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LETTER TO THE EDITOR

Remembrances of Corwin Hansch

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Thoughts on Corwin Hansch from Al Leo

The challenging way Corwin Hansch taught organic chemistry at Pomona College, when he was a newly minted professor and I a junior student, set my course in life to make chemistry my career. After receiving my PhD from the University of Chicago, I settled into a position that did not offer satisfying research, and so when Corwin offered me a post-doctoral position under an NIH grant to study anti-leukemic drugs via his ground-breaking QSAR methodology, I packed up family and belongings and left the Chicago area to work with him back at Pomona College. It seemed somewhat of a daring move at the time, but it was the wisest choice I could have made. Not only was I now becoming a 'cog' in an important research 'machine', but I worked with and became friends with some of the brightest lights in medicinal chemistry from all corners of the globe who were drawn to spend months or even years under Corwin's tutelage. So I can attest to the fact that Corwin Hansch has played an immensely important, positive role in many lives, especially my own.

Thoughts on Corwin Hansch by Cynthia Selassie

I first met Corwin in 1979 when I interviewed for a post-doctoral fellowship in his laboratory at Pomona College. I was taken aback by his stern and imposing presence and vowed that I would not be returning to Claremont. After some nudging by my graduate advisor, Eric Lien, I reluctantly agreed to sign on for only 2 years, which eventually stretched on to the present! As his postdoc and then his collaborator, I came to know him well through our long conversations and some vigorous but beneficial discussions.

Corwin was a brilliant and dynamic person, blessed with a curious and probing mind—he was always eager to "pick the brain" of anyone that he conversed with—be it a noted scientist, a first-year undergraduate student or a janitor. I was always amazed to see him totally engaged and engrossed in these conversations even though they could have involved something as mundane as the removal of paint stains from granite or how to jump on/off moving trains!

He could be a "smart aleck" and stubborn but he was always reflective in his thinking and flexible enough to listen intently to one's arguments, and then alter his stance on an issue. He knew how to have fun and nothing thrilled him more than driving his Corvette at high speed; sometimes when I accompanied him to the UCLA library at the other end of town, I had to hang on for dear life as he hurtled down the freeway. Our day trips to San Francisco to work with Jeff Blaney at UCSF were also done at breakneck speed—Corwin hated to waste valuable, research time.

I was privileged to have worked with Corwin and collaborated with him. He was a strong, teacher/scholar-role model and a wonderful mentor for me. He empowered me and challenged me to "think outside the box." He was big-hearted—always generous with his time, energy and words of wisdom. He was truly a "giant among men."

Thoughts on Corwin Hansch from Ki-Hwan (Paul) Kim

He was a true scholar, teacher, researcher, adviser, mentor, and colleague. He was like a father to me, who introduced me to the field of Medicinal Chemistry and QSAR in 1971, and who later asked me to call him Corwin when I was

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reluctant to call him other than Dr. Hansch. He was enthusiastic about learning new things even from his student, generous, wise, and open-minded, and was always kind and friendly. Corwin, I will miss you greatly. I send my sincere condolences to Gloria. Love, Your only graduate student, Paul Ki-Hwan Kim.

Thoughts on Corwin Hansch from Hugo Kubinyi

In my book "QSAR: Hansch Analysis and Related Approaches", published in 1993 by VCH and dedicated to Corwin Hansch, I wrote a "Personal Foreword" about the role of Corwin Hansch in the development of QSAR and how he brought me to this field: (Note: The following edited comments from pages III–IV of the book are reproduced with permission from the copywright holder Wiley–VCH Verlag GmbH & Co. KGaA.)

"The discipline of quantitative structure–activity relationships (QSAR), as we define it nowadays, was initiated by the pioneering work of Corwin Hansch on growth-regulating phenoxyacetic acids. In 1962–1964 he laid the foundations of QSAR by three important contributions: the combination of several physicochemical parameters in one regression equation, the definition of the lipophilicity parameter π, and the formulation of the parabolic model for nonlinear lipophilicity-activity relationships…

This was the time when I started my Ph. D. thesis on irritant and tumor-promoting phorbol esters, their isolation, partial synthesis, and structure–activity relationships at the Max Planck Institute of Biochemistry in Munich. Indeed one diagram in this book (Figure 43, Chapter 7.4) refers to these compounds. Although I recognized a nonlinear relationship of the biological activities on the chain length of the ester groups (I even measured partition coefficients and found a nice linear dependence on the chain length of the ester groups), the small step from drawing a diagram to formulating a mathematical model, i.e. deriving a parabolic equation, was too large for me at that time. Shortly afterwards, then doing research in pharmaceutical industry, I became aware of the work of Corwin Hansch, Toshio Fujita, William Purcell, and others on quantitative structure–activity relationships. Like some of my colleagues in pharmaceutical industry I noticed this new approach but did not consider to apply it in practical drug design. For years I lived with the prejudice that QSAR is a tool to describe only more or less nonspecific biological effects, like antibacterial, antifungal, hemolytic, narcotic, and toxic activities.

My conversion from Saulus to Paulus happened after a discussion with Rudolf Gompper (recall: years before, Corwin Hansch had spent a sabbatical year in Gompper's group) in Munich in 1974. In his seminar on theoretical chemistry he also mentioned the pioneering contributions of Corwin Hansch to medicinal chemistry. I presented my skepticism but, at the same time, felt ashamed of my ongoing ignorance and decided to read some more papers. Three fortunate circumstances worked hand in hand: William Purcell's book "Strategy of Drug Design. A Molecular Guide to Biological Activity" had just arrived in our library and I read it in 1 day, fascinated by its content and style. An experienced technician helped me with his statistics programs (some months later I had discussions with a professional statistician who insisted that everything we QSAR people do is forbidden for this or that reason. I never would have started QSAR work if I had spoken to him first; now it was too late, I already was infected). A colleague provided a data set on antihistaminic compounds for which, another day later, a beautiful π–σ relationship could be derived. A compound of this series came to preclinical and clinical development, but unfortunately it turned out to be only a drug for guinea pigs; it had almost no activity in humans…

The publications of Corwin Hansch helped me to proceed. A two-month sabbatical in his group at the Pomona College followed in 1978. The visit led to a deeper understanding of quantitative structure–activity relationships and their physicochemical and biological foundations on my side. On the other hand, it stimulated Corwin Hansch to apply the bilinear model in the QSAR of enzyme inhibitors; the most interesting applications of this new model resulted from his work, from 1980 onwards…

Corwin Hansch initiated QSAR and he contributed the most to its development. Correspondingly this book is dedicated to him on the occasion of his 75th anniversary in October 1993. He taught us how to apply QSAR in a proper manner to gain more insight into structure–activity relationships and biological mechanisms. The one and only way to thank him is to feel responsible to use and to develop the QSAR discipline in his sense."

In my 2 month sabbatical I did not only meet Corwin Hansch and Al Leo, but also Carlo Silipo. Once a week we had discussions with Corwin, on different subjects. When I proposed to him that he should deal with pKa value prediction, he commented that he would like to leave this problem for younger people. By and by, I commented some publications of other scientists, in a critical manner, which finally ended in Corwin's comment "Hugo and his nightmare stories".

It must have been at his 70th birthday, which was celebrated in a restaurant, sponsored by Daylight. As a present he got a speaking parrot (of course a toy, not a living animal), which repeated all words that were said to him. And there was a birthday cake, with the inscription "Happy birthday, Corwin all cap"—this was the result of an order by phone, which asked for all letters being capital letters!

Thoughts on Corwin Hansch from Asim Debnath

Twenty-four years ago the very first morning I came to Pomona College to join Corwin's lab I greeted him with "Good morning, Sir". Corwin, with an inquisitive look replied—what? what is "Sir"? I had to explain the Indian tradition (from British). He was amused and told me "I am not your Sir or boss, I am your colleague". That set the tone of our relationship. He realized that I came from a foreign land and helped to ease my anxiety as a newcomer from the onset. Corwin was a father figure to me. He even taught me how to drive in his own famous "Camaro"—I do not know how many had that fortune from their mentors. Corwin was the architect and inspiration in building my career in "Drug Design". I am indebted to his mentorship and generosity. I will miss him very much. I pray to God to give Gloria and her family the strength they need to cope up with this loss.

Thoughts on Corwin Hansch from Andy McCammon

Corwin personally convinced me to attend Pomona College, and by his passion for QSAR, convinced me that the quantitative study of biological molecules was exactly what I wanted to pursue in my own career.

Thoughts on Corwin Hansch from Hua Gao

I worked with Corwin Hansch as a postdoctoral research fellow for several years. Corwin guided my career path in many ways including working behind the scenes to advance my career. The concept of QSAR was a catalyst for my career as a computational chemist in pharmaceutical industry. QSAR is ubiquitous in medicinal chemistry and biology and has broad impacts on drug discovery in many aspects including molecule design and in silico ADMET modeling. From Hansch π constants to Hammett constants, all the elements in QSAR analysis are the fundamentals for medicinal chemists in SAR analysis in drug discovery. They are also the fundamentals for computational chemists in analog design. In recent years, Corwin's concept of comparative QSAR laid the foundation for mechanistic studies of chemico-biological interactions based on physical organic chemistry.

Thoughts on Corwin Hansch from Yvonne Martin

Although it took 50 years, log *P* is now the favored molecular property used by medicinal and agricultural chemists. This fact alone shows Corwin Hansch's tremendous influence. Without his continuing publications, hydrophobicity still might not be appreciated for its central role in the biological activity of compounds.

Professor Hansch will be remembered not only for his enthusiasm for QSAR, but also for the personal warmth with which he interacted with others. He welcomed discussions on the chemical basis of biological activity with anyone, regardless of their knowledge of the field. Although the research for which we know him focused intently on QSAR, he was intellectually curious, telling me that he tried to sit in the front row at seminars "to get the speaker's energy". Not a moment was to be wasted!

Professor Hansch's enthusiasm and warmth affected me personally in 1967—1968. At that time I accompanied my husband to Pomona College where he was to spend the academic year on a Ford Foundation program. At a dinner to welcome new faculty and administration, faculty returning from sabbatical, and spouses, the place cards put me next to Corwin Hansch. Because I was working in pharmacokinetics and drug metabolism I knew nothing of his work at that time; but from the PK work I did appreciate regression analysis, and from my graduate work I knew about hydrophobicity and Hammett sigma constants. Hence, when he explained QSAR, I was fascinated. When I told him that I had brought along a set of data on the rate of in vitro metabolism of a number of common drugs, we agreed to meet the next morning in his office. To my delight he had measured partition coefficients of the compounds on my list. We trotted down to the room with the keypunch, entered the data, and then walked across to the computer center and deposited the cards. In a couple of hours, we found that there was a good correlation. (This work is published in Martin, Y. C.; Hansch, C. "The Influence of Hydrophobic Character on the Relative Rate of Oxidation of Drugs by Rat Liver Microsomes." *J. Med. Chem.* 1971, *14*, 777–779.)

Prior to this meeting the Pomona chemistry department had agreed that I could use a lab in their building, but after the new results, Corwin insisted that I share space with his post-docs. I didn't do any more correlation work at Pomona, but instead tried to extend my in vitro metabolism to Phase II conjugations, which didn't work out. However, the many conversations with Corwin and Eric Lien made me eager to introduce QSAR to Abbott, which I did part-time when I returned in 1968. Ultimately QSAR and all aspects of computer-assisted drug design were my full-time efforts for the next decades.

The chance meeting with Hansch changed the direction of my career. I admire his graciousness in telling me about his method when of course I should have known about it and then including me informally in his group. His personal warmth, enthusiasm, and graciousness were an inspiration to many who met Professor Hansch.

Thoughts on Corwin Hansch from Dick Cramer

Corwin's exclusive dedication to his vision of physical organic chemistry principles being realized within biological structure/activity relationships was uncompromising and lifelong.

Thoughts on Corwin Hansch from Alex Tropsha

As a founder of Quantitative Structure Activity Relationship (QSAR) modeling, Corwin Hansch has been a monumental figure in the field of computer-aided drug design. The depth, intensity, and exceptional longevity of his research in the field spanning more than five decades has had a deep influence on several generations of researchers in medicinal chemistry and fueled many diverse applications of QSAR that remains one of the major research disciplines in computational molecular modeling. Yet as many truly great scientists Corwin was one of the most modest and easily approachable human beings genuinely interested in conversations about science with any researcher, from undergraduate and graduate students to academicians. Those of us who were fortunate to know Corwin Hansch personally will always remember his tall, towering figure and a kind, quiet smile he almost always had when he talked to you. As a true pioneer and the greatest contributor in our field, Corwin leaves scientific legacy that will surely outlive any, even the youngest, of his contemporaries.

Thoughts on Corwin Hansch from Tudor Oprea

'He's taller than I expected', I told myself upon meeting him. It was a small road trip, from Anaheim to Pomona, that I decided to take in the spring of 2004, together with Peder Svensson and Alex Tropsha. This was my second scientific hero encounter, after having meet Sir James Black in 1993. Undeniably influential to generations of computational and medicinal chemists, the work of Corwin Hansch was beautifully summarized in "Exploring QSAR", a book he co-authored with Al Leo and David Hoekman. The concept of "lateral validation", which he enabled by comparing QSAR equations on un-related series, was not the only gem from "Exploring QSAR" that I took to heart. But it was the one that I continue to apply, in QSAR and in virtual screening. And it was the topic of my discussion with Corwin that spring day, as we looked at various examples from the C-QSAR database. We talked about indexing chemicals, and capturing data from literature, about errors and mis-conceptions, and about life, in general. It dawned to me that day that QSAR is a way of life, one that Corwin embraced wholeheartedly. As scientists, we thirst for meaning and understanding, for causality. QSAR is a tool that can lead to the "eureka" moment, when structures and properties rearrange themselves into patterns and knowledge. And Corwin had that unique insight, more than five decades ago. His work reshaped several industries, from pharmaceutical to agro-chemical, flavor and fragrance and materials. More importantly, it reshaped generations of scientists. For that reason, he will remain one of the tallest scientists.

Thoughts on Corwin Hansch from Federico Gago

The opportunity to meet Prof. Corwin Hansch and listen to his talks on "QSAR and molecular graphics" and "QSAR and drug resistance" was given to me when I was a Ph. D. student in Alcalá under the supervision of Prof. Julio Alvarez-Builla and I had to go to Barcelona to participate in a seminar to which this legendary figure was attending. This was mid-May 1985 and another distinguished speaker was W. Graham Richards, who gave a talk on "Quantum Pharmacology" and a second one on "Enzymes as targets". No wonder I was quite overwhelmed when the last day I presented my modest results on relations between chromatographic retention times and octanol–water partition coefficients! When Corwin projected a video that showed the journey of an enzyme inhibitor towards the active site and graphically explained the structure-based rationale behind the numbers that he had previously produced in one of his famous equations to account for structure–activity relationships I was completely flabbergasted. My reaction was comparable only to what I felt when I saw Richard Fleischer's 'Fantastic voyage' as a child. To my dismay, however, by the time I finished answering questions and talking to some fellow students, Prof. Hansch had disappeared from the lecture room and I was meant to consult him a few doubts about some awkward results we were obtaining for several disubstituted benzene derivatives… So I had to pluck up my courage and go to his hotel, which I thought was extremely rude. But he received me very kindly, offered all sorts of help and allowed me to discuss these results at length.

After this life-marking experience, and having been entirely taken by the movie and firmly convinced of the incredible possibilities in pharmacology of applying a combination of physico-chemical methods, theoretical chemistry calculations and molecular graphics, I decided to pursue further studies in this emerging field of research and joined Graham's lab as an upstart in 1987. This experience gave a complete turn to my scientific and academic life, and I am very grateful to both Corwin and Graham for that.

Thoughts on Corwin Hansch from Terry Stouch

QSAR is so common and ingrained in our work that it is now difficult to imagine a time when it didn't exist, much less wasn't pervasive. Further, to us now-a-days the distinctions between biology, physical chemistry, and computation are so completely blurred that their confluence seems completely obvious. Yet it was not always so. Corwin was a true pioneer in the exploration of this new territory and one of the chief catalysts in formulating the framework of our current thought processes and approach to the chemistry of biology. His explorations and observations gave rise to a huge number of intellectual progeny and all of us owe our vision to our positions standing on his shoulders, a crowded place to be sure. In addition to his vision, passion, and leadership, Corwin was a genuinely nice, genteel man always willing to talk with anyone about his or their science. Let's celebrate that he was with us for 91 years.