A WOMAN IN BIOCHEMISTRY AND TOXICOLOGY: THE POLISH-BRITISH REFUGEE REGINA SCHOENTAL

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For over three decades from 1939, Polish-born Regina Schoental (1906-1995) studied, successively, at Oxford and Glasgow, syntheses and identification of polycyclic aromatic hydrocarbons (PAHs), metabolites of carcinogenic PAHs, and, at the Medical Research Council, Carshalton, Surrey, the carcinogenic action of pyrrolizidine (*Senecio*) alkaloids, and diazomethane and nitroso compounds. In particular she demonstrated the relationship between plant-derived hepatotoxic pyrrolizidine alkaloids and primary liver tumors. The role of Schoental and colleagues in the history of the development of synthetic methods for PAHs is also of interest because some are strong candidates for use in electronic devices.

Introduction

On February 2, 1995, the London *Times* recorded the death at the age of almost ninety of biochemist, cancer researcher, and toxicologist Regina Schoental. At that time I was preparing to travel from Jerusalem to London, where I had hoped to meet Dr. Schoental to discuss the transfer of her archive to the Hebrew University's Sidney M. Edelstein Center. It was to have been our first meeting; she had not long before made contact after reading my articles published in the *Biochemist*.

In the event, after arriving in London, I accompanied her solicitor and a member of the family to her apartment in Wallington, Surrey, to examine the archive. It filled at least one large room; there were notebooks, reprints, research notes, correspondence, conference programs and reports, trade and government literature, travel brochures, monographs, obituary notices on her former colleagues, manuals, textbooks, and slides and photographs, as well as exotic dried plants and shrubs and samples of chemicals. Subsequently this material arrived at the Hebrew University, and, after selective reduction, is now held at the Edelstein Center. Most of the manuscripts and publications deal with toxic substances in plants, mycotoxins, polyaromatic hydrocarbons (PAHs), and various other carcinogenic chemicals. These sources reveal that Regina Schoental's research, described in over 250 published papers, contributed to industrial hygiene, diet, including nutritional factors in carcinogenesis, the understanding of the relationship between structure and activity in natural and synthetic carcinogenic organic chemicals, and toxicology in general. Though the archival collection remains largely uncataloged, it includes many items of interest to the history of chemistry, particularly of a woman scientist struggling not only to survive in a mainly male-dominated field, but also in a harsh and changing world outside the laboratory. The following is a summary of her life and career, with an emphasis on chemical studies, based on fragments, some quite substantial, from the archive (1).

Among the many letters in the archive is an item dated September 26, 1983, in which Regina Schoental congratulates a former colleague, the cancer expert Isaac Berenblum, on reaching his eightieth birthday, and in-

forms him that on November 11 of that year she would complete "45 years of my wanderings in the British Desert (2)." These few words spoke reams on her career as a scientist-refugee who survived through a series of appointments in England and Scotland, helped by some colleagues, used by others, but all the time contributing to new knowledge in aromatic chemistry, biochemistry, and toxicology. That she never gained a tenured academic post was, in the opinion of Berenblum, in large part a result of her constant and sometimes voluntary moves. Perhaps more likely was the general difficulty faced by women in gaining academic and leadership posts. Biochemistry, toxicology, and industrial hygiene—areas in which Regina specialized—certainly did offer decent openings for several women, some of whom, like Dorothy Hodgkin and Ethel Browning, were appointed to senior research positions or posts as government inspectors, respectively. The chemist Gertrude Belle Elion, after a difficult start, benefited from male staff shortages during World War II, which enabled her in 1944 to embark on drug development at Burroughs Wellcome; in 1988 she shared the Nobel Prize for Physiology or Medicine, and in 1991 was the first woman to be inducted into the National Inventors Hall of Fame. In most cases, however, in order to overcome career discrimination, outstanding women scientists not only had to rely on strong support from male colleagues in senior positions, but were also expected to conform to prevailing social and cultural norms. As for Schoental, an excellent scientist and world authority in two important areas of toxicology, and with considerable male respect, if not always support, her own tensions with colleagues, as also suggested by Berenblum, did not help her to gain advancement. That may also explain why she has remained hidden among the second rank of exceptional immigrant scientists whose contributions are frequently overlooked. Along with current interest in the role that skilled technicians, as well as ordinary scientists, play in research this makes her achievements of even greater interest. Here they are set into a context that highlights their significance.

Early Life

Regina Schoental was born on June 12, 1906, in Dzialoszyce, a small Polish town northeast of Cracow, where her Jewish family was engaged in industrial pursuits. Her mother was from Cracow and a cousin on this side of the family was the well known bacteriologist Phillip Eisenberg, who in 1914 had published on bacterial variability. Life in Dzialoszyce during the early 1900s was subject to constant political change, including in 1907, when the town was occupied by Russia. After 1914 Regina's private education was frequently interrupted, as the German and Russian armies fought over control of Polish land. In 1916 Regina left home for Cracow, probably to stay with her mother's family. In 1922 she "passed the Entrance Examination to the VIIth Form of the 1st Private High School for Girls." After two years at the school she passed the "Matura" examination that allowed her to study chemistry at Cracow's Jagellonian

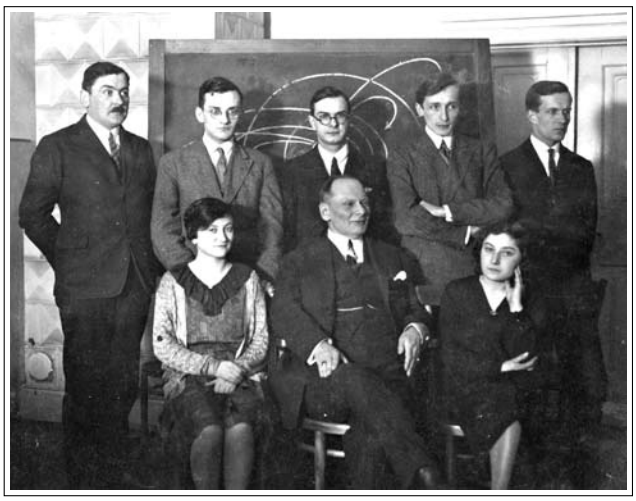

Figure 1. *Regina Schoental, seen here front row at right, with her Ph.D. supervisor, Professor Deodatus Szyszkowski, seated at center, and colleagues at the Department of Physical Chemistry, Cracow, around 1930. Date and photographer unknown. Schoental Archive, Edelstein Center.*

University, where she also attended classes in bacteriology and biology. The course lasted four years and was followed with postgraduate studies. In 1929 she was awarded the M.Chem., and in 1930 the degree of doctor of philosophy. Her thesis, on "a physico-chemical topic," was not published because of the death of her supervisor, Deodatus Szyszkowski, and, later, her departure from Poland. She spent 1931 in Paris at the Pasteur Institute and other clinical laboratories, gaining experience in clinical biochemistry and bacteriology (3).

During 1932-1936 Regina undertook postgraduate research at the Clinical Laboratory of the Military Hospital, Cracow, and also at the "Cancer Laboratories of the University Clinic." After this, she opened a private diagnostic laboratory and was a part-time researcher at the University of Cracow Institute of Forensic Medicine, associated with the medical academy (1936-1938). (Regina also stated that during 1933-1938 she was affiliated with the "Cancer Research Laboratory, Department of Internal Medicine, Cracow.")

In 1938 Cambridge biochemist and emerging historian of science, Joseph Needham, while visiting Cracow, encouraged Regina to pursue her research in the United Kingdom. At that time Needham was seeking out chemists to join his planned research program at Cambridge on the chemical basis of embryonic induction and probably considered Regina a good candidate, even though he did not have access to funds to support her. He was particularly anxious to bring in immigrants, both to assist them and also because their employment costs would be low, or they would be self-funded (4). A recommendation from the head of the institute of forensic medicine, J. Olbrycht, enabled Regina to obtain a "scientific passport" from the Polish authorities. With the promise of financial support from her parents, she wrote to the cancer expert (later Sir) Ernest Laurence Kennaway at the research institute of London's Royal Cancer Hospital. She may have chosen to write to Kennaway on the recommendation of Needham, who hoped that this would be a way of getting her to be close at hand, even if not immediately to join his team (in the event Needham abandoned his project for lack of funds and infrastructure). She was no doubt aware of Kennaway's work on carcinogenic natural tars and PAHs, including his synthesis in 1924 of carcinogenic tars by pyrolysis over hydrogen of isoprene and acetylene, and his demonstration that 1,2:5,6-dibenzanthracene (dibenz(*a*,*h*) anthracene) and its derivatives, and then 3,4-benzo(*a*) pyrene, produced tumors in mice (5). This followed the 1915 publication by Japanese workers K. Yamagiwa and K. Ichikawa of experiments that demonstrated the presence of carcinogens in coal tar; the tars were found to induce skin cancer. Regina Schoental later noted that Kennaway was the first to demonstrate that "a pure chemical can induce tumors in experimental animals." She appears to have done some work on polyaromatic hydrocarbons at Cracow, perhaps as a postgraduate, judging from reprints she retained of 1925 and 1927 papers authored by Karol Dziewoński and coworkers published in the *Bulletin de l'Académie Polonaise des Sciences et des Lettres*. She also retained mid-1930s reprints of work on natural products, including quinine, undertaken by Jerzy Suszko and others at Poznan.

Chemists and Cancer

It is pertinent here to introduce a little more background on chemists and others engaged in cancer research between the two world wars, particularly those with whom Regina Schoental would later work. The chemist (later Sir) James W. Cook had joined Kennaway at the London cancer hospital in the autumn of 1929, and during 1931-1932 they and coworkers isolated and identified a carcinogenic component in coal tar, namely 3:4-benzo(*a*) pyrene. This followed the observation by W. V. Mayneord in 1927 that the carcinogenic coal tar fractions showed a striking fluorescence. Subsequently Cook and colleagues synthesized various derivatives of 1,2-benzanthracene, several of which were cancer-producing. These carcinogenic derivatives exhibited fluorescence bands that, like the tar fractions, were shifted to longer wavelengths. Then in 1931, Israel Hieger (at the London hospital since 1924), obtained from two tons of gas-works soft pitch, via the picrate, 7g of crystalline hydrocarbon which proved to be 3:4-benzo(*a*)pyrene. It was highly carcinogenic, which correlated with the fluorescence spectrum. Independent synthesis from pyrene and structural determination, by comparison with synthetic 1,2-isomer, by Cook and C. L. Hewett, was crucial to confirmation of identity and further progress.

An undated note of Regina, alluding to the different personalities of Kennaway and Cook, written long after the death of Kennaway (in 1958), adds a slightly different slant to the story, and contributes to how Cook rose to fame. It is particularly interesting in view of the fact that Regina's most productive and probably happiest years in Britain before the mid-1950s were spent in Cook's Glasgow laboratory. Reminiscing on the time that she had sat in a lecture theatre with an unwell Kennaway towards the end of his life listening to Cook recount some of his own achievements, perhaps in Regina's mind not giving sufficient credit to others, she compared the "humility" of Oxford-educated Kennaway with the "self assurance and pride" of Cook (6):

> …a self made man—hence probably lacking this ease and certainty that appropriate upbringing in higher classes can give. He was neither in Oxford or Cambridge, but at John Cass College, University of London, not distinguished in any way…[Kennaway] turned to him for samples of PAH, for Hieger to examine their fl[uorescence] spectra to compare with those given by coal tar fractions. Hieger, who slaved with fractionation of coal tar for a long and laborious time, was deprived from his just record, crystallization of 3,4BY[Benzpyrene], because he was not enough of an organic chemist. So the honour and glory went to Cook.

Notwithstanding personal feelings over credit and priority (that were certainly not apparent at the time the work was reported), this identification of a carcinogenic factor in coal tar stimulated extensive synthesis and animal testing of PAHs. At the end of the 1930s, it was a novel and

exciting area for original research in cancer, following concerns, particularly in England and Germany, over lung cancer caused by tars from cigarette smoking (7). Other notable workers in the fields of chemistry of PAHs, and PAHs and cancer, included in Czechoslovakia Erich Clar, in a private laboratory, in the United States Louis F. Fieser, at Harvard, and in Mandate Palestine Ernst David Bergmann and Chaim Weizmann at the new Daniel Sieff Institute (later the Weizmann Institute), Rehovot, who investigated anthracene and phenanthrene derivatives. Kennaway and Fieser independently led investigations into the correlation between chemical structure and carcinogenic activity. Cook had expanded on Clar's synthesis of various 1,2-benzanthracene derivatives, reported in 1929, during his first studies with Kennaway's group in London.

Kennaway was interested in cancers caused by other aromatic molecules, particularly the so-called aniline cancer, named after the aniline dye industry, which used a variety of aromatic amines in dye manufacture. The most potent carcinogens were found to be β-naphthylamine and benzidine, both in use as intermediates for dye manufacture since the 1880s, and since the 1930s known to cause tumors in humans (8). These amino compounds were investigated by Kennaway from the mid-1920s and soon after by Isaac Berenblum and G. M. Bonsor at Leeds. In August, 1932 Berenblum published a comprehensive review of "Aniline Cancer," focusing on bladder cancer (9). During the mid-1930s investigations into bladder cancer caused by dye intermediates were carried out by George H. Germann and Wilhelm C. Hueper at DuPont in the United States (10).

Cook and Kennaway coauthored reports on the literature related to "Chemical Compounds as Carcinogenic Agents" for the *American Journal of Cancer*. These were predecessors of the *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, which first appeared in 1941, compiled by Jonathan L. Hartwell for the National Cancer Institute. Of the 696 compounds listed in the survey, 129 were reported as active. The second edition appeared a decade later, with 1,329 compounds listed, of which 322 were active (the survey was reprinted in 1963 by the U.S. Public Health Service).

At the end of 1938 Regina's interest was drawn to Kennaway's several lines of research in cancer. However, as she later reminisced (11):

> I wrote to Kennaway and without waiting for his reply arrived in London on the 10th November, 1938, only to learn that Kennaway wrote that he is not able to accept me; the Chester Beatty Institute [the expanded research facility at the hospital] was then under construction).

The Chester Beatty Research Institute (now the Institute of Cancer Research) opened in 1939.

Figure 2. *Ernest L. Kennaway. Date and photographer unknown. Schoental Archive, Edelstein Center.*

Cambridge, Oxford, Glasgow, and Chicago

Regina arrived in England with fifty pounds sterling, all she was allowed to take, little knowledge of English, and no research position. She managed, perhaps through Needham, to spend a few weeks in Cambridge, at the Molteno Institute, with biologist and discoverer of cytochromes David Keilin, also of Polish-Jewish origins, who sympathized with her plight. It was through registration at Chelsea Polytechnic "so as not to be returned to Poland" and this brief unpaid post that her visa was extended. Regina then joined, as a volunteer researcher, funded by her parents, the Sir William Dunn School of Pathology at Oxford, directed by Howard W. Florey. After the Nazis marched into Poland in September 1939, she was forced to remain in Britain as a refugee. She later recorded, "The outbreak of the war interrupted [my] cancer research." Regina found herself "cut off from my people and resources." She considered joining the Hebrew University in Mandate Palestine, which was also engaged in cancer research involving studies on PAHs, and was accepted by Leonid Doljanski of the university's cancer laboratories, department of experimental pathology. The war put an end to plans for going to Palestine.

However, "Thanks to the unforgettable kindness of Professor (now Sir) H. W. Florey, F.R.S.…I was given a grant from the Nuffield Trust, and this enabled me to remain in the Department (12)." Her good fortune from this time was to undertake research with outstanding, and later leading, biochemists, toxicologists, chemists, and cancer researchers. At Oxford she worked with

Ernst Chain, who left Nazi Germany in 1933, biochemist Norman George Heatley, who from the late 1930s, after working with Needham at Cambridge, had been engaged in the investigation of metabolism of cancer tissues, and Isaac Berenblum (whose Polish-Jewish family had left Bialystock in 1906 following Tsarist pogroms). Chain, Florey, and Heatley were then developing penicillin. "Florey and Chain suggested that I try to isolate the antibiotic substances from Ps. Pyocyanea, which according to Trueta had beneficial effects upon the wounds (13)." Joseph Trueta, former professor of surgery in Barcelona, and from early 1939 a refugee from Franco's Spain, was, with the support of Florey, at the Sir William Dunn School during 1939-1941. Regina published her research on this topic in 1942, though her main interest was in cancer. By then she had become a member of the Oxford University Research Centre of the British Empire Cancer Campaign, under Berenblum's direction (1938-1948). The research staff consisted of just three members: Berenblum, experimental pathologist, Chain, chemical adviser, and Regina Schoental, "Biochemist—Part-time voluntary worker." In 1942, Berenblum and Regina began to publish jointly on 3:4-benzo(*a*)pyrene (benzpyrene) and its toxicity. They isolated and identified phenolic metabolites of the benzpyrene, chrysene, and 1:2-benzanthracene (14). At Oxford, the mechanism of carcinogenesis was investigated on two fronts: Berenblum's biological approach based on three separate steps, using croton oil; and, through collaboration with the Dyson Perrin Laboratory, Sir Robert Robinson's chemical approach, an attempt to correlate chemical structure with carcinogenic potencies. Robinson and colleagues synthesized sulfur-containing derivatives of PAHs as part of the contribution to Berenblum's research.

Regina, supported with grants from the cancer campaign, remained with the Oxford cancer center until 1946. On behalf of the center, she was at the chemistry department of Glasgow University during 1943-1944, engaged in collaborative research. At Glasgow, Regina was associated with James Cook, since 1939 Regius Professor of Chemistry and Director of the Chemical Laboratories. This brought her into both carcinogenesis and the synthesis and characterization of novel PAHs, an endeavor that would continue until at least the late 1950s. The facilities were excellent, a dedicated chemistry building (the first in Britain) comprised of two substantial wings opened in 1939 (a third, according to the original plan, would be added after 1945), directed by the leading British chemist engaged in the synthesis of carcinogenic aromatic hydrocarbons. Regina's work at Glasgow was originally stimulated by interest at Oxford in the possible inhibition of tumor growths by metabolites of carcinogenic substances, and the need to synthesize a number of metabolites. The facilities were also attractive to the Admiralty that had commandeered a large laboratory for wartime research.

A reprint of Cook's 1942 review of "Polycyclic Aromatic Compounds," in the *Annual Reports of the Chemical Society*, the first such review since 1933, was no doubt a treasured possession of Regina, since it still retains the carefully applied protective wrapping. One of her notebooks, marked "Department of Organic Chemistry, University of Glasgow, Syntheses of Hydroxy-derivatives of Polycyclic Hydrocarbons," with entries for October 1943-December 1945, shows that she maintained close contact with both Kennaway and Berenblum. This suggests that Regina's post at Glasgow may have come about through Kennaway's connections, or, probably more likely, Berenblum's own interest in PAHs. Either way, at a time of depleted ranks among male researchers called away for war-related work, her efforts were invaluable. Various reference compounds for the study of biochemical actions were synthesized mainly by Regina in Cook's laboratory and forwarded to Berenblum at Oxford. At Glasgow, Regina and Cook established the structures of metabolites of the benzpyrene. Regina showed considerable interest in another aspect of Kennaway's work, primary cancer of the liver, as a result of her own pre-war study of such cancers at the Cracow university clinic through measurement of the lactic acid content of blood in normal subjects and those with various diseases.

Regina returned to Oxford late in 1944, probably at her own request, but she must have soon had second thoughts. Personal difficulties, particularly with Berenblum in 1945, prevented concentration on her work. No doubt concern over the absence of contact with her family in Poland was a cause of deep distress. Regina thought of leaving the Oxford group and joining Kennaway, who in March, 1945 offered her a short term post in London. "It was very hard to make a decision," she wrote to Cook on March 20, 1945, "the more so, as Prof. Kennaway prefers me to finish the synthesis of the 8-benzpyrenol in Oxford. In spite of all that I decided however in favour of London, realizing that this is my last chance to work with Prof. Kennaway (15)." Regina, desperate to leave Oxford, advised Cook: "A lot of work remains to be done (I am expected in London in June), in order to finish some of the problems I have been concerned with—but I shall try to concentrate in the first place on the synthetic work, as the prospects of continuing it later are rather bad (unless

you would care to take me back to Glasgow at some later date!)." Regina added notes in pencil to her draft, suggesting that she was not at all happy, even with a post in London, and yearned to return to Glasgow (16):

> In this fine weather—Oxford often painfully beautiful—obviously does not induce much enthusiasm for work.

Kennaway, however, though highly sympathetic, particularly towards a Jewish refugee, expressed concern over the lack of future employment prospects. Regina was prepared to accept the temporary post in London since her intention was to join the Hebrew University. Cancer research in Jerusalem, where conditions were very difficult in other ways, seemed to be a strong option now that the war was entering its final phase (17). This, however, did not materialize, due to lack of facilities for chemical research and animal experiments, restricted research opportunities, and her failure to obtain a grant from the British Empire Cancer Campaign, notwithstanding support from Berenblum, Florey, and Kennaway. Regina had even suggested that the chemical problem could be overcome through collaboration with Ernst David Bergmann. In the event, Regina decided not to take the London post. Kennaway, who always showed great kindness to Regina, would in any case retire one year later from directorship of the Beatty.

Still at Oxford, Regina undertook the further synthesis of various benzpyrene derivatives, particularly 10-methoxy-3,4-benzpyrene, while maintaining close contact with Cook (18). The work was highly challenging, and the product elusive. "I think we got the real 10-MeO-BP," wrote Schoental to Cook on one occasion, though the product could not be fully characterized (19). Separation of chlorinated benzpyrenes "proved a rather difficult job," though it eventually afforded an "embarrass[ment] of riches," namely, four products (20). There was also work on the hydroxyl derivatives, stimulated by the belief that they were important intermediate metabolites of benzpyrene during carcinogenesis. Progress, however, was increasingly hampered by growing personal difficulties at Oxford. Regina considered obtaining a position in the United States, but in October, 1945 wrote to Cook that "My prospects for the USA seem rather bad," and ended her letter: "I do not know what to do. Why did I ever agree to leave Glasgow, all my troubles started since (21)!"

A practical problem was the absence of a stock of benzpyrene, at least until 30 g were obtained in January, 1946. Regina, discovering that IG Farben had filed a patent for benzanthrone-1'-aldehyde, asked Cook whether there was any way of procuring a supply from Germany, which Cook thought unlikely. Both were interested in the forthcoming availability of C-13 for research purposes from the Medical Research Council (22).

After many enquiries for a research post, including with Albert Claude at the Rockefeller Institute in New York, had led nowhere, Regina requested, or at least suggested to Cook, a post back in Glasgow. Hinting again of her dissatisfaction with Oxford, on February 6, 1946, Regina wrote to Cook (23):

> The new scheme you put forward for the two hydroxybenzpyrenes is certainly most interesting and I would be only too anxious to undertake it. I feel however that my continuing synthetic work in Oxford, somehow as a side line besides other problems, without your advice on the spot, is not quite satisfactory; it would certainly give quicker results if I could be in your Department, if this would suit you.

Cook immediately offered her a vacant bench in a small research laboratory. His space and resources were extremely limited, so much so that had Regina's letter arrived one day later the position would already have been filled. Cook expressed the hope that the large laboratory previously occupied by the Admiralty would be made available for research later in the year. Early in April, not long before her departure from Oxford, there was another indication of frustration (24):

> Oxford is now so incredibly beautiful with the pink almond trees etc., as if it tried to make me sorry for leaving it, which I am not.

At the end of April, 1946 Regina began working in Glasgow, funded with her existing grant. Later in the same year she published with Berenblum a paper in which they showed that metabolites of 3:4-benzo(*a*)pyrene were 8- and 10-hydroxyphenolic derivatives (benzpyrenols) and benzpyrenequinones (25). By April, 1947 her funding was transferred from Oxford, extended, and increased, for a period not exceeding three years (26). Despite the personal problems in 1945, Regina maintained a close connection with Berenblum, who invariably offered her support with funding; they remained on first name terms, the affectionate "Gina" and "Berry," respectively.

Now back in Scotland, Regina must have been delighted, even though she was probably aware of the limited long term prospects, particularly for women. The increasing numbers of women recruited into laboratories during the war did not immediately improve their status, irrespective of their qualifications. They were far more poorly paid than men. Kennaway's wife, Nina, even undertook research in close collaboration

with her husband as a volunteer, a situation that lasted over thirty years! Furthermore, cancer research was less prestigious than drug design, and less likely to attract substantial research funds. At a more mundane level, for women at least in British laboratories, there were even restrictions on dress, including on the wearing of trousers, except in the winter (27). The wartime winters, and that of 1947, were particularly severe, though cold laboratories did sometimes favor recrystallizations. It is not without interest that of three issues of the *Chemical Bulletin* that Regina retained after a visit to Chicago in 1953, one highlighted the "Professional Problems of Women Chemists (28)."

At Glasgow there were major compensations. The international standing of the chemistry department was maintained by its first-rate scientists, including the X-ray crystallographer John Monteath Robertson, who not only solved the phase problem that enabled the determination of structures of biological macromolecules, including proteins, but also for Cook undertook bond length measurements on naphthalene, anthracene, and other aromatic hydrocarbons and their hydroxyl derivatives. Prominent guests included, in 1948, Linus Pauling. Regina appears to have enjoyed her time back at Glasgow. She participated in social events and took an interest in the chemistry department's Alchemists Club that catered mainly to undergraduates. She retained just one issue of the club's newsletter, *The Alchemist*, perhaps because it included the article, "Devils, Drugs, and Chemists," that noted (29):

> Penicillin was an English discovery, i.e. the greater part of the work was done by Fleming, a Scotsman; Florey, an Australian; and Chain, a German of Russian descent.

In late 1946 Erich Clar, pioneer in synthesis and identification of polycyclic aromatic hydrocarbons and leader in the field, had joined the chemistry department at Glasgow. In the 1920s Clar had studied at the technical institute in Dresden, from around 1930 he was at the Ronzini chemical institute in Milan and by the end of the 1930s had opened a private laboratory in the Sudetenland at his home town of Herrnskrestchen, southeast of Dresden. He continued to publish in Germany during World War II, including, in 1941, *Aromatische Kohlenwasserstoffe* (30). After the war prior to joining Glasgow he was at the central laboratory of Rütgerswerke A.G. At Glasgow he was supported with an ICI research fellowship.

Cook and Regina, using oxidation with osmium tetroxide as described in 1942 by R. Criegee, B. Marchand, and A. Winnowius, found that benzpyrene and ten other carcinogenic PAHs afforded novel products, since they were attacked at positions not sought by other oxidizing agents. Moreover, in the case of the benzpyrene derivatives the products were, unlike those from oxidations with the usual reagents, close analogs of metabolic products (31). Following the extensive use of fluorescence spectra in PAH studies, Cook and Regina drew upon Clar's studies to survey UV spectra in order to establish relationships between bond structure and the longest UV absorption of various PAHs (32). Significantly, many compounds prepared and characterized by Clar have in recent years proved important in the development of pentacene (five fused linear rings)-based semiconductors.

In 1945 Regina Schoental discovered that most of her family had perished in the Holocaust, including Phillip Eisenberg (d. 1942). A sister-in-law and her thirteen-year-old daughter survived, by escaping to the Soviet Union, where they were sent to Boukhara. Regina's brother, Wincenty, died there in 1942, of typhus. After the war the child was repatriated to Poland and placed in a clearing camp for orphans at Lodz. At the end of 1946, Regina brought the girl, Marya (Matylda Maria Ludwika [Marion]), to Britain and arranged for a home and education; in the early 1950s Marya studied medicine at the University of Glasgow. The trauma brought on by the loss of family led Regina after 1948 to develop close contacts with colleagues in Israel, where from the mid-1950s she attended conferences dealing with cancer, diet, toxic plants, and related topics. Regina, incidentally, never recorded her attitude toward Clar, who during the war had remained in Nazi-occupied Sudetenland, where he continued his research. However, he appears to have had little interest in politics and no sympathy for the Nazis. Regina's professional connection with Clar was certainly congenial.

Regina was awarded the D.Sc. by Glasgow University in 1950 as a result of her syntheses of PAH derivatives and study of the metabolic products of PAHs. This work was continued, for example, with Friedel-Crafts succinoylations of anthracene. At that time she began looking for more permanent employment. In 1950, she joined the Glasgow Royal Cancer Hospital Research Department (from 1952 the Cancer Research Department, Royal Beatson Memorial Hospital), directed by Peter R. Peacock, and continued studies mainly on the metabolic fate of carcinogenic and related PAHs in mice and rats. Tobacco alkaloids were another topic. As a result, during 1951, Regina published a note on the dangers of cigarette smoke in the *Lancet* (33). Much of her research was carried out in close collaboration with Cook (34).

From September 1952, Regina spent just over one year with the Oncology Department, Chicago Medical School, working on the synthesis and metabolic fate of C-14 labeled 8-methoxy-3:4-benzpyrene. Since on her arrival the laboratories were not complete, she took the opportunity to travel to research institutes on both the east and west coasts. Later she wrote up her impressions of the trans-Atlantic trip for a lecture before an audience of British biochemists. The draft reveals humor and amazement, as she emphasized bigness, the overriding role of instruments and even casual dress (35).

> The thing that strikes immediately a visitor from [Britain] is the terrific activity in Scientific Quarters. Enormous research laboratories are either under construction or have just been finished everywhere you go. The American approach to expanding research is a bit different from what it is here. Once they have the money for an institute they build one which obviously has to be bigger and better than any other; then they equip it with the most modern instruments and gadgets available on the market, then they start to think what actually to do with all this, and whom to appoint for the work. This last item, to find appropriate research workers, causes a lot of headache to directors and administrators. So many new laboratories, Scientific and Industrial, have grown up like mushrooms in the last few years, that there are not enough people to go round and staff them.

As for the obsession with instrumentation:

> During my stay in Chicago I isolated an impurity present in starting material used for the manufacture of detergent which was suspected of being carcinogenic. Naturally the manufacturers became alarmed and sent their chemists to discuss the matter with me. In the course of our discussion, on the possibilities of the identification of this substance, these industrial chemists just casually said: "We shall have a couple of x-ray analyses done, some infra-red and ultra-violet absorption spectra, and then see what more is needed." No one suggested that a simple oxidation or reduction may give a lot more information.

Woods Hole on Cape Cod produced some surprises, especially for a European lady accustomed to somewhat formal sartorial standards (35):

> All wear just jeans and short sleeve shirts or blouses, men, women and children, young students, or Nobel prize winners, half a dozen of whom you can find there any time of the summer.

Regina also found time to attend a Gordon Research Conference on cancer at New London, New Hampshire, a symposium on organic chemistry at Ann Arbor, Michigan, and three major scientific meetings in Chicago.

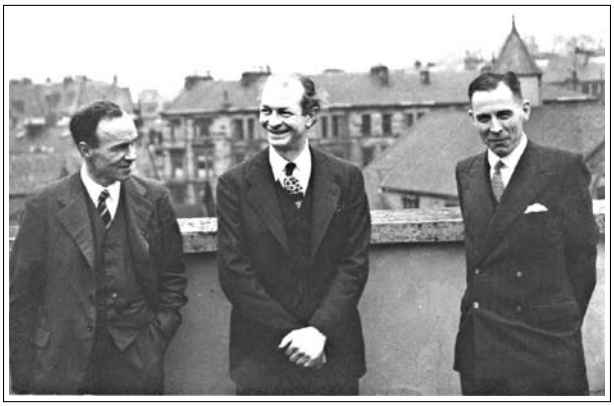

Figure 3. *From left to right: John M. Robertson, Linus Pauling, and James W. Cook, on the roof of the chemistry building, Glasgow University, April 1948. Photographer unknown. Schoental Archive, Edelstein Center.*

Pyrrolizidine Alkaloids

In 1953 Regina returned to the Beatson, but in January 1955, either because funding from the British Empire Cancer Campaign ran out, or of her own accord, she left the Glasgow hospital. One reason was that the cancer campaign would not support her work on a new topic, toxic pyrrolizidine alkaloids and liver disease, in which she had taken a serious interest in Cook's laboratory. There in 1949, Regina and Cook, in collaboration with E. Duffey of the Glasgow hospital, investigated the connection between alkaloids extracted from the weed ragwort and primary liver tumors. An undated draft research report noted (36):

> This would be the first instance of a natural product exhibiting carcinogenic action (all the known carcinogenic substances are synthetic chemicals or products of chemical industries), and would obviously open new fields for further investigation.

By early 1955, as a result of this change in research interests, Regina was again seeking a new post. During April and May, residing at The Brangwyn Hotel in London, she was in touch with Derek H. R. Barton, then at Birkbeck College, University of London, and about to take on the regius professorship at Glasgow, with a research proposal based on the toxic alkaloids to be undertaken in Glasgow (in 1954, after Cook became principal of University College Exeter, his former post was split; Robertson became head of the chemical laboratories). Barton could gain no support for her proposal in Glasgow. When Regina advised him that she intended to apply for a Council of the Royal Society Tropical Fellowship, as advertised in *Nature*, she received his endorsement (37). This research work, however, would have to be done elsewhere. The

tentative proposal, a topic connected to the alkaloids, was entitled "The Chemical and Biological Study of Herbal Medicines Used in Tropical and Subtropical Countries for the Treatment of Women and Infants, with Special Reference to the Hepatotoxic Constituents in Such Herbs." Regina's research application was based on statistical information of liver disorders, particularly liver cirrhosis, in Israel, that showed significant increases with the immigration of Jews from "oriental" countries (Yemen, Iraq, Iran, and North Africa). These immigrants had brought with them various herbal remedies that Regina wished to study as potential hepatotoxic agents. It was a unique opportunity, though it did not suit the needs of Glasgow's chemistry department, that would couple Regina's interest in Israel with a medical problem there that was relevant to many other countries in the Near East, Africa, and Asia. She had on her first visit to Israel in February, 1955, shortly after leaving Glasgow and at the invitation of Berenblum, attempted to stimulate interest into herbal remedies, but without success. Regina later noted that despite this lack of interest in Israel, as well as from the Medical Research Council and Colonial Office in England, a Palestinian Arab in Kuwait and Egyptians had recognized and studied the problem of toxic herbs.

The successful award of the fellowship marked the beginning of a change in the direction of Regina's research; at least, until around 1960, it opened a second branch. On July 1, 1955 Regina joined the Medical Research Council (MRC) Toxicology Research Unit, at Carshalton, Surrey, directed by toxicologist John M. Barnes. The unit was established by Barnes, who had served as a Royal Army Medical Corps officer associated with the Biology Department, Porton Down, during World War II, at the Porton site in 1947; the unit was moved to Carshalton in 1950. Regina, initially funded with the Royal Society research fellowship, was "very happy to have left the Peacock's Department—there is so much more scope and facilities for work here (38)."

Carshalton, "Epping Jaundice," Australia, Africa, and London

In addition to her new research topic, Regina continued with aromatic chemistry, mainly on PAHs, at Carshalton, collaborating with colleagues at Glasgow University and at the Beatson. In 1957 she isolated 3,4:9,10-dibenzpyrene from coal tar. Fortunately, it had been prepared in 1939 by Clar, and his assistance enabled identification. Interest in its carcinogenic activity was stimulated by the fact that in 1956 it had been reported as a constituent of cigarette smoke. In 1964 Regina, now a world authority on the toxicity of carcinogenic PAHs, published an extensive review of carcinogenesis caused by PAHs in Clar's new book, *Polycyclic Hydrocarbons*. In her historical introduction dealing with the discovery of coal-tar carcinogens, rather than engage in polemics over the matter of where most credit was due she simply noted, with references, that (39):

> The story of the exciting and successful discovery of the first carcinogenic constituent of coal tar, 3,4-benzopyrene…has been told by Cook and Kennaway, who recorded the contributions of each individual worker associated with this problem.

Toxicological problems associated with industrial hygiene and cancer in general led to appointments on various committees. Her assignments included the investigation of an outbreak of poisoning known as "Epping jaundice" in February, 1965. Regina established that the cause was contamination of bread in the Epping district of London by the epoxy resin hardener 4,4'-diaminodiphenylmethane, used in the CIBA resin araldite. The hardener, during transport by road, had escaped from containers and mixed with flour later used to make whole meal bread. Some 84 people were hospitalized after they had consumed the affected bread. The results were published in *Nature* (40). Other aromatic amines investigated included β-naphthylamine, benzidine, and azo dyes. Unlike carcinogenic PAHs, whose effects were at the site of application or injection, the target organs for aromatic amines, mainly the bladder, were distant from the place of administration.

The emphasis on aromatic hydrocarbons declined as novel areas of research became available through association with the prestigious MRC unit and its wide ranging contacts outside Britain. As a result, the pyrrolizidine (*Senecio*) alkaloids, those found in the herbal remedies, particularly in the tropics and subtropics, featured increasingly in Regina's research interests from the late 1950s. They were also available from products sold by herbalists in Britain. The study of their carcinogenic action, particularly their ability to induce chronic lesions and tumors in the liver, pancreas, etc., was often undertaken in collaboration with Peter N. Magee at the MRC unit (Magee later moved to the Courtauld Institute of Biochemistry at Middlesex Hospital). Pyrrolizidine alkaloids are phytotoxins prevalent throughout the plant kingdom. Ingestion by animals of these "pyrrole" derivatives in plants is a common cause of poisoning. Over 150 members have been isolated and identified, including their structural determinations. Most are toxic after

both acute and chronic exposure, and have continued to stimulate research in toxicology.

Opportunities for work-related travel, including attendance at conferences and convenient stopovers on long haul flights, aided considerably the interest in toxic substances in plants. For five months in 1960, Regina was at the Commonwealth Scientific and Industrial Research Organization (CSIRO) chemical research laboratories in Melbourne, Australia. On the outward journey she visited African countries and on return, early in 1961, several Asian countries, including India, where she lectured on hepatotoxic plants and liver disease (41). In 1963 she produced liver disease in experimental animals comparable to those encountered in humans. During 1964-1967, with Björn B. Afzelius of Stockholm, Regina collaborated in studies on the toxic action of retrorsine, an alkaloid found in certain South African *Senecio* species. Some of this work was done while Afzelius was on sabbatical leave at the University of St Andrews, Scotland, in 1964. The contacts made during the 1961 trip were of tremendous importance in gaining information for a comprehensive review of liver disease and its connection with both natural and synthetic hepatotoxins. Studies on human toxicity following the ingestion of pyrrolizidine alkaloids in foods and folk medicines took Schoental back to African countries, where she was warmly welcomed. During 1970-1971 she was in Ethiopia and East Africa (Tanzania, Uganda, Kenya), mainly in search of plants used as herbal medicines, beverages or foods, in order to continue and broaden investigations into the role of hepatotoxic plants in liver disorders. The health hazards connected with the herbal remedies, particularly in Ethiopia, were of great interest to her.

Regina also studied, from around 1960, the toxicity of diazomethane ("the simplest alkylating agent," and among carcinogens "the simplest of them all"), and certain nitroso compounds (42). Around 1965 she investigated human nasal tumors, particularly in furniture workers and wood machinists. This followed her work (with S. Gibbard) on carcinogens in Chinese incense smoke, again as a result of the MRC's international standing, and which, since the products were derived from wood, was extended to a study of cancer of the nasopharynx in English furniture workers (43). Among the Chinese population, the highest incidence of cancer of the nasopharynx was found in the south, in Kwangtun Province, Hong Kong, and Macao. Several PAHs, including 3:4-benzo(*a*)pyrene, were isolated from incense smoke by thin layer and column chromatography, with detection by UV. The benzpyrene was estimated fluorimetrically. In the search for suitable aldehydic constituents of lignins, as an extension of this work, samples of tannins were procured from the British Dyewood Company, Glasgow, in 1969. This was an example of Regina's special interest in different pathological conditions that appeared to be prevalent in certain countries. In this case the study of a Chinese problem was found to be applicable to conditions in a sector of British industry, as well as in Kenya (44). There were also studies on metabolites of *Fusarium* and other microfungi (45). In 1967 Regina supplied Stephen Mason at the University of East Anglia samples of high-polymer DNA and the methylated DNA for optical rotatory dispersion (ORD) and circular dichroism (CD) measurements. Other topics around 1970 included the carcinogenicity of oestrogens. Her work on the possible impact of tricothecene toxins in human diseases attracted considerable interest in the early 1980s.

At the end of September, 1971 Regina reached statutory retirement age and left the MRC toxicology unit. In the same year she joined as a visiting worker, at first without research funds, the Department of Pathology, Royal Veterinary College, University College, London, where she continued research into pyrrolizidine alkaloids and nitroso compounds until final retirement in 1988. The publication in the same year of *Pyrrolizidine Alkaloids* by the World Health Organization clearly demonstrated her pioneering role in the understanding of these toxic natural products (46). She maintained contact with colleagues in Africa and Israel, including Isaac Berenblum (who had joined the Weizmann Institute at Rehovot in 1950 to inaugurate its cancer research program).

Berenblum and Schoental

Isaac Berenblum's correspondence with Regina hinted at the professional tensions and rivalries at Oxford in the mid-1940s, and the breakup of the group of cancer researchers there. By early 1947, he was considering taking up a post at the Sieff Institute in Palestine (from 1949 the Weizmann Institute), after spending two months in the United States (47). However, in October, 1948 he joined the National Cancer Institute, National Institute of Health, in Bethesda, Maryland, as visiting special fellow, working on skin cancer induced by 9,10-dimethyl-1,2-benzanthracene. In September 1949, shortly before he emigrated to what had now become Israel, Berenblum told Regina that he was glad that she enjoyed a conference at Cambridge, "if even the presence of Chain did not put you off…," a reference to Chain's volatile and abrasive personality, as much as cultural differences (48). (Chain had also left Britain in 1948, for Italy, after

declining the post at the Sieff Institute that was taken up by Berenblum, returning in 1961 to Imperial College.) In 1949 Regina had wanted to test the carcinogenecity of 8-benzpyrenol at Oxford, but she was advised by Berenblum that the cancer unit was being closed down: "Florey made this decision when he heard that I was not coming back. I always knew, and told you myself, that he never had any love for keeping cancer going (48)." Regina had also enquired about the possibility of joining Berenblum at Rehovot, but their own strong differences around 1945 no doubt influenced Berenblum's decision (48):

> On the matter of the possibility of your joining me at Rehovoth, I wished you had not put me in the position of having to answer it. You know that I think highly enough of your work, and that I have always tried to fight your battles against those who were prejudiced against you, and even those who pretended to be your friends but never went out of their way to help you. But you must surely remember the last year of our collaboration. I remember it only too well, and cannot see myself doing anything that might lead to a repetition of it. Please believe me that I am not harbouring any grievances; I really do hope that, from a distance, we could forget the unpleasantness of that association and only remember the years of amicable and fruitful collaboration.... Please let us forget it all and continue as friends.

Certainly they remained good friends, often exchanging information about scientific and family matters, and making use of their several contacts. In 1955, for example, Regina arranged for pure anthracene to be sent to Rehovot by Cook, who had generously provided samples to several research groups.

As mentioned at the outset, Berenblum opined that Regina's constant travels and moves, sometimes as a result of her own preoccupations, particularly with liver disorders, including cancer, in many ways prevented her from gaining a tenured or senior academic post. There were also the personal difficulties, hinted at by Berenblum, and by colleagues at the MRC. Nevertheless, she was very highly regarded, particularly by Berenblum and Cook, while Barnes appreciated her as an extremely competent scientist and a valuable member of his MRC team.

Regina Schoental contributed a chapter to *Chemical Carcinogens* (ACS Monograph no. 173) (49), edited by C. E. Searle, and to the enlarged two-volume work (ACS Monograph no. 182) (50), and co-edited, with T. A. Connors, *Dietary Influences on Cancer: Traditional and Modern* (51). She was Member of Council, Royal Society of Medicine, Section of Oncology, during 1979-1982 and a member of both the Chemical Society and Biochemical Society. In later years she spent much time applying scientific theories, often based on her toxicological studies, to speculate, for example, on the causes of catastrophic events recorded in the Bible, George III's attacks of madness, the deaths of homosexual lovers of great musicians, and HIV infections and AIDS.

Regina Schoental's portrait appeared on the cover of *Cancer Research* in February, 1988 and again on September 1, 1991, this time accompanied with a one-page review of half a century of research, written by biochemist and cover editor Sidney Weinhouse of Philadelphia (52). She published widely in leading international journals, including *Journal of the Chemical Society*, *British Journal of Cancer*, *Lancet*, *Nature*, *Biochemical Journal*, and *Cancer Research*, as well as in journals published in Poland, Australia, East Africa, India, and Israel. Regina Schoental never married. She passed away on January 29, 1995 and is buried in Jerusalem.

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Jack H. Stocker
1924-2009

An ACS Councilor since 1972, Jack was Chairman of the Division of the History of Chemistry in 1990, ACS Representative to the Chemical Heritage Foundation (CHF) Council, and a dedicated member of the Bolton Society. At the family's request, memorial gifts in Jack's name can be sent for Project SEED Scholarships to ACS Office of Development, 1155 16th St, NW, Washington, DC 20036.