NATIONAL ACADEMY OF SCIENCES

LINUS CARL PAULING

1901—1994

A Biographical Memoir by

JACK D. DUNITZ

Any opinions expressed in this memoir are those of the author(s) and do not necessarily reflect the views of the National Academy of Sciences.

Biographical Memoir

COPYRIGHT 1997

NATIONAL ACADEMIES PRESS
WASHINGTON D.C.

Linus Pauling

LINUS CARL PAULING

February 28, 1901–August 19, 1994

BY JACK D. DUNITZ

LINUS CARL PAULING was born in Portland, Oregon, on February 28, 1901, and died at his ranch at Big Sur, California, on August 19, 1994. In 1922 he married Ava Helen Miller (died 1981), who bore him four children: Linus Carl, Peter Jeffress, Linda Helen (Kamb), and Edward Crellin.

Pauling is widely considered the greatest chemist of this century. Most scientists create a niche for themselves, an area where they feel secure, but Pauling had an enormously wide range of scientific interests: quantum mechanics, crystallography, mineralogy, structural chemistry, anesthesia, immunology, medicine, evolution. In all these fields and especially in the border regions between them, he saw where the problems lay, and, backed by his speedy assimilation of the essential facts and by his prodigious memory, he made distinctive and decisive contributions. He is best known, perhaps, for his insights into chemical bonding, for the discovery of the principal elements of protein secondary structure, the alpha-helix and the beta-sheet, and for the first identification of a molecular disease (sickle-cell anemia), but there are a multitude of other important contri-

This biographical memoir was prepared for publication by both The Royal Society of London and the National Academy of Sciences of the United States of America.

butions. Pauling was one of the founders of molecular biology in the true sense of the term. For these achievements he was awarded the 1954 Nobel Prize in chemistry. But Pauling was famous not only in the world of science. In the second half of his life he devoted his time and energy mainly to questions of health and the necessity to eliminate the possibility of war in the nuclear age. His active opposition to nuclear testing brought him political persecution in his own country, but he was finally influential in bringing about the 1963 international treaty banning atmospheric tests. With the award of the 1962 Nobel Peace Prize, Pauling became the first person to win two unshared Nobel Prizes (Marie Curie won one and shared another with her husband). Pauling's name is probably best known among the general public through his advocacy, backed by personal example, of large doses of ascorbic acid (vitamin C) as a dietary supplement to promote general health and prevent (or at least reduce the severity of) such ailments as the common cold and cancer. Indeed, Albert Einstein and Linus Pauling are probably the only scientists in our century whose names are known to every radio listener, television viewer, or newspaper reader.

EARLY YEARS

Pauling was the first child of Herman Pauling, son of German immigrants, and Lucy Isabelle (Darling) Pauling, descended from pre-revolutionary Irish stock. There were two younger daughters: Pauline Darling (born 1902) and Lucile (born 1904). Herman Pauling worked for a time as a traveling salesman for a medical supply company and moved in 1905 to Condon, Oregon, where he opened his own drugstore. It was in this new boom town in the arid country east of the coastal range that Pauling had his first schooling. He learned to read early and started to devour books. In 1910

the family moved back to Portland, where his father wrote a letter to *The Oregonian*, a local newspaper, asking for advice about suitable reading matter for his nine-year-old son, who had already read the Bible and Darwin's theory of evolution. We do not know the replies, but Pauling later confessed that one of his favorites was the *Encyclopaedia Britannica*. Soon tragedy struck. In June of that year Herman Pauling died after a sudden illness, probably a perforated stomach ulcer with attendant peritonitis, leaving his family in a situation with which the young mother could not adequately cope.

Linus did well at school. He collected insects and minerals and read omnivorously. He made up his mind to become a chemist in 1914, when a fellow student, Lloyd A. Jeffress, showed him some chemical experiments he had set up at home. With the reluctant approval of his mother he left school in 1917 without a diploma and entered Oregon Agricultural College at Corvallis as a chemical engineering major, but after two years his mother wanted him to leave college to earn money for the support of the family. He must have impressed his teachers, for in 1919, after a summer working as a road-paving inspector for the State of Oregon, he was offered a full-time post as instructor in qualitative analysis in the chemistry department. The eighteen-year-old teacher felt the need to read current chemical journals and came across the recently published papers of Gilbert Newton Lewis and Irving Langmuir on the electronic structure of molecules. Having understood the new ideas, the "boy professor" introduced them to his elders by giving a seminar on the nature of the chemical bond. Thus was sparked the "strong desire to understand the physical and chemical properties of substances in relation to the structure of the atoms and molecules of which they are

composed," which determined the course of Pauling's long life.

The following year Pauling resumed his student status and graduated in 1922 with a B.Sc. degree. In his final year he was given another opportunity to teach, this time an introductory chemistry course for young women students of home economics. This new teaching episode also had important consequences for his future. One of the students was Ava Helen Miller, who became his wife in a marriage that lasted almost sixty years.

PASADENA

Pauling came to the California Institute of Technology as a graduate student in 1922 and remained there for more than forty years. He chose Caltech because he could obtain a doctorate there in three years (Harvard required six) and because Arthur Amos Noyes offered him a modest stipend as part-time instructor. It was a fortunate choice both for Pauling and for Caltech. As he wrote towards the end of his life, "Years later . . . I realized that there was no place in the world in 1922 that would have prepared me in a better way for my career as a scientist" (1994). When he arrived the newly established institute consisted largely of the hopes of its three founders, the astronomer George Ellery Hale, the physicist Robert A. Millikan, and the physical chemist Arthur Amos Noyes. There were three buildings and eighteen faculty members. When he left, Caltech had developed into one of the major centers of scientific research in the world. In chemistry Pauling was the prime mover in this development. Indeed, for many young chemists of my generation, Caltech meant Pauling.

Pauling's doctoral work was on the determination of crystal structures by X-ray diffraction analysis under the direction of Roscoe Gilkey Dickinson (1894-1945), who had obtained

his Ph.D. only two years earlier (he was the first person to receive a Ph.D. from Caltech). By a happy chance, Ralph W. G. Wyckoff (1897-1994), one of the pioneers of X-ray analysis, had spent the year before Pauling's arrival at Caltech and had taught Dickinson the method of using Laue photographic data (white radiation, stationary crystal; a method that fell into disuse but has newly been revived in connection with rapid data collection with synchrotron radiation sources). Wyckoff taught Dickinson, and Dickinson taught Pauling, who soon succeeded in determining the crystal structures of the mineral molybdenite MoS_2 (Dickinson and Pauling, 1923) and the intermetallic compound MgSn (1923). By the time he graduated in 1925 he had published twelve papers, most on inorganic crystal structures, but including one with Peter Debye (1884-1966) on dilute ionic solutions (Debye and Pauling, 1925) and one with Richard Tolman (1881-1948) on the entropy of supercooled liquids at 0 K (Pauling and Tolman, 1925). Pauling had already made up for his lack of formal training in physics and mathematics. He was familiar with the quantum theory of Planck and Bohr and was ready for the conceptual revolution that was soon to take place in Europe. Noyes obtained one of the newly established Guggenheim fellowships for the rising star and sent him and his young wife off to the Institute of Theoretical Physics, directed by Arnold Sommerfeld (1868-1951), in Munich.

They arrived in April 1926, just as the Bohr-Sommerfeld model was being displaced by the "new" quantum mechanics. It was an exciting time, and Pauling knew he was lucky to be there at one of the centers. He concentrated on learning as much as he could about the new theoretical physics at Sommerfeld's institute. Pauling had been regarded, and probably also regarded himself, as intellectually outstanding among his fellow students at Oregon and even at Caltech;

however, he must have become aware of his limitations during his stay in Europe. The new theories were being made by men of his own generation. Wolfgang Pauli (1900-58), Werner Heisenberg (1901-76), and Paul Dirac (1902-84) were all born within a year of Pauling and were more than a match for him in physical insight, mathematical ability, and philosophical depth. Pauling was not an outstanding theoretical physicist and was probably not particularly interested in problems such as the deep interpretation of quantum mechanics or the philosophical implications of the uncertainty principle. On the other hand, he was the only chemist at Sommerfeld's institute and saw at once that the new physics was destined to provide the theoretical basis for understanding the structure and behavior of molecules.

The year in Europe was to have a decisive influence on Pauling's scientific development. In addition to Munich, he visited Copenhagen in the spring of 1927 and then spent the summer in Zurich. In Copenhagen it was not Bohr but Samuel A. Goudsmit (1902-78) who influenced Pauling (they later collaborated in writing *The Structure of Line Spectra*, New York: McGraw-Hill, 1930), and in Zurich it was neither Debye nor Schrödinger but the two young assistants, Walter Heitler (1904-81) and Fritz London (1900-54), who were working on their quantum-mechanical model of the hydrogen molecule in which the two electrons are imagined to "exchange" their roles in the wave function—an example of the "resonance" concept that Pauling was soon to exploit so successfully.

One immediate result of the stay in Munich was Pauling's (1927) first paper in the *Proceedings of the Royal Society of London*, submitted by Sommerfeld himself. Pauling was eager to apply the new wave mechanics to calculate properties of many-electron atoms and he found a way of doing

this by using hydrogen-like single-electron wave functions for the outer electrons with effective nuclear charges based on empirical screening constants for the inner electrons.

THE NATURE OF THE CHEMICAL BOND

In 1927 Pauling returned to Caltech as assistant professor of theoretical chemistry. The next twelve years produced the remarkable series of papers that established his worldwide reputation. His abilities were quickly recognized through promotions (to associate professor, 1929; full professor, 1931), through awards (Langmuir Prize, 1931), through election to the National Academy of Sciences (1933), and through visiting lectureships, especially the Baker lectureship at Cornell in 1937-38. Through his writings and lectures, Pauling established himself as the founder and master of what might be called structural chemistry—a new way of looking at molecules and crystals.

Pauling's way was first to establish a solid and extensive collection of data. By means of X-ray crystallography, gas-phase electron diffraction (installed after Pauling's 1930 visit to Europe, where he learned about Hermann Mark's pioneering studies), and infrared, Raman, and ultraviolet spectroscopy, interatomic distances and angles were established for hundreds of crystals and molecules. Thermochemical information was already available. The first task of theory, as Pauling saw it, was to provide a basis to explain the known metric and energetic facts about molecules, and only then to lead to prediction of new facts. At this stage of his development Pauling was attracting many talented co-workers, undergraduates, graduate students, and postdoctoral fellows, and their names read like a Who's Who in the structural chemistry of the period: J. H. Sturdivant, J. L. Hoard, J. Sherman, L. O. Brockway, D. M. Yost, G. W. Wheland, M. L. Huggins, L. E. Sutton, E. B. Wilson, S. H. Bauer, C. D.

Coryell, V. Schomaker, and others. Here are the major achievements.

Pauling's ionic radii: Once the structures of simple inorganic crystals began to be established it was soon seen that the observed interatomic distances were consistent with approximate additivity of characteristic radii associated with the various cations and anions. Among the several sets that have been proposed, Pauling's are not merely designed to reproduce the observations but, typical for him, are derived from a mixture of approximate quantum mechanics (using screening constants) and experimental data. His values, derived almost seventy years ago, are still in common use, and the same can be said for the sets of covalent radii and nonbonded (van de Waals) radii that he introduced.

Pauling's rules: Whereas simple ionic substances, such as the alkali halides, are limited in the types of crystal structure they can adopt, the possibilities open to more complex substances, such as mica, $KAl_3Si_3O_{10}(OH)_2$, may appear to be immense. Pauling (1929) formulated a set of rules about the stability of such structures, which proved enormously successful in testing the correctness of proposed structures and in predicting unknown ones. As Pauling himself remarked, these rules are neither rigorous in their derivation nor universal in their application; they were obtained in part by induction from known structures and in part from theoretical considerations. His second rule states essentially that electrostatic lines of force stretch only between nearest neighbors. In the meantime, as structural knowledge has accumulated, this rule has been modified by various authors to relate bond strengths to interatomic distances, but it seems fair to say that it is still the basis for the systematic description of inorganic structures. W. L. Bragg, who may

have felt somewhat beaten to the post by the publication of these rules, wrote (1937): "The rule (the second one) appears simple, but it is surprising what rigorous conditions it imposes upon the geometrical configuration of a silicate. . . . To sum up, these rules are the basis for the stereochemistry of minerals."

Quantum chemistry: In 1927 Ø. Burrau solved the Schrödinger equation for the hydrogen molecule ion H_2^+ in elliptic coordinates and obtained values for the interatomic distance and bonding energy in good agreement with experiment. Burrau's wave function fails, however, to yield much physical insight into the stability of the system. Soon afterwards, Pauling (1928) pointed out that although an approximate perturbation treatment would not provide any new information, it would be useful to know how well it performed: "For perturbation methods can be applied to many systems for which the wave equation cannot be accurately solved . . . ." Pauling first showed that the classical interaction of a ground state hydrogen atom and a proton is repulsive at all distances. However, if the electron is not localized on one of the atoms, and the wave function is taken as a linear combination of the two ground state atomic wave functions, then the interaction energy has a pronounced minimum at a distance of about 2 a.u. This was the first example of what has come to be known as the method of Linear Combination of Atomic Orbitals (LCAO). For the hydrogen-molecule ion, the LCAO dissociation energy is only about 60% of the correct value, but the model provides insight into the source of the bonding and can easily be extended to more complex systems. In fact, the LCAO method is the basis of modern molecular orbital theory.

A few months earlier Heitler and London had published their calculation for the hydrogen molecule. This was too

complicated for an exact solution, and their method also rested on a perturbation model, a combination of atomic wave functions in which the two electrons, with opposite spins, change places. More generally, the energy of the electron-pair bond could now be attributed to "the resonance energy corresponding to the interchange of the two electrons between the two atomic orbitals." As developed by Pauling and independently by John C. Slater (1900-76), the Heitler-London-Slater-Pauling (HLSP) or Valence Bond model associates each conventional covalent bond with an electron pair in a localized orbital and then considers all ways in which these electrons can "exchange."

Much has been made of Pauling's preference for Valence Bond (VB) theory over Molecular Orbital (MO) theory. The latter, as developed by Fritz Hund (born 1896), Erich Hückel (1896-1980), and Robert S. Mulliken (1896-1986), works in terms of orbitals extended over the entire molecule, orders these orbitals according to their estimated energies, and assigns two electrons with opposite spin to each of the bonding orbitals. Electronic excited states correspond to promotion of one or more electrons from bonding to antibonding orbitals. Nowadays, MO theory has proved itself more amenable to computer calculations for multicenter molecules, but in the early days, when only hand calculations were possible, it was largely a matter of taste. The main appeal of the MO model was then to spectroscopists. Chemists, in general, were less comfortable with the idea of pouring electrons into a ready-made framework of nuclei. It was more appealing to build molecules up from individual atoms linked by electron-pair bonds. The VB picture was more easily related to the chemist's conventional structural formulas. Both models are, of course, drastic simplifications, and it was soon recognized that when appropriate correction terms are added and the proper transformations

are made they become equivalent. In particular, the MO method in its simplest form ignores electron-electron interactions, while the VB method overestimates them.

Pauling was fully acquainted with early MO theory—there is at least one important paper (Wheland and Pauling, 1935) on the theory of aromatic substitution. But he clearly preferred his own simplified versions of VB theory and soon became a master of combining them with the empirical facts of chemistry. A remarkable series of papers entitled "The Nature of the Chemical Bond" formed the basis for his later book with the same title. In the very first paper Pauling (1931) set out his program of developing simple quantum mechanical treatments to provide information about "the relative strengths of bonds formed by different atoms, the angles between bonds, free rotation, or lack of free rotation about bond axes, the relation between the quantum numbers of bonding electrons and the number and spatial arrangements of bonds, and so on. A complete theory of the magnetic moments of molecules and complex ions is also developed, and it is shown that for many compounds involving elements of the transition group this theory together with the rules of electron pair bonds leads to a unique assignment of electron structures as well as a definite determination of the type of bonds involved." To a large extent Pauling developed his own language to describe his new concepts, and of the many new terms introduced, three seem indelibly associated with his name: hybridization, resonance, and eletronegativity.

Only the first of these truly originates from him. In the first paper of the series Pauling took up the idea of spatially directed bonds. By a generalization of the Heitler-London model for hydrogen, a normal chemical bond can be associated with the spin pairing of two electrons, one from each of the two atoms. While an *s* orbital is spherically symmetri-

cal, other atomic orbitals have characteristic shapes and angular distributions. It was not difficult to explain the angular structure of the water molecule H_2O and the pyramidal structure of ammonia H_3N. But the quadrivalency of carbon was a problem. From its ground state ($1s^2 2s^2 2p^2$) carbon ought to be divalent; from the excited state ($1s^2 2s^1 2p^3$) one might expect three mutually perpendicular bonds and a fourth weaker bond (using the *s* orbital) in some direction or other. As a chemist Pauling knew that there must be a way of combining the *s* and *p* functions to obtain four equivalent orbitals directed to the vertices of a tetrahedron. Atomic orbitals can be expressed as products of a radial and an angular part. Pauling solved the problem by simply ignoring the former. The desired tetrahedral orbitals are then easily obtained as linear combinations of the angular functions. Pauling called these hybrid orbitals and described the procedure as hybridization. Other combinations yield three orbitals at 120° angles in a plane (trigonal hybrids) or two at 180° (digonal hybrids). With the inclusion of *d* orbitals other combinations become possible. In his later years Pauling stated that he considered the hybridization concept to be his most important contribution to chemistry (Kauffman and Kauffman, 1996).

Resonance: In attempting to explain the quantum-mechanical exchange phenomenon responsible for the stability of the chemical bond, Heitler and London had used a classical analogy originally due to Heisenberg. In quantum mechanics a frequency $\nu = E/h$ can be associated with every system with energy E. Two noninteracting hydrogen atoms are thus comparable to two classical systems both vibrating with the same frequency ν, for example, two pendulums. Interaction between the two atoms is analogous to coupling between the pendulums, known as resonance. When coupled

the two pendulums no longer vibrate with the same frequency as before but make a joint vibration with frequencies $\nu + \Delta\nu$ and $\nu - \Delta\nu$, where $\Delta\nu$ depends on the coupling. Going back to quantum mechanics, it is as if the system now has two different energies, one higher and one lower than before. Heitler and London interpreted the combination frequency $\Delta\nu$ as the frequency of exchange of spin directions.

Pauling first used the term resonance more or less as a synonym for electron exchange, in the Heitler-London sense, but he went on to think of the actual molecule as "resonating" between two or more valence-bond structures, and hence lowering its energy below the most stable of these. Thus, by resonating between two Kekulé structures the benzene molecule is more stable than these extremes, and the additional stability can be attributed to "resonance energy." Through his resonance concept Pauling reconciled the chemist's structural formulas with simplified quantum mechanics, thereby extending the realm of applicability of these formulas, and he proceeded to reinterpret large areas of chemistry with it.

In the mid-years of the century resonance theory was taken up with enthusiasm by teachers and students; it seemed to be the key to understanding chemistry. Since then, its appeal has declined. It has now a slightly old-fashioned connotation. Certainly, it had some failures. Resonance theory would lead one to expect that cyclobutadiene should be more stable as a symmetric square structure than as a rectangular one with alternating long and short bonds, whereas the contrary is true. (It seems ironic that in the 1935 classic *Introduction to Quantum Mechanics* by Pauling and E. Bright Wilson, Jr., qualitative MO theory was applied to only one example, four atoms in a square. In contrast to the Valence Bond method, which gave a typical "resonance energy" to

this system, the MO model gave none. Of course, cyclobutadiene was then still only a synthetic chemist's dream.) Similarly, it does not explain the stability of the cyclopentadienyl anion compared with the corresponding cation; in these and other cases simple molecular orbital theory provided immediate and correct answers. In the index of a modern textbook on physical chemistry "resonance" is likely to appear only in an entry such as "resonance, nuclear magnetic." It does not fare much better in textbooks on inorganic and organic chemistry; a few pages on resonance formalism are usually followed by a more extensive account of simple molecular orbital theory.

Electronegativity, the third concept associated with Pauling's name, is still going strong. It emerged from his concept of partially ionic bonds. The energy of a bond can be considered as the sum of two contributions—a covalent part and an ionic part. The thermochemical energy of a bond D(A—B) between atoms A and B is, in general, greater than the arithmetic mean of the energies D(A—A) and D(B—B) of the homonuclear molecules. Pauling attributed the extra energy Δ(A—B) to ionic resonance and found he could assign values x_A, etc., to the elements such that Δ(A—B) is approximately proportional to $(x_A - x_B)^2$. The x values form a scale, the electronegativity scale, in which fluorine with $x = 4$ is the most electronegative element, cesium with $x = 0.7$ the least. Apart from providing a basis for estimating bond energies of heteropolar bonds, these x values can also be used to estimate the dipole moment and ionic character of bonds. Other electronegativity scales have been proposed by several authors, but Pauling's is still the most widely used—it is the easiest to remember. According to Pauling, electronegativity is the power of an atom *in a molecule* to attract electrons to itself. It therefore differs from the elec-

tron affinity of the free atom although the two run roughly parallel. Many other interpretations have been proposed.

These and many other topics were collected and summarized in the book based on Pauling's Baker lectures, *The Nature of the Chemical Bond*, probably the most influential book on chemistry this century. In my opinion the 1940 second edition is the best; the 1939 edition was short-lived, and the 1960 edition, although it contains much more material, did not evoke the same feeling of illumination as the earlier ones.

Like so many others, I first encountered Pauling through this book, which I discovered sometime in my second year as an undergraduate at Glasgow University. It came as a revelation. Setting out to offer an introduction to modern structural chemistry, it explained how the structures and energies of molecules could be discussed in terms of a few simple principles. The essential first step in understanding chemical phenomena was to establish the atomic arrangements in the substances of interest. To try to understand chemical reactivity without this information or with dubious structural information was a waste of time. This was just what I needed to help me make up my mind that my future was to be in structural chemistry.

PAULING AND MOLECULAR BIOLOGY

The Nature of the Chemical Bond marks perhaps the culmination of Pauling's contributions to chemical bonding theory. There were achievements to follow, notably an important paper (1947) on the structure of metals, but the interest in chemical bonding was being modified into an interest into the structure and function of biological molecules. There are intimations of this in the chapter on hydrogen bonds. Pauling was one of the first to spell out its importance for biomolecules:

Because of its small bond energy and the small activation energy involved in its formation and rupture, the hydrogen bond is especially suited to play a part in reactions occurring at normal temperatures. It has been recognized that hydrogen bonds restrain protein molecules to their native configurations, and I believe that as the methods of structural chemistry are further applied to physiological problems it will be found that the significance of the hydrogen bond for physiology is greater than that of any other single structural feature.

Like many of his comments it seems so obvious, almost a truism, but it was not obvious then. Essentially the same idea had been expressed in Mirsky and Pauling (1936), but hydrogen bonds are not even mentioned, for example, in Bernal's (1939) article on the structure of proteins.

Two remarkable observations from 1948 deserve to be mentioned here. One is a forerunner of the 1953 Watson-Crick DNA double-helix structure and explains what had not yet been discovered (1948,1;1976):

The detailed mechanism by means of which a gene or a virus molecule produces replicas of itself is not yet known. In general the use of a gene or a virus as a template would lead to the formation of a molecule not with identical structure but with complementary structure . . . . If the structure that serves as a template (the gene or virus molecule) consists of, say, two parts, which are themselves complementary in structure, then each of these parts can serve as the mold for the production of a replica of the other part, and the complex of two complementary parts thus can serve as the mold for the production of duplicates of itself.

And in the same vein, although nothing whatsoever was known about the structure of enzymes, the other (1948,2) announced what became clear to biochemists in general only many years later:

I think that enzymes are molecules that are complementary in structure to the activated complexes of the reactions that they catalyse, that is, to the molecular configuration that is intermediate between the reacting substances and the products of reaction for these catalysed processes. The attraction of the enzyme molecule for the activated complex would thus lead to a

decrease in its energy, and hence to a decrease in the energy of activation of the reaction, and to an increase in the rate of the reaction.

The message seems to have laid in oblivion until well after "transition-state binding" had become popular; it is not mentioned, for example, in Jencks's classic work (1969) on enzyme catalysis.

Both of these prescient statements depend on the concept of complementarity, which arose out of Pauling's early work on proteins and antibodies. This started because, in the search for funding during the depression, Pauling obtained a grant from Warren Weaver, director of the Rockefeller Foundation Natural Science Division, but only for research in life sciences. With his knowledge of inorganic structural chemistry, hemoglobin was the first target, and within a few months he solved an important problem. By magnetic susceptibility measurements it was shown that, whereas hemoglobin contains four unpaired electrons per heme and the oxygen molecule contains two, oxyhemoglobin (and also carbonmonoxyhemoglobin) contains none (Pauling and Coryell, 1936). This result showed that in oxygenated blood, the O_2 molecule is attached to the iron atom of hemoglobin by a covalent bond—that it was not just a matter of oxygen being somehow dissolved in the protein. Magnetic susceptibility measurements could also yield equilibrium constants and rates for many reactions involving addition of molecules and ions to ferro- and ferrihemoglobin. It is interesting that Pauling had introduced the magnetic susceptibility technique at Caltech in connection with the prediction and identification of the superoxide radical anion, a molecule whose biological significance was recognized only many years later (1979).

In 1936 Alfred E. Mirsky (1900-74) and Pauling published a paper on protein denaturation, which was known to be a

two-stage process, one under mild conditions partially reversible, the other irreversible. Pauling associated the first stage with the breaking and reformation of hydrogen bonds, the second with the breaking of covalent bonds. The native protein was pictured as follows: "The molecule consists of one polypeptide chain which continues without interruption throughout the molecule (or, in certain cases, of two or more such chains); this chain is folded into a uniquely defined configuration in which it is held by hydrogen bonds . . . . The importance of the hydrogen bond in protein structure can hardly be overemphasized." Loss of the native conformation destroys the characteristic properties of the protein. From the entropy difference between the native and denatured forms of trypsin, about 10^{20} conformations were estimated to be accessible to the denatured protein molecule. On heating, or if the pH of the solution was near the isoelectric point of the protein, unfolded segments of acidic or basic side-chains would get entangled with one another, fastening molecules together, and ultimately leading to the formation of a coagulum. This was perhaps the first modern theory of native and denatured proteins.

Complementariness enters the picture in 1940, when Max Delbrück (1906-81) and Pauling published their refutation of a proposal of Pascal Jordan, according to which a quantum-mechanical stabilizing interaction between identical or nearly identical molecules might influence biological molecular synthesis in such a way as to favor the formation of molecular replicas in the living cell. After dismissing this proposal the authors went on to say that complementariness, not identity, should be given primary consideration. They continued:

The case might occur in which the two complementary structures happened to be identical; however, in this case also the stability of the com-

plex of two molecules would be due to their complementariness rather than their identity. When speculating about possible mechanisms of autocatalysis it would therefore seem to be most rational from the point of view of the structural chemist to analyze the conditions under which complementariness and identity might coincide.

The use of the word "complementariness" instead of the more usual "complementarity" is striking. According to Delbrück, his only role in the publication, apart from suggesting a few minor changes, was to have drawn Pauling's attention to Jordan's proposal, and it seems quite likely that "complementariness" was one of these minor changes, introduced in order to avoid the epistemological connotations that Delbrück associated with "complementarity" in Bohr's sense.

By this time Pauling was thinking about antibodies. In 1936 he had met Karl Landsteiner (1868-1943), discoverer of the human blood groups and instrumental in establishing immunology as a branch of science. According to Pauling (1976), Landsteiner asked him how he would explain the specificity of interaction of antibodies and antigens, to which he replied that he could not. The question set Pauling thinking about the problem, and it was not long before he had a theory (1940) that guided his research on antibodies for years to come. Eventually, it turned out to be wrong, or at least only half right.

The correct part was that the specificity of antibodies for a particular antigen is based on complementarity: "Atoms and groups which form the surface of the antigen attract certain complementary parts of the globulin chain and repel other parts." The wrong part was his assumption "that all antibody molecules contain the same polypeptide chains as normal globulin and differ from normal globulin only in the configuration of the chain." Pauling was clearly not too happy about this assumption, which he adopted only be-

cause of his inability "to formulate a reasonable mechanism whereby the order of amino-acid residues would be determined by the antigen." He could not know then about the genetic basis of amino-acid sequence. So he was right about how antibodies work and wrong about how they are produced. It was still a long time before a better theory emerged, based not on instruction but on selection, and involving hypervariable regions of the amino-acid chain and shuffling genes. In retrospect then it is not surprising that Pauling's immunochemistry program, carried out mainly by his Caltech collaborator Dan Campbell, never achieved the successes he had hoped for. During World War II there was a brief flurry of excitement when they claimed to have made "artificial antibodies" from normal globulins, but the claim proved to be ill founded and was soon retracted.

In 1941 Pauling's intense work schedule was temporarily stemmed when he was diagnosed as having Bright's disease, regarded then by many doctors as incurable. Under the treatment of Dr. Thomas Addis, he slowly recovered. Addis, a controversial figure, put Pauling on a low-protein, salt-free diet, which was effective in healing the damaged kidneys. After about six months Pauling was more or less back to normal, but he kept to Addis's diet for many years afterwards. Pearl Harbor brought further distractions when Pauling's energies were diverted to war work, mainly on rocket propellants and in the search for artificial antibodies. Earlier he had used the paramagnetism of oxygen to design and develop an oxygen meter for use in submarines.

By the end of the war Pauling felt well enough to travel abroad again. In late 1947 he came as Eastman visiting professor with his family to England, where he gave lectures to packed audiences in Oxford and elsewhere, received medals, and suffered from the climate. In 1948, confined to bed with a cold, he began thinking again about a problem

that had briefly occupied him a decade earlier—the structure of α-keratin. By this time, thanks to the X-ray crystallographic work of Robert B. Corey and his associates, the detailed structures of several amino acids and simple peptides were known, and although the interatomic distances and angles did not differ much from the values derived earlier by resonance arguments, Pauling could now take them as facts rather than suppositions—especially the planarity of the amide group. With the help of paper models he then set himself the problem of taking a polypeptide chain, rotating round the two single bonds but keeping the peptide groups planar, repeating with the same rotation angles from one peptide group to the next, and searching for a helical structure in which each N-H group makes a hydrogen bond with the carbonyl oxygen of another residue. He found two such structures, one of which also fulfilled the condition of tight packing down the central hole. The structure in question repeated after 18 residues in 5 turns at a distance of 27 Å, hence 5.4 Å per turn, whereas X-ray photographs of α-keratin seemed to show that the repeat distance was 5.1 Å. The discrepancy could not be removed by minor adjustments to the model and was large enough for Pauling to put the problem aside (1996).

It was taken up again after his return to Pasadena, with the help of Corey and a young visiting professor, Herman Branson, who checked details of the model and searched for alternatives, but without coming up with anything really new. Then came a paper from the Cavendish Laboratory by Bragg, Kendrew, and Perutz (1950), who described several possible helical structures for α-keratin, all unacceptable in Pauling's view because they allowed rotation about the C—N bond of the amide group. This paper provoked Pauling to publish his ideas in a series of papers that described the now famous α-helix (essentially the one modeled in Oxford

with 3.7 residues per turn), the so-called γ-helix (disfavored on energetic grounds), and the parallel and anti-parallel pleated sheets with extended polypeptide chains (Pauling and Corey, 1950;1951,1,2. Pauling, Corey, and Branson, 1951). By this time X-ray photographs of synthetic polypeptides had clarified the apparent discrepancy concerning the repeat distance along the helix; it was 5.4 Å after all. Max Perutz has vividly described his consternation on first reading Pauling's proposed structure and how he managed to corroborate it by observing the 1.5 Å reflection corresponding to the step distance along the α-helix, which everyone had missed until then (Perutz, 1987).

Very soon evidence began to accumulate that the α-helix is indeed one of the main structural features and that the two pleated sheet structures are also important elements of the secondary structure of globular proteins. Just as a few rules concerning the regular repetition of simple structural units had sufficed twenty years earlier to successfully predict the structures of minerals, now a few simple principles derived from structural chemistry were enough to predict the main structural features of proteins.

Pauling's next essay in model building was not so successful. In the summer of 1952 he learned about the Hershey-Chase experiment proving that genetic information was carried not by protein but by DNA, deoxyribonucleic acid, a polynucleotide. Pauling felt it should be possible to decipher the structure of this substance by model building along lines similar to those in the protein work. The available X-ray diffraction patterns showed a strong reflection at about 3.4 Å, but nothing much else. Having convinced himself that a two-stranded helical structure would yield too low a density, he went on to the assumption of a three-stranded helical structure held together by hydrogen bonds between the phosphate groups of different strands—that is, the struc-

ture rested on the tacit assumption that the phosphodiester groups were protonated! They were closely packed about the axis of the helix with the pentose residues surrounding them and the purine and pyrimidine groups projecting radially outward. When this structure was presented at a seminar, Verner Schomaker is credited with the remark, "If that were the structure of DNA, it would explode!" Nevertheless, the structure was published (Pauling and Corey, 1953), a pre-publication copy having been sent to Cambridge, where it stimulated Watson and Crick into their final spurt, culminating in their base-paired structure, which was immediately acclaimed as correct by everyone who saw it—including Pauling. The Watson-Crick structure conformed to the self-complementarity principle that Pauling had enunciated many years earlier and then apparently forgotten.

Much has been written about this spectacular failure. Why was his model-building approach so successful with the polypeptides and so unsuccessful (in his hands) with DNA? First was the time factor. Pauling had thought about polypeptide structures for more than a decade before he risked publishing his conclusions; he thought only for a few months about DNA.

Secondly, the available information: for the polypeptide problem, precise metrical and stereochemical data for amino acids and simple peptides, mostly from Pauling's own laboratory, were at hand; for DNA almost nothing was known about the detailed structures of the monomers or oligomers. The X-ray photographs available to Pauling were obtained from degraded DNA specimens and were essentially noninformative (they were later recognized to be derived from mixtures of the A and B forms of DNA), and he made a bad mistake in neglecting the high water content of the DNA specimens in his density calculations.

Yet Watson and Crick succeeded with Pauling's methods

where Pauling failed. There is no doubt in my mind that *if* Pauling had had access to Rosalind Franklin's X-ray photographs, he would immediately have drawn the same conclusion as Crick did, namely, that the molecule possesses a twofold axis of symmetry, thus pointing to two chains running in opposite directions and definitely excluding a three-chain structure. Then there were Chargaff's data about base ratios; Pauling later admitted that he had known about these but had forgotten. It seems clear that Pauling was in a hurry to publish, although, according to Peter Pauling's entertaining account twenty years later (P. Pauling, 1973), he never felt he was in any sense "in a race." Finally, as described in the next section, he was by this time under severe harassment from the FBI and other agencies for his political views and activities. This must have taken up much of his mental and emotional energies during these months.

Pauling's standing as a founder of molecular biology rests partly on his identification of sickle-cell anemia, a hereditary disease, as a molecular disease—the first to be recognized as such. The red blood cells in the venous systems of sufferers adopt sickle shapes which tend to block small blood vessels, causing distressing symptoms, whereas the cells in the more oxygenated arterial blood have the normal flattened disc shape. When, towards the end of the war, Pauling heard about this it occurred to him that it could be due to the presence of hemoglobin molecules with a different amino-acid sequence from normal. The abnormal molecules, but not the normal ones, could contain self-complementary patches such as to lead to end-to-end aggregation into long rods that twist the blood cells out of shape. Oxygenation could cause a conformational change to block these sticky patches. It took several years to confirm the essential correctness of what was no more than an intuitive guess. In the preliminary studies attempts to identify any difference be-

tween the hemoglobins of normal and sickle-cell blood were unsuccessful, but with the advent of electrophoresis it could be shown that molecules of sickle-cell and normal hemoglobin moved at different rates in the electric field; the two molecules have different isoelectric points and must indeed be different (Pauling, Itano, Singer, and Wells, 1949). When, much later, it became possible to determine the amino-acid sequence in a protein, sickle-cell hemoglobin was found to contain valine instead of glutamic acid at position 6 of the two β chains. A single change in a single gene is responsible for the disease.

A decade later the further study of mutations in hemoglobin led to yet another fundamental contribution to molecular biology—the concept of the "molecular clock" in evolution (Zuckerkandl and Pauling, 1962). By this time, amino-acid sequencing of proteins had become standard. Hemoglobins obtained from humans, gorillas, horses, and other animals were analyzed. From paleontological evidence the common ancestor of man and horse lived somewhere around 130 million years ago. The α-chains of horse and human hemoglobin contain about 150 amino acids and differ by about 18 amino-acid substitutions, that is, about 9 evolutionary effective mutations for each of the chains, or about one per 14 million years. On this basis the differences between gorilla and human hemoglobin (two substitutions in the α- and one in the β-chain) suggest a relatively recent divergence between the species, on the order of only 10 million years. On the other hand, differences between the hemoglobin α- and β-chains of several animals suggest divergence from a common chain ancestor about 600 million years ago, in the pre-Cambrian, before the apparent onset of vertebrate evolution. From this work it became clear that comparison of protein sequences (now replaced by comparison of DNA sequences) is a powerful source of

information about the origin of species. Evolution of organisms is bound with the evolution of molecules.

POLITICAL ACTIVISM

By 1954, when Pauling was awarded the Nobel Prize in chemistry for his "research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances," he was famous not only as a scientist; he was also a well known public figure, at least in the United States. Although he was not connected in any way either with the Manhattan Project or the Radiation Laboratory, his wartime research on antibodies and rocket propellants brought him into government advisory agencies such as the Office of Scientific Research and Development (OSRD) under Vannevar Bush and earned him the Presidential Medal for Merit, the highest civilian honor in the United States, awarded by President Truman in 1948. A few years later he was being vilified in the local and national press, being cited for "un-American activities," being denied the possibility to travel outside the United States, and his government research contracts were being terminated. How did this happen?

Almost immediately after August 1945 Pauling became concerned with the implications of the atomic age for international relations and the necessity for controls. His lectures and writings on this subject soon attracted the attention of the FBI and other government agencies. Far from being intimidated by these attentions, he began, with the encouragement of his wife, Ava Helen, to take a more active stance. He signed petitions, joined organizations (such as the Emergency Committee of Atomic Scientists, headed by Albert Einstein, and the American Civil Liberties Union), protested against the loyalty oaths demanded of public em-

ployees, and spoke eloquently against the development of nuclear weapons.

In the McCarthy era and especially during the Korean War this was enough to make him suspect as a security risk. Pauling was invited to lecture at a Royal Society meeting on protein structure to be held in London in May 1952. In February his application for a passport was refused because his proposed travel "would not be in the best interests of the United States." Renewed applications up to the end of April met with renewed refusals. A few hours before the start of the meeting Pauling telegraphed his regrets to London. I was present when the news came that Pauling had not been granted a passport and was therefore unable to attend. It was a grave disappointment, for we had all looked forward to Pauling's presence at the meeting, and there was also a feeling of outrage. The action of the State Department was seen as an insult not only to Pauling and The Royal Society, but to the scientific community at large. Pauling was certainly not the only U.S. citizen whose right to travel was denied by the State Department, but the incident provoked such widespread criticism that it probably helped lead to a reexamination and ultimate change in the State Department's policy. Later that year Pauling was permitted to travel to France and England (where he did not see Rosalind Franklin's X-ray diffraction photographs of DNA!) and the following summer he was again in Europe (where he did see the Watson-Crick DNA structure). This freedom to travel was bought at the cost of temporary, self-imposed political restraint, and was in any case a fragile privilege which he lost again a few months later, when he spoke out in defense of J. Robert Oppenheimer.

In March 1954, following the Bikini Atoll explosion of a "dirty" thermonuclear superbomb, Pauling was in the news again when he began to call attention to the worldwide

danger of radioactive fallout in the atmosphere. In the summer his renewed application for a passport was again turned down, but in November, when his Nobel Prize was announced, the State Department found itself in a public relations dilemma. The fuss created by Pauling's absence in London in 1952 would be nothing compared with the international outcry that could be imagined if Pauling were refused permission to travel to attend the Nobel Prize ceremony. So Pauling went to Stockholm, where he was a tremendous success, and followed this by visits to Israel, India, Thailand, and Japan. Everywhere—outside his own country—he was welcomed with enthusiasm, not only for his scientific accomplishments but even more for his political stance.

In the United States, too, the public was becoming increasingly concerned about radioactive fallout, not only from American tests but also from ever more powerful Soviet nuclear explosions. Increasing levels of strontium 90 and carbon 14 made newspaper headlines. Pauling claimed that the increased level of radioactive isotopes in the atmosphere was a danger not only to the living but also to future generations. The spokesmen on the Atomic Energy Commission countered that, although radiation might be harmful, it was not harmful in the doses produced by the tests and that Pauling vastly exaggerated the dangers. In fact, all the estimates were tentative at best, but since the Atomic Energy Commission was responsible both for developing nuclear weapons and for monitoring the associated health hazards, its estimates were probably no more objective that those who demanded a stop to the tests. Andrei Sakharov (1990) estimated that every one-megaton test cost about 10,000 human lives.

In January 1958 Pauling, together with his wife, was instrumental in collecting thousands of signatures from scientists all over the world for a petition to end nuclear bomb

testing, which was presented to Dag Hammarskjöld, secretary general of the United Nations. A few months later the Soviet Union called for an immediate halt to nuclear testing, and in October, after more tests by both sides that added markedly to world concern about fallout, talks began in Geneva to discuss details of a possible test ban. During the talks there was an informal moratorium on testing by the Soviet Union, the United States, and the United Kingdom. In the meantime, Pauling's book *No More War!* was published.

In 1960 the Senate Internal Security Subcommittee (SISS) headed by Senator Thomas Dodd issued a subpoena to Pauling to answer questions about Communist infiltration of the campaign against nuclear testing. At Pauling's request the hearings were open and they soon turned into a public relations fiasco for Dodd and the SISS. This was partly because the members of the SISS had not done their homework and partly because it gave Pauling the excuse to lecture them about elementary civic rights and duties: "The circulation of petitions is an important part of our democratic process. If it is abolished or inhibited, it would be a step towards a police state." By this time public opinion was mostly on Pauling's side, but the whole affair must have been experienced by him as an emotional strain—and a tremendous waste of his time and energy.

In 1961 there was a new petition, an "Appeal to Stop the Spread of Nuclear Weapons," again presented to the United Nations, and he also helped to organize the Oslo conference on the dangers raised by the proliferation of nuclear weapons. But in September there was a new spate of Soviet tests of even more powerful bombs—fifty within a couple of months—and in March 1963 President Kennedy announced that the United States would also resume testing. This time the tests did not last long; they were stopped in the sum-

mer, when new proposals were made to forbid atmospheric tests while permitting underground tests. In August both sides signed a treaty to ban all tests in the atmosphere, in outer space, and under the sea. The treaty went into effect on October 10 and the following day Pauling was awarded the Nobel Peace Prize for 1962.

At the present time, especially in the aftermath of the Chernobyl disaster, the cultural climate has changed so much that this short account of atomic politics until 1963 must strike younger readers as almost inconceivable. In the summer of 1996, when France exploded some "nuclear devices" several hundred meters underground below a remote atoll in the South Pacific, there was an international outcry of protest by governments, the press, and the public. Forty years ago, when tons of radioactive material were being spewed into the atmosphere by test after test, there was no such outcry, at least not in the United States and the Soviet Union, the two countries most responsible for the pollution. One can assume that the majority of people believed the tests were necessary. Small groups of people organized protest marches, but there were no social structures in these nuclear states to resist the continuation of testing and the spread of atomic weapons. Pauling was one of the few who consistently spoke against the dangers of atmospheric testing, against the spread of nuclear weapons, for efficient control of such weapons, and for a more rational approach to solve international conflicts. These sentiments found a ready ear in the non-nuclear countries, and eventually public opinion in the United States also swung in his direction. Whether he had any effect in the Soviet Union is another matter; he is not mentioned in Sakharov's (1990) autobiography.

APOSTLE OF VITAMIN C

A few days after the news of the Nobel Peace Prize Pauling announced that he was leaving Caltech to become a member of the Center for the Study of Democratic Institutions in Santa Barbara. He was disappointed with the lukewarm reaction of the administration and some of his colleagues. Perhaps he had intended to move anyway. In the mid-1950s he had become interested in phenylketonuria (mental deficiency due to inability to metabolize phenylalanine) as a further example of a molecular disease arising from the lack of a specific enzyme. At about this time he was also developing his theory that xenon acts as anesthetic because it forms crystalline polyhedral hydrates; microcrystals of such hydrates in the brain could interfere with the electric oscillations associated with consciousness (1961). He obtained a $450,000 grant from the Ford Foundation to study the molecular basis of mental disease and turned his laboratories more and more away from traditional chemistry, not to the unanimous approval of his colleagues. In 1958 he resigned from his position as department chairman, a position he had held for more than twenty years, and found himself under pressure to give up research space to a new generation of researchers. In these years of intense political activity and world travel he was in any case spending less and less time with his own research group and in keeping up with new developments in chemistry. When he left Caltech he vanished without a trace. In the 1963-64 annual report of the chemistry department his name appears in the list of professors with more honors and degrees than anyone else; in the corresponding report a year later his name has disappeared.

The next few years were not the happiest in Pauling's life. Not only did he sever his connection with Caltech, he

resigned from the American Chemical Society as well. The move to Santa Barbara was not a success. He turned to theoretical physics, but his close-packed spheron theory of the atomic nucleus met with little acceptance. He became engaged in actual and threatened libel suits. He moved briefly to the University of California at San Diego (1967-69) and then on to Stanford University (1969-72), where he was closer to his ranch at Big Sur, but he had no stable position in which to continue his planned research into "orthomolecular" psychiatric therapy. Meanwhile, he was deeply unhappy about the American involvement in Vietnam and about American politics in general.

One consolation was that after passing his sixty-fifth birthday Pauling's health took a sudden turn for the better. Thanks to Dr. Addis's unconventional low-protein diet, he had recovered well from the kidney disease that had laid him low in his forties, but he had always suffered from severe colds several times a year. In 1966, following a suggestion from Dr. Irwin Stone, the Paulings began to take three grams of ascorbic acid per day each. Almost immediately they felt livelier and healthier. Over the next few years the colds that had plagued him all his life became less severe and less frequent. This experience made Pauling a believer in the health benefits of large daily amounts of vitamin C. It was not long before he was enthusiastically promulgating this belief in lectures and writings, which, not too surprisingly, brought on him the displeasure of the American medical establishment. After all, the then recommended daily allowance (RDA) of vitamin C was 45 mg; it was well known that there was no known cure for the common cold, and, in particular, previous studies had shown conclusively that vitamin C had no effect. Nevertheless, the NAS Subcommittee on Laboratory Animal Nutrition was then recommending daily intakes around 100 times that of the human RDA

(adjusted for body weight) to keep laboratory primates in optimal health.

In his 1970 book *Vitamin C and the Common Cold,* Pauling gave evolutionary arguments why much larger amounts of vitamin C than the RDA may be conducive to optimal health. He cited studies supporting its efficacy in preventing colds or at least in lessening their severity. He criticized studies that claimed the opposite and he argued that since vitamin C is not a drug but a nutrient there is no reason why a large daily intake should be harmful. Pauling's arguments did not win the approval of the medical profession but they caught on with the general public. The book rapidly became a best seller. As a result, in America and later in other countries, millions of people have been persuaded that a daily intake of 1-2 g of ascorbic acid has a beneficial effect on health and well being, essentially agreeing with Pauling that "we may make use of ascorbic acid for improving health in the ways indicated by experience, even though a detailed understanding of the mechanisms of its action has not yet been obtained."

One result of the book was a collaboration with a Scottish surgeon, Ewan Cameron, from Vale of Leven, who had observed beneficial effects of high doses of vitamin C in treating terminal cancer patients. Cameron thought that vitamin C might be involved in strengthening the intracellular mucopolysaccharide hyaluronic acid by helping to inhibit the action of the enzyme hyaluronidase produced by invasive cancerous cells. A paper by Cameron and Pauling (1973) advocating vitamin C therapy in cancer was submitted to the *Proceedings of the National Academy of Sciences* (PNAS), which, in an unprecedented move, rejected the paper (it was then published in the specialist journal *Oncology*). During the next few years Cameron continued his trials. Since a double-blind trial was ethically unacceptable, he compared

results obtained with one hundred ascorbate-treated terminal patients and one thousand other cases, ten controls for each patient, matched as closely as possible, and found that the ascorbate-treated patients lived longer and felt better subjectively. A paper describing these results was eventually published in PNAS (Cameron and Pauling, 1976) but only after long arguments with referees. The Cameron-Pauling collaboration culminated in their 1979 book *Cancer and Nitamin C*, which was again more popular with the public than the medical profession, which continued to regard claims about the effectiveness of vitamin C in treating or preventing cancer as quackery. But by this time several important changes had occurred in Pauling's life.

At Stanford Pauling's demands for more laboratory space for his orthomolecular medicine studies had been turned down. A solution was found by a younger colleague, Arthur B. Robinson, who had left a tenured position at San Diego to work with Pauling at Stanford. Instead of working in cramped quarters at the university they would set up their own research institute nearby. A building was rented, initial financial help was forthcoming, and the Institute for Orthomolecular Medicine was founded in 1973. Once the initial funding ran out the institute found itself in financial straits. Soon it was renamed the Linus Pauling Institute of Science and Medicine with Pauling as president. By this change, it was hoped, fund-raising possibilities would be improved—a hope that proved illusory. Since Pauling was frequently away on travels and in any case disliked administration, Robinson took over in 1975, but the fiscal problems of the institute dragged on for several years until support began to be provided by private foundations and individual donations.

Personal and scientific difficulties between Robinson and Pauling led to Robinson's dismissal in 1979 and to lawsuits that dragged on for years. Meanwhile, Pauling continued to

defend his unorthodox views and became once again a controversial figure, regarded by some as a crackpot, by others as a sage. In 1986 he wrote another popular book *How to Live Longer and Feel Better*, which, based on his own experiences, gave advice about how to cope with aging.

In July 1976 Ava Helen underwent surgery for stomach cancer. Instead of post-operative chemotherapy or radiation treatment she adopted vitamin C therapy to the tune of 10 g per day. She was soon well enough to accompany Pauling on his various travels, but she finally succumbed five years later in December 1981. Pauling continued to travel, appear on television, write, and receive honors—his energy seemed unabated. When quasi-crystals with forbidden fivefold symmetry were discovered in 1984 Pauling took a contrary position and argued that the fivefold symmetry seen in Al/Mn alloys resulted merely from twinning of cubic crystallites (1985). He was probably wrong, but the resulting controversy was nevertheless useful in forcing the proponents of quasi-crystals to seek better evidence for their view.

He even became reconciled with Caltech, where his eighty-fifth and ninetieth birthdays were marked by special symposia in his honor. In 1991 he was diagnosed with cancer. Surgery brought temporary relief, and megadoses of vitamin C kept up his spirits. He spent his last months at the ranch at Big Sur and died there on August 19, 1994.

In the meantime, the medical establishment is no longer so totally dismissive of Pauling's views about possible therapeutic benefits of vitamin C on the common cold and on cancer. A recent review of several studies concludes that although supplemental vitamin C does not decrease the incidence of the common cold it does diminish the duration and severity of symptoms (Hemilä, 1992). This review also states that the level of vitamin C intake derived from a

normal or balanced diet may be insufficient for optimal body function and that the substance is safe even in large amounts.

The connection between vitamin C and cancer has also become a respectable topic of discussion. It was the subject of a conference organized by the National Cancer Institute in Washington, D.C., in 1990. Vitamins C and E (and other anti-oxidants) inhibit the endogenous formation of N-nitroso compounds in animals and humans (Bartsch, Ohshima, and Pignatelli, 1988). Such compounds are known to be carcinogenic in animals. Conclusive proof that they are dangerous at the levels naturally present in man is lacking, but the evidence seems suggestive. Thus, although the effectiveness of vitamin C in treating cancers may still be debatable, there is good reason to believe that it has at least an important preventative role.

The final word about the effect of large doses of vitamin C on health has still to be said. If you have a full, healthy diet rich with fruit, grains, and fresh vegetables, then you probably do not need supplemental vitamins and minerals. But in the modern world many people have, and may even prefer, an unhealthy diet. For them vitamin supplements are probably beneficial. After all, Pauling not only recommended large doses of vitamin C but also advised people to stop smoking, eat less, and cut down on sucrose.

PAULING THE MAN

Pauling lived a long and productive life. As scientist, through his writings and personal impact, he influenced several generations of chemists and biologists. As political activist he challenged the political and military establishment of the United States and helped to change them. As health crusader he took on the medical establishment and persuaded millions of people to eat supplemental vitamins.

He could be very persuasive indeed. His lectures were spellbinding, and he had a characteristically simple and direct literary style.

I remember his lectures at Oxford in early 1948. The lecture hall was too small to hold all who wished to attend; there was standing room only. He told those of us who had never studied electrostatics to go home and read Sir James Jeans's book on that subject before coming to his lectures on chemical bonding. I had never studied electrostatics but I stayed, spellbound. I had never heard anyone quite like him, with his jokes, relaxed manner, seraphic smile, slide-rule calculations, and spontaneous flow of ideas (only much later did I realize that much of that apparent spontaneity was carefully studied). He had great histrionic skills.

Vain? Conceited? Pauling was certainly aware of his own intellectual superiority, but he could be patient in dealing with the slowness of the slow witted. On the whole he was fairly tolerant of young, insecure seminar speakers, although, as I remember, he could also be intimidating at times. I am referring here to Pauling in middle age; I am told he became more intolerant in his later years. Political harassment during and after the McCarthy era must have taken its toll. Ambitious? Self-centered? Undoubtedly. Without these traits he would not have been able to accomplish as much as he did. But he often had a merry twinkle in his eyes and could be very charming, both as a public personality and in private.

In personal matters he kept most people at a distance. I believe he was basically rather shy. When he talked about science or politics or anything that caught his interest there was no stopping him. He read widely and was extremely knowledgeable in many areas—a result of having pored over the *Encyclopaedia Britannica* in his youth? In conversation one sometimes sensed a faraway look in his eyes; one felt

that he was already thinking about something else. Probably he was, and, indeed, he was a formidable thinker, both at the problem-solving level and about fundamentals. With his prodigious memory he could call up facts and derivations, what so-and-so had written in 1928, the unit cell dimensions of an obscure mineral, the standard heat of formation of ethane; and he had a remarkable capacity to visualize complex three-dimensional structures. I once asked him why he had never discussed the application of group theory to problems of chemical bonding. "Jack," he replied, "if you need group theory to solve that sort of problem then you're in the wrong line of business."

In addition to his Nobel Prizes Pauling was awarded dozens of honors and distinctions, including honorary doctorates from Oregon State College, Brooklyn Polytechnic Institute, Reed College, and the Universities of Chicago, Princeton, Yale, Cambridge, London, Oxford, Paris, Toulouse, Montepellier, Lyon, Liège, Humboldt (Berlin), Melbourne, York (Toronto), New Brunswick, and Warsaw. His election to membership in the National Academy of Sciences, Royal Society of London, Académie Française des Sciences, and Akademiya Nauk SSR may be specially mentioned.

His name will be remembered as long as there is a science of chemistry.

I HAVE LEARNED MUCH about Pauling's life from the excellent biography by Tom Hager (1995) and am grateful for information and advice from many friends and colleagues, among them David Craig, Durward W. J. Cruickshank, Albert Eschenmoser, Edgar Heilbronner, Barclay and Linda Pauling Kamb, Paul Kleihues, Alan Mackay, Peter J. Pauling, Alexander Rich, John D. Roberts, and Verner Schomaker.

REFERENCES

Bartsch, H., H. Ohshima, and B. Pignatelli. 1988. Inhibitors of endogenous nitrosation. Mechanisms and implications in human cancer prevention. *Mutat. Res.* 202:307-24.

Bernal, J. D. 1939. Structure of proteins. *Nature (London)* 143:663-67.

Bragg, W. L. 1937. *Atomic Structure of Minerals.* Ithaca, N.Y.: Cornell University Press.

Bragg, W. H., J. C. Kendrew, and M. F. Perutz. 1950. Polypeptide chain configurations in crystalline proteins. *Proc. R. Soc. Lond.* A203:321-57.

Cameron, E., and L. Pauling. 1973. Ascorbic acid and the glycosaminoglycans: An orthomolecular approach to cancer and other diseases. *Oncology* 27:181-92.

Cameron, E., and L. Pauling. 1976. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proc. Natl. Acad. Sci. U.S.A.* 73:3685-89.

Debye, P., and L. Pauling. 1925. The inter-ionic attraction theory of ionized solutes. IV. The influence of variation of dielectric constant on the limiting law for small concentrations. *J. Am. Chem. Soc.* 47:2129-34.

Dickinson, R. G., and L. Pauling. 1923. The crystal structure of molybdenite. *J. Am. Chem. Soc.* 45:1466-71.

Hager, T. 1995. *Force of Nature: The Life of Linus Pauling.* New York: Simon & Schuster.

Hemilä, H. 1992. Vitamin C and the common cold. *Br. J. Nutr.* 67:3-16.

Jencks, W. P. 1969. *Catalysis in Chemistry and Enzymology.* New York: McGraw-Hill.

Kauffman, G. B., and L. M. Kauffman. 1996. An interview with Linus Pauling. *J. Chem. Educ.* 73:29-32.

Mirsky, A. E., and L. Pauling. 1936. On the structure of native, denatured, and coagulated proteins. *Proc. Natl. Acad. Sci. U.S.A.* 22:439-47.

Pauling, L. 1923. The crystal structure of magnesium stannide. *J. Am. Chem. Soc.* 45:2777-80.

Pauling, L. 1927. The theoretical prediction of the physical properties of many-electron atoms and ions: Mole Refraction, diamag-

netic susceptibility and extension in space. *Proc. R. Soc. Lond.* A114:181-211.

Pauling, L. 1928. The application of the quantum mechanics to the structure of the hydrogen molecule and hydrogen molecule-ion and to related problems. *Chem. Rev.* 5:173-213.

Pauling, L. 1929. The principles determining the structure of complex ionic crystals. *J. Am. Chem. Soc.* 51:1010-26.

Pauling, L. 1931. The nature of the chemical bond. Application of results obtained from the quantum mechanics and from a theory of paramagnetic susceptibility to the structure of molecules. *J. Am. Chem. Soc.* 53:1367-1400.

Pauling, L. 1940. A theory of the structure and process of formation of antibodies. *J. Am. Chem. Soc.* 62:2643-57.

Pauling, L. 1947. Atomic and interatomic distances in metals. *J. Am. Chem. Soc.* 69:542-53.

Pauling, L. 1948. Molecular architecture and the processes of life. Sir Jesse Boot Foundation Lecture. Nottingham, U.K.

Pauling, L. 1948. The nature of forces between large molecules of biological interest. *Nature (London).* 161:707-709.

Pauling, L. 1961. A molecular theory of general anesthesia. *Science* 134:15-21.

Pauling, L. 1970. Fifty years of progress in structural chemistry and molecular biology. *Daedalus* (Fall):988-1014.

Pauling, L. 1979. The discovery of the superoxide radical. *Trends Biochem. Sci.* 4:N270-71.

Pauling, L. 1985. Apparent icosahedral symmetry is due to directed multiple twinning of cubic crystals. *Nature (London)* 317:512-14.

Pauling, L. 1994. My first five years in science. *Nature (London)* 371:10.

Pauling, L. 1996. The discovery of the alpha helix. *Chem. Intell.* 2:32-38.

Pauling, L., and R. B. Corey. 1950. Two hydrogen-bonded spiral configurations of the polypeptide chain. *J. Am. Chem. Soc.* 72:5349.

Pauling, L., and R. B. Corey. 1951. The structure of synthetic polypeptides. *Proc. Natl. Acad. Sci. U.S.A.* 37:241-50.

Pauling, L., and R. B. Corey. 1951. The pleated sheet, a new layer configuration of polypeptide chains. *Proc. Natl. Acad. Sci. U.S.A.* 37:2451-56.

Pauling, L., and R. B. Corey. 1953. A proposed structure for the nucleic acids. *Proc. Natl. Acad. Sci. U.S.A.* 39:84-97.

Pauling, L., R. B. Corey, and H. R. Branson. 1951. The structure of proteins: Two hydrogen-bonded helical configurations of the polypeptide chains. *Proc. Natl. Acad. Sci. U.S.A.* 37:205-10.

Pauling, L., and C. D. Coryell. 1936. The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proc. Natl. Acad. Sci. U.S.A.* 22:210-16.

Pauling, L., and M. Delbrück. 1940. The nature of intermolecular forces operative in biological processes. *Science* 92:77-79.

Pauling, L., H. A. Itano, S. J. Singer, and I. C. Wells. 1949. Sickle cell anemia, a molecular disease. *Science* 110:543-48.

Pauling, L., and R. C. Tolman. 1925. The entropy of supercooled liquids at the absolute zero. *J. Am. Chem. Soc.* 47:2148-56.

Pauling, P. 1973. DNA—The race that never was? *New Sci.* 58:558-60.

Perutz, M. G. 1987. I wish I'd made you angry earlier. *Scientist*, (Feb. 23):19.

Sakharov, A. 1990. *Memoirs* (English translation by R. Laurie). New York: Knopf.

Wheland, G. W., and L. Pauling. 1935. A quantum mechanical discussion of orientation of substituents in aromatic molecules. *J. Am. Chem. Soc.* 57:2086-95.

Zuckerkandl, E., and L. Pauling. 1962. Molecular disease, evolution and genetic heterogeneity. In *Horizons in Biochemistry*, eds. M. Kasha and P. Pullman, pp. 189-225. New York: Academic Press.

BIBLIOGRAPHY

A complete bibliography, by permission of the Linus Pauling Institute, is available from The Royal Society, London.