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Spinach on the Ceiling: A Theoretical Chemist's Return to Biology

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Annu. Rev. Biophys. Biomol. Struct.
2006. 35:1–47

The *Annual Review of Biophysics and Biomolecular Structure* is online at
biophys.annualreviews.org

doi: 10.1146/
annurev.biophys.33.110502.133350

1056-8700/06/0609-
0001$20.00

Key Words

molecular dynamics, NMR coupling constants, trajectory calculations, reaction kinetics

Abstract

I was born in Vienna and came to the United States as a refugee in October 1938. This experience played an important role in my view of the world and my approach to science: It contributed to my realization that it was safe to stop working in fields that I felt I understood and to focus on different areas of research by asking questions that would teach me and others something new. I describe my experiences that led me from chemistry and physics back to my first love, biology, and outline some of the contributions I have made as part of my ongoing learning experience.

Contents

EARLY YEARS IN EUROPE

I was born in Vienna, Austria, in 1930 and seemed destined to become a physician. For several generations, there had been one or more physicians in the family, partly because medicine was a profession in which Jews in Austria could work with relatively little hindrance from discrimination. Neither my brother nor any of my numerous cousins displayed any interest in becoming a doctor, unlike me who at the age of five went around bandaging chairlegs and other substitutes for broken bones. I was fascinated by the stories of various relatives, including my Uncle Paul, who was a superb clinician. So, my family concluded that I was to become "the" doctor.

My paternal grandfather, Johann Paul Karplus, was a professor at the medical school of the University of Vienna, where his research led to the discovery of the function of the hypothalamus. My maternal grandfather, Samuel Goldstern, ran a private clinic that specialized in the treatment of rheumatological diseases by use of a mildly radioactive mud. The clinic, which I visited often because my grandparents had their apartment on an upper floor of the building, was called the *Fango Heilanstalt*. I had always assumed that *Fango* was a made-up name and learned decades later that *fango* is nothing more than the Italian word for *mud*. Many of the patients at the Fango were wealthy Arabs from the Middle East, an example of how the history of Arabs and Jews has long been intertwined and not always in the present destructive manner.

My childhood home was located in the Viennese suburb named Grinzing, well known as a wine growing area. There were small informal inns (Heurige) where we sometimes went in family groups for relaxed evenings eating and drinking (mainly the adults) the fruity young white wine of the region. The Heurige were also great places for children because between eating sausages, cheese, and bread, they could play in the garden.

In the early 1930s, when owning an automobile was still relatively rare, we already had a small car, a "Steyer Baby." One day when it was parked in front of our house, I scooted into the driver's seat and pretended to drive. I inadvertently released the brake, and the car started to roll downhill. I was terribly frightened as the car approached a pit at the end of the street. Miraculously, I steered the car so it turned just before reaching the pit and stopped. I recall the slope of the hill as being steep and the pit as very deep. Forty-five years later on a visit to Vienna with my family, we went to see my childhood home, which

had been appropriated by the Nazis during the Second World War. I discovered that the "steep" hill was a very gentle slope and the "pit" a shallow ditch, so that the danger was more in my young mind than in reality.

Stories from my early childhood, most of which I know from their retelling by my parents, aunts, and uncles, indicate that I was a strong-willed independent child (in a positive sense) and a brat (in a negative sense). One such story concerns my "escape" at the age of three from a summer daycare center, where I apparently did not like the way I was being treated. One morning I simply walked out and somehow, despite the center being several miles from our house, I made my way home. Both the daycare people and my parents, who had been notified, were extremely worried about my disappearance and were searching for me. Although I was scolded, my parents were so happy to see me that my punishment consisted of a mild reprimand. The venture was justified in my mind because after that I was allowed to stay home. Then there was the infamous "spinach incident." My beloved nanny, Mitzi, told me that I must eat my spinach. (Popeye did not exist in Austria, but unfortunately spinach did.) With all the vehemence I could muster, I took a spoonful of the spinach and threw it at the ceiling. The spinach stain remained visible on the ceiling for a long time and was pointed out at appropriate moments when my parents wanted to indicate what a naughty child I was.

Traditionally we summered at an Austrian lake or on the Adriatic coast of Italy with several families that were either relatives or friends with children of similar ages. Such extended family activities were an integral part of my growing up and gave me confidence and a sense of belonging. One day at the beach, a friend of my parents picked me up and cuddled me, much to my dismay. I yelled out, "*Ich bin ein Nazi*" ("I am a Nazi"), which so shocked her that she dropped me. Clearly, I had somehow realized, presumably from listening to my parents and others, that being a Nazi was the worst possible thing to be.

Already before the Nazis entered Austria in 1938, our life had changed significantly, even from the viewpoint of an eight year old. Among our neighbors were two boys of ages comparable to my brother, Robert, and me. They were our "best friends," and we played regularly with them. In the spring of 1937, they suddenly refused to have anything to do with us and began taunting us by calling us "dirty Jew boys" when we foolishly continued to try to interact with them. Similar problems occurred at school with our non-Jewish classmates. Prior to this, my school experience in first grade and the beginning of the second had been wonderful, in part because I had a great teacher, Herr Schraik, not the least of whose outstanding attributes was that his wife ran a candy store. When my class was ready to advance to second grade, the parents petitioned that Herr Schraik be "promoted" with us and, because of his outstanding record as a teacher, this request was granted. Nevertheless, in the middle of that school year (1937–1938) he was no longer allowed to teach. He was Jewish and the authorities had decided that any contact with him would contaminate the minds of the children. The new teacher was incompetent and blatantly anti-Semitic—he constantly criticized the Jewish students like myself, independent of how well or poorly we were doing. The situation became so bad that my parents took me out of school.

One small, but not insignificant, part of my schooling in Austria had to do with my being left-handed. When I started first grade, I was obliged to learn to write with my right hand. Whatever the supposed psychological consequences of that may be, I have always been grateful that right-handedness in writing was imposed on me. This was particularly true when I first went to the United States and saw the contortions children went through to write with their left hand. Clearly everything, at least in Western European languages (not Hebrew or Arabic), is set up for right-handed people.

On March 13, 1938, the German Nazi troops crossed the border into Austria and

completed the *Anschluss*, the "joining" of Austria with Nazi Germany, which had been specifically forbidden by the Versailles Treaty after the First World War. The Germans had been "invited" into Austria by the puppet Seyss-Inquart, who took over the Austrian government after Chancellor Schuschnigg was forced to resign. The night before, my family and some friends were listening to the radio in the living room, which was darkened to conform to the curfew and black-out requirements in case of air attacks. I was furious, not because of what was happening politically, but rather because my parents had planned an early birthday party (my actual birthday being March 15), and I was far from being the center of attention. Hitler entered Austria in triumph and his troops were welcomed by enthusiastic crowds. (To this day, more than 65 years later, I have mixed feelings about visiting Austria, which I rarely do, because anti-Semitism seems nearly as prevalent now as it was then. However, I recently learned that I am still officially an Austrian citizen, so I have dual nationality.) A few days after the *Anschluss*, my mother, brother, and I left Austria by train for Switzerland. My parents had been concerned about Hitler's takeover of Austria for some time. For the previous three years, my Aunt Claire, who had studied in England, had been teaching English to me and my brother, Bob. Well before March 13, train tickets had been purchased and a bed-and-breakfast "pension" had been reserved in Zurich.

The most traumatic aspect of our departure was that my father was not allowed to come with us and had to give himself up to be incarcerated in the Viennese city jail. In part, he was kept as a hostage so that any money we had would not be spirited out of the country. My mother reassured my brother and me, saying that nothing would happen to him, though of course she herself had no assurance that this was true. At that time, the Nazi government still allowed Jews to leave Austria, as long as they left their money behind. One way of spiriting money out of the country was to buy diamonds and hide them in clothing and food. During our train trip to Zurich, the guards at the German/Austrian border meticulously reduced a beautiful large sausage to thin slices, presumably searching for hidden diamonds. Fortunately, the sausage could still be eaten, and Bob and I were not too bothered by this event.

My parents hoped to go to America, but visas to the United States were granted only to applicants who had an "affidavit," a document from an American citizen guaranteeing their financial support. Many would-be immigrants would have been allowed to leave Austria (or Germany) but were not permitted to enter the United States. Some of them ended up in other countries (South America, Australia, and New Zealand), but, as history has recorded, many were not able to leave and died in concentration camps. My father's older brother Edu had immigrated to the United States some years earlier and had become chief engineer at the General Radio Corporation in Boston, where he invented the Variac, then a widely used device for continuously varying the electric voltage. The president of General Radio, Mr. Eastman, provided the required affidavit, enabling us to obtain visas for the United States.

Arranging for the journey to the United States took several months. After leaving Austria, my mother, brother and I lived in Zurich. Bob and I enrolled in a neighborhood public school where we rapidly learned *Schwyzertütsch* (the Swiss German dialect). Speaking *Schwyzertütsch* was not only a way of belonging, but it also provided us with a secret language which my mother did not understand. When summer came, we left Zurich and went to La Baule, a beach resort in Brittany, France, on the Atlantic coast, where our Uncle Ernst Papanek had established a summer colony for refugee children. The children were mainly from Jewish families, though there also were some whose parents were political refugees. During the late 1930s and early 1940s, Ernst organized a number of these children's homes, which saved the lives of many children. He described these efforts

in his autobiography, *Out of the Fire*. Ernst's philosophy was that one could rely on the common sense and intelligence of children; one of the hallmarks of the homes was that they were run as cooperatives, with the children's input playing a significant role. Bob and I, and our cousins Gus and George (Ernst's children), as well as newfound friends, spent a blissful summer in La Baule swimming and building sand castles. Although food was in short supply, we were well nourished. I did not realize it then, but my mother and the other grownups were extremely worried about the future. Somehow they kept this from us and gave us a happy summer. Both Bob and I looked back on this period as a wonderful experience. Roberto Benigni's film *Life Is Beautiful* brought back memories of those days.

The visas finally arrived, passage was booked, and the three of us were ready to leave for the United States. Although there had been no news from my father, he miraculously turned up at Le Havre a few days before our ship, the *Ile de France*, was scheduled to depart for New York. From my point of view, it was exactly what my mother had told me would happen: We would all go to America together. When my father joined us in Le Havre, Bob and I asked him what jail had been like. He told us that he had been treated well in jail and cheerfully described how he had passed the time teaching the guards to play chess. One aspect of my father's personality, which strongly influenced both my brother and me, was to make something positive out of any experience.

We never learned the full details of my father's release from jail. My Uncle Edu had posted a $5000 bond for his release and after the war, several Viennese (e.g., a jailer, someone concerned with running the prisons) wrote us claiming credit for his release. There was no evidence as to who had done what, if anything. Nevertheless, my parents sent CARE packages to all the claimants and wished them well. (CARE, Cooperative for Assistance and Relief Everywhere, was a humanitarian organization that distributed nonperishable food packages after the Second World War to help overcome food shortages in the war-torn countries.) My parents directed food packages to people who might have helped free my father, as well as to many other people we knew (e.g., my nanny, Mitzi) who had survived the war.

A NEW LIFE IN AMERICA

We arrived in New York Harbor early in the morning on October 8, 1938, and I stood on the deck watching the Statue of Liberty appear out of the mist. The symbolism associated with the Statue of Liberty may seem trite today (and somewhat deceptive given our present immigration policies), but in 1938 it was special for me. Most of the immigration formalities had been taken care of by Uncle Edu, so that a few hours after our arrival we boarded a train to Boston. (My uncle had a house in an exclusive part of Belmont, a suburb of Boston, which at that time did not allow Jews to live there. We rarely were invited to visit him when we first came, and when we did we had to hide our "Jewishness"; in particular, we were not to say anything before entering the house to avoid the neighbors' being aware of our foreign accent.) During our initial weeks in the United States, we were lodged in a welcoming center in Brighton, where a large mansion had been transformed into an interim home for refugee families. We were taught about America (what it was like for foreigners to live in Boston), given lessons to improve our English, and aided in the steps required to be allowed to remain in the United States as refugees.

Soon we were ready to start a new life. My parents rented a small apartment in Brighton (part of Greater Boston), and Bob and I immediately entered the local public schools, as we had in Zurich. I was in the third grade and had the good fortune to have a teacher (I had a crush on her) who gave me special English lessons after school. At the age of eight, my English advanced so rapidly by being in school and by playing with the neighborhood

children that these special lessons, alas, lasted only a few months.

I very much wanted to be accepted by my new country, and while living in Allston I was a street kid in every sense, hanging around with my friends, playing stick-ball and other such games, occasionally stealing candy just for the fun of it. For a while, I refused to speak German at home, despite my parents' limited English. One afternoon when I was playing in the street, I tripped in my haste to get out of a car's way and ended up with my foot under the car's rear tire. The driver had stopped and gotten out to see what was wrong, but with me screaming and crying it took him a while to understand that he should move the car off my foot. Once he did, thankfully my foot was only mildly sore. He wanted to drive me home and report to my parents what had happened, but I insisted that I was fine and would get home by myself. It was true that I was not hurt, but my primary concern was to keep my parents from knowing what had happened, how I spent my time, and specifically that I played in the streets.

After we came to the United States, our comfortable life in Vienna was a thing of the past. We were now relatively poor, although my father had brought some money in the form of valuable stamps, which he had purchased while we were still in Austria. Despite our economic straits, my parents did everything to ensure that our lives were as unchanged as possible. The first summer we were in the States, both of my parents worked as domestics—my father as a handyman and my mother as cook and cleaning woman—for a wealthy family who had a summer house in New Hampshire. We lived in a small house on the grounds, where Bob and I had an idyllic summer. The next summer my parents were similarly employed at a boys' camp, again to enable Bob and me to spend the summer as campers. My parents both took courses to help them find better employment. My father studied machining at the Wentworth Institute and my mother studied home economics at Simmons College. With the United States entering the War, employment was high, and my father joined an airplane pump factory after he graduated from a one-year course. He rapidly advanced in the company to become a quality inspector and worked at this company until he retired 20 years later. My father frequently told stories to Bob and me about problems he had solved or how he had suggested improvements in the pumps. The way he described his ideas (he had been educated in physics at the University of Vienna) helped arouse our scientific curiosity. After finishing an undergraduate program, my mother found a position as a hospital dietician, similar to the type of work she had done in Vienna at the Fango, her father's hospital. She continued her education and received a Master's degree at the age of 65.

Motivated by their concern for our education, my parents moved to Newton (a suburb of Boston), where the schools were recognized as superior to the Boston public schools. My parents bought a small house in a pleasant neighborhood in West Newton, and I attended the Levi F. Warren Junior High School. To my knowledge, we were the first Jewish family to live there. One Saturday, after we had lived in West Newton for about six months, an FBI agent knocked on the door and politely requested to see my father. The agent explained that he was investigating a complaint from our next-door neighbor, who had telephoned the FBI to report that every morning as he was leaving for work, my father would step out on the front porch, turn around, and make the Nazi salute while shouting "Heil Hitler." The FBI agent appeared rather embarrassed and said that he realized that such an accusation against a Jewish refugee from Nazi Austria was ridiculous. After some questioning (about our family history and present status), he got up to leave and told us that nothing further would happen.

My junior high teachers soon realized that I was bored with the regular curriculum, so they let me sit in the back of the classroom and study on my own. What made this experience particularly nice was that another student, a very pretty girl, was given the same privilege,

and we worked together. The arrangement was that we could learn at our own pace without being responsible for the day-to-day material but had to take the important exams. Several dedicated teachers at Warren Junior High helped us when questions arose, particularly with science and mathematics. With this freedom, we explored whatever interested us and, of course, did much more work than we would have done if we were only concerned with passing the required subjects.

In nonacademic activities, I participated like everyone else (I was not particularly good in sports, though I enjoyed soccer a lot) and made a number of friends that formed a close-knit group throughout high school. As part of our education, we had to choose several technical courses. The two I chose were printing and home economics, the latter not because it was essentially all girls, but because the students did real cooking. I had become interested in cooking early on and used to spend time in the kitchen with my mother and grandmother, who both cooked simply but well with the freshest ingredients. The final exam had us prepare a dinner for the class, with each group responsible for one course.

BEGINNING OF SCIENTIFIC INTERESTS

Soon after we moved to Newton, Bob was given a chemistry set, which he augmented with materials from the school laboratory and drug stores. He spent many hours in the basement generating the usual bad smells and making explosives. I was fascinated by his experiments and wanted to participate, but he informed me that I was too young for such dangerous scientific research. My plea for a chemistry set of my own was vetoed by my parents because they felt that this might not be a good combination—two teenage boys generating explosives could be explosive! Instead, my father had the idea of giving me a Bausch and Lomb microscope. Initially I was disappointed—no noise, no bad smells, although I soon produced the latter with the infusions I cultured from marshes, sidewalk drains, and other sources of microscopic life. I came to treasure this microscope, and more than 60 years later it is still in my possession. One especially rewarding aspect of my working with the microscope was that my father, who was a thoughtful observer of nature (he liked to fish with a simple line, not to catch fish, but because it gave him an excuse to sit by a stream and watch the fish and observe their behavior), spent a lot of time with me and was always ready to come and look when I had discovered something new. I had found an exciting new world and looked through my microscope whenever I was free. The first time I saw a group of rotifers I was so excited by the discovery that I refused to leave them, not even taking time out for meals. They were the most amazing creatures as they swam across the microscope field with their miniature rotary motors. (The rotifers come to mind today in relation to my research on the smallest biological rotatory motor, F_1-ATPase.) My enthusiasm was sufficiently contagious that I even interested some of my friends. It was a special occasion when they came to my house and looked at the rotifers through the microscope.

This was the beginning of my interest in nature study, which was nurtured by my father and encouraged by my mother, even though it was still assumed that I would go to medical school and become a doctor. One day my closest friend, Alan MacAdam, saw an announcement of the Lowell Lecture Series (a Boston institution, originally supported by a Brahmin family—the Lowells), which organized evening courses on a wide range of subjects at the Boston Public Library that were free and open to the public. The organizers invited excellent lecturers from the many universities in the Boston area, as well as from nonacademic disciplines. The series that had caught Alan's eye was entitled "Birds and Their Identification in the Field," to be given by Ludlow Griscom, the curator of ornithology at the Museum of Comparative Zoology at Harvard University. Alan and I occasionally walked in

the green areas in Newton, particularly the Newton Cemetery, and looked for birds with my father's old pair of binoculars. Together we attended the first lecture, which had a good-sized audience, although it was not clear whether most of the people came simply to have a nice warm place in winter rather than because of their interest in birds. I was enthralled by the lecture, which provided insights into bird behavior and described the large number of different species one could observe within a 50-mile radius of Boston. I was amazed that it was possible to identify a given species from "field marks" evident even from a glimpse of a bird, if one knew how and where to look. Alan did not attend the subsequent lectures, but I continued through the entire course. At the end of the fourth or fifth lecture, Griscom came up to me and asked me about myself. He then invited me to join his field trips, and a new passion was born. From that time on, my treasured microscope was relegated to a closet, and I devoted my free time to observing birds on my own, as well as with Griscom and his colleagues, with the Audubon Society, and other groups that organized field trips.

The culmination of these trips was the annual "census," usually held at the height of the bird migration in May. This was an activity sponsored by the Audubon Society, and the objective was to observe (see or hear) the largest number of different species within a given 24 hours. Each year, Griscom organized one such field trip, inviting only a select group of "birders" to participate. The census lasted a full 24 hours, starting just after midnight to find owls in the woods and rails and other aquatic species in the swamps. There was a carefully planned route, based on known habitats and recent sightings of rare species. The specific itinerary was worked out in a meeting, at which everyone contributed what interesting birds they had sighted recently, but Griscom made the final decision on how we would proceed. As the youngest (by far) in the group, I was assigned special tasks. One of these tasks—perhaps not the most pleasant—was to wade into the swamp at night (fortunately there was a moon) and scare up birds so that they would fly off and could be identified by their calls. On this census trip we found 160 or so different species, a record at the time for the area.

I became intrigued by alcids, of which the now extinct, flightless Great Auk was the most spectacular member of the family. I persuaded my family to go for summer vacation to the Gaspé Peninsula in Canada because there was a famous rocky island just offshore that had nesting colonies of two kinds of alcids, puffins and guillemots, as well as gannets, spectacular large black and white sea birds. Although one could not visit the island sanctuary (it was forbidden in order to protect the nesting birds), I borrowed a telescope from the Audubon Society to view the birds. We drove through the Gaspé Peninsula by car and spent the nights in bed-and-breakfast places. One strong impression of the trip through New Brunswick and the Gaspé area was that the houses in most of the villages were in much poorer condition than those on the coast, which were supported by the tourist trade. Moreover, each such small village was dominated by an outsized church, indicating the power of religion in these communities.

Many of the alcids go south to New England for the winter. Usually, they are far out to sea, but when there is a storm they are likely to be blown close to shore, so that such storms (particularly Nor'Easters) present the best opportunity to see rare species, such as the tiny Little Auk, which is only eight inches in length but can survive in the roughest seas. In the winter of 1944, school was closed because of a heavy snowstorm, and I took the early morning train up to Gloucester, a town on Cape Ann north of Boston, and hiked out to the shore. I sat on the steps of one of the large mansions, shuttered for the winter, and looked out to sea through my binoculars. The day started well as I quickly spotted several alcids in the cove below. As I was getting chilled after a couple of hours and ready to walk back to the train station, a car pulled up. A couple of

men got out and walked toward me. At first, I naively presumed they were other birders, interested in what I had seen. I soon realized that they did not look like birders—no binoculars for one thing and not really dressed for a day in the snow. Moreover, they approached me in a rather aggressive manner, asking me what I was doing and why. They did not believe that I was sitting in such a storm looking for birds. Shortly after, they showed me their police badges and bundled me into the car, not for a ride to the train station, but instead to the Gloucester police station. I was only 14 years old and very frightened and became even more so when I realized from their questions that they thought I might be a German spy. That I was an immigrant from Austria, spoke German, and had German-made Zeiss binoculars did not help. They suspected me of signaling to submarines off the American coast, preparing to land saboteurs or whatever. It took hours of interrogation and several phone calls to the Audubon Society before the officers finally decided that I was not doing anything wrong and drove me to the train station. That was the last time I ventured on such a trip by myself.

On one of the field trips to Newburyport with Griscom, I spotted an unusual gull. When I pointed it out to him, he concluded, after looking through his telescope, that he had never seen a bird like that and that we should try to "collect" it, a euphemism for shooting the bird. He had a license to carry a "collecting gun" with a pistol grip and a long barrel that made it easier to aim. Because the bird was far away and separated from us by mud flats, only partly exposed at low tide, I was given the task of collecting the bird. I waded out fairly close to the bird and successfully shot it, even though I had never fired a gun other than at fairs. After a careful comparison with birds in the Museum of Comparative Zoology collection, Griscom was convinced that we had found something new, a hybrid between a Bonaparte's gull (common in America) and a European black-headed gull (common in Europe but rare in North America), which had somehow crossed the ocean. The bird was in the museum collection with its wing feathers, which were essential for its identification, beautifully spread out (**Figure 1**). (I say "was" because when I went recently to find it, the gull had disappeared. My reason for going to look for it was to discuss with Scott V. Edwards, the newly appointed Professor of Ornithology at Harvard, the possibility of sequencing the DNA to find out whether the result would confirm Griscom's identification.)

Figure 1

A photograph of me with the hybrid gull showing its wing feathers, which played the essential role in its identification.

I entered Newton High School in the fall of 1944 but soon found that I did not have the same supportive environment as in elementary and junior high school. My brother, Bob,

had graduated from Newton High School two years before and had done exceedingly well. My teachers presumed that I could not measure up to the standards set by my brother. Since I had always been striving to keep up with Bob and his friends, this just reinforced my feelings of inferiority. Particularly unpleasant were my interactions with the chemistry teacher. When my brother suggested I compete in the Westinghouse Science Talent Search, the chemistry teacher, who was in charge of organizing such applications, told me that it was a waste of time for me to enter and that it was really too bad that Bob had not tried instead. However, I talked to the high school principal and he gave me permission to go ahead with the application. I managed to obtain all the necessary papers without encouragement from anyone in the school. A test was given as part of the selection process, and I found a teacher who was willing to act as proctor. I did well enough to be invited as one of the 40 finalists to Washington, DC. Each finalist had a science project for exhibition in the Statler Hotel, where we were staying. My project was on the lives of alcids, based in part on the trip to the Gaspé Peninsula and some of the field studies I had made during New England winters. The various judges spent considerable time talking with us, and the astronomer Harlow Shapley, who was the chief judge, charmed me with his apparent interest in my project. I was chosen as one of two co-winners. (At that time, there was one male and one female winner; Rada Demereck and I were co-winners.) The visit to Washington, DC, was a great experience, especially because we met President Truman, who welcomed us as the future leaders of America. Moreover, winning the Westinghouse Talent Search made up for the discouraging interactions with some of my high school teachers. Their attitude contrasted with that of my fellow classmates, who voted me "most likely to succeed."

My final forays into ornithology took place during several summers at the end of high school and after I entered college. In 1947, I had a summer internship at the Maryland Patuxent Research Refuge of the Fish and Wild Life Service, the only National Wildlife Refuge established to conduct research. Publicity about the harmful effect of DDT on bird life had prompted studies at the refuge. We collected eggshells as part of a field survey of two several-acre plots, one sprayed with DDT at the normal level and the other without DDT. My task was to analyze eggshells for their DDT contents and to determine the differences between shells from the two plots (their thickness and other features). I also conducted a census twice a day of the birds in the two areas, determined the number of nesting pairs, and collected any dead birds I found. The summer was an exciting one for me and a fine introduction to field research and laboratory work as part of a team. It was a very hot summer, and all my (older) colleagues drank beer to relax in the late afternoon, so I joined them. I did not like the bitter taste initially but rapidly learned to enjoy beer.

Thanks to a meeting with Professor Robert Galambos, who did research on the echolocation of bats in the basement of Memorial Hall at Harvard, I was invited by his collaborator, Professor Donald Griffin, to join his group in a study of bird orientation that was to take place in Alaska during the summer of 1948. (Griffin and Galombos had demonstrated in 1940 that bats used echolocation to orient themselves and find their prey, though Lazzaro Spallanzani had already suggested this in 1794, but apparently no one believed him.) Our team was based at the Arctic Research Laboratory in the town of Point Barrow, Alaska, which is located at latitude 71° north, the northern-most point of land on the North American continent. The laboratory was run by the Office of Naval Research (ONR), primarily to study how humans (presumably soldiers and sailors) can adapt to life in the arctic winter. Its director, Lawrence Irving from Swarthmore College, had a broad view of the laboratory mission and had invited our group to use the facilities. (It is worth mentioning that before there were

organizations to support civilian research, like the National Science Foundation, ONR was the leading government agency in this area.) Our primary interest was in golden plovers, which nested on the tundra in areas not far from the laboratory. Atlantic and Pacific golden plovers nested together, and the two species separated in the fall to migrate over a thousand miles or more southward to their respective winter homes. We trapped some plovers of both species and attached radio transmitters to all of them and magnets to half of them. We then released the plovers 20 to 50 miles from their nests, both in the Atlantic and Pacific direction, and followed them at a distance with a small airplane. The idea was to ascertain if the birds with magnets would have a more difficult time returning to their nesting area. There were suggestive results (the birds with magnets seemed to get more disoriented than those without, though they all found their way home), but Griffin felt that what we had found was not conclusive proof that the plovers had a magnetic sense, and the work was never published.

In Umiat, an observation camp at a distance from the main laboratory, I organized my first experiment with the aid of the other scientists, who must have been amused by my youthful enthusiasm. (I was 17 years old and by far the youngest member of the research team.) The experiment involved several nesting pairs, including robins. Three people participated in the observation of the nests; each person stood a 4-h shift twice a day because there were 24 hours of daylight. We found that the parents fed the robins over the entire 24-h period and, interestingly, that the young robins left the nest earlier than did their cousins, who nested in Massachusetts. I wrote a paper (50) describing the results, with the conclusion that the survival value of the shorter time in the nests, which were highly exposed to local predators, made up for the dangers of the longer flights required to reach the summer nesting area in the Arctic. It is not clear whether my youthful conclusion was correct, although it did stimulate a number of papers, both pro and con, and the paper continues to be cited (106). Also, I noticed that at Umiat, where we were on our own, the normal 24-h day stretched to about 30 h; we stayed awake for 22 or so hours and then slept for about 8 hours.

The following summer Griffin invited me to Cornell University, where he was on the faculty before joining the Biology Department at Harvard. In addition to conducting experiments in the Griffin lab, I enjoyed "hanging out" with college students and school teachers who were taking summer courses at Cornell. I initially worked on bat echolocation and was very impressed by the way the bats were kept in the refrigerator between experiments; they went to sleep, hanging from a rod all in a row. At Griffin's suggestion, I then focused on trying to condition pigeons to respond to a magnetic field to test the results of an article that had concluded that pigeons use the earth's magnetic field to navigate. I was doubtful about the paper because I thought the analysis was flawed. My attempts at conditioning the pigeons proved elusive, but we never published our negative (to me, positive) results. Subsequently, other experiments have shown that pigeons, as well as wild birds, do use the earth's magnetic field as an aid in navigation. This experience taught me that being skeptical is essential in science, but that it is also important to be receptive to new ideas—even if you do not like them.

COLLEGE YEARS

I entered Harvard in the fall of 1947. There was never any question about my wanting to attend Harvard and I did not apply to any other school. In addition to the Westinghouse scholarship, I received a National Scholarship from Harvard to cover the cost of living on campus. Otherwise I would have had to live at home to save money. I would not have minded this, since I was not a rebellious teenager eager for independence and distance from my

parents. However, as I soon discovered, much of the Harvard experience took place outside of classes at dinner and in evening discussions with friends.

At first I still intended to go to medical school but changed my mind during my freshman year. My teenage ornithological studies, fostered by Griscom and Griffin, had already introduced me to the fascinating world of research, where one is trying to discover something new (something that no one has ever known); I began to think about doing research in biology. I had concluded that to approach biology at a fundamental level (to understand life), a solid background in chemistry, physics, and mathematics was imperative, and so I enrolled in the Program in Chemistry and Physics. This program, unique to Harvard at the time, exposed undergraduates to courses in both areas at a depth that they would not have had from either one alone. It had the additional advantage, from my point of view, that it was less structured than chemistry. For example, it did not require Analytical Chemistry, certainly a good course as taught by Professor James J. Lingane, but one that did not appeal to me. Although I shopped around for advanced science courses to meet the rather loose requirements, I also enrolled in Freshman Chemistry because it was taught by Leonard Nash. A relatively new member of the Harvard faculty, Nash had the deserved reputation of being a superb teacher. Elementary chemistry in Nash's lectures was an exciting subject. A group of us (including DeWitt Goodman, Gary Felsenfeld, and John Kaplan—my "crazy" roommate, who became a law professor at Stanford) had the special privilege that Nash spent extra time discussing with us a wide range of chemical questions, far beyond those addressed in the course. The interactions in our group, though we were highly competitive at exam times, were also supportive. This freshman experience confirmed my interest in research and the decision not to go to medical school.

Harvard provided me with a highly stimulating environment as an undergraduate. One aspect was the laissez-faire policy, which allowed one to take any courses with the instructor's permission, even without having the formal prerequisites. The undergraduate dean said it was up to me to decide and, if a course turned out to be too much for me, that would be "my" problem. I enrolled in a wide range of courses, chosen partly because of the subject matter and partly because of the outstanding reputation of the lecturers; these courses included one in *Democracy and Government* and another in *Abnormal Psychology*. More related to my long-term interests were some advanced biology courses, which I registered in without having to suffer through elementary biology and biochemistry. Two memorable courses were George Wald's *Molecular Basis of Life* and Kenneth Thimann's class on plant physiology with its emphasis on the chemistry and physiology of growth hormones (auxins) in plants. Both professors were inspiring lecturers and imbued me with the excitement of the subject. These courses emphasized that biological phenomena (life itself) could be understood at a molecular level, which has been a leitmotif of my subsequent research career. Wald's course also introduced me to the mechanism of vision, which led to my first paper on a theoretical approach to a biological problem (42).

Although I remember my undergraduate career at Harvard as a formative experience that furthered my interest in the world of science, it was reminiscent of my high school days in that my brother had preceded me, had been a stellar student in the Program in Chemistry and Physics, and was in the process of completing a PhD at Harvard with E. Bright Wilson, Jr., and Julian Schwinger. I spent considerable time with Bob and his fellow graduate students in Wilson's group. I was tolerated, I suppose, as Bob's little brother, though one day I made my mark when I solved a problem (they were always "challenging" each other) before any of them did. Given the importance of this "success" in my life, I am fond of the problem and restate it here: "It is agreed that to divide a pie between two

people so that both are satisfied, one is allowed to cut the pie in two and the other chooses. The problem is how to extend this concept (dividing or choosing) to three or more people, so that everyone is satisfied." There is a special solution for three people and a general solution for any number. After solving this problem, I was accepted as part of the group by my brother and his friends, and during the afternoons when I could escape from the many labs I had to do, I would often join them. Their discussions of science exposed me to new ideas that I would not have come across otherwise.

The legendary *Elementary Organic* course taught by Louis Fieser was a standard part of the Program in Chemistry and Physics, but I thought it would be a waste of time: The course had the reputation of requiring a very tedious laboratory and endless memorization. An early version of the well-known textbook by Louis Fieser and Mary Fieser was available in lecture-note form and, rather than enrolling in the course, I tried to learn organic chemistry by reading it on my own, not with complete success. After studying the lecture notes, I enrolled in Paul Bartlett's Advanced Organic because that course taught the physical basis of organic reactions. It was an excellent course, though difficult for me because one was supposed to know many organic reactions, which I had to learn as we went along. At one point, Bartlett suggested that we read Linus Pauling's *Nature of the Chemical Bond*, which had been published in 1939 based on his Baker Lectures at Cornell. The *Nature of the Chemical Bond* presented chemistry for the first time as an integrated subject that could be understood, albeit not quite derived, from its quantum chemical basis. The many insights in this book were a critical element in orienting my subsequent research in chemistry.

At the end of three years at Harvard I needed only one more course to complete the requirements for a bachelor degree. During the previous year I had done research with Ruth Hubbard and her husband, George Wald. (Although Hubbard was scientifically on par with Wald, she remained a Senior Research Associate, a nonprofessorial appointment, until very late in her career when she was finally "promoted" to Professor. This was not an uncommon fate for women in science.) I mostly worked with Hubbard on the chemistry of retinal, the visual chromophore, because she had a deeper knowledge of chemistry than Wald. When I brought up my need to find a course for graduation, Wald suggested that I enroll in the physiology course at the Marine Biological Laboratory in Woods Hole, Massachusetts. This course was one of the few non-Harvard courses that were accepted for an undergraduate degree by the Faculty of Arts and Sciences. The physiology course was widely known as a stimulating course designed for postdoctoral fellows and junior faculty. The lectures in the physiology course by scientists who were summering at Woods Hole, while doing some research and enjoying boating and swimming, offered students a state-of-the-art view of biology and biological chemistry. (The course still exists, although its subject matter has shifted toward cell biology, of greater current interest.) For me, the only undergraduate in the course, it was a wonderful experience. I not only learned a great deal of biology but I also met several people, including Jack Strominger and Alex Rich, who became lifelong friends.

Woods Hole was an exciting place. Among the famous scientists that I met there were Otto Loewi, who had received a Nobel Prize in Physiology and Medicine (1936) for the discovery of the chemical basis of the transmission of nerve impulses, and Albert Szent Gyorgi, who had won a Nobel Prize, also in Physiology and Medicine (1937) for discovering vitamin C and showing that it existed in high concentration in paprika, a staple of the Hungarian diet. His little book, *Nature of Life*, *A Study of Muscle* (116), helped inspire my interest in doing research in biology. Like the *Nature of the Chemical Bond*, its stress on the logic of the subject helped to arouse my interest. These scientists held court in the afternoons at the Woods Hole beach and

fascinated us young people with their discussions of new experiments and scientific gossip. In addition, there was an active student life, since many of the senior researchers brought along students from their labs. One of the justifications for having the laboratory in Woods Hole was that there were a wide range of marine animals which were caught for use in experiments. A prime example is the squid, whose giant axon was the ideal system for studies of the mechanism of nerve conduction. Because most of the experiments used only a small fraction of the animal, each week or so I collected some of the leftover laboratory squids and lobsters and prepared a feast for myself and friends, who provided bread, wine, and salad.

In considering graduate school during my last year at Harvard, I had decided to go to the West Coast and had applied to chemistry at the University of California at Berkeley and to biology at the California Institute of Technology (Caltech). Accepted at both, I found it difficult to choose between them. Providentially, I visited my brother, Bob, who was working with J. R. Oppenheimer at the Institute of Advanced Studies in Princeton, New Jersey. Bob introduced me to Oppenheimer, and briefly to Einstein. When Oppenheimer asked me what I was doing, I told him of my dilemma in choosing between U.C. Berkeley and Caltech for graduate school in chemistry or biology. He had held simultaneous appointments at both institutions and strongly recommended Caltech, describing it as "a shining light in a sea of darkness." His comment influenced me to choose Caltech, and I discovered that Oppenheimer's characterization of the local environment was all too true. Pasadena itself held little attraction for a student at that time. However, camping trips in the nearby desert and mountains and the vicinity of Hollywood made up for what Pasadena lacked.

I had become very interested in films and organized a classic film series at Caltech during my time there. This enabled me to preview many films that I had always wanted to see. The series showed mainly silent films accompanied by live piano music played by fellow students. (One of them was Walter Hamilton, a crystallographer, who died very young.) In searching for films, I gained access to several production studios, where I would ask the librarians to lend me films for our nonprofit Caltech series. The high point was my visit to the Chaplin studio. The receptionist was not particularly forthcoming, but then Charlie Chaplin himself walked in and asked what I wanted. He seemed intrigued by the idea that a science student was interested in films, and I asked him about the possibility of showing Monsieur Verdoux. He said it had been withdrawn (for political reasons), but told the librarian to let me have some of his early short films which at the time were not available to the public. I had always been a Chaplin fan and this meeting was one of the very special events of my graduate career.

At Caltech, I first joined the group of Max Delbrück in biology. He had started out as a physicist but, following the advice of Niels Bohr, had switched to biology. With Salvador Luria and others, he had been instrumental in transforming phage genetics into a quantitative discipline. His research fascinated me, and I thought that working with such a person would be a perfect entrée for me to do graduate work in biology. There were many bright and lively people working with Delbrück. I particularly remember Seymour Benzer, like Delbrück, a former physicist. We had discussions of phage genetics, biology, and a variety of subjects of mutual interest. Among other things, it was Seymour who introduced me to horsemeat, which became a staple of our household in Altadena. The law in Los Angeles was such that at the supermarket horsemeat was sold only as meat for dogs. Not deterred by that, horse filet, which cost a fraction of the corresponding cut of beef, turned up in my cooking as horse stroganoff, horse Cordon Bleu, and so on. Each of the members of our household, which included Sidney Bernhard, Gary Felsenfeld, and Walter Hamilton, had specific tasks to do. Mine,

with Sidney, was cooking, and the horsemeat (as well as the local seafood) was regularly served.

After I had been in the Delbrück group for a couple of months, Delbrück proposed that I present a seminar on a possible area of research. I intended to discuss my ideas for a theory of vision (how the excitation of retinal by light could lead to a nerve impulse), which I had started to develop while doing undergraduate research with Hubbard and Wald. Among those who came to my talk was Richard Feynman; I had invited him to the seminar because I was taking his quantum mechanics course and knew he was interested in biology, as well as everything else. I began the seminar confidently by describing what was known about vision but was interrupted after a few minutes by Delbrück's comment from the back of the room, "I do not understand this." The implication of his remark, of course, was that I was not being clear, and this left me with no choice but to go over the material again. As this pattern repeated itself (Delbrück saying "I do not understand" and my trying to explain), after 30 minutes I had not even finished the 10-minute introduction and was getting nervous. When he intervened yet again, Feynman turned to him and whispered loud enough so that everyone could hear, "I can understand, Max; it is perfectly clear to me." With that, Delbrück got red in the face and rushed out of the room, bringing the seminar to an abrupt end. Later that afternoon, Delbrück called me into his office to tell me that I had given the worst seminar he had ever heard. I was devastated by this and agreed that I could not continue to work with him. It was only years later that I learned from reading a book dedicated to him that what I had gone through was a standard rite of passage for his students—everyone gave the "worst seminar he had ever heard."

After the devastating exchange with Delbrück, I spoke with George Beadle, the chairman of the Biology Department. He suggested that I find someone else in the department with whom to do graduate research. However, I felt that I wanted to go "home" to chemistry and asked him to help me make the transfer. Once in the Chemistry Department, I joined the group of John Kirkwood, who was doing research on charge fluctuations in proteins, as well as on his primary concern with the fundamental aspects of statistical mechanics and its applications. I undertook work on proteins and research started out well. It was complemented by a project involving Irwin Oppenheim and Alex Rich. Kirkwood's course in *Advanced Thermodynamics* was famous for its rigor, and the three of us, with Kirkwood's encouragement, worked together to prepare a set of lecture notes for the course. Each of us was responsible for writing up some of the lectures and the other two read them over. This was very useful for our learning thermodynamics and the set of notes was circulated widely. Some years later, Irwin Oppenheim prepared an improved version of the notes and it was published as a text entitled *Chemical Thermodynamics* (75).

In the spring of 1951, as I was getting immersed in my research project, Kirkwood received an offer from Yale. Linus Pauling, who was no longer taking graduate students, asked each student who was working with Kirkwood whether he would like to stay at Caltech and work with him. I was the only one to accept and, in retrospect, I think it was a very good choice. Initially, I was rather overwhelmed by Pauling. Each day upon arriving at the lab, I found a handwritten note on a yellow piece of paper in my mailbox which always began with something like "It would be interesting to look at. . . ." As a new student I took this as an order and tried to read all about the problem and work on it, only to receive another note the next day beginning in the same way. When I raised this concern with Alex Rich and other postdocs, they laughed, pointing out that everyone received such notes and that the best thing to do was to file them or throw them away. Pauling had so many ideas that he could not work on all of them. He would communicate them to one or another of his students, but he did not expect a response. After I got

over that, my relation with Pauling developed into a constructive collaboration.

Given Pauling's interest in hydrogen bonding in peptides and proteins, he proposed that I study the different contributions to hydrogen bonding interactions for a biologically relevant system, but I felt this would be too difficult to do in a rigorous way. Because quantum mechanical calculations still had to be done with calculating machines and tables of integrals (something difficult to imagine when even log tables have followed dinosaurs into oblivion), we had to find a simple enough system to be treated by quantum mechanical theory. I chose the bifluoride ion (FHF^-) because the hydrogen bond is the strongest known, the system is symmetric, and only two heavy atoms are involved. (Today, such "strong" hydrogen bonds have become popular in analyses of enzyme catalysis, although there is no convincing evidence for their role.)

I sometimes felt intimidated when I went in to talk with Pauling, but it was wonderful to work with him and be exposed to (although not necessarily understand) his intuitive approach to chemical problems. One day I asked Pauling about the structure of a certain hydrogen bonded system (i.e., whether the hydrogen bond would be symmetric, as in FHF^-). He paused, thought for a while, and gave a prediction for the structure. When I asked him why, he thought again and offered an explanation. I left his office and soon realized that his explanation made no sense. So I went in to ask Pauling again, thinking that perhaps he would come up with a different conclusion. Instead, Pauling said that he believed that the predicted structure was correct, but he proposed an entirely different explanation. After going over his analysis, I was again dissatisfied with his rationale and caught up with him as he was leaving his office. He said that he still believed the conclusion was valid and produced yet another rationale. This one made sense to me, so I did some crude calculations which indicated that Pauling was indeed correct. What amazed me then, and still does today, is that Pauling came to the correct conclusion, apparently based on intuition, without having worked through the analysis. He "knew" the right answer, even if it took more thought to figure out why.

The research was very rewarding, all the more so because of the intellectual and social atmosphere of the Chemistry Department at Caltech. The professors—like Pauling, Verner Schomaker, and Norman Davidson—treated the graduate students and postdoctoral fellows as equals. We participated in many joint activities that included trips into the desert, as well as frequent parties held at our Altadena house, where Feynman would occasionally come and play the drums. At one such party, Pauling disappeared for a while and I discovered him out in the backyard on his knees collecting snails, which had infested our yard, for his wife Ava Helen to cook for dinner. (It was only later in France, when I collected my own snails, that I learned how complicated it was to prepare them—the snails had to fast for a week—so that now, looking back, I am not sure what the Paulings did with their snails.)

Pauling's presence attracted many postdoctoral fellows to Caltech. When I was there the group included Alex Rich, Jack Dunitz, Massimo Simonetta, Leslie Orgel, Edgar Heilbrunner, and Paul Schatz. Interacting with them (as a graduate student, I was the "baby" of the group) was a wonderful part of my Caltech education and many of them became my friends. Sadly, Massimo Simonetta, who remained a dear friend and colleague after his return to Italy and whom I visited regularly in Milan, as well as on ski trips to Courmayeur in the winter and Portofino in the summer, died suddenly from virulent leukemia in 1986.

My parents had given me their old car as a graduation present, and several times during my Caltech career I drove across the country to our home in Newton, Massachusetts, for part of the summer. Each time I took a different route, once through Canada with visits to

the Banff and Jasper National Parks, and another time through the Deep South. On one such trip while driving through Texas on a very hot summer day, my friends and I decided to take a swim and cool off. We passed one swimming area, but it was full of people. Because we were unshaven and dirty from the long drive, we looked along the river for a quieter place to swim. About a mile downstream we came upon another swimming area with broken-down steps leading to the water. As it was deserted, we decided it was the perfect place. After we had been in the water for about 10 minutes, a couple of pickup trucks drove up and several men jumped out with guns at the ready. What turned out to be the local law enforcement officers ordered us out of the water and demanded to know what we thought we were doing... "white folks swimming in an area reserved for niggers." They had noticed the Massachusetts license plate on the car and had concluded we were Northern "troublemakers." After some effort we succeeded in explaining that, given our scruffy state, we had just not wanted to bother other (white) people and the officers let us go, with the admonition that we had better drive straight through Texas without stopping anywhere, which we did.

My initial attempt at a purely ab initio approach to the bifluoride ion failed and I soon realized that it was necessary to introduce experimental information concerning the atomic states to obtain a meaningful estimate of the relative contribution of covalent and ionic structures. I developed a method for doing this and completed my work only to discover that William Moffitt (who was to be my predecessor at Harvard) had just published a similar approach called the method of *Atoms in Molecules*. He had presented the method in a more general and elegant formulation (91) compared with my treatment, which focused specifically on the bifluoride ion. Although there were significant differences in the details of the methodology, I felt so discouraged by the similarities that I never published "My Great Idea," as Verner Schomaker, one of the members of my thesis committee, called it. Not too surprisingly, I was having a difficult time writing my thesis. (I retained my interest in this type of approach, and some years later Gabriel Balint-Kurti joined my group as a graduate student, and we proposed an improved version of the theory, which we called the Orthogonalized Moffitt method, and applied it to the potential energy surfaces for simple reactions (4).) Such calculations are mostly of historical interest today, when fast computers and ab initio programs are widely used without empirical corrections, except for complex systems like biomolecules.

POSTDOCTORAL SOJOURN IN OXFORD AND EUROPE

One day in October 1953, Pauling came into the office I shared with several postdocs and announced that he was leaving in three weeks for a six-month trip and that "it would be nice" if I finished my thesis and had my exam before he left. This was eminently reasonable, since I had finished the calculations some months before and I had received a National Science Foundation (NSF) postdoctoral fellowship to go to England that fall. Pauling's "request" provided just the push I needed, even though the introduction was all I had written thus far. With so much to get done, I literally wrote night and day, with my friends typing and correcting what I wrote. In this way, the thesis was finished within three weeks, and I had my final PhD exam and celebratory party. After a brief visit with my parents in Newton, I left for England and arrived shortly before Christmas 1953.

In my NSF postdoctoral application I had proposed to work with John Lennard-Jones in Cambridge, England. He, however, had left Cambridge to become Principal of Keele University in 1953, and so I had to alter my plans. Instead I joined Charles Coulson at Oxford University, where he had an active group in theoretical chemistry at the Mathematical Institute. One member was Simon

Altmann, who greatly improved my limited knowledge of group theory and who, with his wife, Bochia, "adopted" me while I was in Oxford. In addition, there were visitors such as Don Hornig and Bill Lipscomb, who were on sabbaticals.

I was 23 years old when I arrived in England. Having worked continuously all the way through graduate school, I was eager to have the sojourn in Europe provide experiences beyond science. The NSF postdoctoral fellowship provided a generous (at the time) salary of $3000 per year, which was sufficient to do considerable traveling. I took the NSF guidelines about following the customs of the institution quite literally, perhaps more so than was intended, and traveled throughout Europe outside of the three six-week terms when I was in residence in Oxford. In fact, upon my arrival in Oxford shortly before Christmas, I went in to see Coulson, got him to sign my NSF form, and immediately left on the first of many trips to Paris. Although there were few scientific interactions during these extended trips, I learned much about the peoples and their cultures, art, architecture, and cuisine, all of which continue to play an important role in my life. One trip involved driving a Volkswagen across Europe through Yugoslavia to Athens; another an extended visit to France, Switzerland, and Italy. On the latter, I first saw the Lake Annecy and the Haute Savoie region. I concluded that I wanted to own a chalet in one of the upper valleys for summer and winter vacations, but I could not afford it then and for many years to come.

I became interested in photography at that time. Upon completing my PhD, my family had given me a Leica IIIC, a superb camera, which my Uncle Alex had brought to the United States from Vienna. Throughout my travels, I took photographs, particularly of people, using a trick I had developed. The Leica had a long focus lens with a reflex viewer, which enabled me to face away from my subject; I could take photographs of crowds and individuals without their being aware of it. Although the resulting Kodachrome slides are now more than 50 years old, they remain in excellent condition. My wife, Marci, had the idea that the slides, which had hardly been looked at over the years, should be printed and enlarged. This endeavor has, in a sense, come full circle. During the academic year 1999–2000 I was Eastman Professor at Oxford. While there, we were introduced to a marvelous photographic craftsman, Paul Sims (Colourbox Techunique). He made beautiful prints from the collection of slides, and a selection was exhibited at my 75th birthday celebration at NIH in Bethesda, Maryland (101).

During the two years in Oxford as a postdoctoral fellow, I spent more time thinking about chemical problems than actually solving them. My aim was to find areas where theory could make a contribution of general utility in chemistry. I did not want to do research whose results were of interest just to theoretical chemists. Reading the literature, listening to lectures, and talking to scientists like Don Hornig and the Oxford physicist H.M.C. Pryce, I realized that magnetic resonance was a vital new area. Chemical applications of magnetic resonance were in their infancy and it seemed to me that nuclear magnetic resonance (NMR), in particular, was a field where theory could make a contribution. Chemical shifts, for example, could provide a means of testing theoretical calculations, but, of even greater import, quantum mechanical theory could aid in interpreting the available experimental results and propose new measurements.

My first paper in chemistry on the quadrupole moment of the hydrogen molecule, obtained from different approximate wavefunctions, was in this vein (51). Although this was a short paper, I spent an enormous amount of time rewriting and polishing it before I finally was ready to submit it. When students seem to face similar problems in finishing their first paper, I often tell them about what I went through and that publishing (or being ready to publish) one's

work becomes easier with each succeeding paper.

FIVE YEARS AT THE UNIVERSITY OF ILLINOIS: NMR AND COUPLING CONSTANTS

As my postdoctoral fellowship in Oxford (1953–1955) neared its end, I was looking for a position to begin my academic career in the United States. With my growing interest in magnetic resonance, I focused on finding an institution that had active experimental programs in the area. One of the best schools from this point of view was the University of Illinois, where Charles Slichter in Physics and Herbert Gutowsky in Chemistry were doing pioneering work in applying NMR to chemical problems. The University of Illinois had a number of openings in Chemistry at that time because the department was undergoing a radical renovation; several professors, including the chairman Roger Adams, had retired. Pauling recommended me to the University of Illinois and the department offered me a job without an interview and without waiting for a recommendation from Coulson. The latter was fortunate, because Coulson had written that, although he had no doubt about my intellectual abilities, I had done very little work on problems he had suggested. I accepted the offer from Illinois without visiting the department, something unimaginable today with the extended courtships that have become an inherent part of the academic hiring process. The University of Illinois offered me an Instructorship at a salary of $5000 per year; the department offered nothing like the present-day start-up funds, and I did not think of asking for research support.

Although the University of Illinois was a very good institution with excellent chemistry and physics departments, it was located in a small town in the flat rural Midwest, where I could not imagine living for more than five years. Having had such a good time as a postdoctoral fellow traveling in Europe, I was ready to get to work, and Urbana-Champaign seemed like a place where I could concentrate on science with few distractions. The presence of four new instructors—Rolf Herber, Aron Kupperman, Robert Ruben, and me—plus other young scientists on the faculty, such as Doug Applequist, Lynn Belford, and E.J. Corey, led to a very interactive and congenial atmosphere.

I focused a major part of my research on theoretical methods for relating nuclear and electron spin magnetic resonance parameters to the electronic structure of molecules. The first major problem I examined was concerned with proton-proton coupling constants, which were known to be dominated by the Fermi contact interaction. What made coupling constants of particular interest was that for protons, which were not bonded, the existence of a nonzero value indicated that there was an interaction beyond that expected from localized bonds. In the valence bond framework, which I used in part because of my training with Pauling, nonzero coupling constants provide a direct measure of the deviation from the perfect-pairing approximation. To translate this qualitative idea into a quantitative model, I chose to treat the vicinal coupling constant in a molecule like ethyl alcohol, one of the first molecules to have its NMR spectrum analyzed experimentally. Specifically, I chose to study the HCC'H' fragment as a function of the HCC'H' dihedral angle, a relatively simple system consisting of six electrons (with neglect of the inner shells). I believed that it could be described with sufficient accuracy for the problem at hand by including only five covalent valence-bond structures. To calculate the contributions of the various structures, I introduced semiempirical values of the required molecular integrals. Although the HCC'H' fragment is relatively simple, the calculations for a series of dihedral angles were time consuming and it seemed worthwhile to develop a computer program. This was not as obvious in 1958 as it is now. Fortunately, the ILLIAC, a "large" digital computer at that time, had recently been built at the University of Illinois.

If I remember correctly, it had 1000 words of memory, which was enough to store my program. The actual program was written by punching holes in a paper tape. If you made a mistake, you filled in the incorrect holes with nail polish so that you could continue the program, the output appearing on spools of paper. Probably the most valuable aspect of having a program for this type of simple calculation, which could have been done on a desk calculator, was that once the program was known to be correct, a large number of calculations could be performed without having to worry about arithmetic mistakes.

Just as I finished the analysis of the vicinal coupling constants (52), I heard a lecture by R.V. Lemieux on the conformations of acetylated sugars. I do not remember why I went to the talk, because it was an organic chemistry lecture, and the chemistry department at Illinois was rigidly separated into divisions, which had a semiautonomous existence. Lemieux reported measurements of vicinal coupling constants and noted that there appeared to be a dihedral angle dependence, although the details of the behavior were not clear. The results were exciting to me because the experiments confirmed the theory, at least qualitatively, before it was even published.

E.J. Corey, who was an assistant professor at Illinois and later became a colleague at Harvard, was one of the people with whom I had dinner on a fairly regular basis at the Tea Garden, a passable Chinese restaurant in Urbana-Champaign. We often discussed recent work of mutual interest and one day I described the studies that I had made of vicinal coupling constants. Corey immediately recognized the possibility of using the results for structure determination and published what is probably the first application of my results in organic chemistry (7). Not long after, the theory appeared in a comprehensive review of the use of NMR in organic structure determinations (19), and someone introduced the name *Karplus equation* for the relationship I had developed. This proved a mixed blessing. Many people attempted to apply the equation to determine dihedral angles of organic compounds. They found some deviations of the measured coupling constants from the predicted values for known structures and published their results, commenting on the inaccuracy of the theory.

As happens too often with the application of theoretical results in chemistry, most people who used the so-called *Karplus equation* did not read the original paper (52) and thus do not know the limitations of the theory. They assumed that because the equation had been used to estimate vicinal dihedral angles, the theory said that the coupling constant depends *only* on the dihedral angle. By 1963, having realized organic chemists tend to write and read Communications to the *Journal of the American Chemical Society*, I published such a Communication (56). In it, I described various factors, other than the dihedral angle, that are expected to affect the value of the vicinal coupling constant; they include the electronegativity of substituents, the valence angles of the protons (HCC' and CC'H), and bond lengths. The main point of the paper was not to provide a more accurate equation but rather to make clear that caution had to be used in applying the equation to structural problems. My closing sentence, which has often been quoted, was the following: "Certainly with our present knowledge, the person who attempts to estimate dihedral angles to an accuracy of one or two degrees does so at his own peril."

In spite of my concerns about the limitations of the model, the use of the equation has continued, and the original paper (52) is one of the *Current Contents* "most-cited papers in chemistry"; correspondingly, the 1963 paper was recently listed as one of the most-cited papers in the *Journal of the American Chemical Society* (20a). In addition, there have been many empirical "extensions" of the equation; perhaps the most complex published form (46) uses a 12-term expression. Equations have been developed for vicinal coupling constants involving a variety of nuclei (73) (e.g., ^{13}C-CC'-H, ^{15}N-CC'-H), and they have been applied in areas ranging from inorganic to

organic to biochemistry. An important more recent application is the use of these relationships as part of the data employed in structure determination of proteins by NMR (76, 89). The vicinal coupling constant model, which was developed primarily to understand deviations from perfect pairing, has been much more useful than I would have guessed. "In many ways my feeling about the uses and refinements of the *Karplus equation* is that of a proud father. I am very pleased to see all the nice things that the equation can do, but it is clear that it has grown up and now is living its own life" (59).

I continued to work on problems in NMR and ESR (electron spin resonance) because new areas of chemistry were being studied by these spectroscopic methods and it seemed worthwhile to try to provide insights from theoretical analyses of some of these applications. Examples are a study of the hyperfine interactions in the ESR spectrum of the methyl radical (53) and the contributions of π-electron delocalization to the NMR coupling constants in conjugated molecules (54). My general approach to the magnetic properties of molecules was summarized in an article entitled "Weak Interactions in Molecular Quantum Mechanics" (55). The choice of title was apt because the energies involved in coupling constants and hyperfine interactions are indeed weak relative to the electron volts of bond energies, excitation energies, and ionization potentials that are the bread and butter of quantum chemistry. However, the title also had a facetious aspect in that my brother had been working on what the physicists call "weak interactions" (72).

At Illinois, my officemate was Aron Kuppermann. Our instructorship at Illinois was the first academic position for both of us, and we discussed science, as well as politics and culture, for hours on end. We soon became fast friends. He and his wife, Roza, lived in an apartment next to mine and often invited me for dinner. Our friendship has continued for more than 50 years, even though I left Illinois to go to Columbia University and Aron moved to Caltech. We see each other only once in several years, but having Aron and Roza as friends provides a special continuity in my life.

Aron and I decided that, although we were on the faculty, we wanted to continue to learn and would teach each other. I taught Aron about molecular electronic structure theory [we published two joint papers on molecular integrals (64, 77)] and Aron taught me about chemical kinetics, his primary area of research. Aron is officially an experimentalist, but he is also an excellent theoretician, as was demonstrated by his landmark quantum mechanical study of the $H + H_2$ exchange reaction with George Schatz. This work was some years in the future (it was published in 1975) (78), but in the late 1950s we both felt that it was time to go beyond descriptions of reactions in terms of the Arrhenius formulation based on the activation energy and preexponential factor. My research in this area had to wait until I moved to Columbia University, where I would have access to the required computer facilities.

MOVE TO COLUMBIA AND FOCUS ON REACTION KINETICS

During the summer of 1960 I participated in an NSF program at Tufts University with the purpose of exposing high school and small college science teachers to faculty actively engaged in research. Our task was to present some modern chemical concepts in a way that would help the teachers in the classroom. Ben Dailey, one of the organizers of the program, asked me one day as we were standing next to each other in the washroom whether I would consider joining the chemistry faculty at Columbia University, where he was a professor. Because I had already been at Illinois for four of the five years I had planned to stay there, I responded positively. I heard from Columbia shortly thereafter and received an offer to join the IBM Watson Scientific

Laboratory with an adjunct associate professorship at Columbia.

The Watson Scientific Laboratory was an unusual institution to be financed by a company like IBM. Although the laboratory played a role in the development of IBM computers, many of the scientists there were doing fundamental research. The Lab had been founded in 1945 near the end of World War II to provide computing facilities needed by the Allies. Its director, Wallace Eckart, is perhaps best known for his highly accurate perturbation calculation of the three-body problem posed by the motion of the earth around the sun in the presence of the moon; the H + H_2 reaction, which I studied while at the Lab, is also a three-body problem in the Born-Oppenheimer approximation. When Eckart described the position at the Watson Lab to me, he made clear that staff members were judged by their peers for what they did in their research and not for their contribution to IBM. The presence of outstanding scientists on the staff, such as Erwin Hahn, Seymour Koenig, Alfred Redfield, and L.H. Thomas (of Thomas-Fermi fame), supported this description and made the place very attractive. Moreover, the Watson Lab had a special advantage for me in that it had an IBM 650, an early digital computer, which was much more useful than the ILLIAC because of its greater speed, larger memory, and simpler (card) input. (No more nail polish!) I was to have access to considerable amounts of time on the IBM 650 and to receive support for postdocs, as well as other advantages over a regular Columbia faculty appointment. This was a seductive offer, but I hesitated about accepting a position that, in any way, depended on a company, even a large and stable one like IBM. This was based, in part, on my political outlook, but even more so on the fact that industry has as its primary objective making a profit, and all the rest is secondary. By contrast, my primary focus was on research and teaching, which are the essential aspects of a university, but not of industry. Consequently, I replied to Columbia and the Watson Lab that the offer was very appealing, but that I would consider it only if it included a tenured position in the chemistry department, even though I agreed initially to be at the Watson Lab as well. Columbia acceded to my request, and after some further negotiation I accepted the position for the fall of 1960.

The environment at the Watson Lab was indeed fruitful, both in terms of discussions with other staff members and of the available facilities. I was able to do research there that would have been much more difficult at Columbia. However, not unexpectedly, the atmosphere gradually changed over the years, with increasing pressure from IBM to do something useful (i.e., profitable) for the company, such as visiting people at the much larger and more applied IBM laboratory in Yorktown Heights, essentially doing internal consulting. I decided in 1963 that the time had come to leave the Watson Lab, and I moved to the full-time professorial position that was waiting for me in Chemistry at Columbia. (IBM closed the Watson Lab in 1970.) Given that experience, I always warn my students and postdocs about accepting jobs in industry. They may well have an exciting environment when they first join the staff, receive a significantly higher salary than they could at a university, and not have to worry about obtaining grants to support their research. What I urge them to remember is that a new management team can take over at any time, particularly if the company is not doing well, and decide to cut down on the research budget. (Research in the short run only spends money, even if it can finally produce a profit.) This attitude has led to layoffs of individual scientists or the closing of beautifully equipped research laboratories that were built only a few years before. It is of primary importance that your objectives (in my case, teaching and research) be the same as those of the institution where you work. This requirement is ideally satisfied in a good university but cannot be guaranteed in industry.

I continued research in the area of magnetic resonance after moving to New York.

One reward of being at Columbia was the stimulation provided by interactions with new colleagues, such as George Fraenkel, Ben Dailey, Rich Bersohn, and Ron Breslow. Frequent discussions with them helped to broaden my view of chemistry. In particular, my interest in ESR was rekindled by George Fraenkel and we published several papers together (62, 66, 80), including a pioneering calculation of ^{13}C hyperfine splittings (62). Although the techniques we used were rather crude, the results provide insights concerning the electronic structure of the molecules considered and aided in understanding the measurements. Many of the weak interactions, which could be used to provide information about the electronic structure of molecules, were a real challenge to estimate in the mid-1960s. Now they can be calculated essentially by pushing a button with programs like the widely used Gaussian package. The high-level ab initio treatments that are used routinely today have the drawback that, even though the results can be accurate, the insights obtained by the earlier, simplified approaches are often lost in the complexity of the calculation.

My interest in chemical reaction dynamics had deepened at Illinois through many discussions with Aron Kuppermann, as already mentioned, but I began to do research in the area only after moving to Columbia. There were several reasons for this. There is no point in undertaking a problem if the methodology and means for solving it are not available: It is important to feel that a problem is ripe for solution. (This has been a guiding rule for much of my research—there are many exciting and important problems, but only when one feels that they are ready to be solved should one invest the time to work on them. This rule has turned out to be even more important in the application of theory to biology, as we shall see later.) Given the availability of the IBM 650 at the Watson Lab, the very simple reaction, $H + H_2 \rightarrow H_2 + H$, which involves an exchange of hydrogen atom with a hydrogen molecule, could now be studied by theory at a relatively fundamental level. Moreover, early measurements made by Farkas & Farkas in 1935 (26) of the rate of reaction over a wide temperature range provided important data for comparison with calculations. A second reason for focusing on chemical kinetics was that crossed molecular beam studies were beginning to provide much more detailed information about these reactions than had been available from gas phase or solution measurements. The pioneering experiments of Taylor & Datz opened up this new field in 1955 (117), although it was not until 2000 that Datz received the prestigious Enrico Fermi Award in recognition of this work. Many groups extended their original crossed molecular beam experiments and showed that it was possible to study individual collisions and determine whether they were reactive. Thus, calculated reaction cross sections, rather than overall rate constants, could be compared directly with experimental data.

To do a theoretical treatment of this, or any other reaction (including the protein folding reaction), a knowledge of the potential energy of the system as a function of the atomic coordinates is required; it is necessary to know the potential energy surface or energy landscape, as it is now called. Isaiah Shavitt, who was working with me as a postdoctoral fellow at the Watson Lab on quantum mechanical calculations, had developed new methods for evaluating multicenter two-electron integrals (109), and he used the $H + H_2$ potential surface as his first application (110). Even though this reaction involved only three electrons and three nuclei, the theoretical surface was expected to be useful only for determining the general features, and a more accurate surface was needed for calculating reaction attributes for comparison with experiment. (Five years later Liu (86) was able to calculate an accurate surface for the $H + H_2$ exchange reaction.) Thus, it was necessary to resort to so-called semiempirical surfaces, whose form was given by a quantum mechanical

model with parameters determined from experiment.

Already in 1936, J. Hirshfelder and B. Topley, two students of H. Eyring, had attempted a trajectory calculation of the H + H_2 reaction with the three atoms restricted to move on a line, for simplicity (40). In a trajectory calculation one determines the forces on the atoms, here the three hydrogen atoms, from the potential energy surface and integrates Newton's equation, F = ma, to obtain the positions of the atoms as a function of time. Hirschfelder and Topley used a three-body potential for the reaction based on the Heitler-London method. They calculated a few steps along the trajectory but were not able to finish the calculation, so we do not know (and never will since we do not have the initial velocities) whether the trajectory was reactive. The potential had a well in the region where all three atoms were close to each other ("Lake Eyring" as it was called), which was expected to give a three-body complex under the collision conditions appropriate for the reaction. Ab initio quantum mechanical calculations, such as that of Shavitt, indicated that this was incorrect, i.e., there was a simple activation barrier. Thus, to obtain a meaningful description of the H + H_2 reaction, it was necessary to introduce a more realistic potential function. Moreover, what was needed was the reaction surface in full three-dimensional space, rather than restricting the hydrogen atoms to positions on a line.

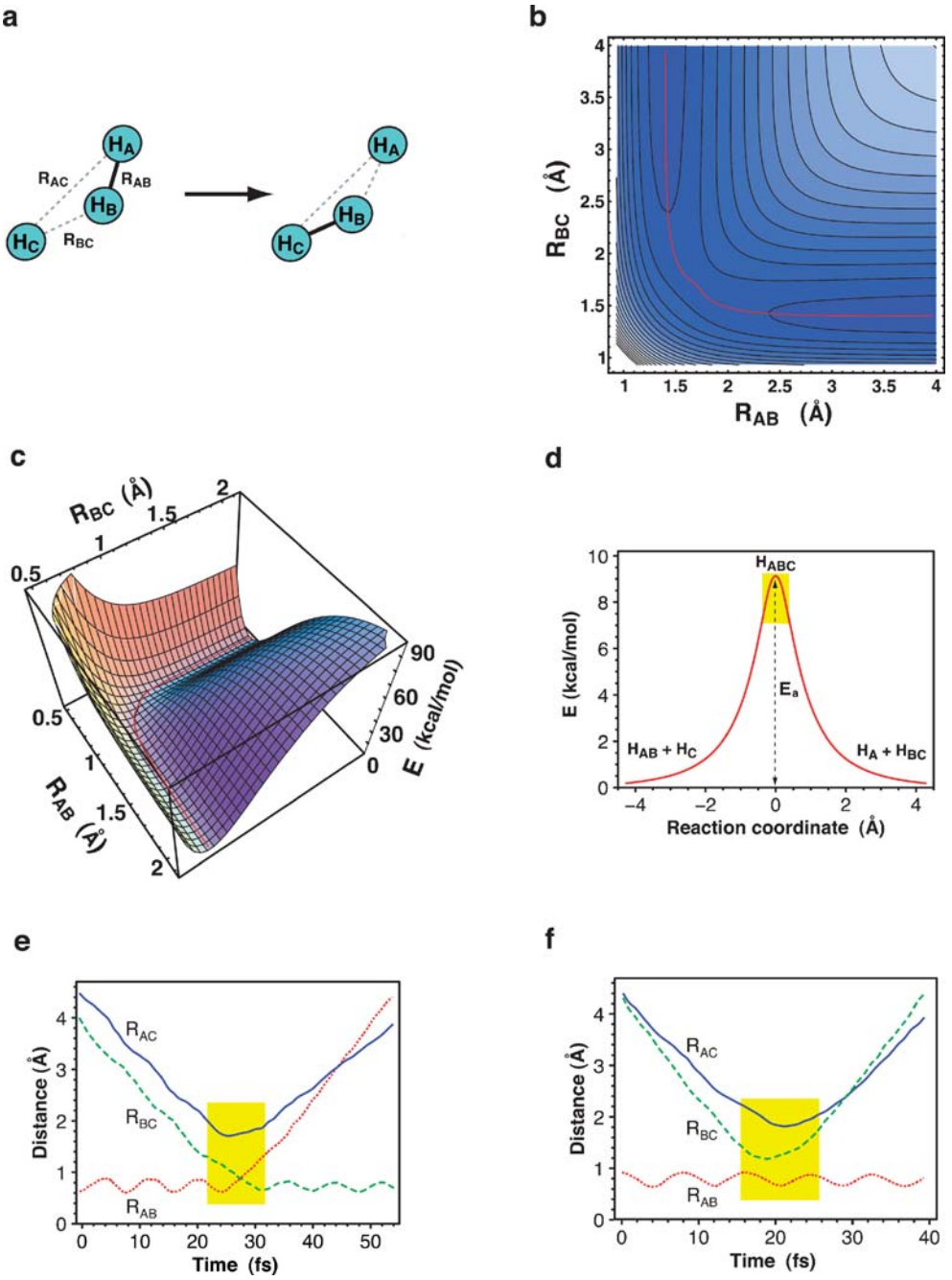
Richard Porter, a graduate student with F.T. Wall, had used a surface without Lake Eyring to improve the collinear collision calculations (119). Much impressed by Porter, I invited him to join my group at Columbia as a postdoctoral fellow. At Columbia, we rapidly developed a semiempirical extension of the original Heitler-London surface for the H + H_2 reaction, based on the method of diatomics in molecules, and calibrated the surface with ab initio quantum calculations and experimental data for the reaction (100). This surface, which is known as the Porter-Karplus surface, has an accuracy and simplicity that led to its continued use in many reaction rate calculations by a variety of methods over the years.

Once the surface was developed, we were ready to undertake the first full three-dimensional trajectory calculation for the exchange reaction. Dick Porter was a fundamental contributor to the H + H_2 research, which also involved R.D. Sharma, another postdoctoral fellow. With the availability of large amounts (by the standards of the day) of computer time on the IBM 650 at the Watson Lab, we were able to calculate enough trajectories to obtain statistically meaningful results (69). Determination of the reaction cross section required the calculation of a series of trajectories with an appropriately chosen range of initial conditions, such as relative velocities and impact parameters. The trajectories start with the reactants far apart (so far that the interaction between the hydrogen atom and

Figure 2

The exchange reaction between a hydrogen atom and a hydrogen molecule. (*a*) Schematic representation of the reaction with definitions for the distances R_{AB}, R_{AC}, and R_{BC}. (*b*) Contour plot of the potential energy surface for a linear collision as a function of the distances R_{AB} and R_{BC} with $R_{AC} = R_{AB} + R_{BC}$; the minimum-energy path is shown in red. (*c*) Same as panel (*b*), but in a three-dimensional representation. (*d*) Energy along the reaction coordinate corresponding to the minimum-energy path in panels (*b*) and (*c*); the transition state is indicated in yellow. (*e*) A typical trajectory for the reactive, three-dimensional collision; the three distances R_{AB}, R_{AC}, and R_{BC} are represented as a function of time. (*f*) A typical trajectory for the nonreactive collision; as shown in panel (*e*). In both panels (*e*) and (*f*) the interactions between the three atoms are limited to a very short time period (yellow background); this mirrors the narrow potential energy barrier in panel (*d*). The figure has been reproduced, with permission, from Reference 24.

hydrogen molecule are negligible), let them collide in the presence of the interaction potential, and then follow the atoms until the products are again far apart. By looking at which atoms are close together, one can determine whether a reaction has taken place (**Figure 2**). As can be seen from the figure, the reaction (i.e., the time during which the three atoms are interacting) takes only a few femtoseconds. This illustrates a fundamental



point, namely that many simple reactions have a small rate constant, not because of the elementary reaction rate, which is fast when it occurs, but because of the large activation energy, which makes most thermal collisions nonreactive. Within the approximation that classical mechanics is accurate for describing the atomic motions involved in the $H + H_2$ reaction and that the semiempirical Porter-Karplus surface is valid, a set of trajectories makes it possible to determine any and all reaction attributes, e.g., the reaction cross section as a function of the collision energy. The ultimate level of detail that can be achieved is an inherent attribute of this type of approach, which I was to exploit 15 years later in studies of the dynamics of macromolecules. Although there are significant quantum corrections for $H + H_2$, the results for the reaction cross section as a function of internal energy and the rate constant as a function of temperature provided insights concerning the fundamental nature of chemical reactions that are as valid today as they were 40 years ago when the calculations were performed.

As in many of my papers in which a new method was developed (69), I tried to present the detail necessary for the reader to reproduce and use what had been done. (We had to work through it all, so why not save others the effort?) The requirement that the work be reproducible is often cited as a standard for publishing papers, but, in practice, few papers are written in this way. Recently, I was pleased to learn that our paper was cited by George Schatz (105) as one of the key twentieth-century papers in theoretical chemistry. Schatz pointed out that what we had called the quasiclassical trajectory method (classical trajectories with quantized initial conditions, which are very important for the H_2 molecule because of its large zero-point vibrational energy, some of which is available in the transition state) was still widely used, even though now full quantum dynamics calculations for the $H + H_2$ reactions and a small number of other reactions are available. Moreover, Schatz states, "The KPS paper stimulated research in several new directions and ultimately spawned new fields."

After the $H + H_2$ reaction calculation, Dick Porter and I collaborated on the textbook *Atoms and Molecules* (68), which developed quantum chemistry at the introductory level for students of physical chemistry. It was based on a lecture course I had given at Columbia and then at Harvard University. (Teaching is a very good discipline, which forces the instructor to understand a subject well enough so it can presented in a fashion clear enough for students to understand.) We thought that writing a book based on the lecture notes would be simple to do, but in fact it was an enormous task. The book was finished only because Dick and I were together for a summer on Martha's Vineyard at a "writing camp" for scientists, sponsored by an imaginative young publisher, Bill Benjamin. Later, while spending a semester at the Weizmann Institute in Rehovot, Israel, I used part of the time to correct the proofs, which in my case inevitably led to significant rewriting. The book has been a success, particularly as a source of material for teachers of physical chemistry.

Unlike quantum dynamics calculations, the quasiclassical trajectory method was easily extended to more complex systems. One study that I remember as particularly interesting was done by Martin Godfrey, that of the $K + CH_3I \rightarrow KI + CH_3$ reaction, in which the collisions involved an orientated CH_3I molecule (63). We were stimulated to do this calculation by an ingenious experiment performed by Richard Bernstein, who was one of the outstanding contributors to the field of crossed molecular chemistry but died young. He, indeed, oriented the CH_3I reactant relative to the incoming K^+ ion so that one could study the effect of the orientation on the reaction and obtain additional information for comparison with the calculation; the two papers were published together in the *Journal of the American Chemical Society* (6).

RETURN TO HARVARD UNIVERSITY AND BIOLOGY

In 1965, it was time to move again. Columbia and New York City were stimulating places to live and work, but I felt that new colleagues in a different environment would help to keep my research productive. I had incorporated this idea into a "plan": I would change schools every five years and when I changed schools I would also change my primary area of research. It was more exciting for me to work on something new, where I had much to learn so as to stay mentally young and have new ideas.

When it became known that I was planning to leave Columbia University, numerous schools invited me to join their faculty. With considerable difficulty, I narrowed the choice down to U.C. Berkeley and Harvard and decided to visit each place for a semester during a sabbatical year (1965–1966). I enjoyed my stay in both places; discussions with colleagues were stimulating and it was very hard to decide between the two schools. I particularly enjoyed my interactions at U.C. Berkeley with Bob Harris, a gifted theoretician who 10 years before had been my very first research student while he was an undergraduate at the University of Illinois. We spent many hours together talking science and politics. This was the era of the Vietnam antiwar movement, and I was introduced to police brutality during some of the marches in Berkeley, a center of the movement, and particularly in neighboring Oakland, which supported the war, in contrast to the Berkeley citizens.

This was not my first experience with political protest, however. I had participated in the 1950s as a Caltech graduate student in meetings organized against the death penalty sentences of Julian and Ethel Rosenberg. In the mid-1970s, my brother, Bob, was initially refused a security clearance to do research at the Livermore Laboratory. Because his participation was deemed important to the laboratory, the administrators appealed and found out that the reason for the refusal was my presence at a Unitarian Church in Los Angeles at a Rosenberg protest meeting two decades previous. Once this item in his FBI file was exposed, Bob rapidly received the necessary clearance.

By contrast, the one time I needed a clearance, it was not granted. I was invited to participate in a disarmament study sponsored in Woods Hole by the National Academy of Sciences in the late 1970s. Every participant had to have a security clearance so that when the report was issued, no one could say that the people involved did not have access to the required information. I had not requested a clearance previously, and it was arranged that I apply for one. I arrived in Woods Hole and attended the opening meeting, which was public, but was not allowed into the sessions after that. While awaiting my clearance to participate in the month-long meeting, I relaxed with my family and worked on my own research in a pleasant nearby hotel with a swimming pool, courtesy of the sponsors. This also permitted me to renew my ties with the Marine Biological Laboratory. The disturbing element in my FBI record was the one that had raised problems for my brother, namely that I had attended the Rosenberg protest meeting. It is still amazing to me that the U.S. government wastes so much time and money recording the attendance at meetings that one should have the right to attend without fear of future harassment or discrimination.

Another such experience occurred while I was on the faculty of the University of Illinois in 1955. Shortly after I moved there, I began to receive a number of visits from FBI agents. There were always two of them; one was from the local (Chicago) office and the other was a different person each time. They questioned me about my political views and focused on the time I had spent in Yugoslavia while I was a postdoctoral fellow at Oxford. I had been there as a tourist and photographer, as already mentioned, but the FBI apparently had other ideas. On one such visit, the "changing" agent suddenly began speaking in a

language I did not understand. It turned out to be Serbian and was apparently meant to trick me. What exactly the FBI was looking for I never discovered. The visits stopped after about six months.

A variety of factors led me to choose Harvard, one of which, in retrospect, was the fact that I had been a Harvard undergraduate. Also, I felt that the Berkeley environment and its weather were just too nice and that the distractions from work were too great, as evident from the activities of a considerable portion of the Berkeley chemistry faculty at that time. I came to Harvard as Professor in the fall of 1966 and received the title of Theodore William Richards Professor in Chemistry in 1979. Although such chairs mean little at Harvard, other than that the funds for one's salary come out of a special endowment, I was pleased to receive this title for two reasons. First, the previous holder of the chair had been E. Bright Wilson, a highly respected member of the department for his science, his humanity in dealing with students, and his high standards of intellectual honesty. Second, this chair was the only one in chemistry named after a scientist (the first American to win the Nobel Prize in Chemistry) instead of the donor of the funds.

At Harvard I continued to do research in the some of the areas that I had developed at Illinois and Columbia, including the study of hyperfine interactions in ESR (102) and the use of quasiclassical trajectory methods for the study of reactions (37). With the results from the trajectory calculations, Keiji Morokuma, B.C. Eu, and I undertook a study of the relation between reaction cross sections and transition state theory as a test of this widely used model in chemistry (93, 94). The application of many-body theory to the electronic structure of atoms and molecules (17, 31), as an extension of methods developed in physics, was also of interest to me, in part to understand better what was involved in this development. I have always found it very helpful when I see a new idea or method to apply it to some problem, even if the specific research is not that significant.

After I had been at Harvard for only a short time, I realized that if I was ever to return to my long-standing interest in biology I had to make a break with what had been thus far a successful and very busy research program in theoretical chemistry. I felt that I had grasped what was going on in elementary chemical reactions and the excitement of learning something new was no longer there. The initial qualitative insights obtained from relatively simple approaches to a new problem are often the most rewarding. This is not to imply that the field of gas-phase chemical reactions has not continued to flourish. It is still active, with ever-finer details concerning reactive collisions being elucidated. For example, I very much enjoyed attending a meeting on reaction dynamics at the Fritz Haber Institute in Berlin in 1982, where I learned about the exciting research going on; I, however, gave a lecture on protein dynamics (58). The meeting also brought home to me that other people with skills different from mine are better able to contribute to the advanced technologies now required in this area.

I planned to take a six-month leave in the fall of 1969 and chose the Weizmann Institute, in part because it had an excellent library. I was aware of Shneior Lifson's work on polymer theory and his reputation of being an open-minded scientist, as well as a marvelous storyteller. I wrote Shneior asking whether I could come for a semester, and he kindly invited me to join his group. The sabbatical gave me the leisure to read and explore a number of areas in which I hoped to do constructive research by applying my expertise in theoretical chemistry to biology. Discussions with Shneior and visitors to his group helped me in these explorations.

A key, although accidental, element in my choice of a problem for study in biology was the publication of *Structural Chemistry and Molecular Biology*, a compendium of papers in a volume dedicated to Linus Pauling

for his 65th birthday. I had contributed an article entitled, "Structural Implications of Reaction Kinetics," (57) which reviewed some of the work I have already described in the context of Pauling's view that a knowledge of structure was the basis for understanding reactions. However, it is not my article that leads me to mention this volume, but rather an article by Ruth Hubbard and George Wald entitled, "Pauling and Carotenoid Stereochemistry." They reviewed Pauling's contribution to the understanding of polyenes with emphasis on the visual chromophore, retinal. The article contained a paragraph, which I reproduce here because it describes an element of Pauling's approach to science that greatly influenced my research:

"One of the admirable things about Linus Pauling's thinking is that he pursues it always to the level of numbers. As a result, there is usually no doubt of exactly what he means. Sometimes his initial thought is tentative because the data are not yet adequate, and then it may require some later elaboration or revision. But it is frequently he who refines the first formulation."

On looking through the article, it was clear to me that the theory of the electronic absorption of retinal and its geometric changes on excitation, which play an essential role in vision, had not advanced significantly since my discussions with Hubbard and Wald during my undergraduate days at Harvard. I realized, in part from my time in Oxford with Coulson, that polyenes, such as retinal, were ideal systems for study by the available semiempirical approaches; that is, if any biologically interesting system in which quantum effects are important could be treated adequately at that time, retinal was it. Barry Honig, who had received his PhD in theoretical chemistry working with Joshua Jortner, joined my research group at that time. He was the perfect candidate to work on the retinal problem. It was known that the retinal (see **Figure 3**) is not planar. It is twisted about the C_{12}–C_{13} single bond, and this was thought to play a role in the photoisomerization reaction (the C_{11}–C_{12} double bond charges, from *cis* to *trans*) that gives rise to the visual signal. No structure of retinal was available, so it was not known whether the twist led to a 12-s-*cis* or 12-s-*trans* configuration (**Figure 3**). Honig did a calculation with a Hückel one-electron Hamiltonian for the π-electron system and a pairwise nonbonded energy function for the sigma bond framework of the molecule (42). The theory predicted that the structure was 12-s-*cis*.

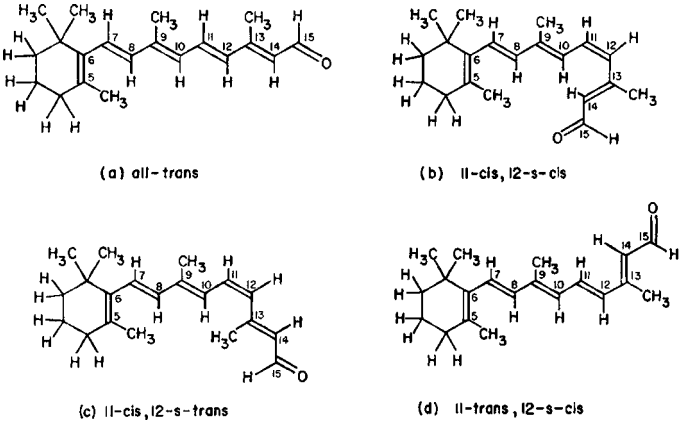


Figure 3

The different form of retinal considered in the calculations. The figure has been reproduced, with permission, from Reference 42.

We felt that this result with its implication for visual excitation was appropriate for publication in *Nature*. We submitted the paper, which received excellent reviews, but came back with a rejection letter stating that because there was no experimental evidence to support our results, it was not certain that the conclusions were correct. This was my first experience with *Nature* and with the difficulty of publishing theoretical results related to biology, particularly in high impact journals. The problem is almost as prevalent today as it was then, i.e., if theory agrees with experiment it is not interesting because the result is already known, whereas if one is making a prediction, then it is not publishable because there is no evidence that the prediction is correct. I was sufficiently upset by this reaction to our work that I called John Maddox, the insightful

Editor of *Nature*, and explained the situation to him. Apparently, I was successful, as the paper was accepted. A subsequent crystal structure verified our prediction (36). In a review of studies of the visual chromophore (43), I noted that "Theoretical chemists tend to use the word 'prediction' rather loosely to refer to any calculation that agrees with experiment, even when the latter was done before the former."

The study of the retinal chromophore gave rise to a sustained effort in my group concerned with the properties of retinal and other polyenes. The continuing effort was fostered, in part, by Bryan Kohler and Bryan Sykes, two assistant professors who had joined the Chemistry Department and were doing experiments that provided challenges for theory. They were part of a group of young faculty (it also included William Reinhardt and Roy Gordon, plus William Miller, a Junior Fellow), which made the department particularly stimulating at that time. Their offices were located along a narrow corridor on the ground floor of Converse Laboratory, with my office at one end. My daily strolls down this corridor provided many occasions for scientific discussion. A collaboration with Sykes led to one of the earliest uses of vicinal spin-spin coupling constants and the nuclear Overhauser effect in NMR to determine the conformations of a biomolecule (retinal in this case) (41). The technique, in a much more elaborate implementation, is now the basis of most protein NMR structure determinations. Kohler and his student, Bruce Hudson, were doing high resolution spectral studies of simple polyenes (e.g., hexatriene) and had observed a very weak absorption below the strongly absorbing transition, which is the analog of the one involved in retinal isomerization. They suggested that there exists a forbidden transition, which was not predicted by simple (single-excitation) models of polyene spectra, such as the one used by Honig in his study of retinal. Klaus Schulten, then a graduate student, working jointly with Roy Gordon and me, introduced double excitations into the Parisar-Parr-Pople (PPP) approximation for π-electron systems and found the low-lying (forbidden) state in hexatriene and octatetraene (108). A number of related studies followed. Arieh Warshel had joined my group at Harvard after we met at the Weizmann Institute, where he had been a graduate student with Lifson. He extended the polyene model by introducing a quantum mechanical Hamiltonian that refined the PPP method for the π-electrons and by treating the sigma-bonded framework by a molecular mechanics approach fitted to a large set of experimental data (120); the method, like the simpler model used by Honig, was an early version of the quantum mechanical/molecular mechanical (QM/MM) approach that is now widely employed for studying enzymatic reactions (28). We used the method to calculate the vibronic spectra of retinal and related molecules (120). Subsequently, a collaboration was initiated with Veronica Vaida, a member of the chemistry faculty, and her graduate student Russ Hemley. He extended the approach we had developed for excited states to molecules such as styrene (39), which Vaida and her students were studying experimentally.

In the 1970s I moved to Mallincrodt from the Converse offices, where the large amphitheatre lecture hall had been renovated into a three-story integrated space to house the physical chemistry faculty and the theoretical students. The renovated area, known as the "New Prince House" (Prince House was an old Cambridge house near the Chemistry Department where the theoretical students had offices for a number of years) promoted interaction among all occupants—senior and junior faculty and the theoretical postdocs and graduate students who had offices in the lower depths of the tri-level complex. Its lounge area equipped with an espresso coffee machine was ideal for generating discussions. Among my many interactions over the 20-year period this complex existed, none proved more fruitful than those with Chris Dobson, who was a junior faculty member in the department from 1978 to 1980 before returning to

Oxford. Our collaborations continue to this day, as described below.

HEMOGLOBIN: A REAL BIOLOGICAL PROBLEM

Another scientific question that appeared ready for a more fundamental investigation was the origin of hemoglobin cooperativity, the model system for allosteric control in biology. Although the phenomenological model of Monod, Wyman, and Changeux (92) had provided many insights, it did not attempt to make contact with the detailed structure of the molecule. I had already begun working on hemoglobin with Robert Shulman, then at Bell Labs, who had measured the paramagnetic NMR shifts of the heme protons, and we had developed an interpretation of the results on the basis of the electronic structure of the heme (111). In 1971 Max Perutz had just determined the X-ray structure of deoxy hemoglobin, which complemented his earlier results for oxy hemoglobin (98). By comparing the two structures, he was able to propose a qualitative molecular mechanism for the cooperativity. Alex Rich, now a professor at the Massachusetts Institute of Technology, had invited Perutz to present two lectures describing the X-ray data and his mechanism. After the second lecture, Alex suggested that I come to his office to have a discussion with Perutz. Perutz was sitting on a couch in Alex's office and eating his customary banana. I asked him whether he had tried to formulate a quantitative thermodynamic mechanism based on his structural analysis. He said no and seemed very enthusiastic, although I was not sure whether he had understood what I meant. Having been taught by Pauling that until one expressed an idea in quantitative terms, it was not possible to test one's results, I went away from our meeting thinking about the best way to proceed. Attila Szabo had recently joined my group as a graduate student, and the hemoglobin mechanism seemed like an ideal problem for his theoretical skills. The basic idea proposed by Perutz was that the hemoglobin molecule has two quaternary structures, R and T, in agreement with the ideas of Monod, Wyman, and Changeux; that there are two tertiary structures, liganded and unliganded for each of the subunits; and that the coupling between the two is introduced by certain salt bridges whose existence depended on both the tertiary and quaternary structures of the molecule. Moreover, some of the salt bridges depended on pH, which introduced the Bohr effect on the oxygen affinity of the subunits. These ideas were incorporated into the statistical mechanical model Szabo and I developed (115). It was a direct consequence of the formulation that the cooperativity parameter n (i.e., the Hill coefficient) varied with pH. This was in disagreement with the hemoglobin dogma at the time and led a number of the experimentalists in the field to initially disregard our model, which was subsequently confirmed by experiments.

When we began working on the model, I discussed our approach with John Edsall and Guido Guidotti, both biology professors at Harvard. Edsall was well known for his deep understanding of protein thermodynamics and Guidotti was an expert on hemoglobin. There were a number of parameters in the model and we had chosen their values by use of physical arguments. Because the values of the parameters were estimated, the results from the model gave only approximate agreement with experiment. Guidotti warned me that such results would not be accepted by the hemoglobin community, in particular, and biologists, in general. Consequently, we inverted the description of the model. We used experimental data to determine the parameters so that the agreement with experiment was excellent and then justified the values of the parameters with the physical arguments we had developed. During the formulation of our ideas, we often asked Guidotti which of certain experiments were to be trusted, since the nearly overwhelming hemoglobin literature contained sets of data that disagreed with each other, without any comment from the

authors indicating which measurements were correct and why.

The paper describing the hemoglobin work was written in Paris, much of it at *Aux Deux Magots*, a left-bank café famous as a meeting place for writers and philosophers from the time of Jean-Paul Sartre. I was on sabbatical leave during 1972–1973 and officially at the Université de Paris XI in Orsay, a suburb of Paris, with the group of Jeannine Yon-Kahn, a pioneer in experimental studies of protein dynamics. However, I spent much of my time in Paris at the Institut de Biology Physico-Chimique on rue Paul et Marie Curie in the 5th Arrondissement. Having often visited Paris since my postdoctoral days and lived there on a sabbatical, I had begun to consider the possibility of moving to Paris on a permanent basis in 1970. I had been at Harvard for the canonical five years, and the idea of returning to Europe was tempting. Given the anti-Semitism and Nazi-leaning parties that still were prevalent in Austria, I had no desire to return to the country of my birth. France offered many attractive aspects of European life and culture, and I believed that I could do high-level research there in theoretical chemistry and its biological applications. After the 1968 revolution, the immense Université of Paris, with more than 300,000 students, had been divided into a dozen campuses. With true French rigor, they were named Paris I, Paris II, etc., although they now have names, instead of merely numbers. Orsay (Paris XI) was one of three science campuses, and it was certainly the best. However, it had the drawback that it was about 40 minutes by the RER (commuter rail) from Paris. If I was going to move to a Paris university, I wanted to live in Paris itself. Consequently, I focused on the two other scientific universities (Paris VI and Paris VII) that were intertwined on the Jussieu campus, a block of ugly modern buildings. Their saving grace was a central location in the area where the Halles aux Vins had been located before World War II. The neighboring streets were still dotted with good inexpensive restaurants dating back to the area's previous existence and now thriving on the faculty and student clientele.

In discussions with colleagues who had urged me to live in France, a serious obstacle became clear. I was a tenured professor at Harvard and not surprisingly was willing to move only if I was offered a permanent position in Paris. However, French university professors were civil servants and only French citizens could be civil servants. Because obtaining French citizenship without losing my American one was out of the question at the time (it is now possible and our son, Mischa, has dual citizenship), I was ready to give up the idea of moving to Paris. Many things in France were achieved then (and still are) by political influence. Jacques DuBois, a chemistry professor at Paris VII with connections to the Pompidou government, said he would try to "arrange the situation." I did not know exactly what he meant but hoped that the tenure problem could be solved. On that basis I took a leave of absence from Harvard.

With only a verbal commitment of a permanent position, I moved the major part of my research group (including David Case, Bruce Gelin, and Iwao Ohmine, among others) from Harvard in the fall of 1974. At Paris VII empty laboratory spaces awaited us. We bought office furniture and computing equipment and went to work. One thing that made the transition much easier was that Marci Hazard, who had joined the lab as secretary in May, came along. Many of the logistical problems (e.g., finding where to purchase what we needed) were solved by her, and she played a key role in the cohesion of the group. As the year went on, DuBois reported on his progress in regularizing my status. I had come as a Professeur Associé, which is an annual appointment open to non-French citizens. Finally, in January a decree was published in the official government register (much of the French government functions by decrees that do not require votes of the National Assembly). This decree exempted university professors from the citizenship requirement, which made possible my appointment as a tenured professor.

Not everything was resolved, however, and the complexity of dealing with the French administration led me to renounce my dream and return to Harvard. The decree remained valid, however, and subsequently I received a number of thank-you letters from non-French scientists who had for many years been appointed annually as Professeur Associé and suddenly received a permanent position. (Jean-Pierre Hanson, who was born in Luxembourg, told me recently that he believes he is one of the first people to have profited from "my" decree.)

During this period I started spending summer vacations with my family in the foothills of the Alps above Annecy and its stunning lake, an area which I had first seen on my postdoctoral trips in the early 1950s. My colleagues at Harvard viewed such absences from Cambridge as improper. However, I found that being away gave me a chance to think, undistracted by everyday pressures. Contemplative hikes in the mountains provided the backdrop for my reading and thinking and played an essential role in developing new areas of research. In fact, I had asked my NSF program director whether these trips were justified under the conditions of my grant. His conclusion was that, given their importance to my research, they constituted an appropriate, even if somewhat unorthodox, summer program. In 1974 I finally found a plot of land with a magnificent view in Chalmont, a small hamlet in the Manigod valley above Lac d'Annecy. A chalet was built, which has been our summer home for 30 years.

PROTEIN FOLDING

In 1969 I was challenged by the mechanism of protein folding during a visit by Chris Anfinsen to the Lifson group at the Weizmann Institute. We had many discussions of his experiments on protein folding, which had led to the realization that proteins can refold in solution, independent of the ribosome and other aspects of the cellular environment (2). [Of course, it is now known that some proteins have more complex folding mechanisms and require chaperones, such as the supramolecular complex GroEL, to fold. This molecular machine is one for which we have used molecular dynamics simulations to elucidate the mechanism (87, 118).] What most impressed me was Anfinsen's film showing the folding of a protein with "flickering helices forming and dissolving and coming together to form stable substructures." The film was a cartoon, but it led to my asking him, in the same vein as I had asked Perutz earlier about hemoglobin, whether he had thought of taking the ideas in the film and translating them into a quantitative model. Anfinsen said that he did not really know how he would do this, but to me it suggested an approach to the mechanism of protein folding. When David Weaver joined my group at Harvard, while on a sabbatical leave from Tufts, we developed what is now known as the diffusion-collision model for protein folding (70, 71). Although it is a simplified coarse-grained description of the folding process, it showed how the search problem for the native state could be solved by a divide-and-conquer approach. Formulated by Cy Levinthal, the so-called *Levinthal Paradox* points out that to find the native state by a random search of the astronomically large configuration space of a polypeptide chain would take longer than the age of the earth, while proteins fold experimentally on a timescale of microseconds to seconds. In addition to providing a conceptional answer to the question posed by Levinthal, the diffusion-collision model made possible the estimation of folding rates. The model was ahead of its time because data to test it were not available. Only relatively recently have experimental studies demonstrated that the diffusion-collision model describes the folding mechanism of many helical proteins (48), as well as some others (49).

Protein folding is an area that has continued to interest me and has led to numerous collaborations in addition to that with David Weaver. When David and I developed the diffusion-collision model in 1975, protein

folding was a rather esoteric subject of interest to a very small community of scientists. The field has been completely transformed in recent years because of its assumed importance for understanding the large number of protein sequences available from genome projects and because of the realization that misfolding can lead to a wide range of human diseases (22); these diseases are found primarily in the older populations that form an ever-increasing portion of humanity. Scientists, both experimentalists and theoreticians—physicists, as well chemists and biologists—now study protein folding. Over the past decade or so the mechanism of protein folding has been resolved, in principle. It is now understood that there are multiple pathways to the native state and that the bias on the free-energy surface, due to the greater stability of native-like versus nonnative contacts, is such that only a very small fraction of the total number of conformations is sampled in each folding trajectory (24). This understanding was achieved by the work of many scientists, but a crucial element was the study of lattice models of protein folding. Such toy models, as I like to call them, are simple enough to permit many folding trajectories to be calculated to make possible an analysis of the folding process and free-energy surface sampled by the trajectories (104). However, they are sufficiently complex so that they embody the Levinthal problem, i.e., there are many more configurations than could be visited during the calculated folding trajectory. The importance of such studies was in part psychological, in that even though the lattice model uses a simplified representation, "real" folding was demonstrated on a computer for the first time. An article based on a lecture at a meeting in Copenhagen (60) describes this change in attitude as a paradigm of scientific progress.

The mechanism of protein folding and the development of methods to predict the structure of a protein from its amino acid sequence continue to be subjects under intense investigation. It is likely that calculations with programs such as CHARMM will permit folding simulations to be done at an atomic level of detail owing to the ever-increasing speed of computers (either localized multiprocessor supercomputers or delocalized grid-based access to many individual processors) before too long. However, this type of brute force approach is of less interest to me than solving the conceptual problem of protein folding, which has been accomplished by more approximate techniques.

ORIGINS OF THE CHARMM PROGRAM

When I visited Lifson's group in 1969 there was considerable interest in developing empirical potential energy functions for small molecules. The novel idea was to use a functional form that could serve not only for calculating vibrational frequencies, as did the expansions of the potential about a known or assumed minimum-energy structure, but also for determining that structure. The so-called consistent force field (CCF) of Lifson and his coworkers, particularly Arieh Warshel, included nonbonded interaction terms so that the minimum-energy structure could be found after the energy terms had been appropriately calibrated (84). The possibility of using such energy functions for larger systems struck me as potentially very important for understanding biological macromolecules like proteins, though I did not begin working on this immediately.

Once Attila Szabo had finished the statistical mechanical model of hemoglobin cooperativity, I realized that his work raised a number of questions that could be explored only with a method for calculating the energy of hemoglobin as a function of the atomic positions. No way of doing such a calculation existed. Bruce Gelin, a new graduate student, had begun theoretical research in my group in 1967. He started out by studying the application of the random-phase approximation to two-electron systems, such as the helium atom. This was still the Vietnam War era and after two years at Harvard, Gelin was drafted.

He was assigned to the military police in a laboratory concerned with drug usage (e.g., LSD). Paradoxically, this work aroused his interest in biology, and when he returned to finish his degree Gelin wanted to change his area of research to a biologically related problem. We decided the time was ripe to try to develop a program that would make it possible to take a given amino acid sequence (e.g., that of the hemoglobin alpha chain) and a set of coordinates (e.g., those obtained from the X-ray structure of deoxy hemoglobin) and to use this information to calculate the energy of the system and its derivatives as a function of the atomic positions. This could be used for perturbing the structure (e.g., by binding oxygen to the heme group) and finding a new structure by minimizing the energy. Developing the program was a major task, but Gelin had the right combination of abilities to carry it out (33).

The result was pre-CHARMM, although it did not have a name at that time. While not trivial to use, the program was applied to a variety of problems, including Gelin's pioneering study of aromatic ring flips in the bovine pancreatic trypsin inhibitor (BPTI) (34), as well as his primary project on hemoglobin. The idea was to introduce the effect of ligand binding on the heme group as a perturbation (undoming of the heme) and to use energy minimization to determine the response of the protein to the perturbation. To attempt to do such a calculation on the available computers (an IBM 7090 at Columbia University was our work-horse at the time, because computing at the Harvard Computer Center was too expensive) required considerable courage, but Gelin's efforts were successful. His work introduced a new dimension to theoretical approaches to understanding protein structure and function. Gelin showed how the effect of undoming of the heme induced by the binding of oxygen was transmitted to the interface between the hemoglobin subunits. The analysis provided an essential element in the cooperative mechanism in its demonstration at an atomic level of detail how communication between the subunits occurred (35). Another application of pre-CHARMM was Dave Case's simulation of ligand escape after photodissociation from myoglobin (16); a study that was followed by the work of Ron Elber (25), which gave rise to the locally enhanced sampling (LES) and multiple copy simultaneous search (MCSS) methods. The latter was developed by Andrew Miranker as a fragment-based approach to drug design (90).

Gelin would have faced an almost insurmountable task in developing pre-CHARMM if there had not been prior work by others on protein energy calculations. Although many persons have contributed to the development of empirical potentials, the two major inputs to our work came from Schneior Lifson's group at the Weizmann Institute and Harold Scheraga's group at Cornell University (107). As I already mentioned, Warshel had come to Harvard and had brought his CFF program with him. His presence and the availability of the CFF program were important resources for Gelin, who was also aware of Michael Levitt's pioneering energy calculations for proteins (82).

Gelin's program has been considerably restructured and has continued to evolve over the intervening years. In preparing to publish a paper on the program in the early 1980s, mainly to give credit to the dominant contributors at the time, we felt we needed a name. Bob Bruccoleri came up with HARMM (HARvard Macromolecular Mechanics), which seemed to me not to be the ideal choice. However, Bob's suggestion inspired the addition of a "C" for chemistry, resulting in the name CHARMM. I sometimes wonder if Bruccoleri's original suggestion would have served as a useful warning to inexperienced scientists working with the program. The CHARMM program is now being developed by a wide group of contributors, most of whom were students or postdoctoral fellows in my group; the program is distributed worldwide in both academic and commercial settings.

THE FIRST MOLECULAR DYNAMICS SIMULATION OF A BIOMOLECULE

Given that pre-CHARMM could calculate the forces on the atoms of a protein, the next step was to use these forces in Newton's equation to calculate the dynamics. This fundamental development was introduced in the mid-1970s when Andy McCammon joined my group. An essential element that encouraged us in this attempt was the existence of molecular dynamics simulation methods for simpler systems. Molecular dynamics had followed two pathways, which come together in the study of biomolecule dynamics. One pathway concerns trajectory calculations for simple chemical reactions. My own research in this area had served as preparation for the many-article problem posed by biomolecules. The other pathway in molecular dynamics concerns physical rather than chemical interactions and the thermodynamic and dynamic properties of large numbers of particles rather than detailed trajectories of a few particles. Although the basic ideas go back to van der Waals and Boltzmann, the modern era began with the work of Alder and Wainright (1) on hard-sphere liquids in the late 1950s. The paper by Rahman (103) in 1964 on a molecular dynamics simulation of liquid argon with a soft-sphere (Lennard-Jones) potential represented an essential next step. Simulations of more complex fluids followed; the now classic study of liquid water by Stillinger and Rahman was published in 1974 (114), shortly before our protein simulations.

The background I have outlined set the stage for the development of molecular dynamics of biomolecules. The size of an individual molecule, composed of 500 or more atoms for even a small protein, is such that its simulation in isolation can serve to obtain approximate equilibrium properties, as in the molecular dynamics of fluids. Concomitantly, detailed aspects of the atomic motions are of considerable interest, as in trajectory calculations. A basic assumption in initiating such studies was that potential functions could be constructed which were sufficiently accurate to give meaningful results for systems as complex as proteins or nucleic acids. In addition, it was necessary to assume that for these inhomogeneous systems, in contrast to the homogeneous character of even complex liquids like water, simulations of an attainable timescale (10 to 100 ps) could provide a useful sample of the phase space in the neighborhood of the native structure. There was no compelling evidence for either assumption in the early 1970s. When I discussed my plans with chemistry colleagues, they thought such calculations were impossible, given the difficulty of treating few atom systems accurately; biology colleagues felt that even if we could do such calculations, they would be a waste of time. By contrast, the importance of molecular dynamics simulations in biology was supported by Richard Feynman's prescient statement in the well-known volumes based on his physics lectures at Caltech:

"Certainly no subject or field is making more progress on so many fronts at the present moment, than biology, and if we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, *it is that all things are made of atoms* (italics in the original), and that *everything that living things do can be understood in terms of the jigglings and wigglings of atoms.* (27; italics added)

More than 25 years have passed since the first molecular dynamics simulation of a macromolecule of biological interest was published (**Figure 4**) (88). This study has stood the test of time, and, perhaps more significantly, it has served to open a new field that is now the focus of the research of an ever-growing number of scientists (10). The original simulation, published in 1977 (88), concerned the bovine pancreatic trypsin inhibitor (BPTI), which has served as the "hydrogen molecule" of protein dynamics because of its small size, high stability, and a relatively accurate X-ray structure (21); interestingly, the physiological function of BPTI

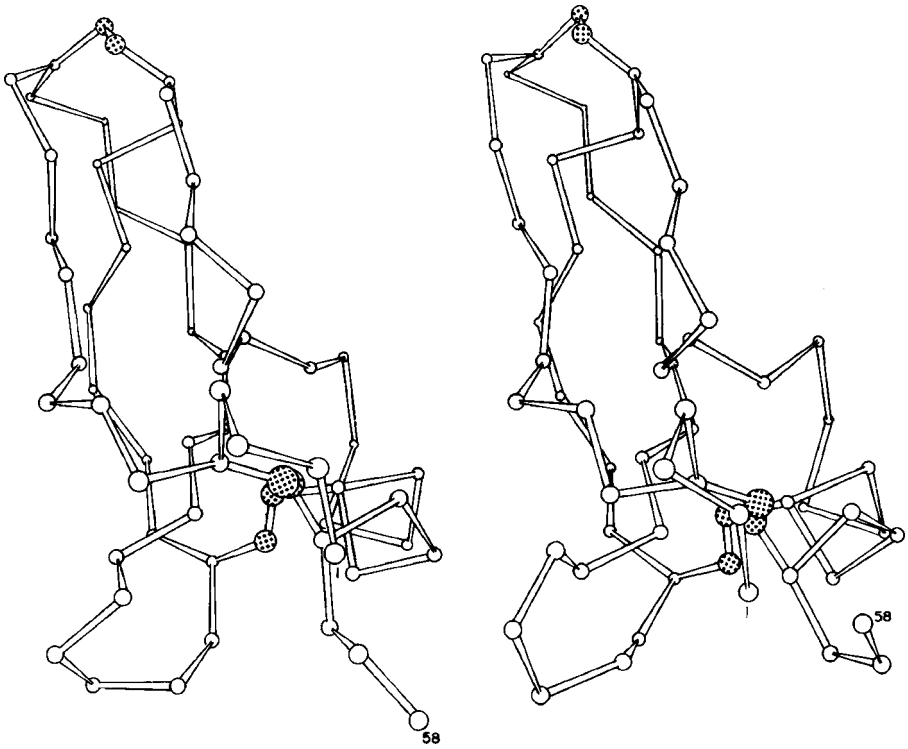


Figure 4

The peptide backbone (α carbons) and disulfide bonds of the bovine pancreatic trypsin inhibitor drawn by Bruce Gelin. (*a*) X-ray structure. (*b*) Time-evolved structure after 3.2 ps of dynamical simulation. The figure has been reproduced, with permission, from Reference 88.

remains unknown. In the mid-1970s it was difficult to obtain the computer time required to do such simulations in the United States. However, CECAM (Center Européen Calcul Atomique et Moléculaire), whose founding director and guiding spirit was Carl Moser, had access to a large computer that was available for scientific research. (Equivalent computers in the United States were found only in the defense agencies and were not generally accessible.) A CECAM Workshop (a two-month *workshop* worthy of its name) was organized by Herman Berendsen in 1976 with the title "Models for Protein Dynamics." As his introduction to the workshop states: "Thus, the simulation of water was a first topic to be studied. The application to proteins was then not foreseen in five or ten years to come." Realizing that the workshop was a great opportunity to do the required calculations, Andy McCammon and Bruce Gelin worked extremely hard to prepare and test a program for the molecular dynamics simulation for the workshop. The initial simulation (88), which was performed at the workshop, introduced many others now active in the field (including H. Berendsen, W. van Gunsteren, M. Levitt, and J. Hermans) to the possibility of doing such calculations (5).

Although the original simulation was done in a vacuum with a crude molecular mechanics potential and lasted for only 9.2 ps, the results were instrumental in replacing the view of proteins as relatively rigid structures [in 1981, Sir D. L. Phillips commented, "Brass models of DNA and a variety of proteins dominated the scene and much of the thinking" (99)] with the realization that they were dynamic systems whose internal motions play a functional role. Of course, there were already experimental data, such as the hydrogen exchange experiments of Linderstrom-Lang and his coworkers (44, 85), pointing in this direction. It is now recognized that the X-ray structure of a protein provides the average atomic positions but that the atoms ex-

hibit fluid-like motions of sizable amplitudes about these averages. Protein dynamics subsumes the static picture. The average positions are essential for the discussion of many aspects of biomolecular function in the language of structural chemistry, but the recognition of the importance of fluctuations opened the way for more sophisticated and accurate interpretations of functional properties.

The conceptual changes resulting from the early studies make one marvel at how much of great interest could be learned with so little—such poor potentials, such small systems, so little computer time. This is, of course, one of the great benefits of taking the initial, somewhat faltering steps in a new field in which the questions are qualitative rather than quantitative and any insights, even if crude, are better than none at all.

APPLICATIONS OF MOLECULAR DYNAMICS

Molecular dynamics simulations of proteins and nucleic acids, as of other systems composed of particles (e.g., liquids, galaxies), can in principle provide the ultimate details of motional phenomena. The primary limitation of simulation methods is that they are approximate. Here experiment plays an essential role in validating the simulation methods; that is, comparisons with experimental data serve to test the accuracy of the calculated results and provide criteria for improving the methodology. Although the statistical errors can be calculated (122), estimates of the systematic errors inherent in the simulations have not been possible, e.g., the errors introduced by the use of empirical potentials are difficult to quantify. When experimental comparisons indicate that the simulations are meaningful, their capacity for providing detailed results often makes it possible to examine specific aspects of the atomic motions far more easily than by using laboratory measurements.

Two years after the BPTI simulation, it was recognized (3, 30) that thermal (B) factors determined in X-ray crystallographic refinement could provide information about the internal motions of proteins. Plots of estimated mean-square fluctuations versus residue number [introduced in the original BPTI paper (88)] have become a standard part of papers on high-resolution structures, even though the contribution to the B factors of overall translation and rotation and crystal disorder persist as a concern in their interpretation (79). During the subsequent decade, a range of phenomena were investigated by molecular dynamics simulations of proteins and nucleic acids. A plethora of experimental data were just waiting for molecular dynamics simulations to elucidate them. Most of these early studies were made by my students at Harvard and focused on the physical aspects of the internal motions and the interpretation of experiments. They include the analysis of fluorescence depolarization of tryptophan residues (45), the role of dynamics in measured NMR parameters (23, 83, 97) and inelastic neutron scattering (20, 113), and the effect of solvent and temperature on protein structure and dynamics (11, 29, 95). The now widely used simulated annealing methods for X-ray structure refinement (14, 15) and NMR structure determination (12, 96) also originated in this period. Simultaneously, a number of applications demonstrated the importance of internal motions in biomolecular function, including the hinge bending modes for opening and closing active sites (9, 18), the flexibility of tRNA (38), the induced conformation change in the activation of trypsin (13), the fluctuations required for ligand entrance and exit in heme proteins (16, 25), and the role of configurational entropy in the stability of proteins and nucleic acids (8, 47). Many of these studies, which were done about two decades ago, seem to have been forgotten; at least, they are rarely cited in the current literature. Of course, when the studies are redone, the more accurate potential functions and much longer simulations (nanoseconds instead of picoseconds) now possible yield improved results, but generally they confirm the earlier work.

Two attributes of molecular dynamics simulations have played an essential part in the explosive growth in the number of studies based on such simulations. As already mentioned, simulations provide the ultimate detail concerning individual particle motions as a function of time. For many aspects of biomolecule function, it is these details that are of interest (e.g., by what pathways does oxygen enter into and exit from the heme pocket in myoglobin). The other important aspect of simulations is that, although the potentials employed in simulations are approximate, they are completely under the user's control. By removing or altering specific contributions, their role in determining a given property can be examined. This is most graphically demonstrated by the use of computer alchemy—transmuting the potential from that representing one system to another during a simulation—in calculated free-energy differences (32, 112, 121).

There are three types of applications of simulation methods in the macromolecular area, as well as in other areas involving mesoscopic systems. The first uses the simulation simply as a means of sampling configuration space. This is involved in the utilization of molecular dynamics, often with simulated annealing protocols, to determine or refine structures with data obtained from experiments. The second uses simulations to determine equilibrium averages, including structural and motional properties (e.g., atomic mean-square fluctuation amplitudes) and the thermodynamics of the system. For such applications, it is necessary that the simulations adequately sample configuration space, as in the first application, with the additional condition that each point be weighted by the appropriate Boltzmann factor. The third application employs simulations to examine the actual dynamics. Here not only is adequate sampling of configuration space with appropriate Boltzmann weighting required, but it must be done so as to properly represent the time development of the system. Monte Carlo simulations, as well as molecular dynamics, can be utilized for the first two applications. By contrast, in the third application, where the motions and their time developments are of interest, only molecular dynamics can provide the necessary information.

FUTURE OF MOLECULAR DYNAMICS

Most of the motional phenomena examined during the first 10 years after the BPTI simulation paper was published continue to be studied both experimentally and theoretically. The increasing scope of molecular dynamics due to improvements in methodology and the tremendous increase of the available computer power is making possible the study of systems of greater complexity on ever-increasing timescales. There are many recent examples of the use of molecular dynamics to obtain information concerning the function of biological macromolecules. At present I am most interested in molecular machines, such as GroEL (87, 118), which require simulations for their understanding. Nature has designed these machines to function through ligand-induced conformational changes encoded in the structure. One of the most fascinating machines is F_0F_1-ATPase, which synthesizes ATP and H_2O, the energy currency of most living cells, from ADP and $H_2PO_4^-$ (**Figure 5**) (32a). Numerous applications by my group and others have been reviewed recently, so that I will not detail them here (61, 65, 67).

It is my hope that molecular dynamics simulations will become a tool, like any other, to be used by experimentalists as part of their arsenal for solving problems. The simulated annealing method for determining X-ray structures originally proposed in 1987 by Axel Brünger, John Kuriyan, and me (14, 15), and so ably developed by Brünger, is now an essential part of structural biology. Without this method, the high-throughput structure determination initiatives would be in considerable difficulty. However, a universal acceptance of molecular dynamics simulations methods for extending experimental data to

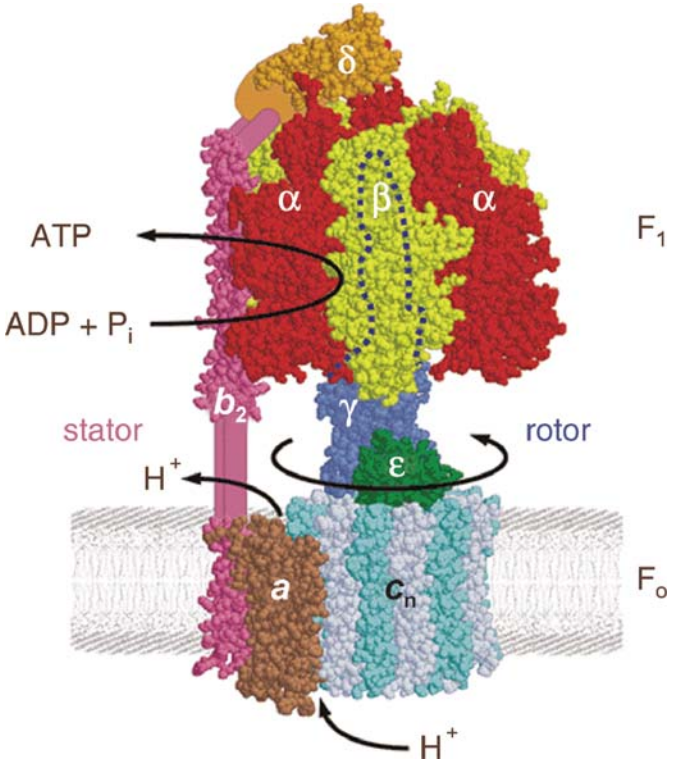


Figure 5

Structural model of F_0F_1-ATP synthase. The figure has been reproduced from Senior AE, Nadanaciva S, Weber J. 2002. *Biochim. Biophys. Acta Bioenerg.* 1553:188–211

learn how biomolecules function is still in the future. The determination of the reaction path involved in conformational change by simulations, is a clear case where, given the structural end point from experiment, simulations are essential, as some crystallographers have already recognized (123).

I still marvel at the insights that simulation methods can provide concerning the functions of biomolecules. Claude Poyart, a dear friend with whom I worked on hemoglobin (81), characterized molecular dynamics simulations of proteins with a beautiful image. He likened the X-ray structures of proteins to a tree in winter, beautiful in its stark outline but lifeless in appearance. Molecular dynamics gives life to this structure by clothing the branches with leaves that flutter because of the thermal winds.

EPILOGUE

As I read through what I have written, I see what a fragmentary picture it provides of my life, even my scientific life. Missing are innumerable interactions, most of which were constructive but some not so, that have played significant roles in my career. The more than 200 graduate students and postdoctoral fellows who at one time or another have been members of the group are listed in **Table 1**. Many have gone on to faculty positions and become leaders in their fields of research. They in turn are training students, so I now have scientific children, grandchildren, and great-grandchildren all over the world. I treasure my contribution to their professional and personal careers, as much as the scientific advances we have made together.

Contributing to the education of so many people in their formative years is a cardinal aspect of university life. My philosophy in graduate and postgraduate education has been to provide an environment where young scientists, once they have proved their ability, can develop their own ideas, as refined in discussions with me and aided by other members of the group. This fostered independence has been, I believe, an important element in the fact that so many of my students are now themselves outstanding researchers and faculty members. My role has been to guide them when problems arose and to instill in them the necessity of doing things in the best possible way, not to say that I succeeded with all of them.

Discussing my scientific family makes me realize that another missing element is my personal family, an irreplaceable part of my life. Reba and Tammy, my two daughters whose mother, Susan, died in 1982, both became physicians (thereby fulfilling my destined role); Reba lives in Jerusalem and Tammy lives on the West Coast. My wife, Marci, and our son, Mischa, who is presently in law school at Boston University, complete my immediate family. As many people know, Marci also plays the pivotal role as the

Table 1 Karplusians: 1955–2005

R. J. Aerni	Kevin Gaffney	Jianpeng Ma	Andrej Sali
David H. Anderson	Jiali Gao	Alexander D. MacKerell, Jr.	Michael Schaefer
Ioan Andricioaei	Yi Qin Gao	Christoph Maerker	Michael Schlenkrich
Yasuhide Arata	Bruce Gelin	Paul Maragkakis	David M. Schrader
Georgios Archontis	R. Benny Gerber	Marc Martí-Renom	John C. Schug
Gabriel G. Balint-Kurti	Paula M. Getzin	Jean-Louis Martin	Klaus Schulten
Christian Bartels	Debra Giammona	Carla Mattos	Eugene Shakhnovich
Paul Bash	Martin Godfrey	J. Andrew McCammon	Moshe Shapiro
Donald Bashford	Andrei Golosov	H. Keith McDowell	Ramesh D. Sharma
Oren M. Becker	David M. Grant	Jorge A. Medrano	Isaiah Shavitt
Robert Best	Daniel Grell	Morten Meeg	Henry H.-L. Shih
Anton Beyer	Peter Grootenhuis	Marcus Meuwly	Bernard Shizgal
Robert Birge	Hong Guo	Olivier Michielin	David M. Silver
Ryan Bitetti-Putzer	Robert Harris	Stephen Michnick	Jeremy Smith
Arnaud Blondel	Karen Haydock	Fredrick L. Minn	Sung-Sau So
Stefan Boresch	Russell J. Hemley	Andrew Miranker	Michael Sommer
John Brady	Jeffrey C. Hoch	Keiji Morokuma	Ojars J. Sovers
Bernard Brooks	Gary G. Hoffman	A. Mukherji	Martin Spichty
Charles L. Brooks III	L. Howard Holley	Adrian Mulholland	David J. States
Thomas H. Brown	Barry Honig	David Munch	Richard M. Stevens
Robert E. Bruccoleri	Victor Hruby	Petra Munih	Roland Stote
Paul W. Brumer	Rod E. Hubbard	Robert Nagle	John Straub
Axel T. Brünger	Robert P. Hurst	Setsuko Nakagawa	Collin Stultz
Rafael P. Brüschweiler	Vincent B.-H. Huynh	Eyal Neria	Neena Summers
Matthias Buck	Toshiko Ichiye	John-Thomas C. Ngo	Henry Suzukawa
Amedeo Caflisch	K.K. Irikura	Lennart Nilsson	S. Swaminathan
William J. Campion	Alfonso Jaramillo	Dzung Nguyen	Attila L. Szabo
William Carlson	Diane Joseph-McCarthy	Iwao Ohmine	Kwong-Tin Tang
David A. Case	Sunhee Jung	Barry Olafson	Bruce Tidor
Leo Caves	C. William Kern	E.T. Olejniczak	Hideaki Umeyama
Thomas C. Caves	Burton S. Kleinman	Kenneth W. Olsen	Arjan van der Vaart
John-Marc Chandonia	G.W. Koeppl	Neil Ostlund	Wilfred van Gunsteren
Ta-Yuan Chang	H. Jerrold Kolker	Emanuele Paci	Herman van Vlijmen
Rob D. Coalson	Yifei Kong	Yuh-Kang Pan	Michele Vendruscuolo
François Colonna-Cesari	Lewis M. Koppel	C.S. Pangali	Dennis Vitkup
Michael R. Cook	J. Kottalam	Richard W. Pastor	Shunzhou Wan
Qiang Cui	Felix Koziol	Lee Pedersen	Iris Shih-Yung Wang
Annick Dejaegere	Christoph Kratky	David Perahia	Ariel Warshel
Philippe Derreumaux	Serguei Krivov	Robert Petrella	Masakatsu Watanabe
Aaron Dinner	Krzysztof Kuczera	B. Montgomery Pettitt	David Weaver
Uri Dinur	John Kuriyan	Ulrich Pezzeca	Paul Weiner
Roland L. Dunbrack, Jr.	Joseph N. Kushick	Richard N. Porter	Michael A. Weiss
Chizuko Dutta	Peter W. Langhoff	Jay M. Portnow	Joanna Wiórkiewicz-K.
Nader Dutta	Antonio C. Lasaga	Carol B. Post	George Wolken

(*Continued*)

Table 1 (*Continued*)

Claus Ehrhardt	Frankie T.K. Lau	Lawrence R. Pratt	Youngdo Won
Ron Elber	Themis Lazaridis	Martine Prévost	Yudong Wu
Byung Chan Eu	Fabrice LeClerc	Blaise Prod'hom	Robert E. Wyatt
Jeffrey Evanseck	Angel Wai-mun Lee	Dagnija Lazdins Purins	Wei Yang
Erik Evensen	Irwin Lee	Lionel M. Raff	Robert Yelle
Jeffrey Evenson	Sangyoub Lee	Mario Raimondi	Swarna Yeturu Reddy
Thomas C. Farrar	Ronald M. Levy	Walter E. Reiher III	Darrin York
Martin Field	Xiaoling Liang	Nathalie Reuter	Hsiang-ai Yu
Stefan Fischer	Carmay Lim	Bruno Robert	Vincent Zoete
David L. Freeman	Xabier Lopez	Peter J. Rossky	Yaoqi Zhou
Thomas Frimurer	Paul Lyne	Benoît Roux	

Laboratory Administrator, adding a spirit of continuity for the group and making possible our commuting between the Harvard and Strasbourg labs. Without my family, my life would have been an empty one, even with scientific success.

ACKNOWLEDGMENTS

Much of the research described here was supported in part by grants from the National Science Foundation, the National Institutes of Health, the Atomic Energy Commission, and the Department of Energy, as well as the royalty income from the CHARMM Development Project. As is evident from the references, the research would not have been possible without my many coworkers, only a few of whom are mentioned in the text. Frontispiece was kindly provided by Nathan Pitt, Department of Chemistry, University of Cambridge, Cambridge CB2 1EW, United Kingdom.

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Annual Review of Biophysics and Biomolecular Structure

Volume 35, 2006

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