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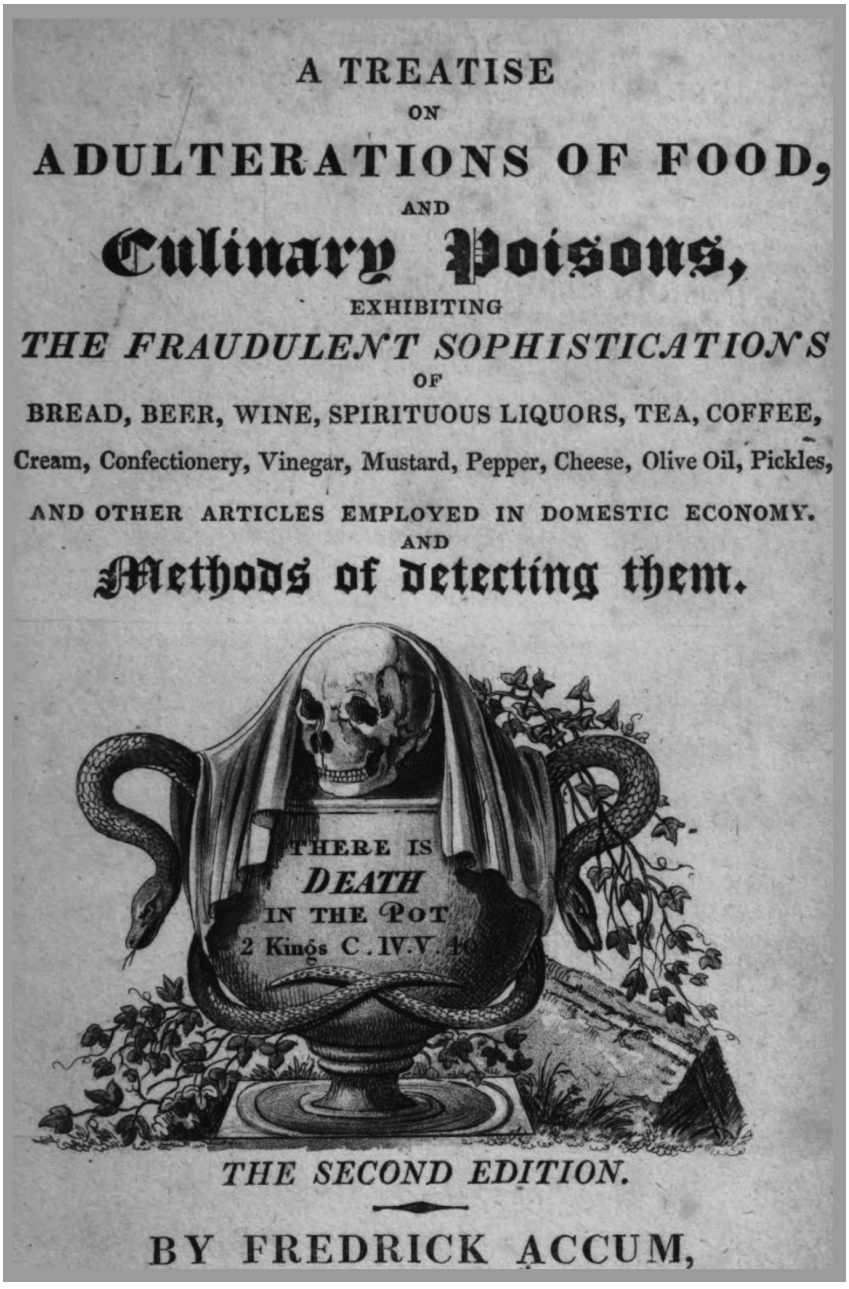

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BULLETIN FOR THE HISTORY OF CHEMISTRY

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The Cover... Fredrick Accum's best known work; see p 79 for more on Accum and p 102 on his American successors.

PROFILES, PATHWAYS AND DREAMS: FROM NAÏVETÉ TO THE HIST AWARD

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Editor's Note

Jeffrey I. Seeman of the University of Richmond is the 2017 recipient of the HIST Award for Outstanding Lifetime Achievement in the History of Chemistry, awarded annually by the American Chemical Society (ACS) Division of the History of Chemistry (HIST). This international award has been granted since 1956 under sequential sponsorships by the Dexter Chemical Company, the Sidney M. Edelstein Family and the Chemical Heritage Foundation, and HIST. Among the highlights of Seeman's work in history of chemistry are numerous articles on the history of 20th-century organic chemistry, service on the executive committee of HIST including a term as chair, founding and administering HIST's Citation for Chemical Breakthrough Award program, the production of video documentaries of prominent chemists, and—the subject of this article—proposing and editing a series of autobiographies of eminent chemists issued as *Profiles, Pathways and Dreams*. More information on the award and on Seeman can be found at http://acshist.scs.illinois.edu/awards/hist_award.php.

A symposium honoring Seeman's achievements in the history of chemistry was held on March 20, 2018, at the 255th ACS National Meeting in New Orleans. Customarily the recipient of the award makes a presentation at the culmination of the award symposium and the *Bulletin for the History of Chemistry* publishes that presentation. Seeman, a strong supporter of the *Bulletin*, preferred to be in the audience rather than lecture at the symposium. Nonetheless, he happily provided an award manuscript for the *Bulletin*. He consulted several colleagues on an appropriate topic for his award paper, and the following article is the result. In what follows, readers will get to know several of the 20th century's prominent organic chemists as well as Seeman.

—Carmen Giunta, Editor

Introduction

Work like you don't need the money. Love like you've never been hurt. Dance like nobody's watching. —Often but not definitely ascribed to Satchel Paige

I published my first article on the history of chemistry in 1983 in the American Chemical Society (ACS) journal *Chemical Reviews* (1). That paper appeared just as I was beginning my sabbatical at the Dyson Perrins (DP) Laboratory in Oxford, England. As I sat in the reading room of the DP those first months, I watched many of the students and staff reading my article. I still receive compliments about that paper, primarily because it was the first article in *Chemical Reviews*—and perhaps in any ACS *research* journal—that contained a history section

Table 1. Books in the Profiles, Pathways and Dreams series of autobiographies published by the American Chemical Society and created and edited by Seeman.

Author	Title	Year Published
Derek H. R. Barton	*Some Recollections of Gap Jumping*	1991
Arthur J. Birch	*To See the Obvious*	1995
Melvin Calvin	*Following the Trail of Light: A Scientific Odyssey*	1992
Donald J. Cram	*From Design to Discovery*	1990
Michael J. S. Dewar	*A Semiempirical Life*	1992
Carl Djerassi	*Steroids Made It Possible*	1990
Ernest L. Eliel	*From Cologne to Chapel Hill*	1990
Egbert Havinga	*Enjoying Organic Chemistry, 1927-1987*	1991
Rolf Huisgen	*The Adventure Playground of Mechanisms and Novel Reactions*	1994
William S. Johnson	*A Fifty-Year Love Affair with Organic Chemistry*	1997
Raymond U. Lemieux	*Explorations with Sugars: How Sweet it Was*	1990
Herman Mark	*From Small Organic Molecules to Large: A Century of Progress*	1993
R. Bruce Merrifield	*The Concept and Development of Solid-Phase Peptide Synthesis*	1993
Koji Nakanishi	*A Wandering Natural Products Chemist*	1993
Tetsuo Nozoe	*Seventy Years in Organic Chemistry*	1991
Vladimir Prelog	*My 132 Semesters of Chemistry Studies*	1991
John D. Roberts	*The Right Place at the Right Time*	1990
F. G. A. Stone	*Leaving No Stone Unturned: Pathways in Organometallic Chemistry*	1993
Andrew Streitwieser, Jr.	*A Lifetime of Synergy with Theory and Experiment*	1997
Cheves Walling	*Fifty Years of Free Radicals*	1995
Autobiographies originally scheduled for publication in the *Profiles* series but published elsewhere		
Teruaki Mukaiyama	*Challenges in Synthetic Organic Chemistry*[a]	1990
Paul von Rague Schleyer	*From the Ivy League to the Honey Pot*[b]	2015

[a]Because Mukaiyama published a similar autobiography in 1990 (2) in the series *International Series of Monographs on Chemistry* by Clarendon Press and edited by Jack E. Baldwin, this proposed volume was deleted from the *Profiles* series.

[b]This volume was never completed by Paul von Rague Schleyer (February 27, 1930-November 21, 2014). An edited manuscript remained in the files of Seeman, however. At Seeman's suggestion, the manuscript was re-edited by Andrew Streitwieser Jr. and published in a collection of chapters written by other James Flack Norris Awardees in a volume edited by E. Thomas Strom and Vera V. Mainz and published by the American Chemical Society in 2015 (3).

with photographs and quotes from eminent chemists. But generally, it was not the chemical kinetics portion of the article about which chemists were enthusiastic, it was the history section. I was convinced that the chemical community was enormously hungry for more history of their own field and especially so for the human side of chemistry.

Between 1990 and 1997, the ACS Books Department published the 20-volume series of autobiographies of eminent organic chemists in the series *Profiles, Pathways and Dreams* (Table 1). The authors came from many countries (Australia, Austria, Bulgaria (born in Austria), Canada, England, Germany, Japan, Switzerland via Sarajevo in the then Austro-Hungarian Empire, and the United States). Their research covered most if not all of the subdisciplines of organic chemistry. Five of the 20 authors were Nobel laureates, and all were recipients of the highest awards bestowed upon organic chemists. While all were men in their 60s to 90s, they nonetheless represented a wide diversity of human beings. This diversity is evident from the styles and content of their stories and the chemistry they studied. I was the editor of each book and of the entire series.

Surely, if the project were to begin today or 10 or 20 years in the future, a steadily increasing number of women would be authors, rising in parallel with the increasing number of women who choose careers in chemistry. And just as surely, had I been initiating the *Profiles* series today, the project would have had several goals not imagined 35 years ago. The books reflect how it was in organic chemistry, from the 1940s to the late 1980s.

As I look back into the years 1983-1997, I am embarrassed by what I asked of and expected from the authors. I had no currency in the history of science. But it was a self-supporting vision and with a sense of purpose that I communicated to the authors a commitment to excellence that propelled the project forward. *It Was the Right Time and the Right Place*, as John D. (Jack) Roberts would later entitle his autobiography (4). The series captures a golden era of organic chemistry in the voices of the greatest of organic chemists of the second half of the 20th century. They are (my) heroes and the icons of that field.

I have elsewhere described how the project came about (5), and I have reminisced a bit about my interactions with several of the *Profiles* authors (6-16). Now, I take this opportunity to relive some of those days with the reader, to share some previously untold anecdotes, and not by coincidence, to describe some of what I have enjoyed and learned in pursuing the history of chemistry. In many instances, my stories will veer off onto more recent tangents. And of course, I can tell only a small portion of the stories collected over a lifetime. Importantly, all the following events and interactions have their roots deep within the *Profiles* autobiographies.

Profiles in Stories

Arthur J. Birch (1915-1995)

It is an honor and it is enormously tricky to edit the autobiography of an eminent scientist, especially an individual who has previously authored hundreds of publications. I felt the real responsibility I had to the authors, for how many autobiographies would any one person write? So, when I reviewed Arthur Birch's manuscript, I was gravely concerned. It read like a jumble of ideas, whipped around like scrambled eggs and then patched together.

There was only one thing to do. I faxed Birch (Figure 1) in Australia. Would he please send me a computer floppy disc of his manuscript? (This was 1987 or 1988, decades before email and Dropbox.) I well remember that what he sent must have been some odd-ball Australian diskette, but fortunately someone in the computer group was able to download it and convert it to WordMARC, the word processor software I used in the late 1980s and early 1990s. I then intensely studied Birch's manuscript, and cut-and-pasted the entire text into an order that made sense, at least to me. Sadly, it did not make sense to Birch. He rejected my organization as I had rejected his. So, he rewrote his entire autobiography, and soon enough, I received a quite excellent manuscript. I also

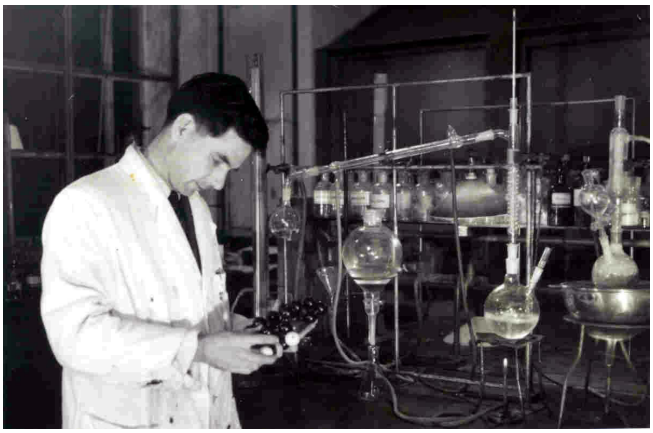


Figure 1. *Arthur Birch at his lab bench during his student days, ca. 1944, at the Dyson Perrins Laboratory, Oxford, England, where he discovered the Birch reduction. Photograph courtesy A. Birch.*

should add that Birch responded to my request that he include additional material on a whole series of topics. Thank you, Professor Birch.

I was soon to meet the man in person!

In 1990, Ronald Breslow invited me to participate in a symposium he was organizing for the 202nd National Meeting of the ACS in New York City on August 25, 1991. The audience was to be science-minded high school students from the New York metropolitan area. My assignment was to present a theme in the history of chemistry to these promising youngsters. I decided to present short biographies of several eminent chemists who had to overcome quite serious challenges in their youth in order to persevere. I spoke of Arthur Birch, Carl Djerassi, Herman Mark, and Ernest Eliel, all of whom had to leave their home countries—in Birch's case, because the Ph.D. degree was not yet given in Australia, or, in Djerassi's, Mark's, and Eliel's cases, to escape the Nazis.

When I finished my lecture to well over 1000 aspiring youth, the lights went up, the applause began, and I recognized—from his photographs, for I had not yet met him—Arthur Birch sitting about 20 rows back, right in the middle. Feeling rather warm in the glow of the hearty applause, I rose to the occasion. "Ladies and gentlemen, here in this audience is one of the individuals I've just been talking about. Professor Arthur Birch, would you please stand up?" So he did, to the thunderous applause of the audience. When the clapping ended, I continued, entirely in a joyful and even self-confident mode, "Professor Birch, did I get it all right?" "No," he responded, "not quite." And then, in front of the entire audience, he began a detailed and rather unanticipated correction.

Carl Djerassi (1923-2015)

I shall never forget Carl Djerassi yelling at me. Carl was not a particularly patient individual, quite the reverse. He was the King of Impatience. Time mattered greatly to Carl, as if the big clock in Grand Central Station was always with him, ticking loudly in his ear. When Carl provided the final manuscript of his first autobiography, he informed me that (5)

> The enclosed manuscript incorporates virtually all requests that you made. … While I will be happy to read any letters from you that acknowledge receipt of this manuscript, or any complimentary remarks, *do not even think* of writing me another letter requesting any more.

Fast forward a few weeks. I was reviewing the galley proofs of Carl's manuscript when I realized that he had not said a single word about his fused knee. As a result of an earlier skiing accident and in much pain, in 1957 Djerassi decided to have a permanent left knee fusion. Thereafter, he was unable to bend his left leg at the knee. One can only imagine the many inconveniences that caused Djerassi for the ensuing 57 years of his life. But it hardly stopped him; he even invented a "skiing technique for stiff-legged persons" (17) (Figure 2).

So I called Carl. He immediately answered the phone. I explained my request. Then the yelling began (18).

> I've done more for you that I have done for any editor. I am in my car, on the way to the airport. I am going to Europe. I don't want to hear from you again.

When the verbal manifestation of his anger was over, I calmly suggested that he simply call his secretary, dictate his answer to my question ("How do you feel, having a fused knee?"), and I would add his text to the caption of the photo of Carl showing off his skiing technique. Within the hour, a fax arrived. An expanded caption to Figure 2 appears on page 66 of his autobiography.

Figure 2*. Carl Djerassi demonstrating his method for skiing, a real skill given his inability to bend his left knee following its being fused, a result of a medical treatment. Photograph courtesy C. Djerassi.*

There were many consequences to me personally and professionally of my editing these autobiographies. One was that friendships developed with many of the authors. Another was that I became a producer-director of videos for academic and history of science themes (19-21). All this ensured together that I knew the life stories of many eminent chemists rather well. Thus I was often asked to lecture and write about them and their history and the history of their era. During the last few years of his life, I wrote two biographical articles on Djerassi (10, 11) and reviews of two of his books (9, 22), one being of *In Retrospect: From the Pill to the Pen* (23). On a phone call near the end of his life, Carl asked me, "Why are you writing these articles? Is it for your own career advancement? Is it for your own publicity?" I paused a moment, to examine my own motivations. "Yes, surely those are factors," I said, "but the real reason, the primary reason is that I have been writing these as a gift to you." I could hear his appreciative nod over the phone.

And unlike many people, I liked Carl, even more so after writing these four articles. I asked him to review my drafts. I had anticipated that he would be fiercely protective of his reputation, how he appeared in print. But no, my Jersey City-born suspicious nature not once detected such behavior. Rather, he was determined that my articles were accurate and complete, even in instances when my descriptions were uncomplimentary, at best. Yes, I admired Carl tremendously. Not everything about him, as I have described (11). But curiously, in those last years, I discovered that I liked him even more than I admired him.

Herman Mark (1895-1992)

Herman Mark, even in his 90s, answered his telephone with a hearty, booming, almost over-the-top "Hello, hello, hello!" I often think of Mark as I begin telephone calls with the same energetic multiplicity of greetings. Recently I shared this memory with his son, Hans, now himself an elderly gentleman. He laughed as one does with a very happy yet respectful common memory.

When I worked with Mark—I met him only once at Brooklyn Polytechnic when he was in his 90s—it was easy to assume that he was just a nice old man. Indeed, he was that, but much more. He was one of the most highly decorated officers (if not the most highly decorated officer) in the Austro-Hungarian Army during World War I. He was an early pioneer in the use of X-ray crystallography for structure determination. In the late 1940s, he helped invigorate, if not establish, academic polymer chemistry in the United States.

Mark died just before his book was completed. Fortunately, his Brooklyn Poly colleague and fellow polymer scientist Herbert Morawetz worked with me to complete Mark's book.

As part of the publishing agreement, ACS Books provided each author with several complimentary volumes. I asked Morawetz, who, besides himself and Mark's surviving son, ought to receive one of the complimentary books. Morawetz suggested Mark's lady friend, Dr. Elfi Braunsteiner, who lived in Vienna. I wrote and asked if she'd like a book. Yes, she responded, and a few weeks after I mailed the volume, she responded again with thanks.

Fast forward several years. I was taking my mother on a tour of Europe, with major stops in Budapest and Vienna. I thought, wouldn't it be fun to contact Dr. Braunsteiner and perhaps meet her. She responded enthusiastically but also asked, would I please bring a copy of Mark's book as she had not received it. Though somewhat puzzled and certainly unwilling to confront her, I carefully added a volume to my luggage.

A week or two later, Dr. Braunsteiner, my mother and I sat in a classic Viennese coffeehouse. Dr. Braunsteiner then explained. "Last night," she said, "I realized that I did have Herman's book. I remembered that, when it arrived, I was still too sad about Herman's death to read it. But last night, I picked it up and could not put it down until I finished every word. It was like I was with Herman once again." There is an infinite number of ways that the practice of and results from studying the history of chemistry can touch people. And when that "touch" is very personal and is communicated to the historian-researcher, the satisfaction is enormous.

I also remain convinced that increasing age need not be an impediment to intellectual achievement. Many of the *Profiles* authors were well into their 80s and even 90s when they wrote their stories. Herman Mark was in his 90s when he was writing his autobiography.

Ernest L. Eliel (1921-2008)

By refusing one of my requests, Ernest provided one of his greatest gifts to me, my friendship with Otto Theodor (Ted) Benfey.

The background is as follows. Vladimir Prelog was Croatian by birth and had fled to the ETH in Zürich in the early days of World War II, welcomed by Leopold

Ružička, who had also fled Croatia for the ETH in the wake of a war, namely, World War I. Ružička, a Croatian-ETH Nobelist, served as a role model for another Croatian-ETH Nobelist, Prelog. Though Prelog's native language was, of course, Croatian, and even though by the 1980s Prelog was fluent in English and German, he felt that he could best describe his life in German, the language spoken in his adopted canton in Switzerland. To his credit, Prelog arranged to have David Ginsburg (24), a competent and erudite chemist, translate his manuscript from German into English. What neither Prelog nor Ginsburg could anticipate was that the latter would have a stroke just before the translation was to be done.

Ginsburg's medical condition necessitated finding a replacement, a task that Prelog hoped he could, and would, transfer to his editor. And thus, I turned to Ernest. Ernest was a perfect choice for translating Prelog's manuscript from German to English: Ernest was a native German speaker. He was an expert in stereochemistry as was Prelog. And he and Prelog were good friends, Ernest having had a sabbatical in Prelog's laboratory in the 1950s.

As it happened, Ernest was also writing his own *Profiles* autobiography while serving as Chair of the Board of Directors of the ACS (1987-1989) and ACS President (1992). He was too busy, so he declined. My disappointment rapidly turned into relief, then joy. Ernest referred me to Otto Theodor Benfey.

Ted Benfey, it turns out, was an even better choice as Prelog's translator. Ted is a physical organic chemist by education, having received his Ph.D. with Christopher Ingold of CIP fame (Cahn-Ingold-Prelog *R,S*-nomenclature) and having held postdoctoral positions with Frank Westheimer and L. P. Hammett (25). Ted is also a historian of chemistry who has translated a number of books from German to English (26). And he was ready and available to translate Prelog's manuscript, which he did expertly and to Prelog's high standards.

One other lasting benefit arose from Ted's participation in the *Profiles* series: he and I became great friends.

The reader may notice that I am now writing more about Ted Benfey than Ernest Eliel. Perhaps that is because I have already written five biographical essays on Ernest (in 2002, 2009, 2014, and two in 2017) including a memoir for the National Academy of Sciences (12-14, 27, 28). I refer the interested reader to those publications.

Vladimir Prelog (1906-1998)

I would always take notes when I spoke with Prelog on the telephone. For an example, see Figure 3. I did so partly because what he said was so worthy that I wanted to be able to recreate his words, and partly it was because I so revered him, that I considered his words rather sacrosanct. I keep such notes of telephone calls with only three other individuals, ironically one being a former mentee and colleague of Prelog's at the ETH, my dear friend Albert Eschenmoser. And in part, I wanted to remember Prelog's stories and his jokes. I often retell one of his jokes, always to much laughter and always with proper attribution.

There are also topics much a part of Prelog's life that I found captivating only after his death, such as Prelog's 1943 partial synthesis of quinine (29). It is an irony of life not to be able to talk with a friend about a topic that, only after his or her death, would become central to one's own research. For example, I did talk a lot with Doering about the Woodward-Doering total synthesis of quinine and Gilbert Stork's claim that the synthesis was a "myth." But today, just a few years after Doering's death, I also wish I had talked with him about my current research on aromaticity, anti-aromaticity, and the Woodward-Hoffmann rules, of which Doering would have had a lot to say.

In one of my telephone conversations with Prelog just a year or so before his death, I discovered that he had not spoken in years with his friend Derek Barton. So, during one telephone call with Prelog, I asked him to hold the phone, for just a moment; I then dialed Barton's number, by good fortune got Barton on the first ring and asked him to hold the phone for a moment. I then pushed the "conference call" button and informed them both that, through the miracle of telephone technology, they could now speak with each other. And so these two old friends spoke for what was likely the last time. (Barton also died within a year.)

Setting up this telephone call between Prelog and Barton remains a happy memory for me.

Michael J. S. Dewar (1918-1997)

The most fascinating aspect of editing Michael Dewar's autobiography was my telephone calls with him, or more precisely, with them, "them" being Michael and his wife Mary née Williamson Dewar ("who was more than my equal" (30)). I felt I was talking with characters from a Jeffrey Archer novel: two elderly English academics, married since their youth, who considered a fierce verbal-

intellectual debate as the opportunity for marital bliss and eternal harmony. When I spoke with one, I spoke with both—or rather listened to both—debate even the most minor point until consensus was reached. I envied their relationship, though I'm not all that certain I could endure its equivalent.

Sadly, Michael did not live long after Mary's death. But he and I did communicate several times in his last years. He asked me to send copies of the photographs that had appeared in his autobiography. Somewhere between Austin, Texas, and Gainesville, Florida, and into his retirement community, the original photographs had been misplaced. And in the midst of those communications, Michael stated matter-of-factly that he didn't know how to use a computer. One of his sons was teaching him! This from one of chemistry's greatest theoretical and computational chemists of the post-1950s era.

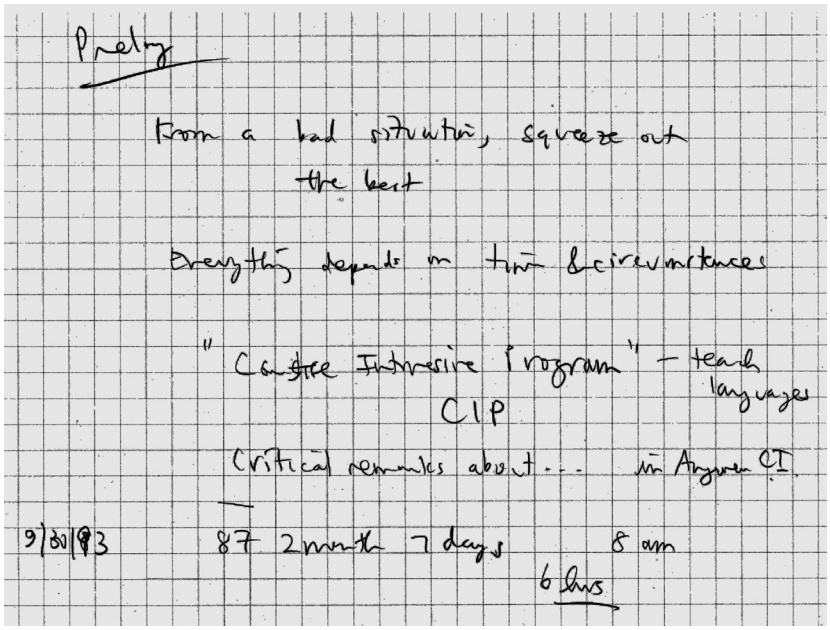


Figure 3. *An excerpt from my notes of a September 30, 1993, telephone call with Prelog. "From a bad situation, squeeze out the best. . . Everything depends on time & circumstances." Then follows what reads to be "Concise [?] Intensive Program," perhaps a joke about the CIP (Cahn-Ingold-Prelog) rules for naming a stereoisomer of a compound. At the very bottom of the figure, Prelog is commenting that he is, on that day, 87 years, two months, seven days, and six hours old. Notes from other telephone calls record the following: "Be a good boy, and if you can't, be very careful." "Seek for simplicity, then distrust it." "Don't worry Prelog, it takes only one minute." "Attack together, march separately."*

William S. Johnson (1913-1995)

I have a streak of sadness when I think of Bill Johnson and his *Profile*. Bill died before his manuscript was completed. But fortunately, four of his close friends and colleagues, several of whom were his former students, completed the manuscript and reviewed and approved the galley and page proofs. His was the last of the 20 volumes to be published, in 1997.

I am also sad because I rejected his request to list all his present and former graduate and postdoctoral students in his book. At the time, it just did not seem to me appropriate for an autobiography. Today I feel very much otherwise. I wish I could reverse that decision.

Bill Johnson intensely identified himself as a chemist. Instead of his name on the sign outside his home in Madison, Wisconsin, he had a plaque manufactured with the tetracyclic skeleton of the steroid backbone (Figure 4). The caption to the photograph that appeared in his autobiography reads as follows (31):

> This is the house we built in the Madison Arboretum on Balden Street, about 1957 (32). The street number plaque with the brass steroid insignia was swiped, shortly before our move to California, presumably by one of my students who made restitution some 20 years later by arranging for the plaque to be placed surreptitiously at my seat while I was at the platform during the memorial ACS symposium for Robert Woodward

Figure 4. *The plaque outside William S. Johnson's home in Madison, Wisconsin. This plaque was stolen by several of his students, then anonymously returned several years later. Photograph courtesy W. S. Johnson.*

> in New York, 1979. I take this opportunity to thank whomever was responsible for the safekeeping and return of the plaque.

On January 8, 2002, I presented a lecture "The Human Side of Chemistry: A Photographic Portrait of Contemporary Heroes" at the Mona Symposium on Natural Products and Medicinal Chemistry at the University of the West Indies in Kingston, Jamaica (33). A highlight of that lecture was the inclusion of many entertaining yet pedagogical photographs that I had collected over the years, many during the editorship of the *Profiles* series. When I showed the photograph in Figure 4, I explained its history: stolen, then returned. Just then, a loud shout came from the back of the room: "I was the one who stole the sign!"

I laughed with everyone else. But I failed to identify the culprit ... and I have blamed myself since 2002 for not having done so. Writing this paper activated the muse. I discovered that the Mona Symposium website has a page that lists the non-West Indies participants at the 2002 meeting (34). And a little sleuthing led me to ... well, I shall not name the individual other than to say that my email to him was promptly answered with an admission, and the revelation that the theft was, as he characterized it, a

> team effort . . . Years after the theft, when [the keeper of the plaque] knew that I would have the opportunity to anonymously return it …

The world of science is a small, compact network of scholars. Its connectivity is amazingly tight. The degrees of separation are few indeed.

Egbert Havinga (1909-1988)

Surely the most touching moment during my editorship of the *Profiles* series was speaking with Louise Havinga, who relayed to her husband Egbert Havinga, on his death-bed, my firm promise: that his book would be carefully and diligently completed and published. I recall saying to Mrs. Havinga, "Please tell your husband my promise. His book will be published."

That promise was fulfilled in large measure due to the collaboration of Havinga's Leiden colleague Harry Jacobs.

Sadly, Havinga and two of the other *Profiles* authors—Herman Mark and Bill Johnson—did not live long enough to hold their autobiographies. But their books were completed with loving care.

Melvin Calvin (1911-1997)

I never actually interacted one-on-one with Melvin Calvin. He wrote his manuscript, I sent my comments to Marilyn Taylor, his long-time high-performing secretary (as administrative assistants were then called), and a final manuscript cleanly and professionally appeared. All questions, requests, and forms were sent to her, and Calvin's responses came promptly from her.

Was Calvin actually alive and participating in this project? I assumed so. Of course, I never questioned the matter.

I do have two postscripts to add. In 1991, when my daughter, Brooke, was in the seventh grade, she had a science project dealing with photosynthesis. Brooke wanted to learn more about Calvin, so I suggest that she write to him. On February 28, 1991, Calvin responded (35),

> I suppose the simplest way to answer is to tell you there is nothing, in my life at least, that surpasses the pleasure which a successful scientific activity gives. Everything else is peripheral to that.

The second postscript involves the 2011 United States postage stamps honoring Calvin, a chemist, and Severo Ochoa, a biochemist. I was asked to serve as the science expert and consult on the design of those stamps. My primary job was to work with the stamps' designers and be certain that the "chemistry" was both accurate and optimal. That was a delightful and totally unanticipated experience—especially so in that, as a youth, I was an avid stamp collector!

Donald J. Cram (1919-2001)

I experienced my most embarrassing moment as editor with Donald Cram. We got the name of his autobiography wrong.

Shortly after Cram's book appeared, he wrote me a lovely and heartwarming letter of thanks. And, almost as aside, he dropped the bomb. His book ought to have been entitled *From Discovery to Design* but was (and is) *From Design to Discovery* (36). How this switch occurred, I do not know. But I do know how it propagated. Once a title is designated, it just self-replicates onto the book's cover, the book's title page, and onto every other page of the volume itself. One click of the computer and off it goes.

But we—both Cram and I—had the opportunity to find and correct the error before the book went to print, and we failed to do so. Cram and I individually and collectively approved the book's cover and both of us

reviewed the galley proofs and the page proofs. On the top of every other page of the page proofs was the book's title. Both Cram and I missed hundreds of the same error. I shared this fact with Cram in a subsequent letter to him for which there was no response.

I might add: we also spelled Arthur Birch's name wrong on the title page of his autobiography. What first appeared was "Author," not "Arthur." Yes, close. Fortunately, this error was caught before the books were distributed. I may own the single uncorrected copy (Figure 5).

Rolf Huisgen (1920-)

My most noteworthy interactions with Rolf Huisgen occurred *after* his autobiography was published. By happy coincidence, in the 1990s and 2000s, my professional life entailed many travels to Europe. And almost all of those involved return travel via Munich, the home of Rolf Huisgen. Countless times, Rolf and I enjoyed the art museums of Munich, especially the Alte Pinakothek, the Neue Pinakothek, and the Pinakothek der Moderne. Rolf introduced me to German Expressionism, most notably what would become one of my favorite artists, August Macke.

My evenings with Rolf and his wife Trudl (Figure 6) form many joyful times in my life and my memory. I had trouble keeping up with Rolf's fast walking pace, just as I had trouble, in days past, keeping up with the much older (than me) Albert Eschenmoser and Dudley Herschbach. I have written more about my times with Rolf and Trudl, and I direct the interested reader to Ref. 15.

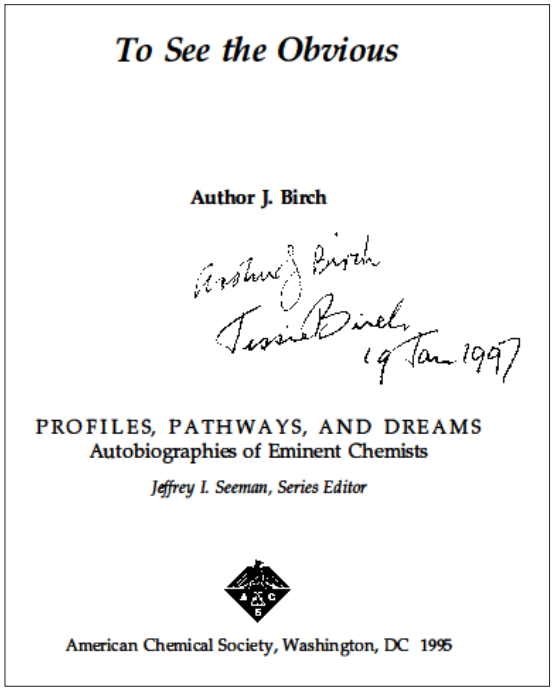


***Figure 5**. The first and erroneous printing of the title page from Arthur Birch's autobiography in the* Profiles, Pathways and Dreams *series. Note the spelling of Birch's first name. Fortunately, this error was caught before the book was distributed. The author of this paper may well have the only otherwise-extinct copy. Note that the spelling notwithstanding, both Birch and his wife Jessie signed the book as a gift to the editor.*

***Figure 6**. Trudl and Rolf Huisgen surrounded by their art, at their Munich home, 2003. Photograph courtesy J. I. Seeman.*

R. Bruce Merrifield (1921-2006)

Bruce Merrifield was a warm, kind and humble gentleman. He also provided to me an early mark of encouragement and approval. I offered to review the early chapters for those authors who wished my input. Bruce was one of those. I'll never forget his response to my praise. "You really like it ..." He was so very pleased with my praise, and I was so very pleased with his gratitude.

Merrifield is also one of the few modern chemists (if not the only one) to be awarded the Nobel Prize in Chemistry for work that he conceived of and did almost entirely by himself, "with his own hands," so to speak. He describes this work, page by page from his laboratory notebook, in his *Profiles* autobiography.

When I last visited Bruce just a few years before he died, he was still working in the laboratory at the Rockefeller University, side–by–side with his devoted wife, Libby. But he expressed to me his concern that he might not be able to retain his laboratory. Space at Rockefeller University was very tight, and even a Nobelist's laboratory and office were not secure. I felt empty, drained with the image.

Koji Nakanishi (1925-)

Koji Nakanishi lives in many worlds simultaneously: first and foremost he is Japanese. But he is also a magician, a chemist, a man of the world, and an American, perhaps in that order. Indeed, he lives in a magic kingdom of natural products and biological systems, his very own fantasy world.

Editing an autobiography can be very personal, and a unique relationship can be established between the author and the editor. One of my remarkable experiences of editing the *Profiles* series was that I met most of the authors in person *only after* their autobiographies had been published. Those were the days of transmitting drafts by mail, typically "airmail" for international service, and less frequently by fax. These processes lengthened the manuscript preparation time considerably. But in a strange way, it made the interactions more personal, or so it seems from today's perspective.

I met Koji for the first time in the spring of 1994 when he gave the Powell Lecture at the University of Richmond, which 13 years later became my home institution. After his lecture, I went up to Koji and introduced myself. He was still standing on the stage; I was a few steps below. Upon hearing my name, Koji let out a deep, honorable "O o o o h!" and bowed deeply. As did I, in return. Koji and I met many times thereafter, including a lovely weekend in 2004 when he visited me, for his first—or perhaps just the second—non-working weekend in his life. I took Koji to meet my horse, an experience that neither he nor I would likely forget (Figure 7).

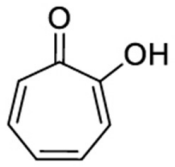
Koji, just as perhaps all prolific scientists, had the ability to sharply focus his attention and shut out distractions. He once told me the story of not recognizing his own daughter in the elevator of their apartment house in Manhattan (19, 37). Nakanishi's daughter later confirmed the story.

Figure 7. *Koji Nakanishi with the author's horse, Awesome, Richmond, Virginia, 2004. Photograph courtesy J. I. Seeman.*

Tetsuo Nozoe (1902-1996)

Circumstances placed Tetsuo Nozoe between a rock and a hard place. Perhaps it was I who placed him there rather than circumstances; you can judge for yourself.

Born in 1902 in Sendai, Japan, Nozoe (independently with Michael Dewar (38, 39)) determined the structure of the first non-benzenoid aromatic compounds (the tropolones). For the next 40 years, Nozoe studied the chemistry of this class of compound. Ultimately, Nozoe never really retired from chemistry, even reviewing a manuscript from his hospital bed on his last day (40, 41). Nozoe was 86 when he began writing his autobiography. Even at that age, he was still commuting several hours (each way, every day) to and from Kao Corporation's laboratories to participate in his experimental research on novel non-benzenoid aromatic compounds.



Tropolone

Nozoe complied with everything I asked of him, and he did so immediately. That is, until I asked him to provide the chemistry genealogy tree of the early 20th century Japanese chemist Riko Majima.

Majima (1874-1962) was the doyen of Japanese organic chemistry in the first half of the 20th century. His students, including Nozoe, and their students were among the most productive and influential Japanese organic chemists for several generations. I asked Nozoe to identify and document for history's sake those influential chemists. But I did not realize the Japanese cultural imperative of saving face; if Nozoe named only some chemists, he would be slighting other chemists by their omission. He wrote to me, apologizing, saying that he had to delete the Majima chemist-family tree based on the warnings of several of his trusted colleagues who had read his draft manuscript.

I urged Nozoe to reconsider. "At age 87, you are the most honored of Japanese chemists. If you do not do this, no one ever will. History of Japanese chemistry will be lost." Nozoe reconsidered and chose history over tradition.

For that and many other reasons, I had a large debt to Tetsuo Nozoe.

That debt was at least partially repaid when, at my urging and under my guest editorship, from 2012 to 2015, *The Chemical Record*—a Wiley journal published for the Chemical Society of Japan—published in 15 consecutive issues the entire Tetsuo Nozoe autograph books, all 1200 pages, along with 19 carefully solicited perspectives (42-44). You see, from 1953 to 1994, Nozoe carried with him to meetings and symposia an autograph book that thousands of chemists and others signed, provided chemical pictographs, wrote poems and otherwise inscribed.

In the editing of the Nozoe Autograph Books project, I was introduced to three of Nozoe's most prominent students, Toyonobu Asao, Shô Itô, and Ichiro Murata. These three "students," then in their 80s, agreed to write two perspectives that appeared with the series. One was a biography of Tetsuo Nozoe (41). The second was on the Tetsuo Nozoe chemist-family tree, which added another generation to the Majima chemist-family tree (45).

Working with what I happily called the AIM team (Asao, Itô, and Murata) brought me back to my time with Tetsuo Nozoe, as if I were working with the great man again. It was an editorial-*déjà vu* experience.

Being a science historian of the modern era has a double advantage. Scientists, in their travels, collect new friends from around the world. And that goes double for historians of science, for they collect as friends both other historians and scientists! A worldwide collection of friends from my professional associations is a continuing benefit that has given me bountiful joys. And unanticipated gifts arrive often to delight one's soul, like the stamp shown in Figure 8 given to me by the AIM team as their thanks—really, my thanks—for being invited to participate in the Nozoe Autograph Books project.

John D. Roberts (1918-2016)

In four papers, I have written about Jack Roberts's personality, professional characteristics and scientific achievements (7, 46), my experiences editing Jack's autobiography (5, 7), and my long and special friendship with him.

Figure 8. *My "Jeffrey Seeman" seal, a gift from Toyonobu Asao, Shô Itô, and Ichiro Murata, three of Nozoe's students and academic chemists of note themselves.*

I treasure the memory (and at the time, the fact) that he would immediately recognize my voice on the phone, when I would say, "Hello Jack!" He would them immediately growl. Actually, he would growl several times. The friendliest and most welcome growls I've ever heard. But they were unmistakably growls, stemming likely from the presumption that I wanted something from him. A realist was Jack.

I treasured my relationship with, and now my memory of, Jack's lovely wife, Edith (Figure 9), as I did the wives of some of the other authors. Edith, a professional in her own right (47), was a warm and gracious person. We spoke frequently, and the memory of her smile upon greeting me still brings warmth to my soul.

Lastly, I treasure my friendship with Marjorie Caserio. After receiving her Ph.D., Marjorie was associated with Jack for nearly a decade, first as a postdoc and then as a research associate. From that era, she is best known as Jack's co-author of several quite popular organic chemistry text books, those often being referred to as "Roberts and Caserio" (48, 49).

***Figure 9**. Edith and Jack Roberts, 2005. Photograph courtesy J. I. Seeman.*

I got to know Marjorie first as the reviewer of Jack's autobiography manuscript. One evening some years after, at an ACS national meeting, she was leaving a reception just as Al Padwa (50) and I were. Al invited Marjorie to join us for dinner, and my two-decade-plus friendship with Marjorie thus began.

One doesn't hear about social connectivity among scientists when one is considering a career in science. Indeed, scientists typically take this value for granted. As mentioned above, that is certainly one of the greatest benefits of a career in science. A historian of modern science shares this benefit in the extreme: such an individual discovers that one's network of friends includes the subjects of one's own research as well as their spouses and their colleagues and friends, too.

F. Gordon A. Stone (1925-2011)

I met Gordon Stone only twice, both times after his autobiography was published. The first time, I was visiting Bristol to see a friend and arranged to meet Gordon. I remember two things about him: first, his wide and welcoming smile; second, the man's organizational skills. All around his office were "in-out" trays in which, he told me, information about different on-going projects or manuscripts in preparation were placed. I wondered how big his pile was for his *Profiles* manuscript, but was too reluctant to ask.

The second time I met Gordon was early on a short holiday I was taking in Wales. I had just completed several days of business in London and decided to visit south east Wales, a region I had visited many times when my family and I lived in Oxford. As I drove toward along the M4 motorway toward Bristol and the Severn Bridge that would bring me into Wales, I recalled that Gordon lived in Bristol. So, I pulled off the motorway, called him, and announced that I would be passing through Bristol and wondered if perhaps I could stop by and say hello. He immediately invited me to have dinner and spend the night.

It was a lovely visit, made especially touching in that Judy, his wife of many years, was in the early stages of what I believe was Parkinson's disease. Gordon was the caretaker, the chef, and the host. His loving demeanor toward his wife enveloped the home. I especially remember his tenderness to Judy and their joint warmth to me.

Andrew Streitwieser, Jr. (1927-)

One of the ironies of my professional career has to do with Andy Streitwieser's 1961 textbook, *Molecular Orbital Theory for Organic Chemists* (51). I used his

***Figure 10**. Andy Streitwieser with the author at the 209th National Meeting of the ACS, Anaheim, California, 1995. Photograph courtesy J. I. Seeman.*

textbook for the one of three courses I was required to take as a graduate student at the University of California at Berkeley. I didn't quite understand much of the book at that time, surely a consequence of my lack of ability or attention, not due to Andy's skill as a teacher. Ironically, that book plays a central role in my current research project, the history of the development of the Woodward-Hoffmann rules (52, 53). And in a real turn-

about, for this current research project I have "deposed" Andy several times regarding the content of that book, the last time questioning him page by page, sometimes line by line and even word by word. *Leaving No Stone Unturned* (54), as Gordon Stone entitled his autobiography (see section immediately above), seems to be my research motto also. Andy has been a very fine deponent.

The student has become the historian-student. The teacher has remained the teacher. And we have become friends (Figure 10).

Reflections on Reflections

Dreams, dreams, dreams.

I could never have dreamed of the personal and professional consequences of the *Profiles* series when I first imagined and "sold" the project to ACS books (5). I refer only in part to all that I learned in the process of editing the project, all the chemistry and the ins-and-outs of scientific publishing. But primarily, I refer to all the relationships that resulted, directly and indirectly, from my participating in this project.

The *Profiles* volumes began to appear in 1990, almost 30 years ago. Sadly, only three of the 20 authors are alive today. When first published, these autobiographies were topical accounts of current chemistry, and many of the authors, though aging, were still the leaders of "present chemistry." Those days are long gone. Today, these autobiographies are sources for the history of chemistry. In only a portion of my own lifetime, the *Profiles* volumes have transitioned from being topical to historical and archival.

Historians of science who study Lavoisier or Priestley, Liebig or Wöhler, Kekulé or Mendeleev, deal with events that are fixed in time and protagonists dead for decades if not centuries, just as insects are locked in the amber of the Baltic shores. But for the *Profiles* series, many of the authors continued their research for years after the publication of their autobiographies. And half of them lived into the 21st century, continuing to publish. The ability to interview the scientists is an enormous benefit when conducting research in the history of *modern* chemistry. There are substantial and sensitive challenges in dealing with eminent chemists who have written many hundreds of publications though few, if any, autobiographical texts. There is a great difference between an autobiography and a scientific paper. The fundamental instruction I gave to the authors was to write about their scientific achievements as well as about the human side of their profession. I have described some of these challenges in other papers and have hinted as some of these in the above brief anecdotes (5-8).

I never anticipated that the *Profiles, Pathways and Dreams* series would serve as a model for other autobiographies. John P. Fackler initiated a series *Profiles in Inorganic Chemistry* in which Fred Basolo (55) and Helmut Warner (56) have published their autobiographies. And separately, Albert Cotton's autobiography was published just after his death (57). These authors and editor have credited the *Profiles, Pathways and Dreams* series as the inspiration for their own autobiographies.

I also never anticipated that I, myself, would use the *Profiles* volumes as source material for my own research. Stephen Weininger asked me recently, "Have you thought about describing the experience of simultaneously being a chemist and an historian of chemistry—sort of being on the inside and the outside at the same time?" When I was editing the *Profiles* series, I was still a full-time practicing and publishing organic chemist, involved in both experimental and computational research. At that time, I considered only other chemists as the customers for the autobiographies. It was my knowledge of and love for chemistry that gave me the ability and perhaps even the permission to interact so intensely with the authors. Today, my interests range more broadly into the history, sociology and philosophy of chemistry, just as the journals I read and in which I publish have moved from the *Journal of the American Chemical Society* and *The Journal of Organic Chemistry* to a much broader set of publications. It is for that internal reason and for external factors mentioned in the introduction that the *Profiles* series, if it began today, would have had a different texture from what it became.

In 1986, Harriet Zuckerman and Joshua Lederberg wrote an insightful article about the nature of discovery. In it, they commented "that personal reminiscence had to be validated by contemporary documents and other testimony as oral history and autobiography are prone to 'unconscious falsification'" (58). During my editorship, I had never considered the possibility that the autobiographies would be anything other than accurate. In the decades since the publication of the *Profiles* autobiographies, I am aware of only one single disagreement with any of the content of those books. That exception is Herb and Sarah Brown's disagreement (59) with Jack Roberts's characterization of an interaction Brown had with Saul Winstein (4). Of course, the matter related to the nonclassical carbocation controversy. On the whole, the *Profiles* series has received major compliments by historians and

chemists alike (60-67), and I often see citations to these volumes in both the chemistry and history of chemistry literature. Thus, these autobiographical representations have withstood the test of intellectual and sociological time and have demonstrated some measure of utility.

What have I learned? What lessons are there, within those volumes, that I should share? When I posed those questions to Djerassi after reading his last autobiography (23) for a review I was to write for *Chemical & Engineering News* (9), he instructed me to read his book again, more carefully! Djerassi never made things easy for others, and in truth, few things are really easy.

Within this article, I have already described much of what I have learned, though some matters are more implicit than explicit. Perhaps the most important are the following precepts. Think big, be creative, and have dreams that far exceed the present. All projects take time and energy, don't waste yours on ideas that, from the get-go, at their best will have limited if any impact. Plan carefully, yet be flexible, keeping your eyes open to new possibilities. Identify the customers of your work and meet their needs, remembering that you are also one of those customers. Find your own special niche. **Have faith in yourself and your ideas. Be an exceptional citizen of our community. Have fun.**

The *Profiles* series has served as the intellectual, emotional and practical foundation for all of my history of chemistry research over the past 30 years. I am deeply appreciative for those experiences, for touching others and for being touched myself. I thank numerous chemists for hundreds of interviews and thousands of email responses and archivists for their boundless welcome and cooperation. I am also deeply appreciative for the HIST Award for Outstanding Achievement in the History of Chemistry. I am enormously touched to find my name associated with many of my heroes who are former Dexter, Edelstein and HIST awardees.

—Dedicated to my teachers, two of many: Ajay K. Bose (Stevens Institute of Technology) and William G. Dauben (University of California, Berkeley).

Acknowledgments

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THE SCIENTIFIC PUBLICATIONS OF ALEXANDER MARCET

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Supplemental material

Abstract

This paper lists all the publications which can be attributed to Alexander Marcet, a physician, chemist and geologist active during the first two decades of the nineteenth century. The contents of each publication are described and assessed. Marcet was a practicing physician at a time and place when many chemists had medical connections. His chemical work is primarily analytical and it also demonstrates how chemistry might eventually shed light on how the human body deals with the materials it has ingested.

Introduction

Alexander Marcet (1770-1822) and his wife Jane Haldimand Marcet (1769-1858) were active in the circles of natural philosophers in London from about 1800 until well into the nineteenth century. Alexander had been exiled from Geneva in 1794 as a consequence of the French Revolution, and he went to Edinburgh to study medicine under Joseph Black (1728-1799) and his colleagues. After graduation in 1797 he moved to London where he practiced medicine and met Jane Haldimand, whom he married. Later he taught chemistry to medical students at Guy's Hospital. He always retained his interest in the growing science of chemistry, and he built a laboratory in each of two homes in London in which he and his wife lived. In his publications he initially cited his name as Alexander Marcet M.D., adding F.R.S. in 1808 when he was elected to the Royal Society. French was his native language and this enabled him to maintain contacts with French and Swiss researchers, and to act as foreign secretary to, for example, the Geological Society of London. He died in 1822. His scientific activities show how, at the beginning of the nineteenth century, chemistry in Britain was professionally and institutionally intertwined with medicine, even while other chemists were breaking free from it.

Detailed information on Alexander and Jane Marcet is still easily available, and Jane's life, in particular, has been described in considerable detail (1). However, Alexander's professional career has been relatively neglected. This paper is an attempt to illustrate that he was no mere helper to his exceptional wife, but a significant figure in his own right. Indeed, Alexander's interests included not only medicine but chemistry, geology, education, and public health (2).

Once exiled, Marcet decided to study medicine at the School of Medicine of Edinburgh University. At the time this was perhaps the foremost in Europe and it drew students from all over the Continent (3). The Head, Joseph Black being concerned with the nature of heat and fixed air (carbon dioxide), the properties of magnesium compounds (as distinct from those of calcium), and the use of the analytic balance (4), is recognized today by chemists a major figure in the development of chemistry as an independent scientific discipline. Black had been appointed Professor of Chemistry and Medicine at Ed-

inburgh in 1766, and he continued to practice medicine for some time afterward. Modern chemists often do not realize that he continued to be active as a physician while researching and teaching chemistry, and that he became principal physician in Scotland to King George III. Black eventually ceased research because of illness and then devoted himself exclusively to teaching. His teaching was very successful and attendance at his lectures increased from year to year for more than thirty years. He had a powerful effect in popularizing chemistry, through his introduction in his chemistry lectures of new concepts and ideas, and his students spread them and practiced them when they left Edinburgh. In fact, one of those students, John Robison, published Black's lectures on chemistry, based on his notes, after his death (5).

Amongst the medical students whom Marcet had met in Edinburgh, and with whom he continued to interact in London were John Yelloly (1774-1842) and Peter Mark Roget (1779-1869). Roget was the son of a Genevan father and an English mother who was the sister of Sir Samuel Romilly, an eminent politician who paid for Roget's university education. Another of Marcet's London acquaintances was William Hyde Wollaston (1766-1828) who also started studying medicine at Edinburgh, but did not complete his studies there, moving to Cambridge. He also made his reputation as a chemist. Another acquaintance was Smithson Tennant (1761-1815), who had intended to study under Joseph Black, but due to family circumstances finally took a medical degree in Cambridge. Being financially secure, he did not long practice medicine and soon spent his time researching chemistry, identifying the new metals osmium and iridium, for which he is still recognized today. At that time it was generally impossible to study chemistry as an independent discipline in universities in Britain, and where chemistry was taught it was usually within a medical curriculum. Marcet's professional career was a prime example.

Alexander Marcet's Publications

A list of Marcet's publications was published in the *Annual Biography and Obituary* (6). (A copy of the obituary is available as Supplemental Material to this paper.) As was usual at the time, this obituary was published without the writer being identified, but it was certainly Roget, who was a great admirer of Marcet. Nick Rennison, in an account of Roget's life (7) quotes several sentences from an unidentified obituary which Roget wrote of Alexander Marcet. These quotations are to be found word-for-word in the "anonymous" 1823 obituary cited above (6).

Alexander Marcet's publications are listed below, in numbered items, exactly as Roget described them in the obituary, though Roget did not number the items. Here Roget's citations are numbered, followed by a full bibliographic citation (including Marcet's by-line, if any), and summarized. Nearly all are available online at Google Books or the Hathi Trust Digital Library. Supplemental material to this paper gives the text of the bibliographic part of Roget's obituary with links to online versions of Marcet's papers.

Item 1: In 1799, he wrote an account of the History and Dissection of a Diabetic Case (published in the London Medical and Physical Journal, vol. ii. p. 209.)

> **"**Case of Diabetes, with an Account of the Appearances after Death, stated in a Letter to Dr. Rollo." By Alexander Marcet, M.D., member of the Royal College of Physicians, London; and Physician to the City Dispensary. *London Medical and Physical Journal*, **1799**, *2*, 209-213.

Marcet came to London in 1797 and worked first at the City Dispensary. The patient discussed here came to the dispensary in March 1798, suffering from diabetes and phthisis pulmonaris (consumption or tuberculosis). Marcet was not aware of the phthisis pulmonaris before he examined the patient. Dissection revealed nothing which had not been observed before in diabetic cases. The patient customarily consumed "seven or eight pounds of beer, or spirits and water in twenty-four hours." Although Marcet studied diabetes in Edinburgh and wrote his graduation thesis on the disease, this account could not have been from his graduation thesis because the case described here came from London. The urine was sweet, and the patient also suffered from mesentery (the attachment of part of the digestive system to the stomach wall.

Item 2: In 1801, a paper on the Medicinal Properties of the Oxyd of Bismuth. (Memoirs of the Medical Society of London, vol. vi. p. 155.) This paper, though read to the Society in 1801, was not published till 1805.

> **"**Observations on the Medical Use of the White Oxyd of Bismuth." By Alex. Marcet, M.D. &c. Sec. M.S., One of the Physicians to Guy's Hospital. *Memoirs of the Medical Society of London*, **1805**, *6*, 155-173.

This paper resulted from a visit to Dr. Odier in Geneva (Louis Odier, 1748-1817). It was read originally in 1801, but Marcet was later asked to publish it. He discovered that Odier was using magistery (oxide) of

bismuth to relieve stomach pains, especially for women used to carrying loads of water on their heads. Bismuth was sold by perfumers, but Marcet describes its preparation and freeing it from a green color, said to be due to oxide of nickel. He includes many back references, some in German and French, and even presents a large chunk of Latin. Marcet describes several of his own cases, mainly women, all with severe stomach pains and sometimes difficulty in holding down food. Most recovered with the bismuth oxide in time, but one required more treatment with mercurial medicines. Many salts had been tried as medicines in such cases, most without success. Marcet cured four cases out of the six described, and later often used the remedy at Guy's.

This was Marcet's first chemistry paper, and it reflects the habit of these early chemists/doctors of trying new compounds on their patients in the hope that they might effect cures. Marcet took pains to describe cases where the oxide of bismuth proved ineffective, and he recommended similar candor in the description of other prospective medicines.

Item 3: On the Hospice de la Maternité at Paris. (Monthly Magazine for May 1801, p. 311.) To this communication he did not affix his name.

"On the Hospice de la Maternité at Paris." *Monthly Magazine*, **1801**, *11*, 311-313.

A footnote to the published paper states that "This valuable and authentic account was communicated to us by a physician, established in London, who had an opportunity last summer of being an eye-witness to all that is mentioned in this report." As a consequence of the French Revolution, hospitals and poorhouses in Paris were funded by the government and never by individuals or charities, unlike normal practice in England. Marcet visited Paris in 1800 and checked that they were as bad as rumored, though recent improvements had been made. He reported that the buildings were good and clean, and the patients were not hungry, cold, or lacking air, but the medical treatment was worse than in England. Patients did not thank their caregivers, as they would do in a charity hospital, such as Guy's Hospital in London, and the caregivers grew discouraged. There were 20,000 distressed persons in 22 hospitals in Paris. The Maternity Hospital delivered 1500 babies per year and accepted any woman in her eighth month. The midwives were female. They received and cared for abandoned children and sent them to "country nurses" to raise them. These children were paid subsistence until the age of 16, when they were told their parents' names and given a birth certificate.

Item 4: In 1802, Translation of the Report to the Institute of France respecting Paul's Manufactory of Mineral Waters; with a Preface written by himself. This pamphlet was published anonymously.

The Report Made to the National Institute of France, in the Month of December, 1799, by Citizens Portal, Pelletan, Fourcroy, Chaptal, and Vauquelin, Respecting the Artificial Mineral Waters Prepared at Paris by Nicholas Paul and Co. G. Woodfall, London, 1802.

The original was written for a session of the National Institute of Sciences and Arts on 21 Frimaire in Year 8 of the French Republic (December 1799). It lists many sources of mineral waters, apparently duplicated by manufacturing in Paris by Nicholas Paul (who was originally from Geneva). The English text contains no name of a translator, though the document is ascribed to Marcet by Roget. Marcet had a deep interest in the medical uses of mineral waters and their chemical contents, and this may be why he was interested in artificial versions. He was also francophone, so he needed no translator to understand it himself.

Item 5: In 1803, a correspondence appeared between Dr. Marcet and Dr. Jenner, respecting a mode of procuring vaccine fluid, in the London Medical and Physical Journal, vol. ix. p. 462.

London Medical and Physical Journal, **1803**, *9*, 462-466.

This set of correspondence between Marcet and Edward Jenner (1749-1823) concerning methods to safeguard vaccination fluid was published without a title. It comprises a brief introductory letter by Marcet to the editors of the journal, followed by extracts of letters from Jenner to Marcet, Marcet to Jenner, and Jenner to Marcet.

Jenner and Marcet were personal friends, and Marcet was very active in encouraging the wide application of vaccination to treat fevers. There is a discussion of cases where the vaccine for smallpox seems to have caused complications. The vaccine taken from a pustule was originally "stored" on a cotton thread, a lancet or between glass plates, and this sometimes caused other illnesses (!). Marcet recommended glass phials with a ground glass stopper (costing one shilling, £0.05 each). Samples should not be too large and should be kept free of air, but light does not damage the vaccine.

Item 6: In 1805, an Analysis of the Brighton Chalybeate, published in Dr. Saunders's Treatise on Mineral Waters, second edition, p. 331.

"A Chemical Account of the Chalybeate Spring, Near Brighton." In William Saunders, *A Treatise on the*

Chemical History and Medical Powers of Some of the Most Celebrated Mineral Waters…, 2nd ed., Phillips and Pardon, London, 1805, pp 331-402.

This is an extensive account of the analysis of a chalybeate (that is, iron-bearing) spring near the Wick in Brighton. There are no medical uses reported, but his many tests showed that 100 parts of residue dried at 160° (Fahrenheit) contains sulfate of iron 21.2 and sulfate of lime 48.2, muriate of soda 18.0 and muriate of magnesia 8.9, and siliceous earth 1.7, with the remaining 2.0 parts attributed to loss. The water itself contains about 1/13 part of carbonic acid gas by volume. The report refers to much then current work due to Black, Humphry Davy (1778-1829), etc., and shows Marcet's careful chemical analysis. He assumes that salts exist in solution very much as what we would term molecules, so that the various sulfates and muriates (chlorides) were considered to be still present as compounds in solution. The chalybeate spring is probably still present in the area, though not exploited for any medicinal properties, as it apparently once was.

William Saunders (1743-1817) was the first president of the Medical and Chirurgical Society, formed in 1805. Marcet was a founding member and foreign secretary (8). Both Saunders and the Medical and Chirurgical Society figure in a few of Marcet's scientific publications in the next several years.

Item 7: Account of the Case and Dissection of a Blue Girl, in the Edinburgh Medical Journal, vol. i. p. 412.

"Case of a Blue Girl, with Dissection." Communicated by ALEXANDER MARCET, M.D., one of the Physicians to Guy's Hospital. *Edinburgh Medical and Surgical Journal*, **1805,** *1*, 412-416.

Description of the dissection of a young woman maid servant, afflicted in winter with a cough, and shortness of breath. She had worked until 7 weeks previously, then could not proceed, and her menses had stopped. She was blue and obviously very ill. Blisters were applied to no effect. She died and the blue color slowly faded in 24 hours. Her heart was slightly enlarged but not changed otherwise, her lungs adhered everywhere to the inner surface of the chest and the pleural cavities were also shrunken and the insides adhered to themselves. All the blood looked venous.

Item 8: In 1807, an Analysis of the Waters of the Dead Sea, and of the River Jordan. (Philosophical Transactions for 1807.)

"An Analysis of the Waters of the Dead Sea and of the River Jordan." By Alexander Marcet, M.D., one of the Physicians to Guy's Hospital. Communicated by Smithson Tennant, Esq. F.R.S., *Phil. Trans. Roy. Soc. London*, **1807**, *97*, 296-314.

Marcet persuaded friends and acquaintances who travelled abroad to collect suitable water samples for him. He did not travel so widely himself. Small samples were collected and held in corked bottles. The paper describes properties of the Dead Sea, noting its earlier English name of Lake Asphaltite. Its water contains muriates of lime and magnesia, and soda, also selenite. Muriate was analyzed by precipitation of luna cornea (silver nitrate). Analyses were checked against standard solutions he had prepared. He checked analyses by two different methods. Sea water contains 25% salts by dry weight. Water from the River Jordan contains only about 1/300 of the dissolved solids as the Sea water, but the same kinds of salt. The same paper was published in *Nicholson's Journal of Natural Philosophy, Chemistry, and the Arts*, **1808**, *20*, 25-40.

Item 9: In 1809, an Account of the Effects produced by a large quantity of Laudanum, taken internally, and of the means used to counteract those effects. (Medico-Chirurgical Transactions, vol. i. p. 77.)

"Account of the Effects Produced by a Large Quantity of Laudanum, Taken Internally, and of the Means Used to Counteract those Effects." By ALEXANDER MARCET, M.D. F.R.S. one of the Physicians to Guy's Hospital. *Medico-Chirurgical Transactions*, **1809**, *1*, 77-82.

An 18 year old man had taken six ounces of laudanum and was very ill. Copper sulfate solution made him vomit, and he was kept on his feet and active for 24 hours, and fed with various materials, especially perfumes which aid breathing (musk, assa foetida, etc.). After several days the patient recovered completely.

Item 10: A Case of Hydrophobia, with an Account of the Appearances after Death. (Medico-Chirurgical Transactions, vol. i. p. 132.)

"A Case of Hydrophobia, with an Account of Appearances after Death." By ALEXANDER MARCET, M.D. F.R.S. one of the Physicians to Guy's Hospital. *Medico-Chirurgical Transactions*, **1809**, *1*, 132-156.

This was the result of a dog bite some days earlier. The patient was treated with opium and iron sulfate and then potassium arsenite (Fowler's solution). He had paroxysms and fits of anger, as is usual with rabies, and died after six days. Dissection showed few abnormalities in the organs.

Item 11: In 1811, a Chemical Account of an Aluminous Chalybeate Spring in the Isle of Wight. (Geological Transactions, vol. i. p. 213.)

> "A Chemical Account of an Aluminous Chalybeate Spring in the Isle of Wight." By ALEXANDER MARCET, M.D. F.R.S., one of the Physicians to Guy's Hospital, and member of the Geological Society. *Transactions of the Geological of London*, **1811**, *1*, 213-248.

This work was undertaken at the suggestion of Saunders, who says that geologists are not interested in medical or chemical properties, but this spring is exceptionally strong in iron sulfate and aluminum sulfate. The environment and the rocks and their general obvious content (iron, little calcium, etc.) are described using notes of a Dr. Berger. Marcet reports specific gravities (*ca*. 1007.5), apparent acidity to litmus, the production of reddish flakes by air, a blue color with potassium "prussiat," a green precipitate with alkali, and white precipitate with silver nitrate, barium nitrate and chloride. Marble was unaffected by being boiled in it, and the residue after drying and redissolving gave an acid solution. Marcet claimed to identify iron, calcium, and aluminum sulfates and maybe magnesium sulfate, also sulfuric and muriatic acids. These are all considered as compounds present in solution, though he states all the muriatic acid exists in the form of muriate of soda. Then comes an extensive discussion of seven ways to analyze such mineral water samples, followed by a detailed account of the identification and quantification of the various sulfates. Silica was also identified. The quantities involved, which included dissolved gas, are greater than in any other chalybeate spring yet recorded. The medicinal properties of the water should be considerable, but maybe it should be diluted with other water before drinking.

Item 12: An Account of a severe Case of Erythema, not brought on by Mercury. (Medico-Chirurgical Transactions, vol. ii. p. 73.)

> "An Account of a Severe Case of Erythema Unconnected with Mercurial Action." By ALEXANDER MARCET, M.D. F.R.S. one of the Physicians to Guy's Hospital. *Medico-Chirurgical Transactions*, **1811**, *2*, 73-84.

A detailed account of a patient who had recurring attacks of erythema (a reddish inflammation of the skin) over some years. He was treated with saline antimonial mixture. The patient had been treated earlier for gonorrhea with mercury, and this was often the treatment at the time. Most authorities had linked erythema to mercury, and often called it erythema mercurial or even hydrargyria, but Marcet could find no reason to connect this patient's disease to mercury. He quoted another patient with a similar history, but he also found many cases where mercury was not involved at all. Perhaps mercury potentiates a patient for the condition, but clearly it is not necessary.

Item 13: Experiments on the Appearance, in the Urine, of certain Substances taken into the Stomach, in a letter to Dr. Wollaston. (Philosophical Transactions, for 1811, p. 106.)

> "Reply of Dr. Marcet on the Same Subject." ALEX. MARCET. *Phil. Trans. Roy. Soc. London*, **1811,** *101*, 106-109.

This is actually a reply to, and in part, a section of the paper that immediately precedes it: "On the Non-existence of Sugar in the Blood of Persons Labouring under Diabetes Mellitus." In a Letter to Alexander Marcet, M. D. F. R. S. from William Hyde Wollaston, M. D. Sec. R. S., *Phil. Trans. Roy. Soc. London*, **1811,** *101*, 96-109.

This discussion originated in about 1800 when Wollaston gave up medicine, but it was widely believed that sugar could be detected in diabetic blood. In 1797, Marcet had also accepted this. However, Wollaston and Marcet had independently searched for sugar in blood and urine, and had communicated together around 1800, but had never concluded their discussion. The paper relates their various experiments on blood and urine. Sugar could not be found, but they did trace iron through the system of various patients, which included subjecting then to doses of prussiate of potash, apparently without harming them. Mercury salts were also imbibed by some patients, without harm. That some chemicals, after a dosage, could reach the bladder without passing through the blood was not, at that time, recognized.

Item 14: A Chemical Account of Various Dropsical Fluids with Remarks of the Nature of Alkaline Fluids Contained in these Fluids, and on the Serum of the Blood. (Medico-Chirurgical Transactions, vol.ii. p. 340)**.**

> "A Chemical Account of Various Dropsical Fluids with Remarks of the Nature of Alkaline Fluids Contained in these Fluids, and on the Serum of the Blood." By ALEXANDER MARCET, M.D. F.R.S. one of the Physicians to Guy's Hospital. *Medico-Chirurgical Transactions*, **1811**, *2*, 342-384.

Marcet examined samples taken from different sources in bodies afflicted with cases of spina bifida, hydrocephalus or several kinds of dropsy. He tried a range of chemical tests, many quantitative, employing reagents such as alcohol, lead acetate, silver nitrate,

barium chloride, oxymuriate of platina (sic). Among the "animal matter" he found albumen in highly variable proportions but not gelatine. The ionic nature of salts in solution had not been recognized in 1811, and analytical efforts were directed to identifying the individual species of salts in solution. He also found potassium in small amounts, but always rationalized in terms of compounds such as muriate of potash. He used specific gravity as a measure of the fluids, but noted that the specific gravity of serum varies with the patient and also with time in a single patient. His results differed from those of Dr. George Pearson (1751-1828), M.D. F.R.S., physician to the Duke of York and his household.

In a footnote (p 356), Marcet pays tribute to the growing power and diminishing discomfort of chemical analysis: "The large dismal, subterraneous laboratory of the old chemists is now changed for the fire-side of a comfortable study; and a new school is arising under his [Wollaston's] auspices, and of those of two or three other British chemists, which promises to give a most essential impulse to the progress of analytical chemistry."

This paper of Marcet's prompted a rejoinder by Pearson, published both in *Philosophical Magazine* and in *Nicholson's Journal* (9). Pearson's letters led in turn to responses by Marcet, summarized under Item 15. Pearson had published papers in 1809 and 1810 on Expectorated Matter and Purulent Fluids, which discussed their alkaline content, and in which some results differed from those reported by Marcet. In particular, Pearson had reported that phlegm and pus contain potash and not the soda which Marcet had found in his biological materials. He promised a few more words on the subject for the next issue of the journals. Pearson was evidently classically educated, and apart from quoting Lord Bacon in Latin also expressed his respect for both Marcet and for his putative collaborator Wollaston.

Items 15: In 1812, he was engaged in a controversy with Dr. Pearson, respecting the nature of the Alkali existing in the Blood. (See Nicholson's Journal, vol. xxxii. p. 37; and Philosophical Magazine, vol. xxxix.)

Together with a correspondence with Dr. Bostock on the same subject. (Nicholson's Journal, vol. xxxiii. p. 148. and 285.)

15a: "An Answer to the Observations of Dr. Pearson (see our last Number) on Certain Statements Respecting the Alkaline Matter Contained in Dropsical Fluids, and in the Serum of the Blood." By Alex. Marcet, M.D. F.R.S. one of the Physicians to Guy's Hospital. *Philosophical Magazine*, **1812**, *39*, 122-127. The same letter also appeared in *Nicholson's Journal of Natural Philosophy, Chemistry, and the Arts,* **1812**, *31*, 230-236.

Marcet professes a disinclination to engage in public philosophical controversy. Nevertheless, he stands by his finding that the only uncombined alkali he found in his fluids was soda and not potash. He had isolated by various procedures subcarbonate of soda, some muriate of soda and a small quantity of muriate of potash, but never any carbonate of potash. He confirmed that there had been a source of potassium present by testing with oxymuriat of platina and with tartaric acid; these reagents yield precipitates with potash but not with soda. But the uncombined alkali he identified as soda on the basis of the crystals formed on combination with nitric acid. He wonders whether Pearson was worried by Marcet working on very small quantities of material, rather than with the large quantities Pearson had used. Even the esteemed Joseph Black used small quantities to analyze Iceland springs. Microscopic examination of crystals, which Marcet had used, and small-scale analysis have enabled the identification of five kinds of urinary calculi, four new metals in the ore of platina, the similarities of meteoric stones, the identity of metallic bases of alkalis, and the bases of crystallography. Repetition of these works on a larger scale has simply confirmed the earlier small-scale results. He also accuses Pearson of misquoting his statements and attributing to Marcet and Wollaston (whom Marcet admires greatly) findings which were Marcet's alone. His work may contain errors, but none which Pearson has claimed to identify.

Pearson, having been prevented by "a severe accident" from writing the further comments he had wished to make on Marcet's paper on dropsical fluids (Item 14) found that he now had an additional letter by Marcet to which he must respond. He did so, again in both *Philosophical Magazine* and *Nicholson's Journal* (10). Pearson does not wish to enter a polemical discussion either, but feels it necessary in the cause of science to write further, in the hope that others may be stimulated to take part in a learned controversy. Nevertheless, his writing is sometimes ironic. There is an argument about the advantages and disadvantages of working on small amounts of test material, which Marcet preferred, but Pearson refers to some lessons he had learned from his teacher, the redoubtable Professor Joseph Black, and claims that results obtained from large samples are more reliable. Pearson hopes that this discussion is now concluded.

15b: "A Correspondence between Dr. Bostock and Dr. Marcet, on the Subject of Uncombined Alkali in Animal Fluids." J. Bostock and Alexander Marcet.

Philosophical Magazine, **1812**, *40*, 176-179. The same letter also appeared in *Nicholson's Journal of Natural Philosophy, Chemistry & the Arts*, **1812**, *33*, 147-151.

This correspondence is essentially a letter from Marcet to John Bostock (1773-1846) introduced by Bostock and forwarded (with Marcet's permission) to the editors of the journals in which the controversy had already appeared. Concerning the Marcet-Pearson discussion, Bostock had originally believed Pearson that the uncombined alkali in blood is potash, but after correspondence with Marcet and repeated experiments Bostock is now convinced that the alkali is soda, as a letter from Marcet shows. (By potash and soda, the researchers were referring to KOH and NaOH respectively.) Marcet repeated his experiments to show that the uncombined material identified by Bostock as potash was, in fact, muriate of potash. Conclusion: "… that the potash which exists in the animal fluids, is in the state of muriat, and that the whole of the uncombined alkali is soda."

Pearson was not convinced, though, as he wrote in both journals (11). He states that Marcet should have produced new facts, not conclusions supported by authority. He questions Marcet's interpretation of his results at considerable length. He also states that he "never contemplated potash as existing in an uncombined state in the animal fluids, but in reality in combination with a destructible acid, or with animal oxide." He believed that the acid was malic acid, and after talking with Berzelius (then in London visiting Marcet!) discovered that Berzelius thought the acid might be lactic acid. He finishes with a note that Marcet should not be offended by his jocular style of writing. No offence was intended. "... a public-spirited man will always make sacrifices for the benefit of the republic." Pearson hopes that if the disagreement continues, then utmost politeness would be observed.

This whole correspondence represents a problem which current science would not recognize as such.

Item 16: In 1813, a paper on Sulphuret of Carbon, written conjointly with Professor Berzelius. (Philosophical Transactions for 1813, p. 171.)

"Experiments on the Alcohol of Sulphur, or Sulphuret of Carbon." J. Berzelius, M.D. F.R.S. Professor of Chemistry at Stockholm and Alexander Marcet, M.D. F.R.S. one of the Physicians to Guy's Hospital. *Phil. Trans. Roy. Soc. London*, **1813**, *103*, 171-188. An appendix due to Berzelius alone follows on pp 188-199.

Jöns Jacob Berzelius (1779-1848) visited the Marcets in the summer of 1812 and worked in Marcet's laboratory. This paper and appendix seem to be the products of this collaboration. The oil treated in the paper was first described in 1796 and shown by Clement (Nicolas Clément, 1779-1841) and Desormes (Charles Bernard Desormes, 1777-1862) to be formed from sulfur and charcoal. Others thought it might contain hydrogen, and perhaps no carbon. The quantitative work reported is due to Berzelius. The paper describes the preparation from sulfur and carbon at red heat, and then distilled. They measured its specific weight, refractive power, vapor pressure ("expansive power"), and boiling point (110-115°F). It does not congeal above –60°F. It is highly flammable. They investigated its chemical properties, including the reaction with oxymuriatic acid gas (which Davy had recently renamed chlorine). Combustion yielded sulphureous acid gas, carbonic acid gas and carbonic oxide gas. They failed to detect combined hydrogen reacting with metal oxides, but they proved presence of carbon by generating carbonate of barytes. Analyses for carbon and sulfur using Mr. Dalton's "particle weights" and Davy's analytical data give C:S as 1:2 and no other element present. (That is, the compound was what would later be named carbon disulfide.) The Appendix contains the experimental data, all weights in grammes rather than grains and consistent with the law of determinate proportions. Berzelius noted that different sulfurets contain different proportions of sulfur S, which they cannot explain, but sulphureous acid gas is S:O as 1:2. Berzelius prepared carbosulfurets by reaction with various "alkalis" (bases including ammonia, lime, barytes, strontian, caustic potash and soda). Aqua regia produces an acid substance which Berzelius calls *acidum muriaticum sulphuroso-carbonicum* and whose analysis he interprets in terms of Daltonian atoms as a combination of one carbonic acid, one sulfureous acid, and two muriatic acid. Berzelius was interested in chemical nomenclature, which was still rather unsystematic in 1816, and in the particle theory of John Dalton (1766-1844), which dates from 1803 (12), and his law of partial pressures which was even slightly earlier (13).

Item 17: On the intense Cold produced by the Evaporation of Sulphuret of Carbon. (Philosophical Transactions for 1813, p. 252.)

"Experiments on the Production of Cold by the Evaporation of the Sulphuret of Carbon." By Alexander Marcet, M.D. F.R.S., one of the Physicians to Guy's Hospital. *Phil. Trans. Roy. Soc. Lond.,* **1813**, *103*, 252-255.

Marcet showed that the compound characterized in the previous item (i.e., carbon disulfide) is so volatile

that it can produce severe cooling on evaporation and he also used a vacuum pump to magnify the effect. He measured the "elastic force" (pressure) of its vapor and found it comparable to that of ether as reported (14) by Dalton. Evaporation of a few drops of the liquid into a Torricellian vacuum at room temperature reduced the temperature to 10°F, lower than with alcohol or ether. A thermometer bulb wrapped in a cloth soaked in the liquid can be brought to –81°F with the aid of a good vacuum pump.

Item 18: On the Congelation of Mercury by means of Ether and the Air-pump. (Nicholson's Journal, vol. xxxiv. p. 119.)

> An Account of some Experiments on the Congelation of Mercury, by Means of Ether. By Alexander Marcet, M.D. F.R.S., *Nicholson's Journal of Natural Philosophy, Chemistry & the Arts*, **1813**, *34*, 119-121.

Marcet was fascinated by attempts to produce low temperatures and demonstrated to family and friends how they could be achieved using ether. This paper mentions an experiment of John Leslie (1766-1832) freezing water by evaporation of water using an air pump, but Marcet could not repeat Leslie's experiment of similarly congealing mercury in the bulb of a thermometer. However, this can be easily achieved using ether rather than water in an arrangement similar to that employed in Item 17. He reached –45°F from a room temperature of above 50°F. The method also works with mercury in an open tube, and so the solid may be examined. In addition he used Wollaston's ingenious cryophorus, which had been described in print in 1813. He also reported seeing what we would now term super-cooling of water.

Item 19: Observations on Klaproth's Analysis of the Waters of the Dead Sea. (Thompson's Annals of Philosophy, vol. i. p. 132.)

> "Observations on Mr. Klaproth's Analysis of the Water of the Dead Sea." By Alex. Marcet, M.D. F.R.S., one of the Physicians to Guy's Hospital. *Thomson's Annals of Philosophy,* **1813**, *1,* 132-135.

The results published by Martin Klaproth (1743-1817) differed from the ones Marcet had published earlier in *Phil. Trans*. (Item 8). Marcet made up standard solutions and analyzed them to check the accuracy of his analytical methods, and then repeated and confirmed his Dead Sea analyses as published. The Dead Sea contains muriates of magnesia and lime, muriate of soda, and sulfate of lime. Marcet attributed the discrepancy between his results and those of Klaproth to "desiccation." Today we would probably ascribe the differences to loss of water of hydration or of crystallization.

Item 20: An easy Method of procuring an intense Heat. (Ibid. vol. ii. p. 99.)

> "On an Easy Method of procuring a very intense Heat. By A. Marcet, M.D. F.R.S. Physician to Guy's Hospital. *Thomson's Annals of Philosophy,* **1814**, *2*, 99-100.

The method simply involves introducing oxygen gas into a lamp flame of burning spirit of wine. This enables higher temperatures to be exerted on larger volumes than hitherto. This enables diamond to be burned and platinum metal to be drawn into wire (as demonstrated by Wollaston).

Items 21: In 1814, the articles Potassium and Platina, in Rees's Cyclopedia.

> "Platina" (in Vol. 27) and "Potassium" (in Vol. 28). In *The Cyclopaedia or Universal Dictionary of Arts, Sciences and Literature*. Abraham Rees … with the Assistance of Eminent Professional Gentlemen. Longman, Hurst, Rees, Orme, & Brown, London, 1819.

The *Cyclopaedia* edited by Abraham Rees (1743-1825) appeared serially over the period 1802-1820. When it was published as a set of 39 bound volumes, each volume carried the date 1819. The volumes containing "Platina" and "Potassium" appeared in 1814 (15). No authors are named in the text, but Marcet is listed in the editor's preface among the contributors on chemistry, along with such luminaries as Dalton and Davy (16). Roget ascribes these particular articles to Marcet (6). Page numbers are not printed. Counting the first page on which an article appears as p 1, the entry "Platina" falls on pp 678-681 (of Vol. 27) and "Potassium" on pp 303-304 (of Vol. 28).

Platina (also called platinum by some recent writers) is a noble metal, unaffected by air and moisture. The ores originate mainly from South America, but now also from Estramadura (Extremadura) in Spain. Ores contain up to 80% pure metal, but also no less than four new metals, iridium, osmium, rhodium and palladium as well as more common metal-based impurities. Marcet describes methods of platinum metal recovery from the ores and ascribes the new metals to Tennant (1804) and also iridium and osmium to Wollaston (1805). Platinum metal utensils were rare but becoming more common, though still expensive. They are useful for experimental chemistry. Wollaston used platinum to make fine wires for electrical experiments, and Marcet copied him in this. There follows an account of the chemistry of platinum and of some of its derivatives. Large platinum vessels

are used in the manufacture and distillation of vitriolic (sulfuric) acid in batches of more than 300 pounds.

Potassium, the basis of potash, arose from early experiments on electrolysis, often in Britain and above all by Davy, an example of "British genius." There follows an account of the chemical properties of potassium. Marcet notes that Davy objects to the name muriate of potash because the compound contains neither muriatic acid nor potash, but potassium and chlorine, though many eminent chemical philosophers disagree with him, so the matter is still "sub judice." Soda also yields a similar reactive metal. Larger quantities of potassium can be obtained without electricity using iron turnings at white heat and melted potash in a curved gun barrel, air excluded. The large quantities so obtained are identical in properties to those described by Davy.

Item 22: Account of the Public Schools at Geneva. (Monthly Mag. for 1814, vol. xxxviii. p. 221. and 307.)

> "A Concise Account of the Public Establishments for Education at Geneva; Extracted from a Letter Written by an English Traveller to a Friend in London." *Monthly Magazine,* **1814***, 38*, 221-225, 307-313.

The letter was published in two parts. There is no writer identified, but some correspondence about ten years earlier between Marcet and the editor of the *Gentleman's Magazine,* Charles Aikin (1775-1847), shows that Marcet had wished to describe in an article the reactions of an Englishman to visiting Geneva. In mid-1803 Alexander was thinking of Jane's work being published as articles in a magazine, not as a book, and was also trying to publish some favorable publicity concerning his home city, Geneva, though an earlier effort had not been accepted. Aikin's letter (17) runs as follows:

> Dear Sir
>
> I return you the account of Geneva which I have read with singular pleasure & satisfaction. With regard to the assumed character of an English traveller, one might perhaps be inclined to suspect him to be a true Genevan at heart, but the real matter of fact which is related is such as amply to justify the esteem for the Republic which is so cordially expressed. In any form it will be a very valuable acquisition for the Magazine, but as I am glad to find it longer than I expected, I should tell you that it will be beyond the length of a single letter in a journal in which variety is always as much as possible consulted. It would make two or even three very interesting letters...

However, the articles do not appear to have been published in the *Gentleman's Magazine*, whatever their length.

The two articles seem to have been derived from the same basis as the report written by Marcet for the Archbishop of Canterbury at a time when the Church of England was considering setting up a system of public schools for the public at large, and Geneva might have been a model. The original of that report is to be found in the library of Lambeth Palace. The account states that the education system in Geneva was open to all citizens and free of cost. The letters describe the Geneva system together with details of persons and contemporary events. Marcet had close contacts with Geneva, but there is no record of him visiting there in 1814. Though there is no doubt that although Marcet wrote the letter as published, the precise source of some of the information contained in it is not evident. However, Marcet had certainly himself passed through that education system before being exiled in 1794.

The articles purport to be a letter to a friend seeking a place on the Continent where his son might learn French. The system of public education in Geneva is devoted to three classes: childhood, adolescence, and professional studies covering divinity, law and physic. The first class, being "similar to our public schools of Eton and Winchester" is called a College. These are not boarding establishments, though the pupils remain there all day from ages 5 or 6 to ages 14 to 15. There is no fagging or flogging. Pupils are assessed each year before being allowed to advance, after a public ceremony which the writer claims to have attended on June 20, 1814. The various lectures and the following handsome collation are described in detail. The adolescent department corresponds in some measure to Oxford and Cambridge and the course lasts four years. Teaching religion is very important, but since the lower classes, and especially the female children did not, in the past, receive more than basic instruction in reading and writing, early morning and late evening schools superintended by clergy have been established, where young people may be instructed without interfering with their ability to work a full day.

All the schools are free, also to foreigners. The School of Divinity has 60 students, candidates for ordination. There is a Department of Law, which includes Philosophy and combines moral and natural Philosophy and Mathematics, taught by several eminent philosophers, including Messrs. Prevost (Pierre Prévost, F.R.S., 1751-1839), Pictet (Marc-Auguste Pictet, 1752-1825, founder and editor of the *Bibliothèque Britannique*) and L'Huilier (Simon L'Huilier, 1750-1840). The professors in the School of Medicine include Odier, De La Rive (Charles-Gaspard De la Rive, 1770-1834), and De

Roches, all Fellows of the Royal Medical Society of Edinburgh, and there are professors of anatomy, zoology, mineralogy, and chemistry. Clearly the system of education in Geneva has been well designed and employs very distinguished teachers.

Item 23: In 1815, some Experiments on the Chemical Nature of Chyle; with a few observations upon Chyme. (Medico-Chirurgical Transactions, vol. vi. p. 618.)

> "Some Experiments on the Chemical Nature of Chyle with a few Observations upon Chyme." By Alexander Marcet, M.D. F.R.S. One of the Physicians to Guy's Hospital. *Medico-Chirurgical Transactions*, **1815**, *6*, 618-631.

Chyle is a milky bodily fluid consisting of lymph and emulsified fats, or free fatty acids, formed in the small intestine during digestion of fatty foods, and taken up by lymph vessels specifically known as lacteals. Marcet analyzed chyle from an animal which had eaten solely vegetable food and from another which had eaten solely animal food. The principal constituent of the former is albumen, but dry distillation also yields carbonate of ammonia and a heavy oil. The latter contains less charcoal but more carbonate of ammonia, oil, and cream-like matter; it also contains much albumen. Chyme or chymus is the semi-fluid mass of partly digested food that is expelled by the stomach, through the pyloric valve. Chyme slowly passes through the pyloric sphincter and into the duodenum, where the extraction of nutrients begins. It contains albumen, but that from vegetable food (the only kind he analyzed) contains much more solid matter than other animal fluids and four times as much charcoal as chyle from animal food, though less saline matter. Neither chyle nor chyme contains gelatine.

Items 24: In the same work there have appeared, at different times, communications from him on the subject of the employment of Nitrate of Silver as a Test of the presence of Arsenic. (See vol. ii. p. 155.; vol. iii. p. 342.; and vol. vi. p. 663.)

> **24a:** "A Case of Recovery from the Effects of Arsenic; with Remarks of a New Mode of Detecting the Presence of this Metal." By Peter M. Roget, M.D. *Medico-Chirurgical Transactions*, **1811**, *2*, 136-160.

This "same work" is *Medico-Chirurgical Transactions*, cited in Item 23 above. The paper details an attempted suicide by consuming "white arsenic," after which the patient was treated with a lot of water, then magnesium sulphate, potassium bicarbonate and tartarised antimony. The patient was kept warm and blistered. Roget also administered Ol. Ricini (Oleum Ricini, or castor oil), Capt. Statim Aq. Menth. Pip. (peppermint water, taken immediately) and Mist. Camphor (an alcoholic solution of camphor) with Aq. Font. (spring water). Marcet helped in the treatment. Castor oil and barley water were also administered. The patient was treated with a range of substances and silver nitrate was used to detect arsenic.

Roget and Marcet tested the sensitivity of their method of detecting arsenic, which employed silver nitrate, on small quantities of arsenic, a Marcet specialty. The last few pages of the paper (155-160) contain an extended description, with appropriate literature references, of Marcet's joint work with Roget to determine whether arsenic was detected in the material ejected from the patient's stomach. In fact none was.

> **24b:** "Some Remarks on the Use of Nitrat of Silver, for the Detection of Minute Portions of Arsenic." By A. Marcet, M.D. F.R.S. one of the Physicians to Guy's Hospital. *Medico-Chirurgical Transactions*, **1812**, *2*, 343-347. The same paper also appeared in *Nicholson's Journal of Natural Philosophy, Chemistry, and the Arts*, **1813**, *34*, 174-177.

This paper notes that Roget's patient described in Item 24a had recovered. Its main purpose was to discuss and surmount an objection raised in the literature to the method used. The objection, raised by Charles Sylvester in a letter to *Nicholson's Journal* (18), was about interference with the test by the presence of muriatic (hydrochloric) acid, likely to be found in the stomach.

24c: "Note on the Use of Nitrat [sic] of Silver, for the Detection of Arsenic, in Reference to a Paper on this Subject in Vol. III of the Society's Transactions." By Dr. Marcet. *Medico-Chirurgical Transactions*, **1815**, *6*, 663-664.

The use of silver nitrate to detect arsenic by causing a yellow precipitate may by misleading if phosphate is also present, since this also causes a yellow precipitate. The precipitate should be checked by heating with charcoal (to produce visible metallic arsenic) or using alkaline copper sulfate (to produce Scheele's Green).

Item 25: In 1816, Particulars respecting the Case of Professor De Saussure. (Ibid. vol. vii. p. 228.)

> "Additional Particulars, Connected with Professor De Saussure's Case." Communicated by Dr. Marcet, M.D. F.R.S. Physician to Guy's Hospital. *Medico-Chirurgical Transactions*, **1816**, *6*, 228-236.

H. Benedict de Saussure (1740-1799), who had been Professor of Medicine at the Academy of Geneva, had

died of hemiplegia (a form of paralysis that affects just one side of the body) in unfortunate circumstances. The case was described by Odier in detail in the paper immediately preceding Marcet's paper noted here (19). Marcet here details that, while he was studying in Edinburgh (1794-1797), he received a request from De Saussure *via* his relative, Professor Prévost in Geneva, to beg Dr. Black to provide the details of the treatment of the historian and moral philosopher Prof. Ferguson (Adam Ferguson, 1793-1816), who also suffered from hemiplegia and who was cared for and cured by Black. These details, "drawn up by Dr. Black, in May, 1797" were sent as requested. It is notable that Black's reputation is now as a chemist, though in 1797, he was still practicing medicine. After receiving the details, De Saussure had written to Marcet thanking Black profusely and, as a sick person and a lover of geology, expressing the wish to visit him to benefit from his acquaintance. However, Black's regime was very demanding and seems to have required fasting. De Saussure could not follow it and he died in 1799.

Items 26: On the Medicinal Properties of Stramonium, with illustrative Cases. (Ibid. vol. vii. p. 551.) And on the Preparation of the Extract. (Vol. vii. p. 594.)

> **26a:** "On the Medicinal Properties of Stramonium; with Illustrative Cases." By Alexander Marcet, M.D. F.R.S, Physician to Guy's Hospital. *Medico-Chirurgical Transactions*, **1816**, *7,* 551-575.

Datura Stramonium (Thornapple) extract reduces pain more effectively than any other narcotic. It can be chopped up and smoked to relieve asthma. Generally the seeds are poisonous but a seed extract can be used with care. It was a folk remedy. The paper contains a general account of several different cases, from asthma, through sciatica to cancer, though the beneficial effects for pain relief were limited.

> **26b:** "Additional Particulars on the Preparation of the Extract of Stramonium, by Dr. Marcet, in Reference to the Paper Published by Him, in the Last Volume of these Transactions, (p. 551)." *Medico-Chirurgical Transactions*, **1817**, *8*, 589-592.

Apparently the efficacy for pain-relief diminishes with repeated use, and this had already been noted by Dr. Hudson. His attached letter describes how the method of extraction affects the quality of the product. Further work is necessary to optimize the extraction of a suitable, stable material.

Items 27: In 1817, appeared his valuable work, entitled "An Essay on the Chemical History and Treatment of Calculous Disorders;" of which a second edition was published in 1819.

> *An Essay on the Chemical History and Treatment of Calculous Disorders*. By Alexander Marcet**,** M.D. F.R.S. Physician to Guy's Hospital. Longman, Hurst, Rees, Orme, and Brown, London, 1817. Second edition, revised and enlarged, 1819.

The publishers of this essay were also Mrs. Marcet's publishers. The essay was dedicated to Wollaston, who was also interested in calculi. Marcet had an interest in lithic acid (now known as uric acid or, systematically, as 2,6,8-trioxypurine), gout and calculous disorders. It was "gout of the stomach," presumably a calculous disorder, which eventually killed him**.** The text covers about 200 pages, and Marcet noted that the nature of the calculi and the occurrence of calculi in his patients seemed to vary with where they lived. He therefore became interested in analyzing them, to discover whether this would inform him of the nature of their generation. (Figure 1, a plate from the monograph, shows some of the common tools of wet analytical chemistry he practiced.) However, he considered such stones to be essentially mineral materials since the idea of organic and inorganic compounds as classes was not yet recognized. However, one of the stones he discovered and characterized was actually the first recorded description of xanthine. He used alkali to dissolve calculi, and considered diet too, advising against animal food. He isolated calcium oxalate from calculi and noted that lithic acid was excreted in some cases. The essay contains pictures of sections of various calculi, and also of a typical laboratory of the period.

The title page lists him as a lecturer on chemistry at Guy's Hospital and a member of various medical societies in in Stockholm, Paris, Edinburgh, Geneva and London. Physician to the Spanish Embassy in London was added in the second edition.

Item 28: In 1819, he published an introductory Clinical Lecture. History of a Case of Nephritis Calculosa, in which the various periods and symptoms of the disease are strikingly illustrated; and an Account of the Operation of Lithotomy, given by the patient himself. (Med.-Chir. Trans. vol. x. p. 147.)

> "History of a Case of Nephritis Calculosa, in which the Various Periods and Symptoms of the Disease are Strikingly Illustrated, and an Account of the Operation of Lithotomy, Given by the Patient Himself." By Alex. Marcet, M.D. F.R.S. one of the vice-presidents of this society. *Medico-Chirurgical Transactions*, **1819**, *10*, 147-160.

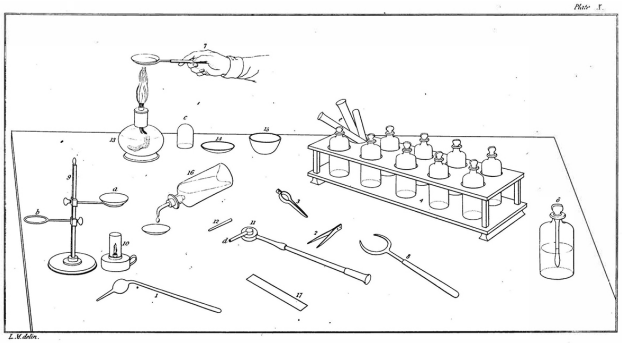

Figure 1*. Plate X from Item 27, second edition (1819) depicting common tools of the wet analytical chemistry Marcet practiced. They include 1) glass blowpipe; 2-3) small platinum tongs; 4) tray for test-bottles and tubes; 6) test-bottle with glass dropper attached to the stopper; 7) use of an appropriate support for suspending a watch glass (or other object) over a spirit lamp; 8) the support used in 7; 9) stand to support watch-glasses or cups over a lamp; 10) lamp; 11) brass blowpipe; 12) a platinum tip for 11, fitting at d; 13) spirit lamp, with a glass cup, c, to cover it, when not used; 14) watch-glass; 15) glass capsule; 16) bottle, with a tube through its cork, to obtain water drop by drop; 17) slip of common window glass.*

The introductory clinical lecture, may be distinct from the published article cited here. Information on Marcet's teaching at Guy's is not easily to hand, though he did contribute to a revised syllabus of chemistry taught to Guy's Hospital students. (See Item 34 below.) An account of the teaching and research on chemistry at Guy's Hospital which includes the period when Marcet was active there has been published (20).

This paper from *Transactions* describes the case of a man who started discharging a white chalky substance, and who later developed pain, retching and constipation. His kidneys had been affected. A stone developed in the bladder. The stone was eventually removed by forceps via the urethra, and the patient himself describes in considerable detail his feelings and reactions during the removal. On the whole, he considered the pain he experienced during the incision and extraction—without anesthesia, of course—to have been less than what the stone itself had caused in one night. The calculus was fusible and Marcet advised discontinuation of alkaline remedies but to take muriatic acid. The patient's health varied, and he did hemorrhage blood. He passed small calculi of phosphate of lime, and magnesia reappeared after the muriatic acid treatment ceased.

Item 29: On the Specific Gravity and Temperature of Sea-Waters, in different parts of the Ocean, and in particular Seas; with some account of their saline contents. (Philosophical Transactions for 1819, p. 161.)

> "On the Specific Gravity, and Temperature of Sea Waters, in Different Parts of the Ocean, and in Particular Seas; with some Account of their Saline Contents." By Alexander Marcet, M.D. F.R.S. &c. *Phil. Trans. Roy. Soc. London*, **1819**, 161-208.

A whole series of measurements in apparatus designed by Marcet on waters sourced from various parts of the globe. Altogether some 68 samples are listed, with the names of the collectors. Marcet attempted to correlate density to characteristics of the source such as temperature and depth. Warmer waters appear to be a trifle denser than colder waters. In general, the deeper the sample origin, the denser the water. The temperature of the water generally drops with depth but sometimes the converse occurs: in Davis Straits in Baffin Bay the surface is warmer than at depth whereas to the east of Greenland and further north the opposite occurs. The differences are perhaps related to the North-west Passage. With Wollaston's urging he detected potassium in sea water, isolating it as potassium chloroplatinate, though he did not use this name. Principal saline contents are muriate of soda and of magnesia, and also sulfuric acid and lime. He imagined the salts (as chlorides or sulfates) persisted in solution, but he did not know which part partnered which. We now know that this is a meaningless question. Marcet calls salt lakes "mere salt ponds," and they may have different composition than the seas. Sea waters, though, contain the same materials in the same relative proportions everywhere but with different total concentrations. Among the various contents Marcet analyzed are muriate of silver (also known as luna cornea), sulfate of barytes, oxalate of lime, and phosphate of magnesia.

Two extended excerpts from this paper, in French and not listed by Roget, were published in the Geneva *Bibliothéque Universelle* (**1819**, *12*). The first part, concerned with specific gravity was classified under physique ("Sur la pesanteur spécifique et la température des eaux de la mer dans diverses parties de l'Océan et dans des mers particulières, et quelque examen des matières salines qu'elles contiennent," 22-34). The second part, concerned with salts dissolved in the waters was classified under chimie ("Sur les matières salines que contiennent différentes mers," 110-117).

Item 30: A paper, in French, on the subject of Vaccination. (Bibliothèque Universelle for November 1819.)

> "Quelques remarques sur la Vaccination, et sur le degré de confiance que l'on peut avoir dans ses effets

préservatifs; adressées au Prof. Pictet, l'un des Rédacteurs de la *Bibliothèque Universelle*." Par le Dr. MARCET, Membre de la Société Royal de Londres, ci-devant Médecin de l'Hôpital de Guy, etc. *Bibliothèque Universelle*, **1819**, *12*, 206-216.

The *Bibliothèque Universelle* succeeded the *Bibliothèque britannique* as a Genevan journal in which to publish important discoveries (21). This article is an account of the value of vaccination, which had been received with skepticism in Geneva. Marcet was a friend of Jenner (see Item 5 above), and used vaccination extensively in his career as a doctor in London. There was also skepticism in London, and Voltaire (1694-1778) had thought the whole process peculiar (22), but it was adopted by members of the Royal Family and after 20 years of practice it was widely accepted. In 1779-1798 there were 38056 deaths from smallpox in London. During the 20 years after the introduction of vaccination (1799-1818) there were 23294 out of a larger population, thus saving the lives of 14672 individuals.

Item 31: Account of a singular Variety of Urine, which turned black soon after being discharged; with some particulars respecting its Chemical Properties. (Medico-Chirurgical Transactions, vol. xii. p. 37.)

"Account of a Singular Variety of Urine, Which Turned Black soon after being Discharged; with some Particulars Respecting its Chemical Properties," *Medico-Chirurgical Transactions*, **1823**, *12*, 37-45.

In 1814 Marcet was shown a sample of urine which looked like licorice solution or port wine with no deposits. It came from a healthy male child aged seventeen months, and it had changed color after emission. Marcet collected samples himself. The samples did not all change color, and the color was stable for years. Carbonate of potash and carbonate of ammonia produced a precipitate. The colored urine was alkaline, smelled of ammonia, and gave a black deliquescent residue on evaporation. This did not contain iron. Alcohol had little effect, and did not dissolve the color. Nitric acid extracted no color. Marcet had once treated a young woman who had paroxysms and also produced black urine. She took Peruvian Bark and later silver nitrate, after which she recovered.

After describing the case of the woman, Marcet returns to the residue of the urine he had begun to describe, and says that he turned it over to Dr. Prout for further analysis, as he did not have lab facilities at his command. Prout reported that the dried urine residue did not contain lithic acid or urea. Adding acid to the urine slowly generated a black precipitate in a clear liquid. Dr. Prout is William Prout (1785-1850), best known to later chemists for his speculation that all elements might be comprised of hydrogen since their atomic weights seemed to be multiples of that of hydrogen (23). As a physician, Prout was expert in diseases of the urinary tract and in analysis of urine (24).

This item was read to the Medical and Chirurgical Society in March 1822. It was published in 1823, after Marcet's death on 19 October 1822.

Item 32: Account of a Man who lived ten years after having swallowed a number of Clasp-knives; with a Description of the Appearances of the Body after Death. (Ibid. vol. xii. p. 52.)

"Account of a Man who Lived Ten Years after Having Swallowed a Number of Clasp-Knives." By ALEX. MARCET, M.D. F.R.S. &c. late physician to Guy's Hospital. *Medico-Chirurgical Transactions*, **1823**, *12***,** 52-75.

Like the previous item, this was read to the Medical and Chirurgical Society in March 1822 and published in 1823, after Marcet's death.

In 1799 an American sailor at a fair in Le Havre saw a man (a magician) "swallowing" clasp knives in a show. He said he could do this, and swallowed one himself. He repeated this several times over many years in different places. He was eventually caught as a smuggler and pressed into a British ship. In December 1805 he became very ill (not for the first time) and he continued under medical care until he died in March 1809. The case was noted in several contemporary London journals. He was reckoned to have swallowed thirty-five clasp knives and occasionally passed pieces of knife. The patient wrote a detailed account of his history of clasp-knife consumption and of his reactions. He was treated with opium from time to time, but suffered great pain. Marcet obtained a sample of the patient's bile, which tested positive for iron (prussiate test). After death, most of the body organs looked normal apart from some membranes being slightly thicker than normal. The stomach seemed capable of accommodating the clasp knives as long as they caused no physical damage. The illustrated stomach contents consisted of a large number of clasp knives both effectively whole and also in pieces. There were at least a dozen, and they were exhibited to the Medico-Chirurgical Society.

Item 33: Some Experiments and Researches on the Saline Contents of Sea-water, undertaken with a view to correct and improve its chemical analysis. (Philosophical Transactions for 1822, p. 448.)

"Some Experiments and Researches on the Saline Contents of Sea-water, Undertaken with a View to

Correct and Improve its Chemical Analysis." By Alexander Marcet M.D. F.R.S. Honorary Professor of Chemistry at Geneva. *Phil. Trans. Roy. Soc. London* **1822**, *112*, 448-456.

Marcet could not detect any mercury in English Channel sea water or the salts obtained from it. Some very careful and quantitative analyses are reported. He concluded that there is no mercury or mercurial salt in ocean water, attributing contrary reports by other researchers to local circumstances. Marcet found ammonia but not nitrates, carbonate of lime but no chloride of lime. He also reported a salt of sulfate with both magnesia and potash in solution. This work was performed before accurate combining proportions had been established (principally by his friend Wollaston in the first place) and before understanding of ions in solution.

This paper was read before the Royal Society on 27 June 1822. It was Marcet's last scientific contribution (25).

Item 34: [not mentioned by Roget]

A Syllabus of a Course of Chemical Lectures Read at Guy's Hospital. William Babington, M.D. F.R.S., Alexander Marcet, M.D. F.R.S., Physicians to the Hospital, and William Allen, F.R.S.& F.L.S. W. Phillips, London, 1816.

To the list of papers Roget mentions in his obituary of Marcet (6), we add this monograph omitted by Roget. Indeed, Marcet was decidedly the junior partner in this endeavor, which had been in print in various forms for many years before his involvement.

William Babington (1756-1833) was apothecary to Guy's Hospital and later, after completing a medical degree from Aberdeen, Physician to Guy's (26). He published the first version of the *Syllabus* in 1797 (27). This course reflected the chemistry established by Lavoisier and his followers, for "… the systems of the older chemists are now exploded, and many of their principles shewn to be fallacious…" A table of nomenclature, including old and new is included at the end of the syllabus, though, to render intelligible the writings of older chemists—which still contain much relevant factual matter. The course starts with sections on Caloric and Oxygen, sure signs of the new chemistry (27). After treating common gases and water, sections on acids, alkalis, earths, metals, and combustibles follow.

William Allen (1770-1843), a chemist (i.e., pharmacist) by trade, was a lecturer in chemistry at Guy's Hospital from 1802 at the invitation of Babington. The two of them published another edition of the *Syllabus* that year. After only five years, there were some changes in organization, if not monumental ones. A discussion of forces including electricity and gravitation precedes the sections on Caloric and Aeriform Substances (gases). Alkalis precede acids; then follow earths, metals, and combustibles and a short new section on "organized bodies" both vegetable and animal (28).

Allen was interested and active in a wide range of scientific and social activities. In the same year he started lecturing at Guy's he was elected a fellow of the Linnean Society of London. Shortly afterwards he was also delivering lectures at the Royal Institution at the invitation of Davy. Allen was a social activist, involved in abolitionist and educational causes (29).

Marcet joined Babington and Allen as an author of the 1816 edition. By this time, the new nomenclature was no longer considered an entirely trustworthy guide: the preface notes that "the new Nomenclature, though admirably contrived, appears from Sir Humphry Davy's late brilliant discoveries, to have in some instances been at variance with facts" (30). For this reason, the table of nomenclature present in previous editions has been replaced by a list of simple bodies, or rather of bodies that have not been decomposed. That list of simple bodies includes three classes, namely the imponderables (Caloric, Light, and Electricity), agents that can unite with inflammable bodies (oxygen, chlorine, and iodine), and the simple combustible bodies (those capable of uniting with oxygen and its class—that is, all of the other simple bodies). The bulk of the syllabus was organized as previously. It is worth noting, though, that the last lines of the syllabus deal with urinary calculi.

Conclusions

Marcet's scientific interests, as exemplified by his publications, were certainly varied. As Table 1 illustrates, chemistry and medicine were the predominant but not exclusive subjects of his interests. We have given more than one subject to several items, so the number of items by subject sums to more than the 34 numbered items presented above. Many of these duplicate classifications were chemistry and another discipline (most often medicine), reflecting cases in which chemical analysis was brought to bear on a problem within another discipline (such as the properties of biological fluids or of seawater).

Table 1. Marcet's scientific publications grouped by subject.

Subject	Number of items	Item numbers
chemistry	24	2, 4, 6, 8, 11, 13-21, 23-24, 27, 29, 33-34
medicine	19	1-3, 5, 7, 9-10, 12-15, 23, 25-28, 30-32
physics	4	17-18, 20, 29
geology	6	6, 8, 11, 19, 29, 33
education	1	22

Marcet's career spanned the period when a great many of the practitioners of chemistry in Great Britain were physicians. If one thinks of the important developments in British chemistry during the first two decades of the nineteenth century, the prevalence of physicians in chemistry may be surprising. The pre-eminent achievements that come to mind include Dalton's atomic theory, Davy's employment of electricity to isolate new elements from familiar compounds, Wollaston's scale of equivalent weights and Tennant's and Wollaston's work on new elements in platinum ores—none particularly related to medicine or even to the chemistry of organisms. Yet much of that chemistry was done by men who had medical degrees.

Indeed, Tennant and Wollaston had earned medical degrees, as has been noted above. Davy was not a physician, but he had been apprenticed to a surgeon and apothecary. Davy launched his scientific career from the Pneumatic Institution Thomas Beddoes (1760-1808) founded to investigate physiological effects of gases (31). Indeed, of the researchers mentioned in the preceding paragraph, Dalton was the only one not connected to medicine. Add to the list of medically connected chemists Humphry's brother John Davy (1790-1868), Prout (of the protyle hypothesis), and Thomas Thomson (1773-1852), who championed both Dalton's and Prout's ideas), and we see that many significant contributors to British chemistry at this time were physicians.

As noted above, medical faculties were among the few educational contexts where chemistry was part of the curriculum in Britain at this time. At this time, chemistry was already intellectually independent as a discipline, having methods and interests of its own distinct from medicine (even though its methods could be useful to medicine). It was also a popular subject—at least for self-improving minds—as evidenced by the success of Jane Marcet's *Conversations on Chemistry* and the popularity of lectures like Davy's at the Royal Institution (32). Chemistry, however, had few institutions devoted to its practice. Davy was fortunate to have a professorship of chemistry at the Royal Institution: there were not many positions in Britain like his. Dalton was a teacher of natural philosophy at a dissenting academy. Medicine was one of the avenues by which a respectable person could pursue an interest in chemistry.

Some of the chemist/physicians mentioned above are better known to posterity as chemists than physicians. Marcet, however, belonged firmly in both camps. For example, at this time and even earlier, it was widely believed that mineral waters had curative properties; spas were very popular in Regency England, as every reader of Jane Austen knows. Hence Marcet's interest in the identities and amounts of the contents of mineral waters, natural and synthetic, as well as his original attempts to discover whether sea water itself varied in content with region and temperature. It must also have seemed evident that investigating the input and output of the human machine would yield valuable information on what might go wrong when such a body malfunctioned. Since the chemists and medical practitioners had little knowledge of the cause of diseases and of what today we recognize as organic chemistry, such researches were bound to be unsuccessful in their basic aim. Marcet's publications (Items 2, 4, 6, 8, 9, 11, 13-15, 19, 23, 27, 29, 33) show the great effort he put into trying to understand bodily function essentially in terms of aqueous chemistry.

Incidentally he isolated several new body products, especially what he termed calculi. However, it should be remembered that physicians of the time, including Marcet, were eager to investigate the effects of newly isolated compounds on their sick patients, and must have caused damage to some. They also asked how and in what form these compounds were excreted, so that the practice of medicine itself was also influenced. The chemistry and medicine interacted reciprocally.

Such calculi had long been recognized as being related to gentlemen's diseases, though presumably women must have suffered similarly. Gentlemen clearly desired some kind of cure. A particular often-cited example is that of Joanna Stephens (d. 1774), who was awarded by Parliament the enormous sum of £5000 for the discovery of a remedy for kidney stones, which were a common and painful affliction. This remedy first publicized in 1738, and subsequently in 1739 and 1741 by the philosopher and physician David Hartley (1705-1757) in a book, *Ten Cases of Persons who have Taken Mrs. Stephens Medicines for the Stone* (33). However, careful reading of the

relevant Act of Parliament (34) makes it clear that the award was not for medical research, but for discovery, in the sense of public disclosure, of her remedy, including its preparation. The award was conditional upon its efficacy being proved by many eminent men, including the Archbishop of Canterbury, the Lord President of the Council, and the Speaker of the House of Commons. Presumably they all suffered from kidney stones. These gentlemen apparently found that the cures worked, though one wonders why. In the entry devoted to Stephens in the *Dictionary of National Biography* (33) the remedy is stated to have been a powder (of calcined egg shells and snails), a decoction (prepared by boiling herbs with soap), and pills (of calcined snails). Such stones were an interest of several chemists of the period, including the great man Wollaston himself (35) and Yelloly (36). Roget, in contrast, seems to have shown an interest in phrenology, theology, the eye, mechanical calculators and, most famously, his Thesaurus (7).

Marcet's research in what we today classify as physical sciences was rather limited. He was interested in methods to obtain both low and high temperatures (Items 16, 17, 18, 20, and 21), and he took pleasure in demonstrating low-temperature effects to his friends and family. His work in his home laboratory with Berzelius (also M.D., F.R.S.) (Item 16) describing the preparation and properties of carbon disulfide is unusual in reading very much like a modern chemistry paper, and it was one of the few of its kind he was concerned with, the others being Items 21 and 24. He also published papers directly concerned with medicine (Item 3), especially but not exclusively with dissections (Items 1, 5, 7, 9, 10, 12, 25, 26, 28, 31, and 32). His interest in the changes caused by the consumption of unusual materials (from arsenic through clasp knives to laudanum) reflected the attitude of a chemist who regarded the human body as a rather complicated chemistry machine somewhat prone to malfunction. Finally Marcet was deeply concerned with the social implications of his work, though also very proud of his original home state of Geneva. This led him to encourage the practice of inoculation (Items 5 and 30) and the adoption for the British population of a type of education like that in Geneva (Item 22).

Acknowledgments

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Supplemental Material

The bibliographic part of Roget's obituary of Marcet (Ref. 6) with links to online versions of Marcet's papers can be found in the Supplemental Material for the *Bulletin for the History of Chemistry* at the journal's website,

acshist.scs.illinois.edu/bulletin/index.php.

A copy of the obituary itself can also be found there.

References and Notes

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About the Authors

G. J. (Jeff) Leigh is an Emeritus Professor at the University of Sussex. After a lectureship at the University of Manchester and a year working in Munich with E. O. Fischer, he spent the rest of his employed career at the Unit (later Laboratory) of Nitrogen Fixation in Sussex, from where he published over 200 papers on the chemistry of nitrogen fixation. He first came upon *Conversations on Chemistry* in 1964 in a second-hand bookshop, and was intrigued by the fact that this book had been written as early as 1806 by a woman who was not a recognized natural philosopher. He has since researched her life intensively and published some papers on her work. During these studies the activities and influence of her husband, Alexander, became very evident and his latest work concerns placing him in an appropriate context of the history of chemistry.

Carmen J. Giunta is Professor of chemistry at Le Moyne College in Syracuse, NY, USA. He is editor of this journal, in which capacity he has enjoyed reading Prof. Leigh's articles on Jane Haldimand Marcet and her husband Alexander. It was his pleasure to work with Jeff on this paper.

2019 Conferences in History and Philosophy of Chemistry

Setting their Table: Women and the Periodic Table of Elements. February 11-12 at the University of Murcia, Spain (www.iypt2019women.es/scientific_topics.php).

Spring 2019 National Meeting of the American Chemical Society will have programming by the division of the History of Chemistry (HIST). March 31-April 4 in Orlando, Florida, USA (www.acs.org/content/acs/en/meetings).

First International Congress on the History of Science in Education. May 30-June at the University of Trás-os-Montes e Alto Douro, Vila Real, Portugal (www.utad.pt/gform/en/event/the-1st-international-congress-on-the-history-of-science-in-education).

Plastics Heritage Congress 2019: History, Limits, and Possibilities. May 29-31 in Lisbon, Portugal (plasticsheritage2019.ciuhct.org).

First International Conference on "Bridging the Philosophies of Biology and Chemistry." June 25-27 at the University of Paris Diderot, France (www.sphere.univ-paris-diderot.fr/spip.php?article2228&lang=en)

International Society for the Philosophy of Chemistry: 23rd annual meeting. July 15-17 in Torino, Italy (www.ispc2019.unito.it).

Fourth International Conference on the Periodic Table, Mendeleev 150, is scheduled for July 26-28 in St. Petersburg, Russia (mendeleev150.ifmo.ru).

12th International Conference on the History of Chemistry (12ICHC). July 29-August 2 in Maastricht (sites.google.com/view/ichc2019).

Fall 2019 National Meeting of the American Chemical Society will have programming by the division of the History of Chemistry (HIST). August 25-29 in San Diego, California, USA.

FREDRICK ACCUM: AN IMPORTANT NINETEENTH-CENTURY CHEMIST FALLEN INTO OBLIVION

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Abstract

The German-born Fredrick Accum (1769-1838), lecturer, author, analyst, industrial chemist, technical expert and trader of chemicals and apparatus was once one of the best-known scientists in the United Kingdom. His efforts to popularize chemistry and to bring it to people of all classes were highly successful as demonstrated by the large audiences of men and women that used to fill the amphitheater of the Surrey Institution to attend his public lectures. His books on chemistry, mineralogy, crystallography and the use of gas for public and home illumination (of which he was an early promoter) were so much appreciated that they were published in several editions and translated into various languages. Numerous distinguished students learned their practical skills in his private laboratory and school.

Despite this considerable success, the very few people who might still remember Accum probably owe that memory to his famous book from 1820 *A Treatise on Adulteration of Food and Culinary Poisons*. And some might also recall the odd events that followed the publication of the book, which eventually forced him to depart from London forever, the city where he had arrived almost three decades before as an assistant pharmacist.

This paper presents the work and legacy of this controversial and once-famous chemist, including a description of the events that precipitated his abrupt departure from the international scene.

Introduction

In the article "The Past and Future of the History of Chemistry Division," published in *Journal of Chemical Education* in 1937, after noting the scientific and pedagogical achievements of the once-famous German chemist Fredrick Accum (Figure 1), its author, Charles A. Browne, states that the latter "suffered the most tragic fate that can befall a scientist—that of going into sudden oblivion with a clouded reputation" (1). Eighty years after publication of that paper, the indifference concerning Accum has probably increased. The above-mentioned journal, for instance, is a good mirror of this fading memory considering that all together only seven papers have been published in which his name appears. Of these publications, only one is entirely dedicated to his biography: "The Life and Chemical Services of Fredrick Accum," also by Browne, published in three parts due to its length (2).

***Figure 1**. Fredrick Accum, 1769-1838 (Courtesy of the Edgar Fahs Smith Memorial Collection, Kislak Center for Special Collections, Rare Books and Manuscripts, University of Pennsylvania).*

Accum is not even the main subject of the other papers. One of these publications (3) describes the beginnings of the study of chemistry in the USA and confirms that some of the first American professors were trained in London by Accum (including for example Benjamin Silliman, Sr., of Yale, William Peck of Harvard and James Freeman Dana of Dartmouth). The author of this paper also identifies another student, Amos Eaton, whose role as a North American botanist, geologist, educator and disciple of Silliman, and whose contribution to the teaching of modern chemistry was described by another writer shortly afterward (4). In Eaton's private publication *Chemical Notebook for the Country Classroom* (*circa* 1820), intended for his students, he indicated the books of Accum as additional reading, placing them at the same level as the famous *Conversations on Chemistry* (London, 1805) of Jane Marcet. As to the three remaining articles they do indeed mention Accum's work. In one of them (5), on the subject of obtaining "silver trees" by the reduction of silver salts in solution, the author comments on the *Arbor Dianae*, one of the many experiments included in Accum's *Chemical Amusement* (London, 1817). In another (6), a short paper entitled "Crystal Model Kits for Use in the General Chemistry Laboratory," its authors remind us that as early as 1813 Accum developed a commercial set of crystal models that accompanied his *Elements of Crystallography* (London, 1813). Finally, a paper from 2011 entitled "A Global Perspective on the History, Use, and Identification of Synthetic Food Dyes" (7) addresses a subject pioneered by the German chemist: food adulteration, on which he wrote a seminal treatise.

Still in *Journal of Chemical Education* Accum is also referred to in a news item (8), in two book reviews (9, 10) and in a list of paper topics (11). The news item announces the donation of Browne's "outstanding collection of the works of Frederick (12) Accum" to a library of the University of Pennsylvania. The older of the book reviews is actually a review of a sales catalog of alchemy and chemistry books. The review's author states that "In the galaxy [of authors] are such names as Accum, Albertus Magnus, Basilium Valentinus, Becher, Berzelius, Black, Boyle, Cavendish, Dalton, Davy, Faraday…" (9). Interestingly, Accum appears also in a list of "Topics for Papers in the History of Chemistry." Amidst 100 topics his name is in 97th position. (William Crookes is the last one.) Considering that two of these allusions to Accum are from 1926, one can imagine they were still an echo of the paper by Browne published the previous year.

A search for "Accum" in the Web of Science does not prove more fruitful, identifying only seven additional papers. Two of them are biographical (13, 14), two others are historical (15, 16), and the remaining publications are related to food safety (17-19), one of them written in Czech (19).

The few citations found in the scientific literature referring to the work of Fredrick Accum tend to be bipolarized: on one hand we find authors who praise him and his work, sometimes even giving him the status of a martyr; on the other hand there are those who consider that his absence from the history of chemistry is fair and understandable. Independently of the opinion that we might defend in this discussion, it is a fact that Accum was one of the most outstanding chemists during the second decade of the nineteenth century. His reputation, which encompassed laboratory practice, consulting, lecturing (privately and in public) and writing, was attested by the multiple editions and many translated versions his books have seen. John L. Comstock—the first author to introduce chemical formulae to secondary school students in the USA (20)—in the preface of his *Elements of Chemistry* (1831), identifies "the authorities which have been consulted in the composition" of his book, and includes the name of Fredrick Accum among

those of luminaries such as Humphry Davy and Michael Faraday (21).

Having been such an important figure in the chemical scene of the early 1800s, his name recognized from Europe to the Americas through his many books, why did he suddenly vanish? Why did he fall into a "sudden oblivion with a clouded reputation" (1)? These are questions that this paper will address.

Life and Work

The main sources of information on Accum's life and work are Browne's paper from 1925 (2), complemented by another (22) based on data he acquired in Germany in 1930 (where he had the opportunity of meeting a great-grandson of the chemist), and Cole's paper from 1951 (13).

Son of a Westphalian soap-boiler of Jewish origin, he was born on March 29, 1769, at Bückeburg, close to Hanover in Germany, and he received the name of Friedrich Christian Accum. Observation of the process of soap manufacture at his father's shop may have inspired him to study chemistry as after completing his studies at the local secondary school, the young Friedrich started working as apprentice in Brande's Pharmacy in Hanover. This was made possible through the connection his parents had with the Brande family, apothecaries to George III of England (who was later also King of Hanover) (23).

The fact that the Brande family had a pharmacy in London, a city in which his scientific interests could be pursued, prompted him to move there in 1793. In his free time as an assistant pharmacist he studied and attended lectures at the Hunterian anatomy school (13). In this period he met William Nicholson and Anthony Carlisle (the two men who in 1800 would discover the electrolysis of water), who became his friends and with whom he collaborated for several years.

In 1798 Accum wrote his first paper ("On the Light Emitted by Supersaturated Borate of Soda, or Common Borax") for the *Journal of Natural Philosophy, Chemistry and the Arts*, that recently had been founded by Nicholson (24). Among other subsequent contributions to this journal over the next few years, his study on the purity of drugs (25) and numerous short notes, such as the occurrence of benzoic acid in old vanilla pods (26), paved the way to the pioneering treatise on food adulteration he would publish in 1820.

At home Accum started conducting experiments and giving private tuition. Resident students with full board were accepted. Among his many students was William Thomas Brande (the son of his former employer), who would succeed Humphry Davy as Professor of the Royal Institution. For many years Accum's laboratory would be the only one of importance in England where students could obtain a practical knowledge of chemistry (2, pt 1).

In 1801 Accum was appointed as assistant chemical operator in the recently founded Royal Institution, almost at the same time that the young Humphry Davy was awarded the positions of lecturer in chemistry and director of the laboratory. Two years later Accum resigned from the Royal Institution (coinciding with the resignation of Count Rumford, one of the founding members of the Institution and a supporter of Accum's appointment).

From 1803 he began a prolific career as an author of scientific books and ultimately also started trading chemicals, apparatus, specimens, models and portable chemistry chests which supported the experiments described in his books, and in which they were advertised. Printed catalogs also described his apparatus, reagents, books, and lessons (27).

One of his many interests was the chemical analysis of mineral waters, and he published several papers on the subject in Alexander Tilloch's *Philosophical Magazine* from 1808 (28). His analytical results show how advanced he was in relation to previous studies of that kind (2, pt 1). His reputation as an exceptional analytical chemist led the inhabitants of Thetford, eager to promote the benefits of the local ferruginous waters, to call on his services. This association resulted in the construction, under Accum's supervision, of a thermal bath establishment endowed with modern conveniences.

In 1809 he was appointed professor of chemistry at the Surrey Institution, an organization dedicated to scientific, literary and musical education and research, founded in 1807 following the model of the Royal Institution. During seven seasons (1808-11, 1818-20) the chemistry course of the Institution was delivered by Accum. There his duties were to provide instruction "for the purpose of initiating into the principles of chemical philosophy those, who possess no previous knowledge of it" (16). His consecutive courses showed the relationship of chemistry with the phenomena of nature, mineralogy and metallurgy, and its application to manufacturing and the crafts. From year to year he changed his lectures, thus maintaining the interest of a regular audience, for whom he also issued a booklet listing the topics present-

ed. For example, his first course (allegedly given gratuitously) dealt with minerals, ores, metals, and their analysis (16). In 1810 he published a companion to his previous courses: *Manual of a Course of Lectures on Experimental Chemistry and on Mineralogy: ... Intended to Illustrate the Lectures Delivered ... in the Theatre of the Surry [*sic*] Institution ...* (29).

***Figure 2**. Thomas Rowlandson's cartoon of Fredrick Accum in one of his public lectures at the Rotunda in the Surrey Institution (Courtesy of the Edgar Fahs Smith Memorial Collection, Kislak Center for Special Collections, Rare Books and Manuscripts, University of Pennsylvania).*

His public lectures became extremely popular, bringing him a great reputation. From that time there is a cartoon depicting him lecturing to an audience of both sexes. In the foreground one can see an old man with a book in his pocket on which is written "Accum's lectures" (Figure 2).

Another subject that caught Accum's great interest was the new gas lighting systems. The first public street illumination with gas was shown in London in Pall Mall, in January of 1807, and some renowned chemists considered it unsafe, including Humphry Davy. As consultant to a new street-lighting company, Accum performed an extensive series of experiments that he subsequently described in his testimony as chemical expert before committees of Parliament. He soon acquired a reputation as a coal gas expert and in 1812, when the "Chartered Gas-Light and Coke Company" was established, his name appeared on the board of directors (2, pt 2).

One of the great qualities of Accum was his capacity to foresee the industrial importance of many chemical novelties. Gas-lighting and the coal-gas industry are important examples, although many others can be found including the industrial processing of beet-sugar and the practical utilization of the distillate from coal tar, a by-product of gas manufacture. The latter would be of special relevance a few decades later, considering that mauveine, the coal tar derived dye accidentally discovered by William Perkin in 1856, was the origin of the British dyes industry (30).

Books

Among his many other activities Accum was a prolific author of books, an activity that he pursued to an extent that is still impressive by today's standards. His first work, *A System of Theoretical and Practical Chemistry*, was published in 1803 (31). This was one of the earliest general chemistry text-books in English presenting Lavoisier's new principles (2, pt 2). In Section III, "History of Chemistry," his praise of the great French chemist is still worth reading. In this book, intended for beginners, the attention the author gave to the chemistry of the simple phenomena of daily life and to that of several crafts (manufacture of soap, conversion of wine into vinegar, silvering of mirrors, etc.) is quite remarkable.

Between 1804 and 1809 he published two works, *A Practical Essay on the Analysis of Minerals* (32) and *An Analysis of a Course of Lectures on Mineralogy* (33). In 1810 the latter would be extended giving rise to his *Manual of a Course of Lectures on Experimental Chemistry and Mineralogy* (29) mentioned above.

Accum's devotion to mineralogy, together with the increasing popular interest in natural sciences led him to publish in 1813 *Elements of Crystallography after the Method of Haüy* (34), the first of its kind in English, also intended for a public with no prior knowledge of the subject.

His publication *A Practical Treatise on Gaslight* saw daylight in 1815 (35) and was the very first work on the subject of illuminating streets and buildings with gaseous hydrocarbons or coal gas. Within three years it was printed in four English editions. Like many of his books, it is handsomely illustrated, with some plates in color (Figure 3). In 1819 he rewrote this treatise, publishing the new version under the title *Description of the*

Process of Manufacturing Coal Gas, for the Lighting of Streets, Houses and Public Buildings (36).

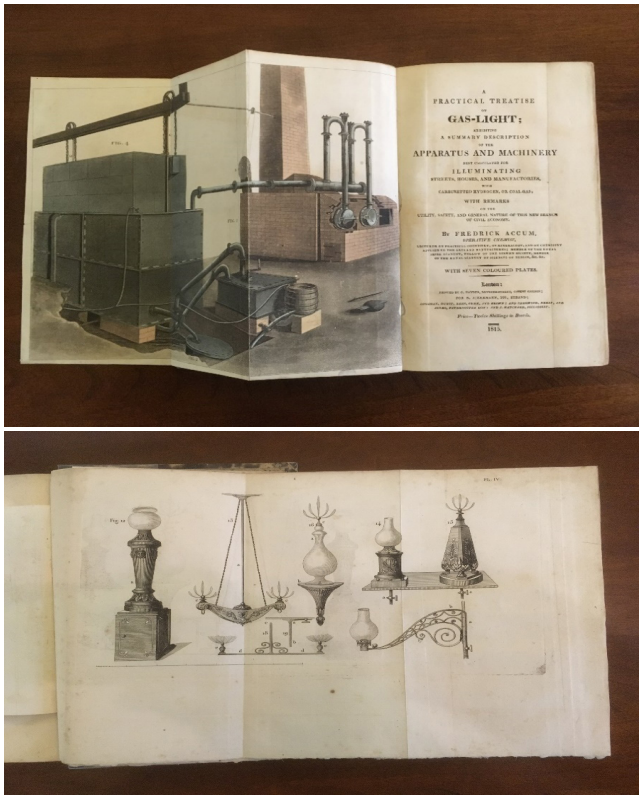

***Figure 3**. Above: Illustration and frontispiece of Accum's* A Practical Treatise on Gaslight *(London, 1815); below: illustration from the French translation* Traité Pratique de l'Éclairage par le Gaz Inflammable *(Paris, 1816). (Courtesy of Science History Institute)*

In 1816 Accum published *A Practical Essay on Chemical Re-Agents or Tests Illustrated by a Series of Experiments* (37), which also had wide dissemination. After revision, a new version was published in 1818 as *Practical Treatise on the Use and Application of Chemical Tests with Concise Directions for Analyzing Metallic Ores, Metals, Soils, Manures and Mineral Waters* (38).

The first edition of his extremely popular *Chemical Amusement, Comprising a Series of Curious and Instructive Experiments in Chemistry, Which are Easily Performed, and Unattended by Danger* (39) sold out in two months in 1817. The second edition disappeared from the bookshops in just one week, and several subsequent editions in English were printed, including one in Philadelphia. The translation of his works into other languages, especially into French and German, was already common, but the popularity of this book surpassed all his previous publications: it was translated into Italian, Spanish and Portuguese in addition to French and German. In this work the author described more than 150 experiments that could be performed at home, providing in each case an accompanying theoretical explanation. It should be added that while these descriptions are now completely out of date, they are still fascinating to read.

In connection with his work related to the ferruginous waters of Thetford, in 1819 he published the *Guide to the Chalybeate Spring of Thetford* (40). In 1820 he published two books dealing with alcoholic drinks: *A Treatise on the Art of Brewing* (41) and *A Treatise on the Art of Making Wine from Native Fruits* (42). A French translation of the former was first reprinted in Paris in 1825 and continued as late as 1853. The latter was as popular as many of his previous publications, offering a general description of fermentation and the manufacture of home-made wines from several fruits. It was printed in London as late as 1860 (and in 1851 in the case of the French version). During the twentieth century, there was a renewed interest in this book in the United States due to Prohibition (2, pt 2), which lasted between 1920 and 1933.

Accum's continued interest in Food Chemistry led him to publish two other books in 1821: *A Treatise on the Art of Making Good and Wholesome Bread* (43) and *Culinary Chemistry* (44). While the first describes the chemical composition and nutritive value of different types of bread prepared from several cereals, in the second book the author explains how to prepare a variety of foods. Among other topics, the latter book describes the preparation of pickles, vinegar, cured meat, preserves, jellies, and marmalades, accompanied by observations on the chemical constitution of these products and the underlying scientific principles of the respective preparative processes. Additionally in *Culinary Chemistry* there are interesting remarks on the origin of some foods (tea, coffee, etc.) as well as historical details, for instances on eating habits in ancient civilizations. The book also includes a section on kitchen fire-places and cooking utensils. Curiously, on page 17 (first edition) the difference between an epicure and a glutton is presented (!).

An important feature of *Culinary Chemistry* is the author's intention to show that culinary processes such as boiling, baking, roasting, stewing, frying and preserving are all chemical transformations. In the preface one may read (44, pp iii-iv):

> The following pages are intended to exhibit a popular view of the philosophy of cookery, to enable the reader to understand the chemical principles, by means of which alimentary substances are rendered palatable

> and nutritious. The subject may appear frivolous; but let it be remembered that it is by the application of the principles of philosophy to the ordinary affairs of life, that science diffuses her benefits, and perfects her claim to the gratitude of mankind.
>
> The art of preparing good and wholesome food is, undoubtedly, a branch of chemistry; the kitchen is a chemical laboratory; all the processes employed for rendering alimentary substances fit for human sustenance, are chemical processes …

In this book, Accum also calls the attention of his readers to the fact that the inappropriate preparation of food is a common cause of disease. Examples include the denunciation of recipes from contemporary cooking books that described procedures including boiling greens with verdigris (basic copper acetate) to improve their color (p 4), or the inappropriate use of copper cooking utensils (pp 331ff).

Also in 1821 his *Dictionary of the Apparatus and Instruments Employed in Operative and Experimental Chemistry* was published (45).

"Death in the Pot"

In the first page of the preface of his *A Treatise on Adulterations of Food, and Culinary Poisons* (46), published in January 1820 (with a second edition in April), Accum wrote (p iii):

> This Treatise, as its title expresses, is intended to exhibit easy methods of detecting the fraudulent adulteration of food, and of other articles, classed either among the necessaries or luxuries of the table; and to put the unwary on their guard against the use of such commodities as are contaminated with substances deleterious to health.

The first book of its genre ever published, this publication appeared after a quarter of a century of enormous developments in chemistry (which actually could favor both the contamination of food and the detection of contaminants). It also introduced the domain of food chemistry, predating other authors' publications by approximately a quarter of a century. This is certainly Accum's most famous book but it may also have contributed to his downfall by creating enemies.

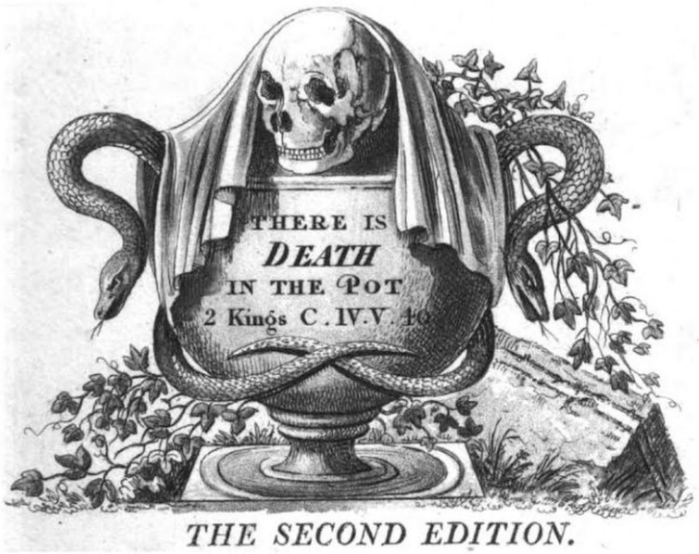

Figure 4. *Left: cover of the first English edition of* A Treatise on Adulterations of Food and Culinary Poisons*. Above: The biblical quotation "There is death in the pot," with somewhat different imagery, was moved onto the title page in the second English edition. Note that the citation of the verse is given incorrectly on the cover of the first edition: it is in chapter 4 of 2 Kings, not chapter 6.*

In this text Accum not only exposed fraudulent practice and toxic contamination in food and drink, providing methods for their detection, but he also identified several traders who had been convicted of fraud, including druggists and grocers who had supplied illegal ingredients. Among the many food adulterations and contaminations of that time one can identify the following examples: the use of alum for whitening bread (p 134), addition of potassium bicarbonate to beer to conceal the effects of acetic fermentation (204), the use of sulfuric acid for fortifying vinegar (311), the addition of copper compounds for coloring pickles (pp 306ff), vermilion (mercurous sulfide—which in turn was often adulterated with red lead, Pb_3O_4) for coloring confectionary products (315f), sugar of lead (lead acetate) for sweetening poor quality wine (109), starch for thickening cream (313f), spices which contained floor sweepings (300), etc.

The cover of Accum's treatise (Figure 4) is, to say the least, peculiar: at the top it shows a skull and below it one can read the biblical quotation "There is Death in the Pot" (2 Kings 4:40); in the center it displays a cobweb with a spider attacking with its fangs a fly; and surrounding the entire composition there are twelve snakes entwining their tails. With such imagery, it is not surprising that the book contains clear moral judgments. For instance, Accum writes (pp 15f)

> The man who robs a fellow subject of a few shillings on the high-way is sentenced to death; while he who distributes a slow poison to a whole community, escapes unpunished.

The treatise, popularly known as "There is Death in the Pot" (a nickname that was also given to its author), immediately became a best seller. It sold 1000 copies of the first edition in one month, and this led to a second edition in 1820 and two further editions by 1822. The book was also published abroad, in several languages. It immediately attracted the attention of the press, which published many reviews (both in favor and against). In the 1920s, Browne alleged that "in all probability [it is] the most extensively reviewed book upon chemistry ever written" (2, pt 2).

If identification of fraudulent practitioners was not enough to create enemies, Accum intensified their hostile response to the second edition by adding (pp x-xi):

> To those who have chosen anonymously to transmit to me their opinion concerning this book, together with their maledictions, I have little to say; but they may rest assured, that their menaces will in no way prevent me from endeavouring to put the unwary on their guard against the frauds of dishonest men, wherever they may originate; and those assailants in ambush are hereby informed that in every succeeding edition of the work, I shall continue to hand down to posterity the infamy which justly attaches to the knaves and dishonest dealers, who have been convicted at the bar of the Public Justice of rendering human food deleterious to health.

The Fall

Before the end of 1820 Accum found himself unexpectedly involved in a scandal that ultimately would force his permanent departure from the UK, which may have taken place between December 23, 1820, and beginning of April, 1821. Seventeen years after his escape, the text of Accum's London obituary described in a very clear and concise way the incidents of 1820 (47):

> … his career was prematurely closed by its having been discovered that, to save himself the trouble of transcription, he had mutilated many valuable books at the latter establishment [Royal Institution's library].

As a sequel to this unfortunate episode, after an initial trial for robbery had failed to condemn Accum, the managers of the Royal Institution turned to the alternative accusation of mutilating property, a charge of which they expected a successful prosecution. The trial was scheduled for April 5, 1821. In January 1821, Accum's friends published a public letter in the *London Times,* addressed to the president of the Royal Institution, in an attempt to persuade him to withdraw the charge. Probably the mentor responsible for this unsuccessful act was Sir Anthony Carlisle. On April 5 Accum failed to appear at the court and apparently no one knew his whereabouts. By that time he probably had already secretly left the country.

Upon his return to his native Germany in 1822, he obtained a double position as Professor of Technical Chemistry and Mineralogy at the Royal Industrial Institute and as Professor of Physics, Chemistry and Mineralogy at the Royal Academy of Construction, in Berlin. His final book, published in 1826, *Physische und Chemische Beschaffenheit der Baumaterialen,* a work in two volumes on building materials, was written as a supporting text for his new activity in Berlin. Accum continued his career as Professor until his death on June 28, 1838.

In the UK, the status of Accum had definitely changed to *persona non grata*. In 1824 one of his former publishers omitted the author's name from the title page

of a reprint of his dictionary on chemical apparatus (45). In later years Accum seemed to accept this situation and either wrote anonymously, or published under the pseudonym of Mucca (the letters of his name in reverse order).

Conclusion

Fredrick Accum, one of the most remarkable chemists working in the UK in the early nineteenth century, in contrast to other famous chemists, for example Humphry Davy or William Hyde Wollaston, two of his contemporary London colleagues, did not leave a consensual mark on the official history of chemistry. To some perhaps, he did not leave any mark at all.

It is certainly true that Accum did not make any important contributions to pure chemistry. Yet some of his vast experimental research and his capacity to foresee the industrial relevance of chemical and technical novelties should be enough to ensure him some recognition. If that is not totally guaranteed, his mercantile inclinations (including selling chemicals and apparatus, renting accommodation with full board to his disciples at his private school or giving remunerated scientific consultancy) may have played a role. And to the list of negative influences in Accum's career we might also add the enemies he provoked by the publication of the *Treatise on Adulterations of Food* and, above all, the book scandal from which he ultimately suffered.

Mercantile activities were certainly not well regarded within the context of the normal public chemistry of that time, largely determined by Davy's behavior which set the model of the disinterested and free chemist (48). From the critical viewpoint of Davy, Accum was considered to be "a cheat and a Quack" (49) although this appreciation deserves to be regarded with some caution as it is well known that Sir Humphry's comments about colleagues could be quite scornful (49; 48 p 246). Nevertheless, in Accum's defense it should be remembered that some of the aspects related to his alleged mercenary behavior were not unprecedented. Regarding the acceptance of private students paying full board, the chemist Thomas Thomson implemented a similar procedure in Glasgow (48). In selling articles publicized in his books he was not alone either. In William Henry's book *An Epitome of Chemistry* (London, 1800), the author advertises two different portable chemical chests: "Invented by William Henry and sold by him at his laboratory in Manchester," giving their description and prices (50). In regard to commercial consultancy, some might consider he was also a pioneer in that respect.

It is recognized that Accum did a great deal of work as a pedagogue and disseminator of chemistry, both orally and in written form. Browne, a great advocate of this idea, stated that "no author understood better than Accum the practical appeal of chemistry to the popular mind and his books acted towards this appeal both as stimulus and a response" (2, pt 2). At the other extreme, others claim that he "leant conspicuously towards the scissors-and-paste school of literary production" (51). His books at least were written in an elegant English and the explanations are clear and concise. Additionally they are beautifully illustrated.

As to his *A Treatise on Adulteration of Food*, which from any point of view is a milestone in the history of the defense of public health, one might say it appeared too soon as the UK only implemented legislation a few decades later. John Mitchell's *Treatise on the Falsifications of Food, and the Chemical Means Used to Detect Them*, published in 1848 (52), and the work of the physician, chemist and microscopist Arthur Hill Hassall contributed to this change. In 1851, together with the Analytical Sanitary Commission, Hassall initiated a series of investigations and, like Accum, made public the names of firms who sold adulterated foods (53). At the time the situation was no better than that exposed by Accum thirty years before. Most of the samples of coffee, bread, cayenne pepper and candies that were analyzed were adulterated or contaminated with toxic heavy metal salts. These results provided grounds for the introduction of the Adulteration Act of 1860, which unfortunately proved to be of limited effectiveness. Eventually in 1875 the Sale of Foods and Drugs Act was passed, which, with the subsequent amendments, proved to be an effective law against frauds in food and drink (54).

Lastly, a further comment should be included about Accum's mutilation of books, which apparently did indeed take place. In view of the nature of the act little can be said in his defense but Browne, his only effective biographer so far, notes that "these faults, however, were the result of thoughtlessness, or neglect, and not of natural depravity," adding that (2, pt 3)

> … those who knew Accum were aware that he was singularly indifferent in the treatment of his own books and never hesitated to despoil them of leaves if it suited his conveniences. Some of his friends believed that, in the almost childish simplicity of his character, he would treat the books of other people in a similar way without any intention or consciousness of wrong doing.

Contrary to the strong statement of Browne that Accum went into "sudden oblivion with a clouded reputation" (1) we only can speak of an almost total forgetfulness in the last eight decades. Accum's reputation was in fact quite weakened when he disappeared from England in 1821 but in what concerns a real oblivion this would take more than one century to happen.

Even if the assessment of his effective contribution to the development of chemistry is not an easy task (especially if one bears in mind prevailing prejudices, such as the belief that his disappearance from the public scene helped to strengthen the concept of pure chemistry, devoid of any commercial interests (51)), it is now time to recognize his scientific and technical skills and his contribution to popularizing chemistry. The man and the scientist surely deserve a deeper comprehensive and unbiased biography.

Nice to have met you Mr. Accum!

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About the Author

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2019 Is International Year of the Periodic Table

The United Nations General Assembly and its Educational, Scientific and Cultural Organization (UNESCO) have declared 2019 to be the International Year of the Periodic Table. Why 2019? It is the 150th anniversary of Dmitri Mendeleev's first periodic table. For more information, see www.iypt2019.org.

The declaration was the initiative of the Mendeleev Chemical Society (Russia). Several international scientific organizations are serving as founding partners, including the International Union of Pure and Applied Chemistry (IUPAC), International Union of Pure and Applied Physics (IUPAP), and the European Chemical Society (EuChemS). Many national chemical societies, including ACS are sponsors.

An opening ceremony will take place on January 29 at the UNESCO House in Paris (www.iypt2019.org/opening-ceremony). An international symposium titled "Setting their Table: Women and the Periodic Table of Elements" will be held at the University of Murcia, Spain, February 11-12 (www.iypt2019women.es/scientific_topics.php). The Fourth International Conference on the Periodic Table, Mendeleev 150, is scheduled for July 26-28 in St. Petersburg, Russia (mendeleev150.ifmo.ru).

The ACS divisions of the History of Chemistry and Inorganic Chemistry are organizing a symposium on the history of the periodic table for the Fall 2019 National Meeting of ACS, set for San Diego, California, August 25-29.

THE CONTRIBUTIONS OF RADIOCHEMISTRY TO MASTERING ATOMIC ENERGY FOR WEAPONS

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Introduction

In 1945, mankind entered into the era of practical use of atomic energy—the atomic age. During the Second World War, American and European scientists, engineers, craftsmen, and laborers created the nuclear industry in the USA leading to the manufacture, in 1945, of the first finished products—nuclear explosives based on the fission of plutonium-239 and uranium-235. In the USSR, 1945 marked the initiation of the nuclear industry which culminated in the first Soviet nuclear explosive, based on plutonium-239, in 1949, and the start-up of the first-ever atomic power station in 1954. Development of the nuclear industry in both countries involved massive contributions by various branches of science—including geology, nuclear physics, radiochemistry, and metallurgy—and all branches of engineering. In the present article, we describe the contribution of radiochemistry to mastering atomic energy and compare and contrast, for the USA and the USSR, the sources of uranium and the first radiochemical technologies in isolation of the plutonium produced by irradiation of uranium and the treatment of the radioactive wastes arising from these separations.

Role of Radiochemical Technology in Mastering Atomic Energy

The roles of radiochemistry in nuclear industry lie in separation and purification of natural uranium from ores, production of uranium hexafluoride for isotope enrichment, production of uranium- and uranium/plutonium-bearing feeds both as nuclear fuel and as fertile material for irradiation in reactors, isolation and purification of plutonium and uranium from the irradiated uranium, and treatment processes for the resulting radioactive waste (1). The key importance of these processes in building atomic weapons was noted by Edward Teller in a 1962 conference in Seattle, observing that once the nuclear material is acquired, it is only a matter of months until a nuclear explosive can be fashioned (2). According to this authoritative physicist and weapons designer, the most complex and difficult part in mastering atomic energy for atomic weapons production lies not in designing the nuclear explosive but rather creating and implementing the technology to produce the fissionable material—^{239}Pu and ^{235}U—in sufficiently high quantities and purity. Of these, plutonium-239 as the ingredient for nuclear explosives is apparently more effective and accessible based on the experience of those states—the USA, USSR, United Kingdom, France, India, North Korea, and Israel (undeclared)—whose first nuclear explosives were based

on plutonium. Only China, Pakistan and (purportedly) South Africa's first nuclear explosives used enriched uranium (3).

The technology of plutonium weapons production consists of neutron transmutation of uranium-238 in reactors, separating plutonium from the uranium and fission products in radiochemical plants, and fashioning the explosive. Of the three steps needed to produce a ^{239}Pu-based nuclear weapon—the reactor, the separation, and crafting the explosive device—two, the first Soviet industrial reactor for plutonium production and the first Soviet nuclear explosive device, were almost exact copies of the American designs, thanks to receipt of clandestine technical information. However the Soviet radiochemists did not receive comparable detail about the American radiochemical techniques and the plutonium separation plant at Hanford, thus necessitating development of indigenous Soviet separations technology.

Acquisition of Uranium Raw Materials for the First Nuclear Projects

Uranium ore from the Shinkolobwe mine in the Katanga Province of the Belgian Congo (now the Democratic Republic of the Congo) provided the raw materials for the first successful American and Soviet nuclear explosive efforts and the unsuccessful German efforts (4). This ore was the richest in the world, a unique deposit now exhausted. In the 1930s and 1940s, the Belgian company *Union Minière du Haut Katanga* produced a uranium concentrate of 65% U_3O_8. More than 90% of the world's uranium stockpile in 1939 arose from the Congo and at this time, the company *Union Minière* sent half of its procured concentrate to Belgium with the second half stored in Africa. In August 1939, a month before World War II commenced, Nobel Prize winner Frédéric Joliot-Curie contacted Edgar Sengier, director of *Union Minière*, explained to the Belgian businessman the value of uranium for potential weapons and, on behalf of the government of France and to the exclusion of Germany, offered a contract to buy the entire stock in Belgium and Africa as well as any future uranium production. Sengier, who had earlier refused a similar request by an English representative, agreed to the French contract but the outbreak of World War II prevented completion of the contract. Belgium soon was occupied by German forces who confiscated and removed to Germany 1200 tonnes of uranium concentrate and used it in their unsuccessful nuclear research. At the capitulation of Germany in May 1945, much of the African-Belgian uranium held by the Germans lay in the American region of occupation and was taken to the USA for nuclear applications.

Meanwhile, the ore concentrates held by *Union Minière* in Africa became the main source of uranium for the Americans' Manhattan Project. With the advent of hostilities in Europe, Sengier, at the advice of Joliot-Curie and unknown to the German occupiers, organized in September 1940 marine transport of uranium concentrates from Africa to the port of New York (in Staten Island) where the concentrate was stored as foreign property nearly two years before the Manhattan Project started in earnest (4). Thus the USA, long before recognizing the need to acquire uranium raw materials, received a unique uranium concentrate not as a military trophy, not as a purchase made in anticipation of future use, but rather through the prescient actions of two Europeans, a critical consignment literally at its doorstep ready for use, subject only to payment. The load contained 1250 tonnes of 65% U_3O_8 concentrate and constituted almost half of the world's separated reserve at that time. This quantity, plus the 3000 tonnes as ore stored in the Congo and later retrieved by the Americans, was more than enough for the first reactors and the first American nuclear explosives of both types. This "gift" to the United States made by Edgar Sengier, at the advice of Frédéric Joliot-Curie, reduced the timeline of American atomic weapons development by years as the United States at that time possessed only poor uranium ores and little indigenous uranium mining and milling capability. The USSR requested some kilograms of pure metallic uranium and uranium compounds from the USA in 1943 under terms of the Lend-Lease program. The USA agreed and provided the USSR 20 kg of metallic uranium, 100 kg of uranium oxide, and 220 kg of uranyl nitrate in April 1943, sufficient to supply materials for laboratory studies for the Soviet atomic project (5, p 98).

The Soviet side likewise benefitted from the seizure of about 200 tonnes of the Congolese mining concentrate, acquired after the surrender of Germany in the Soviet zone of occupation (6, p 108). The Soviet effort also benefitted from the existence of rich uranium deposits in Germany's Sudetenland, in the Joachimstal of the "Ore Mountains" (Erzgebirge). These Congolese concentrates and European minerals served as important, but not unique, uranium sources for the first Soviet reactors and for building of the first Soviet nuclear explosives as the production of uranium from Soviet Asiatic deposits increased quickly—from 14.6 tonnes in 1945 to 129.3 tonnes in 1947 and to 278.6 tonnes in 1949 (5, p 192).

The USSR undertook joint enterprises in 1946-1949 with several Central European countries—the German Democratic Republic (GDR), Czechoslovakia, Bulgaria, and Poland—to make significant addition to the atomic project uranium supply. In so doing, Soviet geologists discovered new uranium ore deposits and more precisely defined established deposits thus augmenting the uranium ore reserves in these countries many fold. Rich uranium deposits were found in GDR's Saxony at Johanngeorgenstadt, Schneeberg, and Oberschlema in the Erzgebirge. The most important uranium deposit was Niederschlema-Alberoda and was the main source of uranium for the Soviet-German corporation "Wismut" until the dissolution of the Soviet Union in 1991. The joint Soviet-Czech enterprise at Jáchymov was created to exploit the old mines Rovnost and Svornost and work the new mines Berg Slavkov and Příbram in western and central Czechoslovakia. A joint Soviet-Bulgarian mining enterprise was created based on a known deposit at Goten with new deposits found at Seslavci. Nevertheless the uranium reserve was small in Bulgaria: 16 tonnes at the beginning of 1946 and 163 tonnes by 1950. A joint Soviet-Polish commission and the enterprise "Kowarski Mines" was created in 1947 with several new uranium deposits discovered. As in Bulgaria, these deposits were poor and the total uranium reserve in Poland was small. The Wolność deposit, the richest in Poland, was exhausted in 1952. The total uranium reserve and concentrations in the ore in these four Central European countries were modest compared with those in the Congo, Canada, and other countries utilized by the USA. The early uranium resources available to the Soviet atomic project by indigenous Soviet and joint Soviet-Central European efforts is given in Table 1. The total uranium delivered to the USSR from Central Europe countries in 1945-1949 thus was ~1700 tonnes, a quantity somewhat less than that available to the USA from Congolese resources at the outset of the Manhattan Project.

Table 1. Uranium ore concentrate production in the USSR and for the USSR from Central European resources, 1945-1949.

Country	Uranium Production, tonnes				
	1945	1946	1947	1948	1949
USSR	14.6	50.0	129.3	182.5	278.6
GDR (East Germany)	–	15.7	150.0	321.2	767.8
Czechoslovakia	–	18.0	49.1	103.2	147.3
Bulgaria	–	26.6	7.6	18.2	30.2
Poland	–	–	2.3	9.3	43.3
From pp 192 and 197 in Ref. 5.					

The First Radiochemical Technologies to Prepare High-Purity Plutonium in the USA

The reactor irradiation of uranium is used to produce plutonium for atomic weapons. The most complex and waste-laden part of this technology is the isolation of plutonium from the admixture of uranium and radioactive fission products in the irradiated uranium fuel. To be used in nuclear armaments, the plutonium, which is present in quantities of only hundreds of grams per ton of irradiated uranium, must be purified from these accompanying elements by a factor of greater than 10^6 (separation factor).

The initial American isolation technology, applied in 1944 to 1956 at the Hanford Site T and B Plants in Washington state, relied on separate coprecipitation of first plutonium and then fission products using bismuth phosphate. In the first step, Pu(IV) in nitrate solution was separated from U(VI) and most of the fission products by coprecipitation with $BiPO_4$. The plutonium-bearing $BiPO_4$ precipitate then was dissolved, the plutonium oxidized to Pu(VI) using Ce(IV) or Cr(VI), and the $BiPO_4$ precipitation repeated, this time capturing residual fission products while leaving the Pu(VI) in solution. The dissolved plutonium then was chemically reduced to Pu(IV) and the Pu(IV)/Pu(VI) steps repeated two more times. A similar cycle followed, this time using lanthanum fluoride, LaF_3, as the carrier, each time further purifying and concentrating the plutonium. Finally, plutonium was isolated from lanthanum by metathesizing the LaF_3 carrier in potassium hydroxide solution to remove the fluoride, dissolving the hydroxide cake in acid, and precipitating the plutonium as the Pu(III)/Pu(IV) peroxide while lanthanum remained in solution.

Edwin McMillan and Philip H. Abelson (Figure 1) in 1940 used an oxidation-reduction coprecipitation cycle of purification in the isolation and discovery of neptunium, the first transuranium element, prepared by bombarding uranium with neutrons using Ernest O. Lawrence's 60-inch cyclotron (7). Stanley Thompson and Glenn Seaborg (Figure 2) adapted this coprecipitation concept to plutonium isolation and patented the $BiPO_4$ portion of the plutonium separation process that used a similar oxidation-reduction coprecipitation cycle (8). The choice of bismuth phosphate as the carrier

was fortuitous and unexpected even for its inventors (9). The Seaborg research group, located at the Metallurgical Laboratory at the University of Chicago, investigated many candidate carriers for plutonium including the nearly insoluble phosphates of zirconium, niobium and thorium, as well as sodium uranyl triacetate as used by McMillan and Abelson for neptunium isolation and identification. Various advantages and disadvantages were found in these investigated carriers. For example, sodium uranyl triacetate carried plutonium but formed small crystals that filtered slowly.

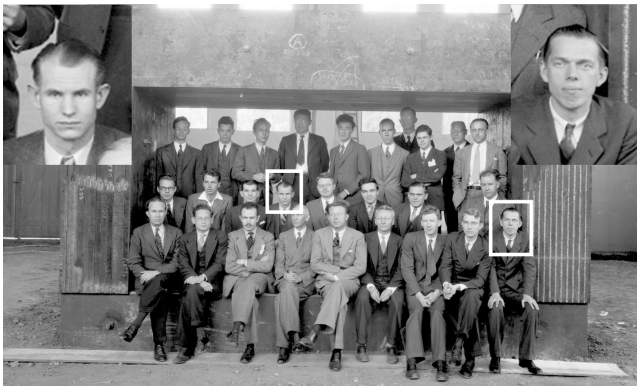

Figure 1. *Edwin McMillan (left) and Philip Abelson (right), co-discoverers of neptunium. Photo taken in the Berkeley 60-inch cyclotron magnet, September 1938. E. O. Lawrence is seated in the front row, middle, and Robert Oppenheimer is standing in the top row, middle, above Lawrence. Photo XBD9706-02525 courtesy Lawrence Berkeley Laboratory, Berkeley, CA, USA (henceforth LBL).*

Figure 2. *Stanley Thompson (left) and Glenn Seaborg at centrifuge in 1948. Photo XBD9704-01812 courtesy LBL.*

It was Thompson (Figure 3), Seaborg's high school and college classmate, invited by Seaborg to join the Metallurgical Laboratory, who suggested trying $BiPO_4$ as a carrier. Thompson knew this carrier as a filter aid from his prior job at Standard Oil. In his testing, Thompson noted that $BiPO_4$ satisfied many requirements for plutonium separation—it is almost insoluble in dilute nitric acid but readily soluble in concentrated nitric acid, it forms large, quickly-settling, and readily-filtered crystals, and the accompanying phosphate retards steel corrosion thereby saving process equipment and minimizing plutonium product contamination. Of course, nothing initially was known about the ability of bismuth phosphate to coprecipitate plutonium in its different oxidation states. Thompson and Seaborg predicted that $BiPO_4$ would co-precipitate Pu^{3+} by its substitution for Bi^{3+} but considered improbable that $BiPO_4$ would trap Pu^{4+}, the most stable plutonium valence in nitric acid solution. Nevertheless,

Figure 3. *Stanley G. Thompson, co-discoverer, with Glenn Seaborg, of the bismuth phosphate process. Photo taken 20 February 1950. Photo XBD200912-01073 courtesy LBL.*

bismuth phosphate was included for investigation. Using ultramicrochemical techniques involving only tens of micrograms of plutonium, Thompson (Figure 3), with Burris Cunningham and Louis Werner (Figures 4 and 5), carefully investigated plutonium coprecipitation, in its various oxidation states, with $BiPO_4$ and found in the period 19 December 1942 to 29 March 1943 that Pu^{4+} is indeed carried with high efficiency (10, pp 223-224 and 258-259) using the uranium concentrations and ~100:1 Bi:Pu ratios corresponding to those envisioned

in the full-scale separation plant (8, Table I). At the same time, Pu(VI), as PuO_2^{2+}, was found not to be captured by $BiPO_4$. Plutonium(V) (as PuO_2^{+}), the other potential oxidation state in solution, does not exist in appreciable concentrations above about 0.4 M HNO_3.

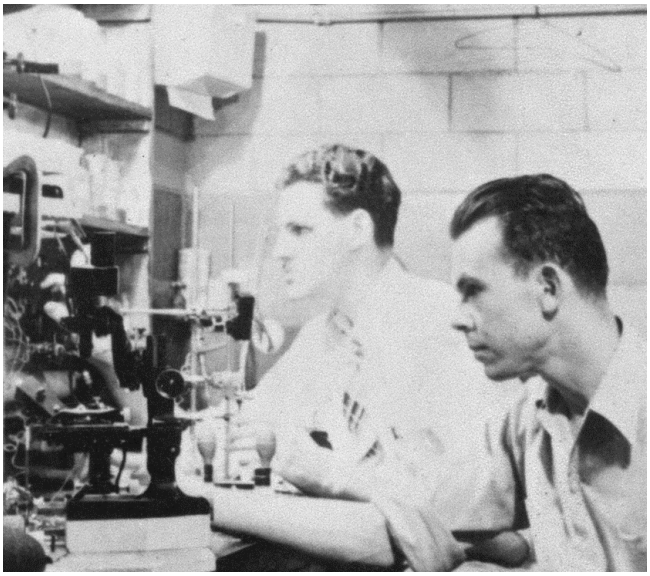

Figure 4. *Louis B. Werner (left) and Burris B. Cunningham (right), early developers of the bismuth phosphate process. Photo taken at the Metallurgical Laboratory, Chicago. Photo XBD9611-05594 courtesy LBL.*

Figure 5. *Burris B. Cunningham demonstrating ultramicrochemical techniques used in early plutonium chemistry investigations at the Metallurgical Laboratory, Chicago. Courtesy LBL.*

Thus the new carrier met the desired process requirements (9). Even though separations from the numerous fission products were incompletely known, DuPont, the Hanford Site engineering firm, proceeded on 7 June 1943 with plant construction on these bases using an ingeniously flexible design (10, p 284). However there remained the concern of scale, multiplying the Metallurgical Laboratory $BiPO_4$ findings done using tens-of-micrograms of plutonium by a factor of ~10^7 to reach hundreds-of-grams batch sizes for the Hanford Site T, B, and U Plants being constructed by DuPont (9). The construction and operation of the plutonium separation plant using $BiPO_4$ technology thus represented a bold calculated risk. As was stated in the official 1945 American report on the Manhattan Project (11, paragraph 7.3):

> In peacetime, no engineer or scientist in his right mind would consider making such a magnification in a single stage, and even in wartime only the possibility of achieving tremendously important results could justify it.

Seaborg assured DuPont that even incomplete plutonium capture by $BiPO_4$ still would provide sufficient yield. Although $BiPO_4$ was the favored initial coprecipitation agent, the selection of $BiPO_4$ process parameters, the subsequent LaF_3 cycle parameters, and the final segregation as plutonium peroxide awaited verbal confirmation by Seaborg to Du Pont plant authorities in a visit to Hanford in 13-15 December 1944. By this time, Thompson had transferred to Hanford to lead the Process Research Group in the Process Chemistry Section (10, pp 576-580). In fact, the initial plutonium separation operations occurred in T Plant on 9 December 1944, before Seaborg's verbal confirmation, using uranium metal slugs irradiated in the Clinton Laboratory (Oak Ridge) X-10 reactor supplemented by non-irradiated slugs (12). The second T Plant run, using a less-than-full charge of uranium metal fuel slugs lightly irradiated in Hanford's B Reactor, supplemented by non-irradiated uranium, occurred on 14 December 1944 while the flowsheet discussions were in progress (Figure 6). Both were "tracer studies" in that the first contained milligram quantities of plutonium product and the second only gram quantities (13). The completeness of extraction gradually exceeded design norms, beginning at 60-70% in the first two months, 90% in the third, 93% after six months, and then above 95% with decontamination factors of 10^8 (14). This success was due to the fortuitous and non-intuitive discovery of the $BiPO_4$ carrier and the creativity and persistence of the American radiochemists. It is noteworthy that, in contrast to the Manhattan Project efforts in reactors and nuclear explosives, whose discoveries were led and fostered in

key areas by European refugees (e.g., Enrico Fermi, Leo Szilard, Hans Bethe, John von Neumann, James Franck, Edward Teller, Rudolf Peierls, George Kistiakowsky), the key radiochemical separation innovations were solely products of US-born contributors.

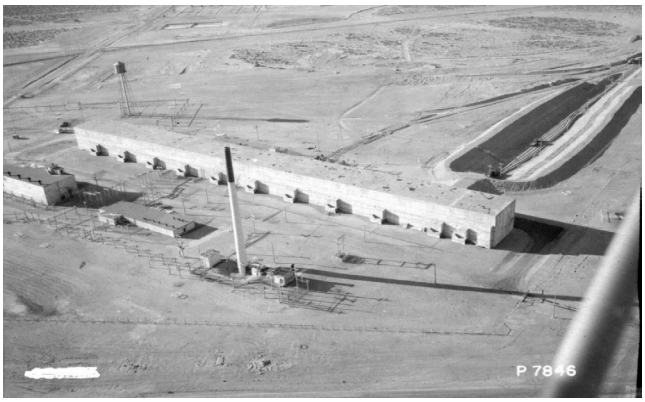

Figure 6. *T Plant, Hanford, based on bismuth phosphate coprecipitation (long building at center) and lanthanum fluoride (building at the left), operated 1944-1956. Photo taken 22 December 1944, during initial start-up operations. Taken from archival original of Ref. 15.*

The First Radiochemical Technologies to Prepare High-Purity Plutonium in the USSR

The initial separations of plutonium from irradiated uranium took place in the Soviet Union on an industrial basis under the scientific direction of Vitaly G. Khlopin (Figure 7), Academician from the Academy of Sciences of the USSR, director of the Radium Institute in Leningrad (now Saint Petersburg), and scientific head in development of the first radium production in the USSR (16). The first Soviet plutonium was produced in industrial scale at the B Plant of Complex 817, now Mayak, at the town of Ozyorsk, Ural, Chelyabinsk Region, using acetate-fluoride coprecipitation technology (17, 18, 19). The plutonium carriers were sodium uranyl triacetate [$NaUO_2(CH_3CO_2)_3$] followed, like the American plutonium separation process, by LaF_3. Each of these agents was used as published earlier by McMillan and Abelson (7) in the discovery and isolation of neptunium, but using LaF_3 in place of CeF_3.

In the Soviet process, the irradiated uranium metal was dissolved in nitric acid, the plutonium oxidized to Pu(VI) by dichromate and the Pu(VI) coprecipitated with U(VI) as $NaUO_2(CH_3CO_2)_3$. Soluble fission products and process impurities (e.g., spent chromium, corrosion

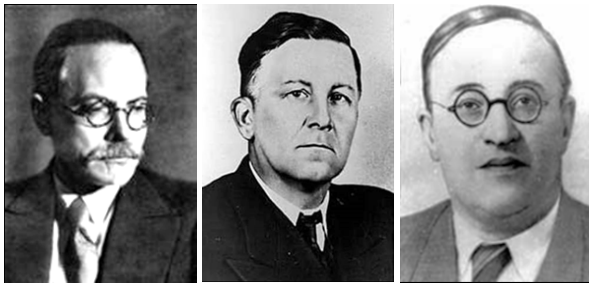

Figure 7. *Left: Academician V. G. Khlopin (1890-1950). Scientific director of plutonium separations at Mayak. Middle and Right: Corresponding Member B. A. Nikitin (1906-1952) and Professor A. P. Ratner (1906-1956), developers of the sodium uranyl acetate and lanthanum fluoride processes for plutonium isolation. All were from the Radium Institute of the USSR Academy of Sciences.*

products) were rejected with the plutonium-denuded solution. An oxidation-reduction cycle of purification ensued—the NaUO2(CH3CO2)3 solids with the coprecipitated Pu(VI) were dissolved, the Pu(VI) reduced to Pu(IV), and NaUO2(CH3CO2)3 again precipitated, leaving the Pu(IV) in solution but NaUO2(CH3CO2)3 solids, destined for separate uranium recovery, carrying much of the remaining fission products. After this cycle, Pu(IV) was coprecipitated with LaF3. The B Plant at Mayak (Figure 8) began operations on December 1948, exactly four years after start-up of Hanford's T Plant, by the successful dissolution of irradiated uranium fuel. However, initial plutonium recoveries within the analyzed solids and solutions were low.

Figure 8. *Plant B in Chelyabinsk-40, based on acetate-fluoride technology, operated 1948-1960.*

To locate the plutonium, a brigade led by the developers of the technology including Corresponding

Member of the USSR Academy of Sciences, Boris A. Nikitin, and Professor Alexandr P. Ratner, both of the Radium Institute, was engaged (Figure 7). Little by little, the causes of the small plutonium recoveries were found and eliminated. Sorption of dissolved plutonium and solid plutonium deposits on walls and pipelines within the plant appear to have been among the causes for the low yields. Technological process parameters were adjusted, such that with each succeeding dissolved irradiated uranium batch the yield increased until, by April 1949, design norms were reached (17, 19). Work to initiate and then adjust operations in the acetate-fluoride technologies was conducted under extreme radioactive exposure. Despite these hazards, the staff worked selflessly such that many received massive doses during the start-up of B Plant. Included in these staff were the process developers. Physicians were not able to thwart development of radiation sickness for Nikitin and Ratner and they died 3 and 6 years after B Plant start-up at the ages of 46 and 49 years, respectively.

It is noted that, along with the acetate-fluoride technology, the USSR scientists considered other plutonium separation methods, including solvent extraction (17, 18, 19). However, only after acetate-fluoride technology began achieving reliable yields did research cease into alternative technologies using diethyl ether as an extractant in Building 102 of the B Plant. Efforts to perform the next chemical step, namely, finishing the separated plutonium into its metallic form at Mayak's C Plant, were led in collaboration by Iliya I. Chernyaev of the Institute of General and Inorganic Chemistry, Anna D. Gelman of the Institute of Physical Chemistry, and Vsevolod D. Nikolsky of the Bochvar Institute (Figure 9). The Cold War necessity to rapidly build atomic weapons, guided by the sense of debt and patriotism, led to willing neglect of safety norms. Thus, the first minister of the Soviet nuclear industry, Vyacheslav A. Malyshev, died early, motivated, with other technological leaders and employees of the nuclear branch, to intentionally run risks to accelerate the work.

Comparing the USA and USSR Radiochemical Technologies

As this account shows, the first American and Soviet plutonium separation radiochemical technologies were similar in exploiting the differences of plutonium oxidation state properties by coprecipitation but were not identical in the primary carrier selected. Thus, the initial

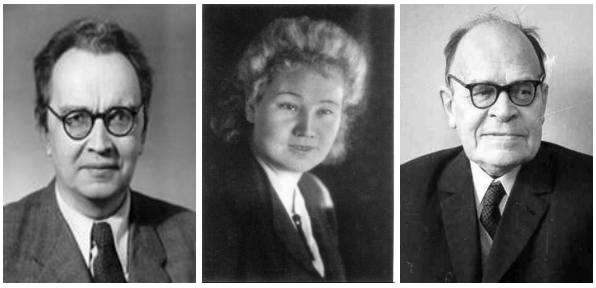

Figure 9. *Left: Academician I. I. Chernyaev, Institute of General and Inorganic Chemistry, USSR Academy of Sciences. Middle: Professor A. D. Gelman, Institute of Physical Chemistry, USSR Academy of Sciences. Right: Doctor of Chemical Sciences V. V. Nikolsky, Bochvar Institute of Inorganic Materials (Institute-9). All worked in devising processes to convert and finish plutonium to metal at C Plant , Mayak, 1949.*

separation at Hanford used Pu(IV) carried by $BiPO_4$ whereas Pu(VI) carried by $NaUO_2(CH_3CO_2)_3$ was used at Mayak. It is noted that the Americans also investigated $NaUO_2(CH_3CO_2)_3$ as a carrier for plutonium separation but, having met with large technical difficulties, including waste neutralization, at the Clinton (Oak Ridge) pilot plant, considered this technology unpromising and chose bismuth phosphate technology. The "Smyth Report" alluded to the separation method choices available to the Manhattan Project but was written elliptically, in the style of Aesop, to avoid, in the interest of military secrecy, concrete statements about specific methods and carriers for plutonium separation except to say that several separation technologies were considered (including volatility, absorption, and solvent extraction) and that, in the end, two coprecipitation processes were involved that took advantage of differences in Pu(IV) and Pu(VI) behaviors (11, paragraphs 8.20-8.26).

Although the Soviet Union (and the world) were aware that coprecipitation processes relying on oxidation state changes were used at Hanford to isolate plutonium, the specific agents, including the primary extraction and subsequent decontamination achieved with high efficiency by bismuth phosphate, were unknown to the Soviet technical leaders through open sources and even, evidently, by espionage at the inception of the Soviet B Plant design. As it was, plutonium recovery by coprecipitation with $BiPO_4$ was investigated in December 1945 by a group led by Corresponding Member Alexandr A. Grinberg, a professor of the Radium Institute and Corresponding Member of the Academy of Sciences of the USSR since 1946. However, under Khlopin's direction, this approach apparently was judged inferior to the acetate-fluoride technologies.

The coprecipitation of Pu(VI) with $NaUO_2(CH_3COO)_3$ proceeds by isomorphous co-crystallisation, wherein PuO_2^{2+} ions readily substitute for UO_2^{2+} ions in the bulk crystal lattice. Because of their isomorphism, capture of Pu(VI) by the uranyl compound precipitate is high at any initial Pu:U solution ratio. In contrast, the coprecipitation of Pu(IV) with $BiPO_4$ proceeds by anomalous mixed-crystal formation wherein the Pu^{4+} and Bi^{3+} ions occupy different places in the $BiPO_4$ crystal lattice. It is known for such cases that the microcomponent (Pu) capture by the bulk ($BiPO_4$) precipitate is incomplete if the microcomponent concentration exceeds some critical value. Therefore, the radiochemists of Radium Institute doubted the effectiveness of the $BiPO_4$ carrier at higher plutonium concentrations. Furthermore, the USSR lacked bismuth production capability (17). The Radium Institute directorate and the Soviet atomic project leadership approved use of the $NaUO_2(CH_3CO_2)_3$ and LaF_3 coprecipitation technologies noting that they provided not only purified plutonium but also recovered the uranium for future isotope enrichment (17).

Radiochemical Treatment Technologies for High-Level Liquid Wastes in the USA and USSR

The American and Soviet/Russian radiochemical plutonium technologies have appreciable differences in radiochemical high-level liquid waste (HLLW) management (20) but some interesting similarities. The big advantage of American plutonium separation technology was that the first Pu(IV) coprecipitation with $BiPO_4$ yielded only kilograms of precipitate for further processing from each 1 to 1.5-tonne uranium metal batch, not tonnes as was the case with the Soviet $NaUO_2(CH_3CO_2)_3$ process which handled all of the uranium with the plutonium in the first plutonium separation step. At Hanford, the uranium- and fission product-bearing mother solution obtained after the first $BiPO_4$ precipitation could be disposed as high active waste for later uranium recovery. Ensuing $BiPO_4$ and LaF_3 precipitations further decontaminated the plutonium of uranium and fission products but yielded only kilograms of waste.

At Mayak, each of the five sodium uranyl triacetate precipitations yielded many cubic meters of high-level liquid wastes or HLLW (1). As a result, Mayak's acetate technology produced perhaps 10 to 20 times more uranium-specific HLLW volume than Hanford's bismuth phosphate technology, the volumes of the latter being initially 64 liters per kg of uranium and decreasing to 20 liters per kg through process improvements. However, the Soviet technology separated both weapon plutonium *and* purified uranium as feed for isotopic enrichment whereas the American bismuth phosphate technology yielded only purified plutonium. Subsequent recovery of the valuable uranium contained in the waste from the first $BiPO_4$ precipitation at Hanford occurred in the 1950s by sluicing waste from the tanks, dissolving the uranium-bearing solids in nitric acid, and tributyl phosphate solvent extraction, separation and purification.

For a variety of reasons, American HLLW treatment differed in other ways from that of the Soviet methods. First, the American nitrate waste chemical composition strongly differed from the high-salt nitrate-acetate Soviet waste. At Hanford, the acidic nitrate liquid wastes were made alkaline by addition of NaOH so that they could be disposed into mild steel-lined underground storage tanks. The Americans also evaporated water from the wastes, both by radiolytic heating and by applied external heat, to decrease waste volume. Although corrosion was expected to be low for the mild steel in contact with the alkaline waste, stress corrosion, the effects of chemical combination and thermal stresses, perhaps accelerated by radiolysis, caused leaks to occur in the steel liners of these concrete tanks, allowing waste solutions to enter the underlying Hanford sand and gravel.

A total of 177 underground tanks were built to store these wastes (now totaling ~200,000 m^3 waste volume), 149 of nominal 20-year lifetime constructed 1943 to 1964 and having a single steel lining within concrete. Beginning in 1968, 28 double-shell (steel) tanks within concrete having a 50-year projected lifetime were constructed. The first confirmation of single-shell tank leakage occurred in 1959, and many more have been confirmed since then (21). Solutions present in the single-shell tanks have been moved to the more secure double-shell tanks. One of the double-shell tanks was recently discovered to have leaked into its annulus but with no confirmed leakage past the second shell into the surrounding soils. Billions of dollars have been spent and will continue to be spent until the waste is removed from the tanks and rendered into more stable forms including glass (22). Meanwhile, extensive characterization of these wastes has been undertaken, including studies of the disposition of plutonium, aided by contributions from French and Russian as well as USA scientists (20, 23).

Neutralization of the first industrial HLLW in Russia at Mayak proceeded more dramatically. The technology of neutralization was developed in laboratory scale in 1949 by members of the Institute of Physical Chemistry

(IPC) of the Soviet Academy of Sciences. However, it was not utilized at Mayak because the B Plant liquid wastes contained salts (sodium acetate and sodium nitrate, $NaCH_3CO_2$ and $NaNO_3$, respectively) and potassium dichromate at higher concentrations than were stated in the detailed design and studied in the laboratory (19, 20). The evaporators designed to reduce HLLW volumes could not function because of salt loading and aggressive equipment corrosion caused by radiation and the high concentration of $K_2Cr_2O_7$ used to oxidize plutonium to Pu(VI). As a result, the B Plant HLLW volume surpassed the waste tank capacity in 1949.

To address this waste storage problem, either replacement of the sodium uranyl triacetate process had to be implemented, production of plutonium stopped, or an alternative means found to handle the waste. The decision to this problem was made in the crucible of the Cold War and the perceived threat of ~200 atomic weapons in the USA arsenal deliverable by air from military bases in countries surrounding the USSR. Under these conditions, the Soviet nuclear design leadership demanded that plutonium production continue and means found to process the B Plant HLLW. Only one option was possible—shunt the HLLW to the Techa River and to adjacent reservoirs such as Lake Karachay.

This expedient was a serious and ecologically dangerous extrapolation of the initial design which called for disposal of only low-level liquid wastes to the Techa River. A commission to ameliorate the ecological effects included representatives of leading research institutes: Corresponding Member Iossef E. Starik (Radium Institute), Corresponding Member Simon Z. Roginsky (IPC; Figure 10), the head of Public Service of Radiation Safety of the USSR, Avetik I. Burnazian, Academician A. P. Aleksandrov (director of the Institute of Physical Problems, Academy of Science), and Corresponding Member Alexandr P. Vinogradov (Institute of Geochemistry, Academy of Sciences). The commission was forced to recommend disposal to the Techa River but to minimize the ecological effect by pre-disposal adjustment of the HLLW to neutral pH and dilution to the maximum possible extent.

Simultaneously in 1949, the design management transferred Corresponding Member Viktor I. Spitsyn from the Lomonosov Moscow State University to deputy director of the IPC as supervisor of waste neutralization studies. From the end of 1949 until the beginning of 1951, Spitsyn, with Neonila E. Brezhneva and Boris A. Zaitsev (Figure 10), developed methods to decontaminate HLLW by carrier precipitation using nickel ferrocyanide (primarily for radioactive cesium) and the oxyhydroxides and sulfides of iron and nickel (primarily for radioactive strontium and rare earths). The settled solids occupied <1% of the initial HLLW solution volume. These co-precipitation schemes were implemented at B Plant to produce sludges of small volume that were stored successfully in stainless steel tanks for more than 50 years and allowed discharge of the decontaminated solutions. Vitrification of this "historical" waste sludge commenced at Mayak at the beginning of the 21st century. Based on nearly contemporaneous research at Mound Laboratory (24), Hanford likewise independently embarked on a very similar program in 1954-1958, and for very similar purposes, to decontaminate the Hanford T and B Plant waste solutions so that they could be discharged to the environment, as well as for uranium recovery. In this case, discharge was underground to the dry sand/gravel

Figure 10. *Top left: Corresponding Member S. Z. Roginsky (1900-1970). Top right: Candidate of chemical sciences N. E. Brezhneva, future doctor of sciences and the winner of the Lenin Award (on left) and Corresponding Member V. I. Spitsyn, elected Academician in 1958 (on right). Bottom: Sergeant, and future doctor of chemistry and winner of the Lenin award B. A. Zaitsev (on the left) with fellow soldiers in the Soviet army, Germany, 1945. All were radiochemists of the IPC of the USSR Academy of Sciences active in devising processes for radioactive waste neutralization and decontamination for Mayak.*

above the water table, leaving the precipitates in the waste tanks, and freeing the tank waste volume associated with the liquids. As at Mayak, the cesium was removed using nickel ferrocyanide. Strontium was removed by dilution with calcium and nonradioactive strontium nitrates and precipitation as the corresponding sulfates and phosphates (25).

It is interesting to note that the storage times and resolutions of these problematic "historical" HLLW from both the Hanford and Mayak technologies have required incubation times of a half-century! This delayed outcome was a consequence of the fact that, at the beginning of the nuclear industry, both in the USA and the USSR, basic attention was given to plutonium production for nuclear arms while radioactive waste treatment was accorded secondary importance. This singlemindedness is apparent by the following example. In 1949 in the USSR, plutonium science and technology occupied tens of thousands of workers in various scientific research institutes and operations sites. At the same time, radioactive waste management was addressed by only one institute. That institute was the IPC, a department of 30 employees, including technicians and scientists devoted to waste management for industrial Complex 817. Only after 1949 did similar research groups arise in other scientific Soviet organizations including the Radium Institute and Bochvar Institute of Inorganic Materials.

Later Developments in Plutonium Separations

Despite the successful experience of the T (and duplicate B) Plants based on bismuth phosphate in Hanford in 1944-1956, plutonium separation was supplemented, in 1951, by solvent extraction by the more effective REDOX process, using methyl isobutyl ketone solvent extraction and then succeeded in 1956 by the PUREX process using tributyl phosphate diluted in kerosene for solvent extraction (26). The PUREX process is now the worldwide baseline plutonium and uranium separation technology for irradiated fuel. The rapid early evolution of plutonium separation technologies in the USA may be contrasted with the extended use of coprecipitation technology in the USSR. The B Plant at Mayak used acetate-fluoride coprecipitation technology from 1948 until 1960. An improved acetate technology conducted without the succeeding LaF_3 steps was used in the DB (double B, or BB) Plant at Mayak with implementation delayed until 1959 because of an HLLW explosion in 1957 (17). The DB Plant successfully operated more than 15 years (19). As the acetate technology was improved, a new unique one-cycle extraction technology to separate weapon plutonium from irradiated uranium was developed based on the PUREX Process. This new technology was tested and introduced into commercial operation at Mayak in 1976 (19). This plant ceased operation in 1989 as an outcome of treaties concluded between the USSR and the USA.

However, the improved acetate technology endured in the USSR until the 1980s (27, 28). One important cause of its longevity was the successful and inexpensive solution of HLLW disposal implemented at the Tomsk Siberian Chemical Combine (SCC) and Krasnoyarsk Mining Chemical Combine (MCC). Through joint efforts of geologists of the Siberian Territorial Management of the Ministry of Geology, radiochemists of the IPC of the Academy of Sciences, specialists from project institutes of the Ministry of Atomic Energy, and employees of the SCC and MCC, a method of underground HLLW injection into clay bed strata at depths greater than 180 m was implemented (27, 28). Russian geologists forecast that the radioactive waste disposed in these isolated layers near the SCC and MCC will remain fixed for many millions of years, sufficient to decay even the longest-lived waste radionuclides. The forecast takes into account the absence of volcanic activity, earthquakes, and significant geological shearing over the past millions of years in the Siberian region of the SCC and MCC. Nevertheless, monitoring for radioactive contamination in observation boreholes around the underground radioactive waste location will be necessary for many years. In contrast, the underground layers in the Ural region near Mayak do not have these favorable attributes for immobilizing HLLW. Therefore, at Mayak, the HLLW treatment method is incorporation into phosphate glass. Large-scale use of underground in-situ HLLW disposal at the SCC and MCC complexes in Siberia has avoided radioactive environmental contamination and considerably reduced capital and operational expenses compared with vitrification and repository storage. These two Siberian industrial complexes' half-century of experience in deep geologic liquid radioactive waste disposal has confirmed the projected reliability and environmentally safety of this disposal method (20).

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Sergey Ivanovich Rovny earned a PhD in radiochemistry from the Leningrad Technological Institute in 1976. He began his career at the chemical combine at Mayak as an engineer and grew to become the director of the central laboratory and director of scientific research at the combine. His research has focused on the chemistry of Pu and Np. The isolation of Tc from waste and preparation of Tc metal for transmutation were developed under his leadership. He retired in 2010 and maintains interest in revealing the history of radiochemical technology.

DRUGS THAT SHAPED THE FDA: FROM ELIXIR SULFANILAMIDE TO THALIDOMIDE

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Introduction

The United States Food and Drug Administration (FDA) currently regulates pharmaceuticals, medical devices and food products. Since the inception of the FDA in 1906, two key pieces of legislation have shaped the FDA into the organization that we recognize today: The Federal Food, Drug and Cosmetic Act (FD&C Act) of 1938 and the Kefauver-Harris amendment in 1962. The FD&C Act of 1938 gave the FDA authority to oversee the safety of food, drugs and cosmetics. The law authorized the FDA to require evidence of safety for new drugs, issue standards for food, and conduct factory inspections. The Kefauver-Harris amendment to the FD&C Act in 1962 required each new drug application (NDA) contain evidence from "adequate and well-controlled studies" demonstrating that a new drug was effective for its intended use and that the established benefits of the drug outweighed its known risks. Companies were required to present animal studies to the FDA *before* obtaining approval to test on humans. Furthermore, clinical studies on humans required informed consent from participants. Each of these pieces of legislation dramatically shaped the FDA and the pharmaceutical industry in the United States (US). They were the product of mounting consumer activism and political pressure, and they were ultimately pushed to passage by high-profile medical disasters: elixir sulfanilamide in 1937 and thalidomide in 1962.

Background

Throughout human history, humans have altered food to prevent spoilage and improve taste (1). As early as Colonial times, lawmakers enacted statutes to protect the health and money of citizens. In the early United States and even earlier, in Colonial times, states and towns sporadically enacted food safety and consumer protection laws. For example, in 1720 Massachusetts outlawed the substitution in bread of "any other grain" than whatever local regulation specified (2). It was not until the Mexican War and a crisis over medications for the troops, that Congress enacted federal legislation to ban adulterated imported drugs. The Drug Importation Act of 1848 required the inspection of imported drugs and medical preparations (3). The problem of food and drug adulteration was already well established in England. In 1820 Friedrich Accum, a German scientist living in in London, published, *A Treatise on Adulteration of Food and Culinary Poisons* (4). Accum used analytical techniques to uncover the use of poisonous substances in food and was the first person to reach a wide audience.

During the second half of the 19th century, the US economy witnessed a dramatic shift from agriculture to industry (5). Locally produced goods were shipped to factories to be preserved, packaged and sold to a growing urban population. With an expanded distribution network, manufacturers no longer interacted directly with their customers and adulteration and deception became more

common and profitable (1). In the US, the most common food adulteration took the form of chemicals to preserve food, hide signs of spoiled food and change a food's color or texture. Examples included the use of copper sulfate to make faded vegetables green, sodium benzoate as a preservative, or borax to make odorous ham acceptable when canned. In other cases, the ingredients were misleading; for example, hayseeds and some apple skins could transform glucose into a substance resembling "strawberry jam" (1).

By the second half of the 19th century there was also a booming "patent" medicines industry in the US. The medicines typically consisted of standard remedies used by doctors at the time. There were often multiple ingredients, and they were sold on the basis of attractive packaging and testimonials that someone claimed to be completely cured by this medicine. The medicine itself was seldom patented, but rather the trademarked labels and shape of the bottle were used to appeal to illiterate consumers. Many products contained alcohol, and some patent medicines contained highly addictive substances such as opium (6).

Although, there were attempts at regulation since colonial times, a well organized push for comprehensive food and drug regulation in the US began during the Progressive Era as activists and political reformers sought to use the federal government to counteract the negative social consequences of industrialization (7). In 1902 Congress passed the Biologics Control Act after the St. Louis Health Department prepared diphtheria antitoxin contaminated with tetanus and thirteen children died (8, 9). In 1906, the Pure Food and Drug Act was passed. The Pure Food and Drug Act established federal government oversight for "preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs or medicines, and liquors" (10). Enforcement fell under the purview of the Bureau of Chemistry in the US Department of Agriculture (USDA), which later became the FDA in 1930. There were weaknesses in the language of the law and Congress did not authorize money for enforcement. But the law did establish, for the first time in US history, that the federal government would oversee commercial abuses and that patent medicines should be considered drugs.

The American Chamber of Horrors

The Pure Food and Drug Act of 1906 was tested many times. In order to be removed from the market, false claims and dangerous products needed to be prosecuted in court. An early challenge to drug regulation came in 1908 when the government seized a large quantity of a product called Johnson's Mild Combination Treatment for Cancer. In U.S. v. Johnson, the Supreme Court ruled against the government, finding that the product's false claims for effectiveness were not within the scope of the Pure Food and Drug Act (11, 12). The challenge with this case and many others was that the bureau had to demonstrate *intent* by the manufacturer to deceive the consumer. For consumer advocates trying to effect change, it made more sense to prohibit the marketing of toxic or ineffective drugs prior to public consumption, rather than trying to retroactively remove one that proved unsafe or misleading.

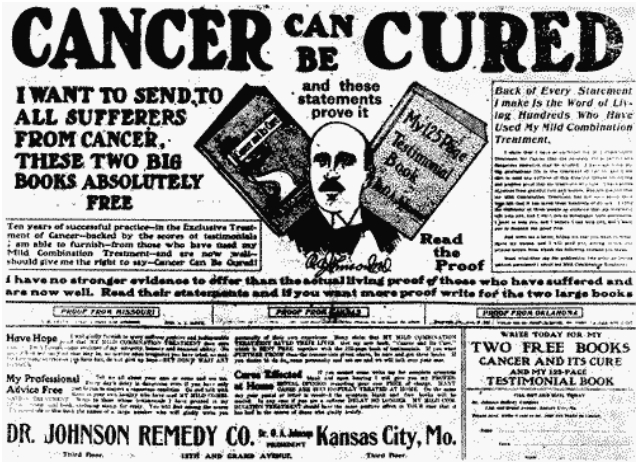

Figure 1. *Advertisements like this one promoted a cure for cancer (13). At the time, the Bureau of Chemistry had to demonstrate that the manufacturer intended to deceive in order to remove unsafe or ineffective products.*

Starting in 1912, FDA officials began to assemble a collection of some of the most egregious products, later named, "The American Chamber of Horrors," by a reporter (14, 15). The exhibit was hardly gruesome, but did contain well-documented examples of manufacturer mislabeling and adulteration of food products. The American Chamber of Horrors was initially an exhibit for Congress, but the 1933 publication of *One Hundred Million Guinea Pigs* by Arthur Kallet and Frederick Schlink (16) brought the exhibit to the public's attention. Some companies changed their production practices in order to be removed from the exhibit.

In addition to the American Chamber of Horrors, the FDA drew upon support from women's groups and organized consumer unions: The General Federation of Women's Clubs (GFWC), the Women's Christian

Temperance Union (WCTU) and Consumers' Research (CR) which were some of the most powerful lobbying organizations at the time (17). In the spring of 1933, FDA commissioner, Walter Campbell, and Paul Dunbar teamed up with Rexford Tugwell, the Assistant Secretary of Agriculture, to draft new legislation (7, 18)

New York Senator Royal Copeland introduced the bill, S1944, to Congress in December of 1933 (19). The bill was an attempt to regulate patent medicines and required manufacturers to apply labels disclosing ingredients. The FDA would have the power to seize misbranded goods and no longer had to prove intent to defraud. The bill also held manufacturers and advertisers legally liable for fraudulent claims (20). The affected industries mounted a well-organized opposition, claiming that Americans have the right to self medicate. Although several factors seemed favorable for the bill to pass (a Democratic Congress and President), the legislation languished in Congress for another five years (7) until the Massengill Company introduced elixir sulfanilamide.

Elixir Sulfanilamide

In his book *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*, Daniel Carpenter discusses the concepts of "policy tragedy" and "political framing" (17)

> In a policy tragedy, someone has been harmed, and wrongly so. The "victim" may be an individual or collective, and the latter is often represented by the former in the manner of an exemplar or "poster child." A culprit (often the system) is responsible in a causal, nearly criminal fashion. The public points a finger at essential and observable features of the regulatory regime, the status quo, as causing or failing to prevent the harm or injustice in question. Yet in a policy tragedy, unlike the criminal or judicial realm, the culprit is less to be punished than reformed.

Political framing links the harm with a condition to create the motivation to push through available solutions. In 1937, elixir sulfanilamide was the policy tragedy and bill S.1944 was the available solution.

In 1937, the Massengill Company in Bristol, Tennessee, was selling a drug called sulfanilamide. Sulfanilamide was one of the first true antibiotics in the family of sulfa drugs in that it specifically killed bacteria. It was used to treat venereal diseases in adults and streptococcal infections (strep throat) in children. The pills themselves were bitter tasting, so at the request of doctors and patients, the company developed an elixir for patients who were unable to swallow the pills. The liquid needed to both dissolve the compound and have a more pleasant taste for children. The solvent chosen: diethylene glycol, a sweet-tasting liquid at room temperature known to cause damage to the blood, kidneys, nervous system and liver (21, 22).

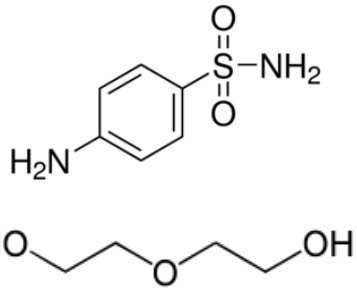

***Figure 2**. The antibiotic sulfanilamide (above) was dissolved in diethylene glycol (below), a sweet tasting, but highly toxic solvent for distribution to adult and pediatric patients in 1937.*

In October of 1937, 240 gallons of elixir sulfanilamide shipped to areas around the US. The first reports of death from the elixir came from the American Medical Association (AMA). On October 11, 1937, the president of the Tulsa, Oklahoma, County Medical Society, Dr. James Stevenson, sent a telegram to the AMA Chemical Laboratory stating that six people had died after taking the elixir. The AMA Chemical laboratory tested a sample of the elixir provided by the Massengill Company. Preliminary laboratory tests concluded that it was the solvent, diethylene glycol, and not sulfanilamide that had caused the deaths. The *Journal of the American Medical Association* (JAMA) issued a public warning on October 18, 1937 (23), and the story was reported by the press in the following days (24, 25).

The FDA learned of the deaths on October 14 and began the arduous recall process. One headline from the *New York Times* read (26)

> **Near End of Chase for Deadly Elixir**
>
> **Government Agents Hope to Recover Today the Last of 700 Bottles**
>
> …Every agent of the United States Food and Drug Administration is scouring the country to recover the bottles, said Dr. Morris Fishbein, spokesman of the medical association. By some time tomorrow, according to J. O. Clarke of the Food and Drug Administration, it is hoped that all the outstanding shipments will be recovered.
>
> –*New York Times*, October 25, 1937

When FDA inspectors reached the Massengill plant, they interviewed the chemists and found that no safety tests had been conducted. At the time, no toxicology testing was required. Under the 1906 law, which still applied in October 1937, the Massengill Company had only broken a mislabeling law. "Elixir" implied alcohol content and elixir sulfanilamide contained no alcohol. FDA Commissioner Walter Campbell was quick to point out that it was only the misbranding that had allowed the FDA to recall the elixir (24). Morris Fishbein, editor of JAMA, was also deeply troubled by the secrecy and absence of standardization from a reliable agency and supported strengthening of the FDA (19). In the four weeks that followed, the FDA was able to recall about 90 percent of the original shipment, but in the end there were 107 deaths (1).

In the aftermath of the tragedy, consumer advocate groups pushed for stronger legislation (27) and on November 16 and 17 of 1937, Royal Copeland (D-New York) and Virgil Chapman (D-Kentucky) successfully pressed for a USDA report, which was presented to Congress on November 26. The USDA report (the Wallace report) detailed the story from the failure of Massengill to test the elixir for toxicity to the technicality that allowed the FDA to enter a case and recall the elixir (28). Two of the most important points were that the elixir was tested for only flavor and not safety, and had the elixir been labeled "solution," no charge of violating the law could have been brought.

The Wallace report was a strong narrative, but it was further strengthened by a copy of a letter written by Maise Nidiffer describing the agonizing death of her beautiful six-year-old daughter after taking the elixir. In her letter, Mrs. Nidiffer begged that similar pain not be caused again and attached a photograph of her child (19). At the end of the report were the following recommendations: Pre-market review and notification for new drugs, prohibition (or withdrawal) authority by the FDA, labeling regulations and compulsory disclosure of drug contents.

The FD&C Act of 1938

President Franklin Roosevelt signed the FD&C Act into law on June 25, 1938 (29). The FD&C Act brought cosmetics and medical devices under FDA regulation, and required that drugs be labeled with directions for proper dosage and use. False therapeutic claims for drugs were clearly addressed and a separate law granted the Federal Trade Commission (FTC) authority over drug advertising. Most importantly, the law required that all new drugs seek approval for safety and efficacy *before* sale (12). Approval required that a company show both efficacy and safety. The new law also corrected abuses in food packaging and created legally enforceable food standards. The law also authorized factory inspections and gave the FDA greater enforcement tools.

The FD&C Act of 1938 dramatically shaped drug development and sales in the US. After passage, companies needed scientists on staff to understand the drugs they were selling and the illness they were intended to treat. Companies were required to produce scientific tests for safety. It was the first US law to require the checking of drugs before they went to market. While initially intended to protect the public, the new law precipitated a shift that ultimately created the drug development industry we know today. After 1938, pharmaceutical companies began to invest large amounts of money to develop effective drugs to treat human illnesses and earn approval before selling their products. Companies adopted aggressive marketing practices to recover the cost of development and generate income before patents expired (1).

More new and effective drugs were invented between 1935 and 1955 than in all the previous years of human history. By the early 1950s doctors had many new and effective drugs in their arsenal to fight diseases. Medicine had become more specialized and new diseases had been identified. The study of clinical pharmacology was developing rapidly and newly hired FDA medical officers were increasingly trained in pharmacology (17).

In 1948, A. Bradford Hill, a British epidemiologist and biostatistician, and Harry Gold at the Cornell Medical School, began to organize formal criteria for drug testing. They introduced the concept of the double-blind study, in which neither the patient nor researcher knows who is receiving drug treatment. (It was well known at the time that doctors introduced bias, both knowingly and unknowingly, and gave drugs to healthier patients while weaker patients would receive the placebo.) In Hill and Gold's protocols, patients were to be selected through formal criteria and randomly placed in treatment and control groups. Drug doses were to be administered according to a fixed schedule, and observations would be recorded at uniform intervals through objective diagnostic technologies (30). More sophisticated trial designs would follow. However, as of 1951, one estimate suggested that 45% of clinical trials still had no control group (31).

The 1938 Act required that new drugs be shown safe for use, but did not specify how this would be demonstrated. As the field of clinical pharmacology advanced, the FDA began to use the NDA as the instrument to enforce standards for efficacy. In 1955 and 1956, the FDA introduced new sections of the NDA requiring full descriptions of clinical results, including adverse effects and therapeutic results (32). Another unresolved issue from the 1938 law was the absence of clear protocols for clinical trials on humans. Some drug companies would circulate "investigational" samples of a drug to practicing physicians and ask for "reports" on safety and efficacy. FDA reviewers found themselves looking at testimonials rather than well-defined and controlled clinical studies (17).

In 1959, the US Senate began hearings to address pharmaceutical pricing. Initially the discussion, introduced by Senator Estes Kefauver (D-Tennessee), focused on profit margins and markups. The pharmaceutical industry, which had one of the highest markups, quickly pointed out that drugs costs covered more than just production expenses; research and development in the pharmaceutical industry were costly (17). The hearings soon turned to other topics, including the cost of clinical trials (17, 30). While Kefauver initially introduced legislation to address truth in labeling and marketing, the FDA contributed ideas to the legislation and pointed out weaknesses in the FD&C act. Ultimately the focus of bill, which had originally been intended (and drafted) to address pricing and truth in labeling, became about safety, efficacy and pre-market testing. Under the FD&C act, safety and effectiveness testing had not been clearly defined and companies could distribute a drug on an investigational basis *before* approval by the FDA.

Newspaper articles from the time reveal that the public was aware of the FDA's policing functions to remove and regulate counterfeit or adulterated products (33) and public awareness of the drug approval process was also growing (34). In the spring of 1961, the Kefauver committee introduced bill S.1552, which was sent to committee and nearly completely gutted (17). A medical disaster was needed to move legislation forward. That disaster came when Morton Mintz published his article about the thalidomide tragedy in Europe and how the FDA had thwarted a similar disaster in the US. The headline read (35):

> **"Heroine" of FDA Keeps Bad Drug Off of Market**
>
> This is the story of how the skepticism and stubbornness of a Government physician prevented what could have been an appalling American tragedy, the birth of hundreds or indeed thousands of armless and legless children.
>
> —*Washington Post*, July 15, 1962

Figure 3. *Frances Oldham Kelsey (36).*

Thalidomide

Frances Oldham Kelsey received her Ph.D. in 1938 in pharmacology from the University of Chicago and joined the faculty from 1938 to 1950. While at University of Chicago, she met her husband, Dr. Fremont Ellis Kelsey, and together they worked on a project to examine the effect of the drug quinine on rabbit embryos. They found that the liver of the mother rabbit contained an enzyme that could break down the drug, but the liver of the unborn rabbits did not contain the enzyme. The work highlighted the fact that some drugs may be safe for an adult, but dangerous to an embryo or fetus (37). Kelsey completed medical school at University of Chicago School of Medicine in 1950 and then served as an editorial associate at the American Medical Association. She taught pharmacology at the University of South Dakota from 1954 to 1957 and practiced medicine from 1957 to 1960. With a background in medicine and pharmacology, Kelsey was a perfect fit for the team of FDA reviewers and joined in 1960.

One of her first assignments at the FDA was to evaluate the drug thalidomide. Although she was pressured by the manufacturer, Richardson-Merrill, to quickly approve

the drug, which was already in widespread use in the rest of the world, Dr. Kelsey found the clinical reports more in the nature of testimonials rather than the results of well-designed and executed studies (38). There were no well-controlled animal or clinical studies, and the chronic toxicology data were incomplete (17). Kelsey also consulted the contemporary literature. She was further troubled by reports of peripheral neuropathy (loss of sensation in the extremities) as a result of thalidomide use (39), a side effect that the manufacturer had initially withheld in their application. She was concerned that the drug had not been adequately tested and cited the need for further study, effectively preventing a disaster in the US.

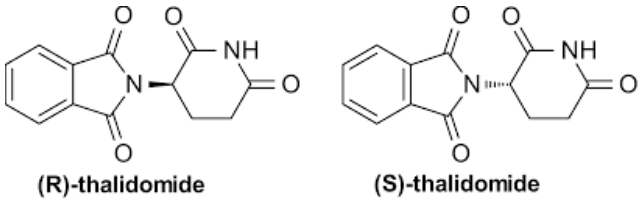

Figure 4*. The enantiomers of thalidomide. The R enantiomer is a sedative and the S enantiomer is a teratogen. Early production methods produced a racemic mixture. However, once inside the human body, the enantiomers readily interconvert.*

Thalidomide, sold from 1957 to 1961, was initially prescribed as a tranquilizer and painkiller. It was later found to be an effective antiemetic (anti-nausea) drug and subsequently prescribed to pregnant women for morning sickness. In 1957 it was sold over the counter in Germany, and by 1960, it was sold throughout Europe and in many other countries. The developer (West German pharmaceutical company, Chemie Grunenethal) claimed it was non-addictive, caused no hangover and was safe for pregnant women (38).

European physicians soon began reporting a disturbing phenomenon. A large number of women were giving birth to babies with severe birth defects. Some had abnormally short limbs and others had malformed internal organs or eye and ear defects. A German pediatrician, Widukind Lenz, began questioning his patients and found the 50 percent of the mothers who had given birth to children with birth defects had taken thalidomide in the first trimester of their pregnancy. In November of 1961, Lenz warned the manufacturer about his discovery of the dangers of thalidomide. Ten days later, German health authorities pulled the drug from the market in Germany (40).

More than 10,000 children in 46 countries were born with severe limb and other deformities as a consequence of their mother taking thalidomide, particularly during the first trimester of pregnancy. The number of children affected in the US was smaller than in Europe. However, the manufacturer had legally distributed thalidomide tablets to over a thousand doctors throughout the US on what was called an *investigational basis*. This was completely legal under the 1938 law. These doctors gave samples of thalidomide to nearly 20,000 patients, some of whom were pregnant (38).

Public awareness of the thalidomide disaster in Europe swiftly moved previously stalled legislation through Congress. In 1962, the Kefauver-Harris Amendments to the FD&C Act required each new NDA contain evidence from "adequate and well-controlled studies" demonstrating that a new drug was effective for its intended use and that the established benefits of the drug outweighed its known risks. Companies were required to present animal studies to the FDA *before* obtaining approval to test on humans. Clinical studies on humans would require informed consent from participants. The amendments further formalized manufacturing practices, required that adverse effects be reported and transferred regulation of advertising from the FTC to the FDA (41).

The 1962 Kefauver-Harris Amendments and the 1963 investigation drug regulations that followed marked a shift in investigation of new drugs in the US. One of the most dramatic changes was the pre-clinical trial process, in which drug developers were required to present evidence that a drug was safe enough to begin clinical trials. The Investigational New Drug (IND) submission and approval currently allows researchers to begin new drug trials on humans for a drug *under development*. In the IND application, companies submit preliminary animal toxicity data, manufacturing process, chemistry background and describe the initial clinical study protocol to be used. The data collected under an IND may later become part of the NDA for formal FDA approval (30).

Off-Label Use and the Comeback of Thalidomide

As thalidomide was being withdrawn from the markets in Europe in the 1960s, doctors at Hebrew University were prescribing it as a sedative for patients with leprosy. They noticed that the drug also alleviated erythema nodosum leprosum (ENL), a type of lesion and nerve deterioration common in leprosy patients.

Later at Rockefeller University in New York, researchers discovered that the drug inhibited a protein called tumor necrosis factor alpha (42), a common cause of inflammation in rheumatoid arthritis, tuberculosis, and Crohn's disease.

In another area of biochemistry, researchers were searching for molecules that would prevent angiogenesis (new blood vessel formation) as a possible treatment for cancer. It was well known that tumors will recruit a new blood supply to feed their rapid growth. Surgeons have long observed that upon removing a tumor, the tumor itself is replete with blood vessels. The idea behind this project was to prevent angiogenesis and thereby starve a tumor. While not an absolute cure, it was a treatment. Thalidomide inhibited angiogenesis for tumor cells in rodents (43). Today there are numerous papers on thalidomide's anti-inflammatory and anti-myeloma activity in adults (44). This discovery explained how thalidomide caused birth defects by targeting blood vessels formation in an embryo.

In 1996, 34 years after the passage of the Kefauver-Harris Amendments, the Celgene Corporation applied for an NDA for thalidomide. In spite of promising results in the area of HIV and cancer, the application was filed for the ENL condition in leprosy (pretty rare in the US), but this is where the company had its strongest data. An advisory committee that included a thalidomide victim, voted to approve thalidomide and a year later the FDA made it official, with the condition of a strict regimen for controlling access to the drug and preventing birth defects (45, 46). The FDA would be more directly involved in selecting and warning patients, an approach used with the drug Accutane that can also cause severe birth defects (47). By 2004, nearly 92 percent of the thalidomide prescriptions were for a type of cancer called multiple myeloma, an unofficial or off-label use. Thalidomide was officially approved for cancer treatment in 2006 (48).

In 1997, Congress passed the Food and Drug Administration Modernization Act to further clarify the role of the FDA with the development of new biotechnologies and treatments from these emerging areas (49). It also formally addressed criticism from activists representing patients with terminal illnesses and the lag time for drug approval. The new law accelerates the review of devices, provides guidelines to regulate advertising of unapproved uses of previously approved drugs and regulates health claims for foods.

The FD&C Act of 1938 and the Kefauver-Harris amendments in 1962 advanced the powers of the FDA and prompted the evolution of the modern pharmaceutical industry in the US. The FD&C act of 1938 opened the door for effective federal food and drug regulation and marked the ending of the quack medicine industry. The Kefauver-Harris amendments in 1962 further strengthened the FD&C Act and clarified regulations for drug testing and clinical trials. Both pieces of legislation were the product of mounting consumer activism, political pressure and were ultimately pushed to passage by high profile tragedies.

Table 1. Some of the landmark Congressional FDA legislation.

•The Biologics Control Act (1902): Ensured purity and safety of serums, vaccines and similar products used to prevent or treat diseases in humans.

•The Pure Food and Drugs Act (1906): Provided for federal inspection of meat and forbade the manufacture, sale or transportation of adulterated food products and poisonous patent medicines.

•The Federal Food, Drug, and Cosmetic Act (1938): Following the elixir sulfanilamide tragedy, the FD&C Act completely overhauled the public health system. Among other provisions, the law authorized the FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections.

•The Kefauver-Harris Amendments (1962): Following the disfiguring birth defects linked to the drug thalidomide, this amendment strengthened the rules for drug safety, required informed consent during clinical studies and required manufacturers to prove their drugs' effectiveness.

•The Medical Device Amendments (1976): Followed a US Senate finding that faulty medical devices had caused 10,000 injuries, including 731 deaths. The law applied safety and effectiveness safeguards to new devices.

•Food and Drug Administration Modernization Act (1997): This law accelerated the review of devices, provided guidelines to regulate advertising of unapproved uses of previously approved drugs and regulated health claims for foods.

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Centennial of IUPAC

The International Union of Pure and Applied Chemistry (IUPAC) will celebrate its 100th anniversary in 2019. It will hold its 50th General Assembly and 47th World Chemistry Congress in Paris, July 5-12, 2019 (iupac.org/100/).

MELVILLE SAHYUN: A LIFE IN BIOCHEMISTRY

M. R. V. Sahyun, Santa Barbara, California; sahyun@infionline.net

Stoutness of heart, humility of soul and open-mindedness are the
Keys to human understanding and happiness;
No one endowed with these virtues can be but honest,
Just and tolerant to his neighbor and himself.
—Melville Sahyun

Abstract

The career of Melville Sahyun comprised three major parts. In the first part he was engaged in diabetes research. In this period his most important contribution was the development of an industrial-scale process for the preparation of a purified insulin solution of standardized potency for clinical application that was based on his studies of insulin crystallization. He then turned to the biochemistry of amino acids and proteins. His major technical contribution in this area was the development of an amino acid supplement solution for intravenous or parenteral administration. In this period he also edited two important monographs on proteins and amino acids. The final phase of his career was devoted to drug discovery. The most noteworthy accomplishment in this period was the invention of the anti-inflammatory molecule tetrahydrozoline, which was formulated for ophthalmic use as Visine™ eye drops.

Introduction

Melville Sahyun (Figure 1) was born in 1895 in Kfarshima, Lebanon, the son of a prominent Beirut physician, Dr. Fares Sahyoun. He graduated (B.A., biology) from the American University of Beirut (AUB), planning to follow in his father's footsteps into a career as a practicing physician. However, he abandoned these career plans in favor of a career in biochemical research. The mantle of medical practice was taken up by his younger brother, Philippe Sahyoun, who ultimately became a distinguished Professor of Pathology at AUB (1). (Note that Melville preferred the Anglophone spelling of his originally Arabic surname, while Philippe opted for the Francophone spelling).

After having served, by his own account (in his personal diary), with British Intelligence in Cairo during World War I, Melville Sahyun emigrated to the United States in 1923. He then began his scientific career, which can be divided into three parts or phases:

1) Diabetes research. This subject had great personal significance for Sahyun, as *diabetes mellitus* (Type 2) was endemic in his family.

2) Proteins and amino acids in nutrition. He was drawn into this area of research by the exigencies of World War II, and became a world recognized expert.

3) Drug discovery. He directed the final phase of his career as the head of his own private research organization, Sahyun Laboratories, in Santa Barbara, California.

This purpose of this article is to review his accomplishments in each of these phases of his career, in turn, and place them in the context of the science of the day.

Figure 1. *Melville Sahyun in the 1930s, at the time he was particularly active in diabetes research. (Author's collection)*

Diabetes Research

Diabetes research in the 1920s and 1930s focused primarily on the chemistry of insulin, following its isolation and the discovery of its therapeutic value by Frederick Banting and Charles Best in the laboratory of Prof. J. J. R. Macleod in Toronto (2). Sahyun's first position in which he could carry out diabetes research was at the Potter Metabolic Clinic of Santa Barbara Cottage Hospital, then headed by Dr. William D. Sansum. This institution subsequently evolved into the Sansum Diabetes Research Institute, as has been documented by Tompkins (3). There Sahyun had the good fortune to collaborate with Dr. Norman R. Blatherwick, Sansum's chief chemist (3).

At the time, insulin was obtained by laborious extraction from the pancreases of slaughtered mammals, usually cattle or hogs, without controls on potency. The response of the blood glucose level in rabbits to a given preparation was used as a method to standardize the dosage of insulin. The problem with this method was that different rabbits responded differently. Sahyun and Blatherwick (4) proposed a method of "calibrating" rabbits used for this standardization by measuring the individual rabbit's response to a reference insulin preparation. In the course of this work they observed that rabbits repeatedly dosed with insulin developed insulin resistance. Their data showed, though the significance of the correlation was not noted at the time, that development of insulin resistance was also associated with weight gain. In this experiment the same rabbits were repeatedly dosed with insulin over a nine-month period, each time with a dose of insulin, *I* (arb. units), just insufficient to produce convulsions. Insulin resistance was demonstrated by the monotonically progressive increase in the required dose; the increase in dosage was reflected in the concomitant weight gain of the rabbits up to a maximum. Their data for two representative rabbits are shown as a semi-logarithmic plot in Figure 2. This observation seems to have anticipated the contemporary understanding of the relationship between weight gain and insulin resistance in humans (5).

A subsequent series of papers (6) continued characterization of the physiological response of rabbits to insulin and established the rabbit as the animal model of choice for pre-clinical evaluation of diabetes therapies. In this work they showed that intraperitoneal, subcutaneous and intravenous administration of insulin were all effective in producing hypoglycemia. Insulin, being a protein. is degraded in the alimentary canal prior to absorption and therefore could not be administered orally, according to the thinking of the day. Although there was the suggestion of an orally active "insulin" even in Dr. Sansum's day (7), an "oral insulin" still remains an elusive target for the pharmaceutical industry.

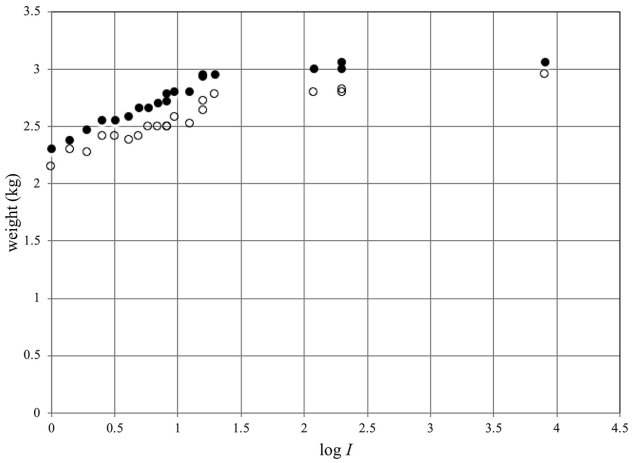
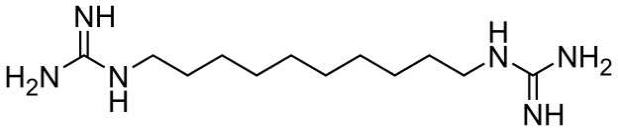


Figure 2. *Weight gain of two rabbits (kg) with increasing insulin resistance, as log I (4).*

Blatherwick and co-workers (8) proposed a standard method for the preparation, isolation and purification of insulin. The potency of their preparation was over twice that reported by Best in Toronto (9). The comparison of methods is offered by H. F. Jensen in his monograph from 1938 (10). By studying the response of their usual preparation to various reagents, Blatherwick et al. concluded that the hormone insulin comprised only a fraction of the material despite its high potency, i.e., despite rigorous purification the best insulin of the day was grossly impure.

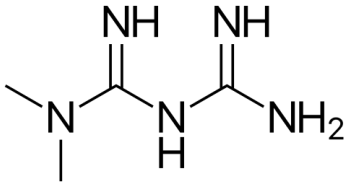
This, of course, is no longer the case, as high potency, high purity insulin (human insulin analog) is now prepared biosynthetically. This biosynthetic insulin, available since 1982, is manufactured using a microbial process based on recombinant DNA technology, in which *E. coli* bacteria have been modified to synthesize insulin identical to the human hormone. As of 2013 this process accounts for the entire US production (11). Some insulin continues to be manufactured abroad by the Sahyun process (see below) or a variant thereof.

Blatherwick, Bischoff, Sahyun, and Hill compared the action of "synthalin" (I) to that of insulin (12, 13). Synthalin was one of the first oral anti-diabetic drugs to be commercialized.



I

Discovered in 1926 synthalin was marketed in Europe by Schering AG of Berlin as "… a synthetic drug with insulin-like properties that could be taken orally" [Author's translation] (14). It was based on the discovery that a guanidine derivative was responsible for the hypoglycemic activity of extracts of French lilac, used since medieval times to treat *diabetes mellitus* (15). Synthalin was never clinically successful owing to its extreme side effects, reviewed by Bischoff, Sahyun and Long (16). The now commonly used drug for treatment of Type 2 diabetes, Metformin (II), is the lineal descendant of this this line of investigation, as described below (17).



II

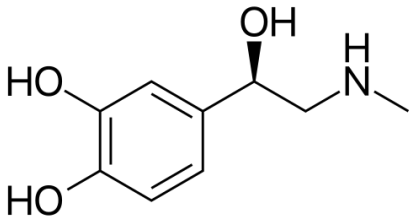
Blatherwick et al. (12, 13) concluded that, in part, the activity of synthalin involved interference with gluconeogenesis (also termed "glycogenolysis," i.e., hydrolysis of glycogen) in the liver. That hydrolysis of glycogen in the liver is a principal source of blood sugar, and thus intimately connected to the etiology of diabetes, had been known since 1857 (18, 19). This understanding laid the basis for the subsequent use of biguanides (now known as AMPK activators (20)), e.g., Metformin, in the treatment of Type 2 diabetes, characterized by excess production of glucose by the liver. Recent research has provided data to support investigation of biguanides for antineoplastic activity (cancer therapy) (21).

The understanding of the mechanism of action of biguanides likewise implied the ineffectiveness of AMPK activators for treatment of Type 1 diabetes, characterized by insufficient insulin production in the pancreas. The distinction between Type 1 and Type 2 was, of course, unrecognized in the 1920s, not being established until 1959 (22). As early as the 1920s, h owever, two separate theories had been advanced to explain the symptoms of *diabetes mellitus*: (1) loss of the capacity of peripheral tissue to metabolize glucose; and (2) overproduction of glucose by glycogenolysis (10). These theories, of course, correspond more-or-less to Type 1 and Type 2 diabetes. Glycogenolysis was later to become the focus for Sahyun's Ph.D. work.

Bischoff, Sahyun and Long (16) further compared the hypoglycemic activity of a variety of guanidine derivatives. These authors concluded that guanylpiperidine, though not clinically useful itself, provided a promising direction for future drug development. The focus on correlating chemical structure with physiological activity in this work presaged Sahyun's future interest in drug discovery and development. More recently, derivatives of guanylpiperidine have shown promise as peptidomimetics for the prevention and treatment of thrombosis (23).

In 1928 Prof. John Macleod, in whose laboratory Banting and Best had first prepared insulin, visited the Potter Clinic and encouraged Sahyun to pursue a Ph.D. in biochemistry rather than the M.D., which had been his

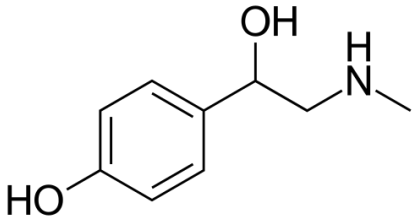
original career goal, and which, according to Tompkins he was still considering (3). Sahyun accordingly applied to and enrolled at Stanford University. In his M.A. thesis work under the direction of Prof. Luck in the Department of Food Science, Sahyun studied the effect of epinephrine (adrenalin, III) on the biochemistry of glycogen in rabbits (24).



III

This work was actually begun at the Potter Metabolic Clinic in Santa Barbara (25). From these studies the authors inferred that epinephrine promotes hepatic glycogenolysis, leading to elevated blood glucose levels. Insulin, on the contrary, was seen as an inhibitor of hepatic glycogenolysis, as well as a promoter of the utilization of glucose by muscle cells.

In one publication on epinephrine from this period, work that was a continuation of his M.A. thesis work, Sahyun and Webster (26) cited the vasodilator properties of epinephrine and related it to other catechol derivatives, e.g., synephrine (IV), studied concurrently by Tainter (27).



IV

In another paper in this series (28) Sahyun noted the effect of epinephrine-like substances on amino acid metabolism, the work of one of his fellow Stanford graduate students, S. W. Morse (29). Morse and Luck, in turn, acknowledged Sahyun's collaboration in their work. This interest appears to have presaged Sahyun's future interest in amino acid metabolism and set the stage for Sahyun's Ph.D. thesis work, under supervision of Prof. Carl Alsberg, on hydrolysis of glycogen, in which he showed *inter alia* that the acid catalyzed hydrolysis is kinetically a first-order reaction (30).

Before leaving Stanford University, Sahyun applied for a patent on a dental preparation which anticipated most modern toothpastes by incorporating a buffer along with the usual surfactants, abrasives, etc. (31). This interesting example of his problem solving creativity had nothing to do with the diabetes research. The patent was cited as prior art in numerous later patent applications on various dental preparations by companies such as Lever Bros. (32) and Colgate Palmolive (33). It has continued to be cited as recently as 2007 (34). Products incorporating Sahyun's technology were not commercialized, however, until after expiration of the original patent, so he derived no financial benefit from the invention.

Sahyun continued his work on insulin when he moved to the laboratories of the pharmaceutical company, Frederick Stearns and Company, in Detroit, Michigan. The company was interested in becoming a supplier of clinically useful insulin, Eli Lilly and Co. being their principal competitor in this market. For their commercialization, Stearns required an insulin that was stable, pure and of reproducible potency. Sahyun focused on exploiting crystalline insulin. (He is sometimes credited with "inventing" crystalline insulin, but this, of course, is not the case). Insulin was first obtained in crystalline form by Abel, reported in 1926 (35).

Sahyun (36) chose to exploit the observations of Scott (37) that crystalline insulin contains zinc, and that if the concentration of zinc is less than "0.04%" (ca. 40 ppm by wt.), the insulin cannot be crystallized. To this end Sahyun and Feldkamp first worked out a method for determining zinc in biological materials (36). Using this method, Sahyun and co-workers were able to show that zinc (ca. 0.02 wt. %) is essential to the stability of insulin preparations (38). This result led to the commercialization by Stearns of crystalline insulin as the zinc derivative in 1938 (39). The actual role of zinc in enabling crystallization was not understood until much later when it was shown that zinc ions assist the assembly of insulin monomers into hexamers (Figure 3) which subsequently crystallize (40).[40] The hexamer is also the form in which insulin is produced and stored in the body; it is converted *in vivo* to the active monomeric form (41).

Sahyun's contribution to the introduction of crystalline insulin to the marketplace may be summarized as developing the findings of Abel, Scott and others into

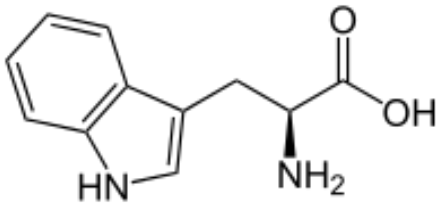
Figure 3*. Insulin hexamer (41b).*

a commercially feasible process. His process patent was issued in 1939 (42). The clinical superiority of this insulin, with respect to both rate of absorption and duration of effect, had already been demonstrated (43). The crystallization, albeit under conditions slightly different to the industrial process, of zinc-insulin by Sahyun's method led to beautiful rhombohedral crystals suitable for crystallographic characterization, which Sahyun provided to the US Food and Drug Administration (44). The actual x-ray structure was not determined until the 1960s by Nobel Laureate Dorothy Crowfoot Hodgkin and co-workers, when techniques for solving such complex structures had finally been developed (45). The structure determination was carried out on rhombohedral crystals, apparently similar to those provided to the FDA by Sahyun, but grown in Hodgkin's own laboratory. According to Vijayan (46) she credited the growth procedure to Scott (37) insofar as she used the citrate buffer preferred by that group rather than the phosphate buffer preferred by Sahyun (42).

Proteins and Amino Acids

With the advent of World War II, research at Frederick Stearns and Company turned to supplements which could facilitate rebuilding tissues of patients with severe wounds and burns, i.e., war injuries, as well as facilitating the recovery of victims of malnutrition due to inhumane imprisonment, e.g., prisoners of war and Holocaust survivors. In the latter case the patients had subsisted on a diet deficient in protein. Such a formulation would also supplement the loss of physiological nitrogen accompanying trauma (47). It would have to be formulated in such a way as to be suitable for use in military field hospitals. It was envisioned that the product in solution form would be administered parenterally or intravenously. In the course of his background research for this ambitious project, Sahyun published a comprehensive review article with over 500 references on the nature of protein deficiency in humans (48).

The scientific context for this work was two-fold. First of all, prior to the 1930s there had been a debate as to whether or not a mixture of pure amino acids could replace dietary proteins in meeting the nitrogen requirements of a growing animal. Willock and Hopkins (49) had identified tryptophan (V) as an essential amino acid, which however tended to be destroyed during acidic hydrolysis of proteins.



V

This specific hydrolysis method had been used to produce amino acid mixtures that failed to provide a dietary replacement for protein, leading to the controversy. It was understood then as now that all ingested protein is hydrolyzed to its constituent amino acids in the alimentary tract, and that it is the component amino acids themselves which are absorbed via the small intestine, i.e., there is no absorption of undigested protein. As noted above, this is the principal problem confronting development of an orally administrable form of the protein insulin.

Secondly, in parallel with this work, was the evolution of the concept of essential amino acids. Essential amino acids are defined as those amino acids that cannot be synthesized by the organism and thus must be supplied from the diet, generally in the form of animal protein. For humans these are now known to be histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine (50). Arginine may be essential in other species, e.g., rats (50).

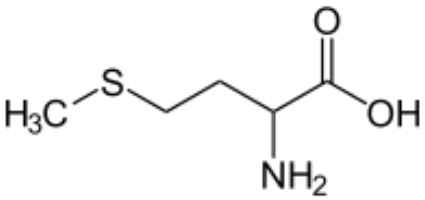
The product developed by Sahyun and his coworkers comprised a solution of amino acids obtained by a combination of acidic and alkaline hydrolysis of a source protein, e.g., casein. Three objectives had to be

met to achieve the goal of a nutritional supplement that could be administered parenterally. First was the need to provide a solution of the amino acids at neutral pH, free from ionic impurities (51). The ultimate process of preparing such a solution involved dividing the protein raw material into two portions, one subjected to acid hydrolysis with H_2SO_4, the other portion subjected to alkaline hydrolysis with $Ba(OH)_2$. These two portions were then combined and purified to yield the neutral solution. The ionic byproduct, insoluble $BaSO_4$, was removed by filtration (52).

Preliminary work, which was not, however, published until 1947, had to address three questions (53):

> (1) Does racemization of amino acids by hydrolysis of a protein occur in such amounts as to reduce the biological utilization of the resulting mixture?
>
> (2) Does the catalytic action of acids on proteins at boiling or at elevated temperature destroy partially or *in toto* any indispensable amino acid or unknown factor other than tryptophane [*sic*]?
>
> (3) Do any appreciable losses of essential amino acids occur during the removal of insoluble inorganic salts and subsequent purification of the hydrolysate?

Secondly, the final solution was likely to be deficient in tryptophan; Sahyun had already published results which showed improved utilization of the amino acids in animal models if the protein hydrolysate was supplemented with tryptophan (54). Tryptophan had to be replaced in an amount sufficient to enable establishment of nitrogen balance (51). A process therefore had to be developed for the isolation and concentration of this amino acid, in this case by adsorption onto activated charcoal from a protein hydrolysate solution (55). Tryptophan could then be added to the protein hydrolysate mixture to fortify the solution in this essential amino acid. The preliminary work (53) had also shown the desirability of supplementing the mixture with methionine (VI) and glycine; casein is deficient in the sulfur-containing amino acids and methionine supplementation is needed to meet nutritional requirements (56). This additional fortification was not, however, disclosed in the final patents (57).



VI

Thirdly, the extreme conditions under which the product might be used in a military theatre of operations and the extended shelf life required for overseas shipment required that the amino acid solution be stabilized against crystallization. To this end Sahyun added a "protective colloid," e.g., pectin (57). The final product was sold under the trade name Parenamine™, and was described in a *Journal of the American Medical Association* editorial as a "…physiologic short cut sparing the need for digestion and absorption in the gastrointestinal tract" (58). The date of this editorial, which accompanied an article disclosing the use of Parenamine in clinical practice (59), indicates that the product, development of which had started as early as 1939, had been made available to the military medical community by 1943.

In the post-War era, Parenamine continued to be marketed. Parenteral amino acids were recommended preoperatively and postoperatively for patients with gastrointestinal disease and/or obstruction (54), and were described as having "…the advantage of producing complete gastrointestinal rest, equal if not superior to that induced by morphine" (47). Much of the above material was used by the Stearns Company to promote the product (60). To the present author's knowledge, Parenamine or its equivalent is still available in the marketplace.

In the course of this work Sahyun became well connected in the community of protein and amino acid researchers and established a strong network among the technical staffs of the suppliers of raw material (e.g., casein, pectin, etc.) as well as in the military medical community, initially US Army Drs. Samuel Altschuler and Helene Schneider. Altshuler had previously been involved in the clinical evaluation of crystalline insulin and was one of the founding officers of the American Diabetes Association (61). This network would prove useful to him in the next phase of his career. Among these colleagues were also Drs. J. D. Fagin and Elaine Pagel at the US Marine Hospital in Detroit. They collaborated on a study that showed that Parenamine therapy in patients with cirrhosis of the liver and chronic alcoholism increased the protein content of their livers, and suggested protective action of protein stores against hepatotoxic agents (62, 63). Branched-chain amino acid supplementation has now specifically been proposed for cirrhosis patients (64).

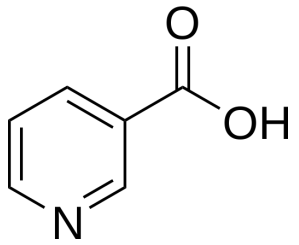
Sahyun was sufficiently highly regarded by his colleagues to be invited to edit a monograph titled *Outline of the Amino Acids and Proteins* (49), which was published in 1944. This book incorporated chapters by academic, industrial and government scientists who

were established authorities in their areas of expertise. In this effort he was strongly encouraged by Prof. Carl Schmidt of the University of California, Berkeley and San Francisco campuses, who wrote the Foreword to the volume. Schmidt had already edited a monograph on this topic (65).

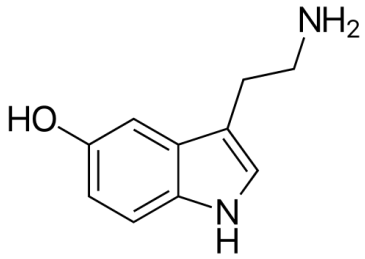
After three generations of family management at Frederick Stearns and Company, in 1946 the Stearns family relinquished management of the firm and sold its businesses to the Sterling Drug Company. Sahyun declined a management position with Sterling, for which he seemed eminently qualified on the basis of his leadership of the Parenamine program, and he chose to re-invent himself as a "Chemist Consultant." He remained in this status for three years, 1946-1949. During this time he maintained an affiliation with the University of Texas Medical Branch in Galveston, Texas.

Sahyun had already arranged in 1945 with his friend and colleague Carl Schmidt to co-edit a more extensive monograph on proteins and amino acids with an emphasis on nutrition. Schmidt, however, passed away in 1946, and Sahyun undertook the editorship of the new volume on his own, he and Schmidt having already agreed on the topics and contributors to be invited. The new book was titled *Proteins and Amino Acids in Nutrition* (66) and comprised 15 chapters. Sahyun's own chapter was entitled "Plasma Proteins and their Relation to Nutrition." The book remains available in facsimile or replica editions (67).

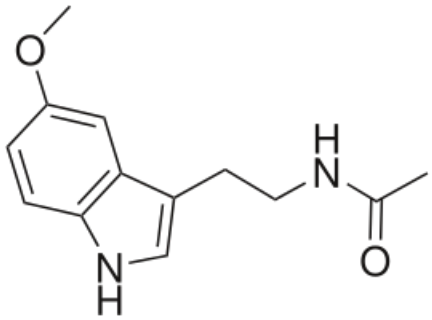
During this time Sahyun chose to enhance his scientific reputation and promote his expertise as a consultant in the field of amino acid and protein chemistry by publishing three definitive review articles. The first (68) dealt with the metabolism and nutritive importance of tryptophan (V). In this paper he summarized the evidence supporting the concept that tryptophan is the precursor of niacin (VII) in *in vivo* biosynthesis and endorsed this theory, even though the biochemistry had not yet been elucidated. This concept is, of course, now well established in the biochemical and popular literature (69). It was not understood at the time, however, that tryptophan is also the precursor of serotonin (VIII) and melatonin (IX). The relationship between tryptophan and serotonin might have been obvious to biochemists from inspection of their chemical structural formulae; serotonin was not isolated and structurally characterized until after 1948, however (70). It was thought at the time that epinephrine (III) was derived in vivo from tryptophan (71).



VII



VIII



IX

Sahyun went on to write a comprehensive review article on the biochemistry of methionine, another of the essential amino acids (72). In this review Sahyun observes that in the course of the work on amino acid supplementation of cirrhosis patients (above) it had been proposed that methionine metabolism might play a role. Subsequently the role of methionine in cirrhosis was confirmed; impaired methionine metabolism is characteristic of the disease (73). More recent research has shown that methionine may have clinically relevant toxicity, depending on the level provided by the supplement (74).

The final review dealt with the relationship of amino acids to the nutritive value of proteins (75). The main point he emphasized in this article was the importance of the simultaneous availability of all the amino acids for protein biosynthesis, an "all-or-none" situation as he termed it. This point had already been made strongly by Sahyun's colleagues, Madelyn Womack and Charles

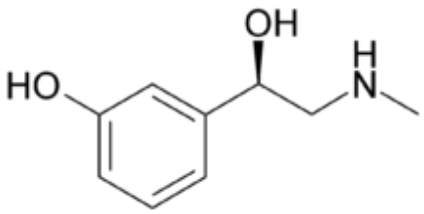
Kade in the earlier monograph he had edited (76). It is now understood that the essential amino acids need to be available not only simultaneously, but in ratios corresponding to the body's requirements (50, 74).

Drug Discovery

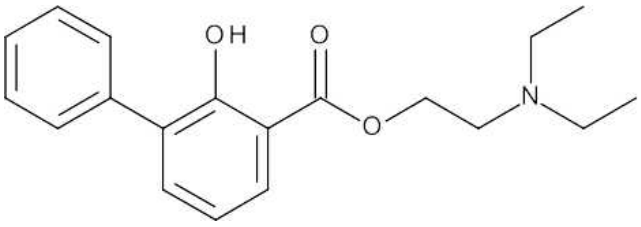
In 1949 Melville Sahyun's career took a new direction. He established an independent research organization, Sahyun Laboratories, back in Santa Barbara, California. He was motivated both by his expressed frustration with the bureaucracy of large industrial organizations, and also by the strong desire on the part of his wife, Geraldine, to live in her home state of California. The focus of his new laboratory was to be drug discovery. To this end he put together a team of synthetic organic chemists, including John Faust, Martin Synerholm, and Leonard Jules, to turn his biochemical intuitions into molecular reality. The facility had the shortcomings of not having any capability for animal research, as well as no ongoing collaboration for clinical testing.

Drug discovery at that time was a much more intuitive, hit-or-miss process than now. The arsenal of current drug discovery techniques, including computational modeling, bioinformatics, "brute force" high-throughput screening, and now artificial intelligence (neural network) methods (77) were, of course, not available 65 years ago, nor would a small independent laboratory have had the resources to implement these capital intensive research strategies had they been available. Although there is no documentation of Sahyun having been involved directly in drug discovery prior to the establishment of Sahyun Laboratories, by his own account (personal communictaion) he had been involved in development work on neosynephrine (phenylephrine, X) marketed as a nasal decongestant by Frederick Stearns and Co. This claim on his part appears to be undocumented; in fact the literature indicates that much of that development work had been carried out prior to Sahyun's arrival at Stearns (78).

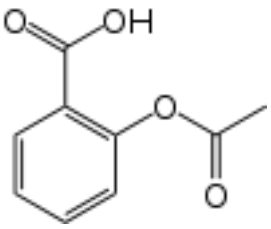
The laboratory's first successful molecule was biphenamine (2-diethylaminoethyl-3-phenylsalicylate mandelate, XI), for which mild antihistaminic, fungicidal, antibacterial, and anesthetic properties were claimed (79). Structurally it may be viewed as a rather elaborate aspirin (XII) analog.



X



XI



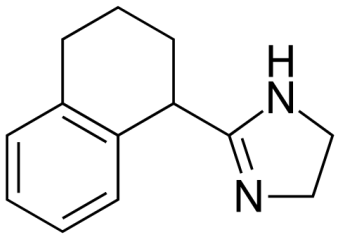
XII

Application of the compound in solution as a urinary bactericidal agent was also proposed. Sahyun went on to formulate it as a topical analgesic-antibacterial preparation for "first aid" application, much as Neosporin™ is used today. Without the backing of a large pharmaceutical manufacturer, the clinical trial data to obtain FDA approval for over-the-counter marketing were not accessible, and Sahyun could only obtain approval for marketing the formulation as an "experimental," prescription-only medication. He tried marketing the product himself under the trade name Melsaphine™ for a short period of time without significant market penetration (79). It turned out to be popular for veterinary applications, however.

One of Sahyun's former Stanford colleagues, Thomas Schulte, MD, who was an equestrian along with being a practicing physician, had noticed in using the product on horses, that biphenamine facilitated debriding of wounds, i.e., cleansing of the wound by removing foreign material and dead tissue, so that the wound would heal without increased risk of infection. After the original patent expired Schulte patented a formulation of biphenamine with aloe vera for this specific application in veterinary medicine (80). Schulte also patented biphenamine, in admixture with dimethyl sulfoxide, as a topical analgesic (81), and as an opthalmological

anti-inflammatory (82). Biphenamine is reportedly the active ingredient in the Sebaclen™ antibacterial shampoo marketed by Carter-Wallace Inc. (83), and is currently manufactured in Germany as a raw material for the pharmaceutical industry (84).

The second important molecule to come out of Sahyun Laboratories was tetrahydrozoline, also known as tetryzoline [2-(1,2,3,4-tetrahydronaphthalen-1-yl)-4,5-dihydro-1H-imidazole, XIII], synthesized by Synerholm and Jules (85).



XIII

While the basis for Sahyun's conception of biphenamine is not at all transparent, the intellectual process leading to the design of tetrahydrozoline is much more apparent and illustrative of the process of drug discovery in those days. It is obvious that the chemical structure of tetrahydrozoline incorporates the β-phenylethylamine framework, common to vasopressors such as epinephrine (III) and neosynephrine (X), with which Sahyun had previously worked. It had already been established by Barger and Dale that the "…optimum carbon skeleton for sympathomimetic activity consists of a benzene ring with a side-chain of two carbon atoms, the terminal one bearing the amino-group" (86). These authors had also observed enhanced pressor (blood pressure enhancement) activity when this optimum structure was rigidized in the form of β-tetrahydronaphthylamine. Development of tetrahydrozoline was thus a matter of optimization of the pressor response by various molecular modifications of the known, active compounds. Since the structure-activity inferences of Barger and Dale had been based in large part on naturally occurring compounds, this strategy exemplifies the confidence of synthetic organic chemists of the day in their ability to improve upon nature. Surprisingly tetrahydrozoline lacks the aromatic hydroxyl groups, which conventional wisdom held to be essential to sympathomimetic action (87). Hydroxylated analogs of tetrahydrozoline showing strong adrenergic activity were subsequently reported by DeBernardis and co-workers at Abbott Laboratories (88).

Like neosynephrine, the pressor activity of tetrahydrozoline results from a vasoconstrictor (blood vessel contracting) action (89). This suggested to Sahyun its application as a decongestant, like neosynephrine, and as an anti-inflammatory agent. He also patented it as a sedative (90), a usually undesirable side-effect for a decongestant. The decongestant application was developed in collaboration with Chas. Pfizer and Co., and marketed as a nose drop preparation under the trade name Tyzine™. The product is currently manufactured for Kenwood Therapeutics by Denison Pharmaceuticals (91), and available by prescription.

About 1952 it occurred to Sahyun that tetrahydrozoline might have ophthalmic application. This was largely because the present writer, then twelve years old, was experiencing serious eyelid irritation from swimming pool chemicals. With myself as principal clinical test subject, he formulated tetrahydrozoline into a standard lubricant eye drop formulation. He (and my mother) thought the product might be successful in the marketplace because of the high level of eye irritation being experienced by Southern California residents at the time, owing to photochemical smog (92). The concept interested drug manufacturer Chas. Pfizer and Co. with whom he was already working on the Tyzine product, and Pfizer brought the eye drops to market as Visine™, but apparently not before 1954 when the Synerholm patent was applied for. Pfizer continued to market the product until 2009 when its consumer product line (and accompanying trademark portfolio) was sold to Johnson and Johnson Inc. At least three other manufacturers now make an ophthalmic product essentially identical to the original Visine, but not sold under that name, according to the Health Canada database for products approved for over-the-counter sale (93).

Interest in tetrahydrozoline continued. Pfizer scientists also patented it as a central nervous system depressant for veterinary application (94). In this patent tetrahydrozoline is described as adrenolytic (sympathomimetic inhibiting), whereas Sahyun had understood that it was adrenergic, as disclosed in the original patent application (85). The preponderance of evidence on human health effects of tetrahydrozoline collected by the National Library of Medicine (95) supports Sahyun's understanding, contrary to the claim in the Gardocki et al. patent. Scientists at Bayer Cropscience AG later also claimed insecticidal activity for compounds of a general class which included tetrahydrozoline, though based on their patent claims it was not their preferred embodiment (96). Human toxicity of tetrahydrozoline, if ingested, is

now well-documented; it is especially severe in children (95). Tetrahydrozoline has allegedly even been used as a murder weapon (97).

The dihydroimidazoline ring in tetrahydrozoline is, of course, an amidine functionality. It was therefore not surprising that the Sahyun Laboratories group addressed amidine chemistry as a route to other pharmacologically active molecules (98), namely compounds that exhibited sedative and adrenolytic properties, similar to the action claimed surprisingly by Gardocki et al. (94) for tetrahydrozoline itself. Another patent described an antifungal salicylamide compound (99). None of the compounds covered by these later patents appear to have been commercialized.

Although Sahyun had published prolifically during the first twenty-five years of his career, he virtually stopped publishing when he redirected his interests to drug discovery. His career in this later phase can only be traced through the patent literature. In summary it appears that though the idea of an independent research organization may have been a dream-come-true for him, his limited scientific contributions during this time, up until his retirement in 1973, made it the least productive period, in terms of publication and significant scientific accomplishment, in his career.

One exception to Sahyun's lack of publication during this period was a tutorial article on "The Discovery of Insulin," which provided a capsule history of diabetes research up to the work of Banting and Best (18). In this paper he emphasizes the role of liver glycogenolysis in the etiology of diabetes. This appears to have been his last published paper. Since Sahyun's mind was still on diabetes, one of the mysteries of this period is that he did not choose to follow up on the lead of guanylpiperidine as an inhibitor of liver glycogenolysis, which he had reported in 1929 (16), and address this target as a route to a diabetes medication. This would have been a high-priority endeavor once the distinction between Type 1 and Type 2 diabetes had been elucidated (21). It is possible, as suggested by one of the reviewers of this paper, that the companies he worked with did not have an interest in entering this market, so were not prepared to support research in this area.

Conclusions

The career of Melville Sahyun comprised three major parts. In the first part he was engaged in diabetes research. In this period his most important contribution was the development of an industrial-scale process for the preparation of a purified insulin solution of standardized potency for clinical application, based on his studies of insulin crystallization. He then turned to the biochemistry of amino acids and proteins. His major technical contribution in this area was the development of an amino acid supplement solution for intravenous or parenteral administration. In this period he also edited two important monographs on proteins and amino acids. The final phase of his career was devoted to drug discovery. The most noteworthy accomplishment in this period was the invention of the anti-inflammatory molecule tetrahydrozoline, which was formulated for ophthalmic use as Visine™ eye drops. Dr. Melville Sahyun died in Santa Barbara, California, in 1977.

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About the Author

M. R. V. (Mel) Sahyun is the son of the subject of this article and figured in at least one of the technological accomplishments described herein. He received his Ph.D. in Chemistry at UCLA under supervision of Nobel Laureate D. J. Cram, and went on to career positions of varying responsibility at the US Public Health Service, 3M Corporate Research, and the University of Wisconsin–Eau Claire. For twelve years he was senior editor of the *Journal of Imaging Science and Technology*, shepherding it from a publication, which emphasized photochemistry, optics and materials science, to one embracing digital technology. Among other awards he is recipient of the Berg Prize of the International Committee for Imaging Science, citing his promotion of international cooperation through science. His most cited paper involves photophysics of TiO_2 analyzed by high-speed laser spectroscopy, work done as a Visiting Scientist at Concordia University, Montréal, in collaboration with Prof. Nick Serpone and his group.

2018 HIST Award to David E. Lewis

The History of Chemistry Division (HIST) of the American Chemical Society (ACS) is pleased to announce that Professor David E. Lewis of the University of Wisconsin-Eau Claire is the winner of the 2018 HIST Award for Outstanding Lifetime Achievement in the History of Chemistry. This international award has been granted since 1956 under sequential sponsorships by the Dexter Chemical Company, the Edelstein Foundation, the Chemical Heritage Foundation, and HIST. A symposium honoring the work of Prof. Lewis, including a lecture by the awardee, was held on August 21, 2018, at the ACS Fall meeting in Boston.

David Lewis was born in the borderline bush area around Adelaide, South Australia. He matriculated from Salisbury High School, and moved on to the University of Adelaide, where he graduated with Honors in Organic Chemistry in 1973. He conducted graduate research in natural products until he was beckoned to the United States and the state of Arkansas in 1977. Professor Lewis earned tenure and the rank of Associate Professor at Baylor University in 1988, then moved to South Dakota State University, where he became a Full Professor in 1993. He was called to The University of Wisconsin- Eau Claire in 1997 as Chair of the Chemistry Department, where he continues a very active program in synthetic organic chemistry. His work was recognized in 2012 with a DSc. Degree from the University of Adelaide, and he was elected a Fellow of the Royal Society of Chemistry in 2015.

Lewis picked up an interest in the history of organic chemistry, joining HIST and starting to publish in its journal (now 15 papers, including two Best Paper Awards in 1997 and 2010). He served as the Chair of the Division from 2003-2005. His focus has been organic chemistry in Russia, especially at Kazan. He is recognized in Russia as the author of "a wonderful series of works devoted to the history of Russian chemistry." His collected works were translated and published in Russian in 2016. His 2012 book, *Early Russian Organic Chemists and their Legacy* has been hailed as the most important contribution to this previously understudied area. More information on Seeman and the award can be found at acshist.scs.illinois.edu/awards/hist_award.php.

RESPONSE TO REVIEW OF *A TALE OF SEVEN SCIENTISTS*

Eric R. Scerri, Department of Chemistry and Biochemistry, UCLA;
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I would like to thank Helge Kragh for taking the trouble to review my recent book (1).

After a few flattering remarks about my previous work in the history and philosophy of chemistry, Kragh immediately goes on the offensive and objects to the fact that my book has two prefaces and a biographical section. Unlike Kragh, I write for a general audience of chemistry educators and the general public, in addition to experts in the history and philosophy of science. I therefore asked a leading chemist, Peter Atkins, to say a few words on behalf of the book. Since Atkins restricted his comments almost entirely to the chemical aspects of the book, I also asked an expert on the philosophy of science to write a few introductory words to address the philosophical issues.

My project of proposing a new philosophy of science is admittedly rather ambitious. Perhaps I could have waited for a further five or so years in order to dot all the i's and cross all the t's, but I chose to go into print and see what others thought about the new direction that I have launched into. Of course, I welcome corrections and suggestions as well as the opportunity to elaborate a little on the ideas that I proposed in the book.

I also chose to include a biographical sketch on my own intellectual journey. Many readers as well as reviewers have told me that they very much appreciated hearing about how I arrived at my current views but obviously one cannot please everybody.

I regard myself as one of the 'little people" in the philosophy of science in general, even if I have succeeded to make a small mark in the far more restricted field of the philosophy of chemistry, as the reviewer so generously acknowledges. My own views on general philosophy of science are like a drop in the vast ocean of diverse opinions in this far larger arena. I believe I am part of the organic web of authors and researchers that I espouse in my book. I think it is therefore quite appropriate for me to forge ahead in the hope that others, might subsequently comment.

Kragh begins by writing,

> One motivation for Scerri's project is, somewhat strangely, his dissatisfaction with standard histories of quantum mechanics which he suggests overrate the contributions of German-speaking physicists and underrate those belonging to the English-speaking world. He does not elaborate and perhaps wisely so. Whether one likes it or not, with the exception of Paul Dirac the emergence of quantum mechanics was almost entirely due to physicists from Germany and Austria.

I find it rather odd that Kragh should feel the need to imply to readers that I did not elaborate. In fact, I explained my statement a good deal further. Here is what I actually wrote on the question of quantum mechanics and German-speaking physicists.

> As the history of quantum mechanics is usually presented, it appears as a mainly German affair. Of

> course, if we think of Schrödinger and Pauli then national allegiances must be widened a little to encompass Austria, Switzerland—and Denmark in the case of Bohr. Certainly, the Frenchman Louis De Broglie is given due coverage as is the Englishman Paul Dirac (who was of partly French origin). Nevertheless, quantum mechanics is generally regarded as a Germanic affair in the wider sense. As I see it there was a great deal of influential work being carried out in the English-speaking world during this period but this is only evident if one drops the emphasis on the heroic approach to the history of science.

I explain why I focus on the seven particular scientists that I do a few pages later.

> … in terms of nationalities they consisted of four from Britain and one each from Germany (Abegg), France (Janet) and The Netherlands (van den Broek). Needless to say, the predominance of authors who wrote mainly in English reflects my own linguistic limitations and perhaps an unfair bias toward the Anglophone world.[18]

What I am saying is that I am concentrating mainly on authors who wrote in English or French for the simple reason that I cannot read German! I am not attempting to claim that "the Brits were somehow better than the Germans."

Kragh bemoans what he sees as my wanting to deglamorize famous scientists when he writes,

> The reason why Scerri focuses on these marginal figures is that they illustrate one of his main theses, that the contributions of the lesser, even obscure figures are no less important to the overall progress of science than those of the famous scientists. This thesis he takes quite seriously, even denying that there are any "outstanding personalities" in science. According to this view there is no reason to celebrate scientists such as Newton, Lavoisier, Maxwell, Darwin and Einstein, for they all belong to the same crowd as the thousands of scientists who have not achieved historical recognition.

Of course there is no harm in celebrating these and other similarly well-known figures, provided that one also acknowledges that each of them stood on the shoulders of what I call the little people, rather than the giants in the famous quotation attributed to Newton. In the final analysis perhaps the famous scientists should *not* be celebrated, although that would make for a rather dull world.

I am criticized for saying that Janet did not catalyze the work of others which leads to the reviewer asking why I included this amateur scientist in my band of seven "little people." Janet's left-step table has been the basis of many studies aimed at finding the optimal form of the periodic table and of the theoretical foundations of the Madelung rule. The point is that Janet's table seems to represent the Madelung rule in a better way than the more traditional formats do (1-, 2, 3, 4, 5, 6). I included Janet's ideas because he represents an excellent example of a little- known scientist who made notable contributions, even if they were not appreciated at the time of his writing.

After finding all manner of faults, Kragh finally turns to the main ideas in the book.

He complains that I have nothing to say on ordinary workers and technicians who are surely equally entitled to be called "little people" in science. Although I agree with Kragh about the value of technicians, this is not a point I chose to make in the book. I deliberately chose to focus on little known individual chemists and physicists. My account regards the unit of evolutionary change to be individuals rather than groups in the way that Kuhn does. This is why I try to distance myself from the sociological approaches to the study of science, which seems to be another aspect that the reviewer finds puzzling.

Support for my choosing this course of action comes from an editorial piece in a recent issue of *Perspectives on Physics* that is appropriately entitled, "On Minor Scientists" (7):

> For decades, historians of science have realized the shortcomings of focusing narrowly on extraordinary individuals—a tendency often called the "great man myth," long recognized by historians in general. Yet this realization has not translated into significantly greater treatment of under-recognized scientists. Rather, it has generally meant scrutinizing large-scale social and institutional currents, collaborative efforts, the role of instruments, and other such processes. When attention has fallen on underrecognized individuals, they have tended to be the technicians, assistants, members of marginalized groups and other scientific laborers whose contributions went uncredited for reasons other than a lack of prize-winning breakthroughs. Scientists who fit squarely within the scientific establishment and did the type of work validated by traditional reward systems yet have long been eclipsed by their more illustrious colleagues find themselves neglected in the very stories that reject the myth of the great man. Can we tell the stories of underrecognized figures without seeking to cast them as secondary to larger processes or to elevate them (with the benefit of hindsight) to the pantheon of greatness? What might we learn from such studies?

Kragh takes issue with my view on truth and ridicules my assertion that scientific ideas should not be regarded as being right or wrong. The view that water is composite is "right" Kragh argues, while the view that water is elemental is simply wrong. However right and wrong, and admittedly the terms are not ideal in this context, should always be asserted within a particular framework. Elements themselves *are* composite as seen from the perspective of the fundamental particles that make up its atoms as the reviewer knows only too well.

My reason for downplaying the view that developments in science are right or wrong is best illustrated by means of a biological analogy. In the animal kingdom the gradual evolution of a new limb in some species, for example, cannot be said to be right or wrong. The new limb, which has resulted from random mutations in the DNA of the animal, may confer an evolutionary advantage in the individuals that possess the mutations. In retrospect we can claim that this development was "right" but always within an environmental context that the animals find themselves in.

Nevertheless, I agree with the reviewer that I have not provided a mechanism for my proposed evolutionary view of the growth of science and will attempt to do so briefly now. Like Kuhn I maintain that the development of science is non-teleological rather than being directed at an objective "out there" reality. But whereas Kuhn believes that the development of science is just analogous to biological evolution, I consider it to be more than an analogy. My appeal to evolution is not merely to biological evolution but to evolution writ large, by which I mean the evolution of the entire universe, the solar system, the geology of the earth as well as the evolution of life on earth. Each form of overlapping evolution of this kind presumably has a different mechanism.

The mechanism for the evolution of science must surely be of a psychological kind and it is not one that I am in a position to spell out at this stage. What I will say, and this *is* by way of an analogy, is that the mechanism may be similar to random mutations that are known to occur in the DNA of biological organisms. Such mutations govern biological diversification followed by natural selection of those organisms that best fit the environmental niche that the organisms find themselves in. So it is with intellectual ideas entertained by scientists. They are not, I suggest, arrived at deductively through clean logical arguments but first emerge in much the same way that biological mutations take place.

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BOOK REVIEW

The Foundations of Physical Organic Chemistry: Fifty Years of the James Flack Norris Award, E. Thomas Strom and Vera V. Mainz, Eds., ACS Symposium Series 1209, Oxford University Press, 2016, 336 pp, ISBN 9780841230712, $170.

The field of physical organic chemistry arose during the 1930s largely because of the kinetic research of Christopher K. Ingold at University College London and of Louis P. Hammett at Columbia University. Ingold's work stressed organic reaction mechanisms, whereas Hammett's emphasized the thermodynamics of free energy relationships of acid-base reactions. The field blossomed with work along these lines in the 1940s and 1950s, but the scope immediately expanded. The principles were applied in organic chemistry to solvent effects, NMR spectroscopy, conformational analysis, reactive intermediates, aromaticity, isotope effects, noncovalent interactions, catalysis, photochemistry, molecular mechanics, and semiempirical and ab initio calculations. Applications moved beyond organic chemistry to embrace inorganic and organometallic chemistry, biochemistry, materials chemistry, medicine, industrial chemistry, and even geology. The defining theme was the relationship between molecular structure and molecular properties, both micro and macro and of interest to both the pure chemist and the applied chemist. The properties included kinetic, thermodynamic, spectroscopic, medicinal, practical, and on and on.

The publication of Louis P. Hammett's classic book *Physical Organic Chemistry* in 1940 is considered to be the founding act of this field. Twenty-five years later, the American Chemical Society (ACS) initiated the James Flack Norris Award in Physical Organic Chemistry, the first two winners of which were Ingold and Hammett, followed by Saul Winstein, who may have been the greatest physical organic chemist because of the originality of his approaches (although many may arguably put Paul D. Bartlett in his place). In 1988 the Award for Early Excellence in Physical Organic Chemistry was initiated by the publisher Wiley to recognize individuals in the early stages of their careers. Many monographs have become physical organic classics, including Edwin S. Gould's *Mechanism and Structure in Organic Chemistry* (1959), Ernest L. Eliel's *Stereochemistry of Carbon Compounds* (first edition 1962), Kenneth B. Wiberg's *Physical Organic Chemistry* (1964), Jerry March's *Advanced Organic Chemistry* (first edition 1968), and today's standard, *Modern Physical Organic Chemistry* by Eric V. Anslyn and Dennis A. Dougherty (2006). In 1959 the first edition of a textbook for undergraduate organic chemistry by R. T. Morrison and R. N. Boyd was released, with a novel approach that employed physical organic concepts, particularly reaction mechanisms and aromaticity. The first journal devoted to the field probably was *Journal of the Chemical Society*, which split in two in 1966, Part B of which was subtitled "Physical Organic Chemistry." The journal, however, evolved into *Journal of the Chemical Society Perkin Transactions II* in 1972. The *Journal of Physical Organic Chemistry*, devoted entirely to the field in all its manifestations, began in 1988.

On the occasion of the approaching 50th anniversary of the Norris Award (and, I might add, the 75th anniversary of the publication of Hammett's *Physical Organic Chemistry*), E. Thomas Strom and Jeffrey I. Seeman organized a symposium at the 247th National Meeting of the ACS in Dallas, TX, in 2014 under the auspices of the Division of the History of Chemistry, to recognize the field and its contributors. This book, edited by Strom and by Vera V. Mainz and published in the ACS Symposium Series (number 1209), brings together papers written by the participants, expanded with an introductory chapter and two chapters by students of key Norris Awardees who are deceased. Unfortunately, two chapter authors passed away soon after the book was published.

The leadoff article by Arthur Greenberg summarizes the life and scientific work of Norris, whose birth in 1871 made him senior to Ingold and Hammett by more than 20 years. Norris in turn was slightly younger than those chemists mentioned by Greenberg who developed many of the concepts on which physical organic chemistry was based—Paul Walden and Victor Meyer for stereochemistry and Julius Stieglitz and Moses Gomberg for reactive intermediates. To these names should be added that of Arthur Lapworth for developing concepts of reaction mechanisms. These chemists, including Norris, set the scene for the research of Ingold and Hammett. Greenberg describes Norris's specific contributions to physical organic chemistry, primarily at MIT, and the endowment provided by his widow, Anne Chamberlin Norris, which resulted first in the Norris Award for Outstanding Achievement in the Teaching of Chemistry (1951) and ultimately in the Norris Award in Physical Organic Chemistry.

Three of the contributing award winners describe work that interweaves theory and experiment. Wiberg briefly discusses his experimental, theoretical, and spectroscopic work, but focuses his discussion on his work with optical activity, almost all of which was published after his retirement from Yale in 1997. Andrew Streitwieser's focus is on isotope effects with almost no mention of theory, although he returns to that topic in a later, collaborative chapter. Interestingly, both Wiberg and Streitwieser began their work as graduate students in the laboratory of William von Eggers Doering. In fact, this volume includes four authors who were Doering students.

Paul von Ragué Schleyer is represented by two chapters in this volume. One chapter constitutes the subject of his lecture at the symposium, the norbornyl cation. It is fitting that this topic be covered in this volume, because of the central role of this cation in the field during the 1960s and 1970s. The so-called norbornyl controversy pitted two giants of the field, Saul Winstein and Herbert C. Brown, who initially debated the topic in classic lectures at UCLA and Caltech in 1963. The debate became so intense and, many thought, extended, that the field of physical organic chemistry itself suffered. Schleyer died just before he could finish his article for this volume, so the editors (Mainz and Strom) carried it to completion to ensure its inclusion. Every conceivable kinetic, structural, theoretical, and spectroscopic tool was applied to the problem, but ultimately it was X-ray crystallography that resolved the issue in favor of the delocalized structure, the so-called nonclassical version. This inapt term fed the controversy but never disappeared. Brown died in 2004, but I am not sure he ever agreed that the norbornyl cation was anything but localized.

Schleyer is represented by a second, autobiographical paper. Jeffrey Seeman had developed an autobiographical series of monographs for the ACS during the 1990s and asked Schleyer to contribute a volume on his work. During an extended hospitalization, he finally had time to write the bulk of the volume, which he entitled "From the Ivy League to the Honey Pot," to emphasize the transition from his position at Princeton, where he was primarily an experimentalist, to Erlangen, Germany, where he was primarily a computational chemist. The title was intended to highlight the fundamental differences in funding mechanisms between the American and European systems, in particular for obtaining computer (and, I add, spectroscopy) time. Basically, the German system enabled Schleyer to carry out the calculations he previously could not afford. The sociological differences between American and German universities also were important in his decision to move from Princeton and ultimately to remain at Erlangen until the compulsory retirement age by German law, the primary flaw in the honey pot. Schleyer never finished his manuscript, although Seeman had a draft. Interestingly, the volume is listed on amazon.com with a publication date in hardcover of June 1, 1998, apparently anticipated as Seeman assured me it was never published. Thus it fell to Streitwiester to complete the task, so that this volume at last presents Schleyer's autobiography to the public.

Edward M. Arnett presents his unique contributions to structure and mechanisms through the use of calorimetry, in addition to providing a brief exposition on the period of physical organic chemistry that immediately followed the publication of Hammett's book, the 1940s and early 1950s. In the true tradition of physical chemistry, Arnett and his students built their own calorimeters.

The results that rolled off of this unique instrumentation included the importance of solvation in solution acidity and basicity, such as the apparently inverted order of basicity of amines from ammonia to tertiary structures. Calorimetry was ideally suited for the quantitative assessment of physical organic concepts. In the true physical organic tradition, Arnett synthesized the unknown *ortho*-di-*tert*-butylbenzene and then determined the strain energy between the closely nestled *tert*-butyl groups to be 22 kcal mol^{-1}.

Ronald Breslow describes his contributions to one of the evergreen subjects of physical organic chemistry. The series of 4*n*+2 (Hückel) cyclic hydrocarbons provided an ineluctable attraction to physical organic chemists, with neutral six-membered benzene at the early center of attention and the charged five-membered cyclopentadienyl anion demonstrating the potential of the series. Then in 1954 Doering and Knox proved the existence of the seven-membered tropylium ion to complete the aromatic triad. The question remained as to whether the extra stability of aromaticity would countermand the expected ring strain in the three-membered cyclopropenium ion. Breslow and his students made the first substituted such cation in 1957 followed by the more satisfying unsubstituted cation in 1967. He also considered the issue of antiaromaticity, which embraced the four-membered constituents of the series, cyclobutadiene and its charged forms. Breslow, along with Myron Bender, was one of the pioneers of applying physical organic chemistry to biochemistry, and the remainder of his chapter is concerned with those contributions.

Three chapters focus on reactive intermediates, as well as the chapter already mentioned in which Schleyer summarized the norbornyl cation field. The editor Strom together with Kathleen Trahanovsky, both graduate students of Glen Russell, celebrated his life and research with a well-illustrated and enjoyable chapter. Free radicals also were the topic of the chapter by Keith Ingold, who was a member of the only father/son pair to receive the Norris Award. Ingold includes not only an insightful summary of his own work, but a pair of remarkable look-alike photographs of himself and his father when both were 12 and when both were in their 70s. Diradicals are the subject of the only chapter by what might be called a younger generation, by Weston Thatcher Borden. His chapter of course is strong on theory, but the focus is on the rich variety of diradicals that he has studied over his very productive career.

Last to be mentioned is the chapter by Ronald Magid and Maitland Jones on "Life in the Research Laboratory of William von Eggers Doering." Based on two "unpublishable" manuscripts by these authors, this expurgated version only makes one want to go to the website cited in the chapter for the full versions. What comes over strongly in the chapter are two highlights of Doering's research—originality and fun. Indeed the title begins with "Lost in the Funhouse." I can attest to the fun that Doering always injected into his research and his lectures. The year after I moved from my position as an undergraduate in Doering's group at Yale to a graduate student in Southern California, the National ACS Meeting came to Los Angeles in 1963, and with it, Bill Doering. I could not miss his lecture, which oddly was held in a movie theater. When he began his lecture on the stage, he discovered he lacked a pointer, and the slides were well above the length of his arm. Despite an acerbic request for a pointer, nothing was forthcoming, so Doering disappeared off stage and came back with … a broom. He preceded to grab its bristly head and point to relevant parts of the slide with the tip of the shaft. At last someone arrived breathlessly with a pointer, and Doering found himself with both a broom and a pointer. He then began sweeping the stage as he took the broom behind the curtain to dispose of it.

This book provides an eclectic group of essays on physical organic chemistry and physical organic chemists, which provides enjoyable as well as edifying reading.

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