ILLINOIS YEARS—1960-1968

Family

This was another period bounded by two sabbatical leaves from the University of Illinois: the Swiss sojourn followed, for me, by the Australian IUPAC Meeting and the New Guinea adventure in 1960 and time spent at the University of Wisconsin, Rockefeller University, and Israel in 1967-1968. The latter sabbatical was also supported by a Guggenheim Fellowship, which was lucky for me because it is no longer the practice of the Guggenheim Foundation to award a second fellowship. For the children, it was a period of concentration on schooling. Ken and Marcia survived the shock of returning from the Progymnasium in Flims, Switzerland, to their respective grades in middle school in Urbana, Illinois. Nell had tutored them a bit in preparation. Ken attended Urbana High School during the period 1963-1966, ran cross-country and track, and was the cartoonist for the school paper. The high school was only two-and-one-half blocks away from our house. Ken applied to a number of schools of architecture and was accepted by the University of Illinois where he shifted to a major in graphic design (1967) after his first year, during which time he lived at home. He claimed a section of the basement and used the side door for entry and exit so that his parents would not have to worry about his comings and goings at odd hours. (We did, anyway!) Jim and Dave remember especially one of his lengthy projects then or later, in which he was carving up pink Styrofoam blocks to assemble some large structure that supposedly had a purpose. It was hard to rid the basement of the flecks of pink Styrofoam that retained static electrical charge, a reminder of his presence and diligence. Ken had a life that was rather separate from his siblings, but we were all together over Christmas/New Year vacations in Aspen, Colorado, and at least one summer month in Dunewood, Manistee, Michigan. Ken lived in a fraternity during his second year at Illinois, then in a rented house with Chip and Chrissie Frey in his third year, and back home in the fourth.

Marcia was on a teen fashion board of one of the local department stores and she kept up with her dancing. She says that she felt somewhat

isolated in Urbana High School because the girls seemed to arrange themselves in cliques. She was being—or becoming—an individualist, as were both of her parents. It is of interest that a group of the ten of the high school girls has met for reunions at approximately five-year periods and has become more cohesive and supportive in recent years, with Marcia as the organizer. The children's separate telephone was on a long cord in the upstairs hallway. Some privacy could be achieved by carrying the telephone into one of the three bedrooms or the bathroom. Social life in the high school years revolved about the Tigers Den in the Urbana Civic Center, where there was dancing to live music on Friday and Saturday nights. The old railroad station in Urbana was converted to a theater for amateur productions and for occasional exhibits. Nell and Marcia had a good mother-daughter relationship, only occasionally tested by the inherited strong personality traits that had come down through the female line of the family from the time of Napoleon. Jointly-held principles of fairness, justice, and equality were modulated by an abiding love. I have talked about Nell's reading to each of the children. David remembers especially Marcia's reading to him "a lot."

Everyone remembers Nell's great meals. They also remember Taina, everyone's dog, standing in Mother's way and staring at her coldly while she was preparing dinner for the family (instead of for her). Taina's main activity in the house during 1959-1970 was to nest under things—bookshelf, chairs, table, desk, or piano. Walking the dog or taking her to the park was an ad lib family assignment. She remained overweight and had a tendency to perfume herself by rolling in unspeakable material; otherwise, she was a very loving dog.

When Marcia went off to college in 1967, namely, to the University of Wisconsin, Madison, we all missed her. She had been an excellent older sister to Jim and Dave all through their growing-up years. Marcia still remains in close contact with her roommate of the first years at Wisconsin, but it took Marcia some time to recognize her own self and her own purpose. Because I had initiated a research collaboration with Professor Folke Skoog, an eminent plant physiologist at the University of Wisconsin, I *had* to visit Madison from time to time, which meant that I could see Marcia and take her and her roommate out to dinner. For more about Marcia's college education, see the next chapter.

During this rather arbitrarily selected time period, James was advancing from 8 to 16 years old and David, from 6 to 14 years old. They were good friends, as I hear from each of them, but they had their own interests and their own friends outside the family. Each now tells of the other's good sense of humor and of some of the mischief that they devised together.

They both joined Little League and, during two years, were on the same team. Both liked to construct things, and Jim took to airplane model building in serious fashion. Jim followed Ken into Boy Scouts. When we offered golf lessons to each of the children in turn during summers in Michigan, Ken enjoyed the lessons but not the practice, we found that Marcia needed glasses because she could not follow the ball when she hit it, and only Jim took it seriously enough to become a tremendous hitter, although not always accurate. Jim liked to earn money, as demonstrated early when he worked a paper route (or two). He still keeps in touch with his Urbana High School classmates, about 30 of them, and claims 10 of them as his close friends. He was an activist President of the Student Senate in his junior year, during which the school dress code, considered restrictive, was changed. Also, the school buses that were used to transport students between the high school and the north end of town were old and ramshackle. The Student Senate convinced the School Board that they were unsafe, and new buses eventually appeared. Jim was on the Tigers Den Council that put on dances at the Urbana Civic Center and was in charge of hiring bands, advertising, security, etc.—in short, of running the club. In one summer, the Council put on a financially successful rock festival. In his senior year, Jim—anticipating his working age somewhat—had a job with his friend, Andy Green, hauling equipment for a rock band that in time became well known. When 16 years old, he had a job in an all-night diner that provided some interesting experiences and fortified his ability to assume responsibility.

When David was in Little League, he liked to talk to his mother about baseball and felt very comfortable in doing so. Nell followed the St Louis Cardinals on the radio while knitting, and she knew a great deal about the players and their relative abilities. David also confided in Maggy Lou Perry when she gave him (a) a lunch that included, if he could convince her, her special fried potatoes, and (b) a snack when he came home in the afternoon. Whenever he was shunned by his older siblings, he had Taina to talk to and play with. Dave regularly arrived home late from school when he was in the 7th grade. Nothing was said, but Nell's curiosity caused her to drive by the schoolyard, where she saw Dave on the front steps surrounded by a group of his black classmates. He was conducting a voluntary tutoring session that was teacher-approved. David started playing the drums in 5th grade and obtained more equipment during the 7th and 8th grades, when other would-be pop musicians started populating the basement in the later hours of the day. I offered the following deal: any member of the family who was serious enough about a musical instrument to take lessons regularly could have that instrument and it would be his

(her) property, even to sell when he (she) tired of it. The same was true for athletic equipment.

It was really Nell who created the home atmosphere. I was working very hard, very long hours and averaging two chemistry trips per month. She was taking on more and more responsibilities in the League of Women Voters. Her tennis and bridge provided recreation, plus golf in the summer. Our circle of friends kept expanding, and the entertainment of my research students became a regular function. The children recall that we seemed to have many dinner parties. I recall that Marcia assisted with the special ones, while the others made brief, polite appearances.

Lecture invitations became plentiful during the 60s, and international meetings provided additional speaking opportunities, i.e., two in Europe in 1962, two in Japan in 1964, and one in Sweden in 1966. The whole family joined in the visit to Sweden, where, in Stockholm, Professor Holgar Erdtman and Gunhild Aulin-Erdtman arranged excellent accommodations for us in a pension that was convenient to the meeting center and to the tourist attractions of the capitol. The public transportation system in Stockholm is so efficient, or at least it was in 1966, that the four young Leonards, ages 12-18, acting as a team, saw everything they wanted to see and ate in automats where they could select from food on display. When Nell and I went to a banquet at the Wenner-Gren Foundation, the Erdtmans provided a separate table for the "team," who behaved admirably. At the end of the meeting, we treated the team to a trip to the North Cape, with travel through Sweden, the north of Finland, and along the fjords of Norway by train, ferry, bus and steamer. On the overnight journey by train going north from Stockholm, the team was amused by their father's standing at the end of the sleeping car so that he could mark our crossing of the Arctic Circle. "But Dad, that's just a geographic term," they said. "You wait and watch carefully," I rejoined. Sure enough, when it came time for crossing, there appeared a line of whitewashed rocks stretching away from the tracks about one hundred meters, labeled "Arctic Circle." The children were suitably amazed and amused. I was certain that there would be some designation of the crossing, and I was happy to hear their ridicule turn to appreciation. We went by bus down into the famous iron mine in Kiruna, Sweden, by ship and bus into the north of Finland, and again by bus to the North Cape (Sweden), then southwest and along the coast of Norway by steamer (fantastic smorgasbord breakfast and lunch). My favorite port on the Norwegian coast was Tromsö, which has a "crystal" church. I was so stimulated by the long hours of sunlight that I roamed the streets at midnight, came upon some boys playing soccer, and was allowed to kick the ball with them. Because there was little

difference at that time of year between day and night, their play outdoors was apparently regulated by when they were tired and felt they needed sleep, not by a strict parental timetable.

We toured further south along the coast of Norway by steamer, then by train across the frontier into Sweden at a ski resort, and back to Stockholm also by train. From Stockholm, we flew to Switzerland. Train from Zürich to Chur and bus to Lenzerheide brought us to a Dutch reunion with Els's family. The combined ten children ate, played, hiked, and climbed together. I was spirited away by Prof Pl. A. Plattner, the Research Director of Hoffmann-LaRoche. How did he find me? I had left an itinerary with my secretary at Illinois, so he knew I was supposed to be in Lenzerheide with my family. He drove from Basel to Lenzerheide in his little Porsche, parked, and started walking through the town. We were staying in a pension, and there are many of them. We would have been hard to find, but luck intervened. He spotted some Leonard kids, either outside the post office or a chocolate shop, pulled out the family Christmas card we had sent him, approached the flock of children and asked them where he might find the particular ones whose photos were on the card. Spectacular reaction! The troop led him to our pension, and I was dragooned to drive back with him to Basel on the following day. I had a long interview with the President of Roche, who was interested in filling the post of Research Director of Chemistry in their U.S. branch, salary unspecified, i.e., as high as necessary. Since I had made the decision of university versus industry employment on several previous occasions, I considered my role to be one of offering advice, which I continued to do, to good avail, when I returned to the United States. Two of my recommendees, in sequence, were offered the position but were retained, with advancement in salaries, at their respective U.S. institutions. The successful appointee was Arnold Brossi, who had received his Ph.D. from the E.T.H. in Zürich—an excellent choice. He generously sought my continued advice, and we became great friends for years thereafter, during which the advice-giving member of the team exchanged place.

I returned to Illinois to complete some university business while the Dutch family reunion continued in Switzerland. When it came time for my family to return home, they got as far as London, where they were halted by an airline strike. The problems to be solved consisted of (1) claiming accommodations for the night, (2) acquiring new reservations for flights to U.S. for five people on the following day, and (3) notifying me at what airport they would be landing. To add to the complications, Nell was ill, so Kenneth took over. The ground personnel must have been charmed by his polite persistence on behalf of the family, for he succeeded in

accomplishing (1) and (2). It was 6 o'clock the following morning when I could learn, at the opening of the telegraph office, where they were arriving. It was to be Detroit. I had further instruction to alert a friend of Ken's who was to be picked up and driven as far as Grand Rapids, there to be ticketed on a bus to Manistee. Of course, all of this required some fast driving on my part, which was detected in Kalamazoo, where a speed limit was posted as 45 miles per hour on the west side of a traffic light (green when I reached it) and 35 miles per hour on the east side. I pointed out to the officer who stopped me the inequity of this arrangement, which he knew very well because of several vehicles and several officers who were in "conference" on the side of the road to the east. I indicated that I knew Kalamazoo well, having sung often at the chapel of Kalamazoo College which was just above us within view. He seemed to be in the mood for chatting rather than for harsh action. We continued our talk until the other stopped vehicles had left; then, he allowed me to continue on my journey. He had cost me time but no money. When we reached Grand Rapids, I realized that I would not be able to arrive at the Detroit airport by the time my family was due. Seeking a solution to this dilemma, I telephoned Carl Johnson, former Ph.D. who was teaching at Wayne State University in Detroit. He volunteered to meet them upon their arrival and did, to which they responded with surprise, some pleasure, and some disappointment that I had not planned my drive well enough to reach the airport on time! After gathering luggage, talking a bit, and some stalling for time on Carl's part, Carl looked at his watch and suggested that I should be driving up the ramp "just about now." That is just what happened. We drove to Cadillac, Michigan, had supper in our favorite restaurant, buffet-style, picked up Ken's friend in Manistee, where he had time to read a book, and drove on to Dunewood. That refreshing place put us all at ease and almost instantly restored Nell's well-being. We stayed there until the beginning of the school year.

Research

New research programs were initiated in 1960. One of these started with the isolation of triacanthine from the new leaves of the honey locust tree (*Gleditsia triacanthos* L.) that James Deyrup had gathered, with the aid of some assigned convicts, in Dixon Springs, Illinois. A thorough study of the structure and chemistry of triacanthine established that it was 3-isopentenyladenine. The position of the group on the 3-position of the ubiquitous adenine nucleus was unusual, and this initiated one branch of

research on 3-substituted adenines in biochemistry. The nature of the substituting isopentenyl group initiated another branch of research in plant physiology. Some of the earlier research problems still had momentum, however, and thus claimed equivalent priority.

One of my graduate students left to see if he could advance in medical school, leaving an obviously gravid project behind. Carl Johnson took it up with alacrity and thereby provided a general, facile method of converting sulfides to sulfoxides by aqueous sodium metaperiodate oxidation. This simple method could be applied to medium-sized rings containing sulfide and carbonyl functionality. Carl found that the monocyclic 8-membered-ring 1-oxo-1-thiacycloöctan-5-one plus perchloric acid underwent a transannular reaction involving protonation of the carbonyl oxygen and formation of a bicyclic system. The conformation of the original monocyclic compound was established by determination of its electric dipole moment, while the structure of the salt, having a positive charge on the sulfur and a new hydroxyl group, was established by infrared spectroscopy and by proton magnetic resonance. Methoxy and acetoxy compounds could be made from the transannular salt, thereby providing unique functionality. Carl resolved the question of the mechanism of hydrolysis of the acetoxy compound elegantly by means of solution kinetics and the use of 0^{18}-water, namely: the transannular transfer of an oxygen atom, i.e., the sulfoxide oxygen becomes the carbonyl oxygen. I asked Carl how he had thought up the foolproof method of determination of the course of the reaction. He replied that he was in the process of writing a letter to his mother when the idea occurred to him. From that time onward, whenever a student ran into a problem for which there was no immediate solution (and the research director also could not provide an immediate solution), I suggested that he (she) write a letter home to mother! The usual student response was a very quizzical look, requiring a retelling of the Carl Johnson story.

Another problem developed from our earlier study of the iminium functional group. One of the reactions of iminium salts, i.e., with diazomethane, led to aziridinium salts. Klaus ("Bob") Jann, a postdoctorate from Germany, made the prototype. The key to isolation of these three-membered-ring compounds, which had been previously postulated mainly as unstable intermediates, was in the selection of a non-nucleophilic anion portion. Once we had found the way to isolate the pure aziridinium salts, we studied them systematically, with the attendant benefit of discovering their potential synthetic utility based upon hitherto unknown ring-expansion reactions. Our research on iminium and aziridinium salts was cited when I received the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry, 1963.

"Spatial Control of Organic Functionality" was the title selected for my Julius Stieglitz Memorial Lecture, 1962, sponsored by the Chicago Section of the American Chemical Society. It covered our findings of transannular interactions and reactions mentioned earlier, in rings of medium size (8-11 members), especially the new functionality created when pairs of donor and acceptor groups are placed diametrically opposite each other: amine and carbonyl, sulfide and carbonyl, sulfoxide and carbonyl, amine and sulfoxide, amine and oxime, and many others.

NJL, University of Illinois, 1963

The most amusing aspect of this research resulted from my placing in the hands of Professor Jack D. Dunitz, E.T.H., Zürich, two crystalline samples of aminoketones that exhibited transannular interaction. If that eminent crystallographer could determine their structures in the solid by X-ray, he could solve the issues of the conformation of the medium-sized rings, the angle of N approach to C=O, and, of course, the interatomic distances. That was my thinking. While the methodology was not yet in place in 1960 for the facile solution of the x-ray structural problems, the situation changed with time. The samples that were placed in Jack Dunitz's desk drawer were forgotten and were rediscovered only years later when Jack was moving to new quarters. The crystal structures, when published in 1975, confirmed that the N—C=O nucleophilic approach trajectory is such that the angle between the developing N-C bond and the C=O bond is about tetrahedral. In a talk in 1974, prior to publication, Dunitz amused his audience by stating that it had taken 14 years to solve the structures of these two small molecules!

It was the 3-isopentenyladenine (triacanthine) that fostered an entirely new area of study. James Deyrup worked out the chemistry, and Richard Laursen's unequivocal synthesis of 3-isopentyladenine provided a means of direct comparison with the dihydro derivative of the natural-source compound. The research suddenly went international when I sent samples of triacanthine to Europe that were found to be identical with the togholamine of Dr. A. Cavé and Dr. R. Goutarel (France) and the chidlovine of Dr. X. G. Monseur (Belgium) that were isolated from diverse natural sources. We published a jointly authored paper in a French pharmaceutical journal. Dr. Tozo Fujii, a visitor in our Illinois laboratory from the University of Tokyo, in the meantime, learned how to place an isopentenyl

group at any of the five nitrogens of adenine by means of suitable blocking groups, thus paving the way for selective synthesis of any desired N-substituted adenine. The 1-isopentenyladenine is interesting because it can be rearranged to N^6-isopentenyladenine by treatment with alkali or by autoclaving. The latter was also made by A. Cavé, as reported in his Doctor of Natural Sciences thesis in the University of Paris.

I could interest Professor Folke Skoog of the Department of Botany (now, Plant Physiology) of the University of Wisconsin, whom I had not yet met, in the testing of these compounds for biological activity, namely, the growth and differentiation of plant callus tissue and in the prevention of leaf senescence, so-called cytokinin activity. My stimulation of his interest was based on the structural similarity of the compounds to kinetin, an unnatural product of the autoclaving of DNA. We were pleased to learn that N^6-isopentenyladenine had ten times the activity of kinetin and that the N1-substituted isomer had fractional activity as a result of its partial conversion to the N^6-isomer during the autoclaving process. We realized that there were many questions to be answered: (a) could the N^6-isomer be found in nature; (b) the rearrangements should be studied further; and (c) determination of structure-activity relationships was in order. Our particular combination of chemistry and plant physiology involved a close collaboration between Illinois and Wisconsin that lasted 18 years, thus well beyond the arbitrarily selected 1960-1968 period under consideration, and it resulted in about 50 publications. It involved many visits back and forth, exchange of students and postdoctorates for the effective mastery of ideas and techniques, and eventual involvement and collaboration with half a dozen other scientists.

N^6-isopentenyladenine was indeed found in nature, in the plant pathogen *Corynebacterium fascians*, by Hamzi and Skoog and was identified and fully characterized in our laboratory. After the first two back-to-back publications, we followed with only joint publications. The Wisconsin-Illinois team's search for other naturally occurring cell-growth, cell-differentiation factors uncovered eight additional highly active substances from plant, animal, bacterial, and fungal sources. We carried out stereoselective syntheses to produce these compounds, and our structure/activity investigations led to agents even more active than the naturally occurring cytokinins. Used in very low concentration, the cytokinins initiate plant, flower, and tree growth in tissue culture. This feature is basic to horticultural and agricultural development. The culture and growing of gerbera in California constitute one example of economic importance that has resulted from tissue culture using added cytokinin, usually N^6-benzyladenine in this commercial case. A very recent finding by Dr. Marvin

D. Siperstein, Professor of Medicine at the University of California, San Francisco, indicates that N^6-isopentenyladenine (now abbreviated iP) is, in fact, an importance link between plant and mammalian systems, and, like mevalonate, it stimulates DNA synthesis specifically during the S phase of the mammalian cell cycle.

Innovation of 3-substitution on the adenine nucleus stimulated us to synthesize 3-isoadenosine, and, through the urging of my student Richard A. Laursen, we ventured into the realm of its 5'-mono-, di-, and triphosphates and the NAD+ analog based on 3-isoadenosine in the anticipation that these would serve as *spatial probes* of enzyme-coenzyme binding sites. Indeed, they are. We were fortunate to secure the collaboration of several laboratories in determining the wide range of biological activity of 3-isoadenosine and its phosphate derivatives, similar to that of the natural adenosine and its corresponding phosphate derivatives. The similarity, while possibly initially surprising, is readily understandable in spatial terms. Thus, the superposition of the purine ring of a 3-isoadenosine derivative over that of adenosine illustrates the close relationship that exists between the two, especially the proximate location of the individual nitrogens in each. When the necessary methodology for oligonucleotide synthesis and X-ray—and NMR—structure analysis came into being some 30 years later, we could confirm the hydrogen-bonding pattern that had been first postulated.

There was another research project in our group that had a major industrial and economic impact many years later (see the Postscript that follows this section). My graduate student G. Edwin Wilson, Jr., initiated the investigation of the hypothesis that a transannular route might be operative in the biosynthesis of penicillin. He made the necessary 7-membered-ring precursor, with all substituents in place, to test the suggestion that oxidation of the monocyclic system could lead to the bicyclic ring system that is present in penicillin. Oxidation with chlorine led instead to rearrangement, with the formation of 3-isothiazolones containing a monoheterocyclic system, i.e., a 5-membered ring. I added a paragraph to the long Leonard and Wilson article in the 1964 issue of the *Journal of the American Chemical Society*, stating that it was of interest that the isothiazolones produced a zone of inhibition when placed on an agar plate seeded with *Bacillus subtilis*. This had been Ed Wilson's method of testing, on the bench top, whether an antibiotic was produced on oxidation of the original 7-membered ring. No, it was not the hoped-for penicillin that had been produced, but the initial disappointment was followed by the excitement that the isothiazolones were biologically active. William D. Crow, a postdoctorate from Australia, joined my research group and

provided a simple, direct method for the synthesis of 3-isothiazolones, illustrating the procedure with the N-ethyl compound. The work was presented at the Chicago meeting of the American Chemical in September, 1964.

In December, 1966, we moved from Noyes Laboratory to the new building, now named Roger Adams Laboratory, where we could test the organic chemistry laboratory facilities so long in design and construction. I learned that there was some intense betting going on as to whether Dr. Leonard would make the deadline for evacuation from Noyes Lab of all his library and research belongings. It must be said that I worked late into the last night and next morning to confound the critics who had predicted my even worse procrastination. The only sad thing about the move was that some overzealous janitors threw away valuable spectroscopic data stacked in a barrel that they mistook for trash. One needs the original data for publishing the findings. The occurrence was so traumatic that I could only forget the work and could never publish the many papers that might have resulted. Perhaps it was not a great loss to science, but it was indeed a loss to me and to my research colleagues.

Postscript

Approximately 20 years after we had published and presented our work on 3-isothiazolones, including the antibacterial activity of the N-ethyl derivative, I received a telephone call from William E. Goode, who had been a Ph.D. student of mine in the late 40s. He had become the Vice President of the Rohm and Haas Company and wanted to know whether I would be willing to make a trip east to visit their new research facilities, all expenses paid plus an honorarium. The rest of the conversation went something like this:

"Would you like me to lecture, and on what topic?"

"No, thank you, just come for a visit."

"What time would you like me to arrive?"

"Any time it would be convenient for you, but preferably before lunch. We would like you to come for lunch."

"When would I return?"

"Oh, possibly mid-afternoon."

"OK. I would like to see you again, but I don't usually fly from Illinois to New Jersey for lunch."

"Let us know when you plan to arrive, and we will have a company car at the airport to meet you."

The transportation worked perfectly. Upon my arrival at Rohm and Haas' new research location and after greetings and a cup of coffee, the enigmatic conversation continued.

"We would like you to sign a secrecy agreement."

"I don't know that I can do that. I have an exclusive consulting agreement with Eli Lilly and Company."

"We are sure that it will be all right. We don't want to ask you for advice. We want to give you some information, as a courtesy."

"Great, I am always receptive to information."

Then, Bill and the others proceeded to tell me that they had read the articles in which we described the synthesis of 2-ethyl-4-isothiazolin-3-one (its systematic name) and its mild antibacterial property. They had decided that a long N-alkyl chain would render this type of compound paint-soluble, would be easy to make from readily available R&H stock, and might retain some of the biological activity of our original compound. They thought I would like to hear of their success before it became public knowledge! I was delighted to learn that a small piece of fundamental research had produced a practical result some years later. Their lead compound was the N-octyl derivative, called "Skane®M-8" in its industrial formulation. Skane®M-8 mildewcide has been formulated into primers, house paints, and trim paints—all latex, oil, and alkyd paints—and has demonstrated effective mildew resistance when applied to bare wood or to repainted surfaces. I am not in the business of advertising the product but the following properties can be expected of it: (a) no side effects on the paint film, (b) stabile, (c) economical, (d) low toxicity, and (e) easy to formulate. It also has microbistatic and fungicidal activity, reflecting our original finding on the N-ethyl compound. There followed (1994) from R&H, Kathon®LX 1.5%, a microbicide and fungicide for preservation of formulated adhesives and construction products, including asphalt, caulking, coating, cement, stucco, and clays. This product is also relatively nontoxic. Sea-Nine™211 (1992) is an antifouling agent containing dichlorinated N-octylisothiazolone. It is used on the hulls of ships to prevent the formation of a slime layer, and thus a loss in ship speed, caused by the usual adherence of bacteria and diatoms, also protozoa, freshwater and marine algae, and especially barnacles. In 2001, R&H was awarded the National Medal of Engineering on the basis of the improvements brought about in preservative painting and realized in efficiency of transport by their products.

If I am asked whether I should have patented our initial 3-isothiazolone and have tried to benefit financially, I can only say that the system worked very well as events occurred. My research was supported by a U.S.

Government grant. The source of the money was taxation. I did not know of the needs in painting and shipping, nor did I imagine what different substitution of the isothiazolone would produce in the way of properties. R&H research read my articles in the open literature, invented new compounds, manufactured, profited, and paid taxes. Thereby, additional fundamental research could be supported. A success for science!