentley, a distinguished statistician in Pomona's Math department had the background in this embryonic science of regression analysis. Bentley helped us greatly in avoiding serious faux-pas with respect to the use of statistics. Also importantly, he helped us to get started on nonlinear regression analysis: a very important idea introduced into QSAR by Hugo Kubinyi.

The next major event, seemingly designed in heaven, was Al Leo's arrival to join our group at Pomona. Leo had graduated from our chemistry department with honors before getting his Ph.D. from Westheimer at the University of Chicago. He then decided to look for an industrial job and was offered a position at Shell. However, on learning from his medical examination that he had been shot in the head during World War II and carried a metal plate to cover the hole, the offer was withdrawn. QSAR is *very* much indebted to the German sniper who shot Leo. A *slight*

move of the shot in one direction and Leo would have gone to Shell. A slight move in the other, and he would have gone to the great beyond. Leo's coming to Pomona in 1968 was no trivial event in the development of QSAR.

It soon became clear to Leo that we would never be able to measure all of the log P values needed to understand chemical–biological interactions. He began to build a data bank of log P values from the literature as well as values for other useful electronic and steric parameters (in addition, we measured many hundreds of values to help Leo's work). These compilations were sold to industrial laboratories around the world to support Leo, who had come to Pomona without a secure position (he soon became known the world over in drug research). In fact, he has earned his own salary and much more ever since. Today, his method will calculate log P for almost any conceivable organic compound. Even a small desktop computer can calculate 100,000 in less than 10 min. This has become extremely important in drug research. Companies now plan on making and testing hundreds of thousands of compounds to find new leads in drug research. In the process, one wants to avoid redundancy in the properties of the chemicals and have a good spread in log P. Scientists are still astonished that this work emanated from a small, undergraduate college. From 1999 to date, Leo's work has received 54,500 citations.

Rekker in Holland had made the first effort on such calculations, but his approach was terribly flawed by the necessity to use 'magic constants'. These were small numbers that had to be added to a primitive calculation to get the right answer. This only worked when one knew the answer. Today I have lost count of the number of approaches that other scientists have published, and continue to invent, to calculate log P. Most are based on a few hundred to a thousand chemicals. Leo's system is based on over 11,000 carefully selected measured values. No serious worker in drug design, pesticide design or environmental toxicology can avoid using these parameters to assess the hydrophobic properties of organic chemicals.

These early years were difficult since the problems were so complex; however, the interest our work provoked was obviously growing. We did not have any idea of the degree of the interest until a publication appeared in *Current Contents* in 1981. The Institute for Scientific Information had started compiling how many times and by whom, each scientific article was cited in all other publications. A seemingly impossible task! They reported for the period of 1965–1978 that I was among the top 300 most cited authors out of over 1,000,000 researchers publishing in all areas of science.

The next chance event in the evolution of QSAR was David Weininger's decision to come to Pomona (he should have been at Harvard). We knew nothing about Weininger (today he is known worldwide), but it was clear he could be of great help to us. Fortunately our chemistry building (built in 1965) had been built much larger than was immediately necessary. This had provided crucial space for over 60 postdocs and technicians who came to help us from all over the world. Hence we had space, in a cubbyhole in the basement, so that Weininger and his brother could work on programming Leo's ideas on the calculation of log P.

College trustee, Frank Seaver, who provided the money for three large buildings for our science center, had been very farsighted and proactive in urging us to include everything we could possibly use in designing our building. Mr. Seaver had only two restrictions: the windows on the second floor could not go to the ceiling and it absolutely had to have slit toilet seats in the men's room. Mr. Seaver was heaven sent for QSAR.

It would have been impossible for us to find someone like Weininger and we are glad that we crossed paths. He had been working on a language at the EPA to enter the complex 2-D structures of organic compounds into a computer in a linear fashion. His method is still the only unambiguous method of naming the untold billions of possible organic compounds. He called the method SMILES. Then Leo, with Weininger's unusual ability at computer programming developed the Clog P program for calculating log P. This *very* successful program began to sweep the world. In fact, the project was so successful that Pomona College wanted to be free of it, even though up to this point it had been run on a nonprofit basis. The reason for this severance was the fear that some company would use such a program to design a drug that would eventually turn out to be highly toxic and the College could then be held liable! Weininger then left Pomona to start-up his own company, Daylight, that for a while had only Leo's Clog P program as it's only offering. The College finally gave up all rights to our work to us, and Leo and I decided to found a small company that he named BioByte, to market our products. Leo has been CEO ever since. His grandson, Michael maintains the computer system. This includes Clog P plus our databases of many thousands of parameters for use in QSAR as well as 18,000 QSAR for a system of bioinformatics. Again, a world-class idea was developed at Pomona.

Although Leo's work brought international attention to Pomona College he held the most unusual position in a small college that I have ever heard of. He has never had faculty status and he has never been on the payroll at the College. He has quietly gone about his business, often helping undergraduate students and postdoctoral fellows in one way or another and playing a central role in the strange development of QSAR. Too much of the credit went to me. For example, in giving a lecture at the National Cancer Institute some years ago, one of the directors who often

traveled in Europe and India told me that everywhere he went (drug and toxicology research) it was Hansch, Pomona; Hansch, Pomona. Sometime after this, a visitor to our lab from China used *exactly* the same words: "Everywhere I go in China, it is Hansch, Pomona; Hansch, Pomona!" Little did these men realize what all lies behind the evolution of QSAR.

Another highly improbable event that greatly influenced our thinking was also the product of a Pomona graduate, Jeff Blaney. On graduating from Pomona, Jeff went to study Medicinal Chemistry at UCSF, after being "infected" at Pomona where his mother Billie was our NIH secretary for many years; she was the last secretary we had who could take dictation, now a lost art. She became extremely adept at drawing the structure of complex organic molecules with the new IBM typewriter that seemed such a remarkable machine but is now completely forgotten. The pace of change has been incredible!

At UCSF, Robert Langridge was just beginning to develop what is today called Molecular Modeling. His student, Mike Connolly, had worked out a program into which the thousands of atoms comprising a protein or enzyme could be entered with proper positioning from their coordinates obtained via X-ray crystallography. Langridge had been working on this for many years; Connolly's contribution was to show how a computerized surface could be placed on the atoms of the proteins. From this one could see in color and in 3-D exactly how small molecules (a drug or toxic chemical) could be positioned on or in the protein. When Blaney had completed much of his experimental work for his Ph.D., his professor was murdered (some thought by his wife, although the mystery was never solved). Jeff now had free time to work with us. I made many trips to UCSF to see from his work, how various chemicals fit into or onto the binding sites of various enzymes. We had synthesized various sets of chemicals at Pomona and Nelson Smith had made an important contribution to our efforts by working out the procedures for assaying these compounds with various hydrolytic enzymes. Then from the formulation of our QSAR, we could deduce the nature of the binding sites. Comparison with Jeff's 3-D pictures was our first solid evidence that our abstract mathematical expressions made real sense. Later Teri Klein replaced Jeff when he went off to DuPont. In the early 1980's from the graphics studies, I began to develop a strong sense that what we had been postulating since 1961 was not crazy. I received many invitations from all over the world (China, India, Russia, Australia, Japan, etc.) to talk and show the beautiful color 3-D pictures made by Jeff and Teri. The use of graphics in QSAR has now become a huge business used throughout the drug industry and academic community.

Of course, our first data for the interactions of chemicals with enzymes had come from Nelson Smith who, after graduating from Pomona, had received his Ph.D. in reaction kinetics at Stanford. The program worked out by Nelson was subsequently used by many postdoctoral associates who came to Pomona to study, especially Cynthia Selassie who is now Chair of the chemistry department.

In 1980, Cynthia Selassie joined our group after completing her Ph.D. under Eric Lien at USC. Eric had been one of our earliest postdocs and had gained wide recognition in the field of QSAR. As chance would have it, Cynthia brought a new technique–that of testing chemicals on various types of cells in culture, to our laboratory. Soon, she showed that we could study a set of chemicals on an isolated enzyme and then on the enzyme in live cells. The results could be compared via QSAR and molecular modeling. This took us an important step forward. In some instances, with data from other laboratories, we have been able to compare QSAR from the isolated enzyme, the enzyme in cells and then in whole animals to obtain a consistent, understandable picture. Recently testing sets of chemicals on fast-growing cancer cells has enabled us to develop a model for estrogenic toxicity. Cynthia is another unorthodox individual who was born of Indian parents in Mombasa, Kenya. After finishing high school, she won a scholarship to Mt. St. Marys College, in Los Angeles, and came to the US against her parent's wishes. After Mt. St. Marys, she completed a M.S. at Duke in physical organic chemistry before receiving her Ph.D. in medicinal chemistry at USC, an ideal preparation for QSAR research. In about 8 years, she became Professor of Chemistry and then Chair of the department. Today, she is one of our most popular faculty members for conducting student research in part because of her interest in the interface between chemistry and biology. She is sometimes referred to as the "QSAR Lady".

In 1988, two more chance events occurred simultaneously to bring us into a new phase of QSAR development. My NIH grant was not renewed. Amazingly, R.J. Reynolds approached me offering to support our work. Naturally, I was uneasy thinking that they wanted our help in making 'better' cigarettes. This was not the case. They simply felt they should be supporting the development of our understanding of toxicology. This was the least restricted support that I had ever received.

At this very moment in space-time, we had another significant piece of exceptional good luck. Al Leo and I began developing a computerized database that we had started in 1972. It was beginning to be too much to carry in our minds. We got some support for 3 years from NIH to build a computerized system. However, at this time computers still operated on IBM cards and real time

interactions were way in the future. Nevertheless, I entered 1,000+ QSAR as I had proposed to NIH. Donald McIntyre had programmed our first effort in this direction. In the late 80's, we needed an imaginative person with the right background to appreciate the importance of what we were doing and to develop it in ways not foreseen by Leo and me. Another former Pomona student, David Hoekman, proved to be ideal for the job. At Pomona he had first majored in math and physics for 3 years, turning to biology for 2 years before graduating. At the same time he had become very interested in computers working with McIntyre who for many years ran our computer 'center'. In fact for a number of years McIntyre was the only person running the computer while at the same time teaching geology and acting as chairman of the department! It was McIntyre's intense interest in computers and high standing in the College that enabled Pomona, with the financial help of trustee, Frank Seaver, to obtain the third IBM 360 produced that had 16 K of memory (1965). What a step forward from the Clarey! Soon he showed us how to do regression analysis and store data on the 360. In many ways, McIntyre helped us get through the early years.

With Reynolds' support and Hoekman's intense work, we were on our way to the development of an astonishingly versatile electronic database for bioinformatics. In the last year of the millennium, it contains over 18,000 equations, 2-D structures on almost 200,000 chemicals, references to the pertinent literature and all of the many thousands of essential parameters organized by Leo over a period of 25 years. A critical element of this complex entity is the language SMILES developed by David Weininger. It can all be managed or updated from anywhere in the world. In fact, Hoekman moved to Seattle, Washington where he continues to develop our truly unique system. A growing number of laboratories around the world (Greece, Japan, Italy, China and the U.S.) do their computing and QSAR comparisons on our computer. What a change from the use of IBM cards! Now our major concern is to get a large fraction of the world's literature into the system in the form of QSAR. Even today, relatively few laboratories publish QSAR on their studies of chemical–biological interactions. The necessary data are present in thousands of articles in hundreds of different journals, but the authors lacked the necessary understanding of physical organic chemistry, biology, computers and ambition to do the job.

Scientists have studied the effects of organic chemicals on all forms of life or parts thereof for the past 150 years. All kinds of plants, animals, fish, insects, cells, enzymes, organelles, etc. have been studied, but no serious attempt was made at systematic organization until our work at Pomona started in 1962. Now that a fast-growing number of mathematical relations are accumulating (Hua Gao entered over 4,000 into our system and his successors Rajni Garg, Alka Kurup and Rajeshwar P. Verma have already added over 1,500 more). The scientific community is now in position to do comparative QSAR. The equations enable us to compare how chemicals react with each other and how they affect biological systems. Also the system provides a means for comparing a QSAR derived by a new method. Alan Shusterman, formerly at Pomona and now at Reed College, has helped us to explore the use of Quantum Chemistry in formulating QSAR and to see how the parameters compare with those in 'Classical QSAR'. Litai Zhang at FMC Corporation and Asim Debnath at the New York Blood Center have also helped us greatly on this problem. No doubt as computers become faster quantum chemical calculations will play a larger role in QSAR.

It has been said that until you can discuss your work in terms of numbers, you do not have a real science. QSAR has now set the stage for the development of a new science of chemical–biological interactions in mathematical terms.

Looking back it is hard to imagine the probability of how such an odd collection of chance occurrences brought me to a small liberal arts college to initiate what today we view as the embryonic new science of chemical–biological interactions. Although such studies had been underway since the mid-1800's, it was our work that placed it on a generalized mathematical basis.

In 1964, Arthur Koestler argued that creativity arises from the sudden interlocking of two previously unrelated skills or matrices of thought. Clearly, this applies to QSAR, where three such areas of thought came together in 1962: mechanistic organic chemistry, quantitative biology and the use of computers. No connection was possible without computers. Teaching mechanistic organic chemistry from 1947 to 1961 while working with Robert Muir on the quantitative testing of plant hormones on oat sections, I developed two areas of thinking that could not be connected until 1961, when the College trustee, Mr. Clarey, gave our department a computer and Donald McIntyre showed me how to use it.

Although many undergraduates and now over 80 postdocs and technicians all made contributions, the development of C-QSAR and Clog P was the result of the few special chance encounters over a period of 50 years. Behind all of this was the unstoppable merging of chemistry, biology and computers. Where this expanding speck in n-dimension will evolve, in say a short period of 100,000 years, would be interesting to foresee. Looking back at over half a century of work at Pomona trying to understand chemical—biological interactions, I sometimes wonder what part I really played in the development of QSAR. I just sat around writing papers and playing with the computer while destiny brought the right elements together to get the job done. However, we have demonstrated that something of great importance could be

developed at a small liberal arts college without the image to attract much attention scientifically.

Epilogue

However, it must not be forgotten that QSAR is far from being a finished science. It has only commenced work on what many still view as an impossible problem. While it is easy to understand this point of view, one only has to consider the alternative of doing nothing. The contrast is enormous. The huge and fast-growing drug industry has caught on and is spending surprising amounts of money to develop the science of QSAR. A single company may spend more in 1 year than we at Pomona have spent in 50 years. Still the odds are formidable.

Consider a single cell. Its DNA encodes the information for the production of 50,000–100,000 different proteins that form the machinery that produces thousands of other elements from small molecules to organelles, such as the mitochondria. This tiny universe works in dynamic concert and cannot be seriously disturbed or it will die in one way or another. Testing a small set of forty different but related chemicals, hopefully affecting only one of thousands of processes to gain mathematical understanding sounds like a fool's errand. Surely any given chemical is apt, in some degree, to affect more than one of the many, many submicroscopic systems. If it were not for the fact that many highly useful relatively non-toxic drugs have been developed and that many convincing QSAR have been derived (by a small number of researchers around the world) we would not want to risk being a chemical Don Quixote!

What we yet do not completely understand is how the myriad processes in a cell and the countless combinations of cells in a mouse are protected from stray chemicals. It is a mystery why some smokers die from cancer in 15–20 years, while others smoke for 60–70 years constantly bathing their lungs with all sorts of toxic chemicals. (The record seems to be held by a French lady who smoked until the age of 117 and then died at 125). Cigarette smoke contains over 4,000 different chemicals.

The many cellular processes have developed over eons of 'learning' how to protect themselves from unwanted interactions. Also repair mechanisms have come into being. A strand of DNA takes thousands of damaging hits daily, yet a set of repair enzymes keeps it functioning. If something happens to these enzymes, mutations can occur in the DNA that can lead to cancer. How these enzymes can run up and down the long strand of DNA that is millions of times larger than the enzymes is truly mysterious. Also, metabolic enzymes (the P450 enzymes for instance) destroy unwanted molecules. The balance is so delicate. For example, the female estrogens are so essential for women, but having a bit too much as in the case of those using the drug Premarin, will cause cancer. Over the eons, mankind has learned to eat fruits and vegetables that contain chemicals that plants have 'discovered' to be protective. We are only *slowly* learning which and how much of these provide protection against cancer, for example.

But it is far more complicated than this. The drug diethylstilbestrol used to prevent miscarriages caused the mother no harm, but their teenage daughters sometimes developed vaginal cancer. This would probably never have been discovered but for the fact that such cancer is very rare in teenage girls. A vastly more tricky problem is that of aging. It has been shown that damage to DNA is an important factor in aging, but given the complexities of lifestyles, eating and drinking habits, plus the quality of the DNA in the newborn, it is by no means clear how to start serious work on the problem. We must learn enough about chemical-biological interactions in simple systems to anticipate problems without using people as guinea pigs.

People now take drugs for years, even decades, and so studying the toxicology of foreign molecules on the parents, to say nothing of the offspring, will be with us for centuries. Still, it is exciting to push ahead. Now by carefully tailoring molecules we produce chemicals that can greatly improve the minds of schizophrenic or greatly depressed people. But what about a lifetime of use? And what about their children?

We believe that QSAR will play a very important role in understanding chemical-biological interactions. Not a molecule at a time, but in piecing together the larger picture. There are essentially an infinite variety of organic chemicals. Only a few million can be given cursory toxicological study. Only a few can be given the thorough testing needed to be sure long-term use will not have serious side effects. Even today QSAR and the knowledge of physical organic chemistry can be used to estimate the toxicity of many chemicals before they have been made. All of the important advances in understanding organic chemistry and chemical–biological interactions have occurred in the last 150 years (mostly in the last 50). This has taken place with essentially no help from the people in the continents of South America and Africa and only small assistance from Asia. The new buzzword 'biotechnology' is changing this. Fundamentally, making money is more important than saving lives!

Still, examining only the last 150 years is a myopic view of things. Imagine oneself looking back at the earth from the relatively short distance of 10,000 light years, almost nothing compared to the 10–15 billions of light years to the "edge" of the universe. Using the most powerful of telescopes, we would see nothing of consequence. Indeed, one would see the earth as it was 10,000 years ago! With little success, the Egyptians had been attempting to discover

'drugs' from plants about 5,000–6,000 years ago. What has been going on in the planets of the other 50,000,000,000 galaxies, each with billions of stars that must contain hundreds or thousands of suitable habitats for intelligent life?

Now with our fast-growing knowledge of the human genome (as well as those of simpler organisms) and the ability to clone life in its various forms, how long will it be before we very slowly but consciously take over our own evolution? 100, 1,000, 500,000 years? If we don't blow the world to pieces, the process will slowly occur.

One must believe that developments in many other parts of the universe are easily 10,000 years ahead of us. Will the use of QSAR and molecular modeling (first initiated by the cooperative effort of our group at Pomona and Langridge's group at UCSF) help us catch up?