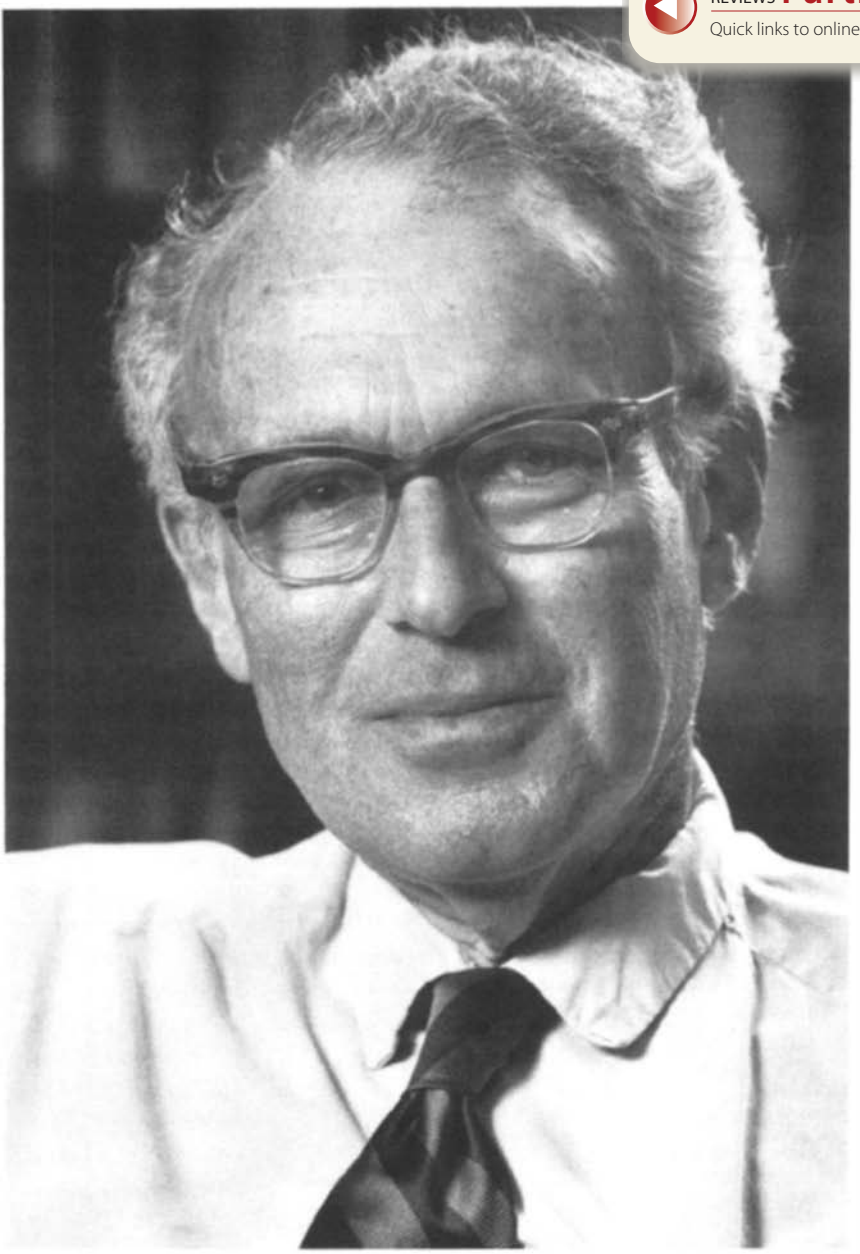

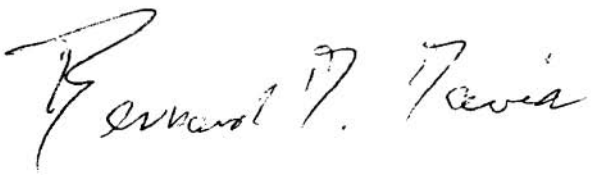

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SCIENCE AND POLITICS: Tensions Between the Head and the Heart

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Evolution, Genetics, and Society

I consider myself very fortunate in having chosen a career in science at such a favorable time. When the study of genetics finally penetrated into microbiology in the early 1940s, it revolutionized the life sciences, and by natural inclination, I was swept up in this venture.

In this essay, I summarize a career that encountered few obstacles and describe the influence of a few individuals on its shape. But in the final section, I take up another, far more sweeping and controversial domain, the relations between science and society. These increasingly drew my attention in the 1970s, a pivotal period in my life, during which I no longer found full-time preoccupation with my research entirely satisfying.

One reason for this restlessness was that the greatest excitement in the life sciences had moved from microbial to molecular genetics, but I had not

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moved with it. But perhaps more important, the world around me was struggling with agonizing questions about justice and race and the meaning of equality and affirmative action. At the time, I was much impressed by a little book by the distinguished humanist and evolutionary biologist T. Dobzhansky (30). He wrote that social equality is a moral and political goal: it is weakened, rather than strengthened, when we tie it to vulnerable assumptions of biological equality, rather than recognizing the reality of biological diversity.

In those turbulent times, Dobzhansky's book fell like a stone. But I shared his concern, as I saw unsound assumptions about human biology being used to distort affirmative action, shifting its aim from equal opportunity to equal numerical results. I therefore decided to spend 1974–1975 at the Center for Advanced Study in the Behavioral Sciences, in Palo Alto, Calif., studying behavioral genetics with the aim of writing a book on human diversity. This work would emphasize the evolutionary aspects of the subject more than the controversial data on IQ. More important, it would articulate the principle that the scientific facts do not prescribe policy, but they should improve it by testing the underlying assumptions.

I did not write the book, partly because the skeptical responses of most of the behavioral scientists at the Center to my nagging about the importance of genetics made it clear that it would be extremely difficult to convince a wider public. During that year, I did publish a transcript of a conference on human diversity, which I organized under the auspices of the American Academy of Arts and Sciences (26). Currently, the academic left is less effective in discouraging study of human behavioral genetics; the public certainly no longer needs convincing that genes are important; and political discussion of problems of affirmative action no longer goes on only under the table.

During the year at the Center, I enjoyed frequent contact with a scholar who had virtually founded the field of the sociology of science, Robert Merton. Toward the end of the year, he remarked that he had never met anyone who had more internalized the canons of science. At the time, this seemed a great compliment. But a decade later, at my retirement party, I offered a different interpretation. It stemmed from my growing fascination with the centrality of evolution, not only for biology but also for our perspective on the nature of the universe and of human beings. This fascination had led me to teach a course for nonscientist undergraduates at Harvard College on evolution, genetics, and society.

Initially, this new and expansive interest led me to share the widely held view that the crowning glory of evolution was the emergence of the human mind, capable of understanding its own evolution. But I gradually became impressed by an additional key principle of evolution: it selects not for maximizing but for optimizing a trait. Hence, if I had internalized the canons

of science maximally—focusing as sharply as possible on logical, analytical approaches to problems, and regarding their emotional aspects as diversions—then I was perhaps suffering from too much emphasis on objectivity, at the expense of what we often vaguely call wisdom.

In fact, in trying to give something of a portrait here, I must recognize that my genes seem to have steered me toward a rather skewed dedication to objective knowledge and truth, and to the importance of building on reality rather than on hope. But I recognize that moral values are more important in our daily lives, and they have competed strongly for my interest.

On the other hand, I have been less interested in esthetic and artistic values. This weakness has made me rather unresponsive to some major areas of cultural achievement. For example, in principle, I can recognize beauty in the multiple levels of meaning and the ambiguities of poetry, yet for me, these conflict with the search for clarity and are less interesting. So too with the visual arts—though here my limited aesthetic responses to details may involve a hereditary problem in dealing with spatial relations; as a student I did badly with morphological subjects.

My interest in moral introspection, in contrast to the classical Greek emphasis on beauty as the major goal of culture, fits the traditions of my Jewish background. And as for many other scientists, for me the extraordinarily abstract beauties and mysteries of the branch of mathematics called music present no conflict with the objective external world, and music has been an important part of my life.

In trying to provide some coherence to the picture, I oversimplify it by focusing on personal tensions between the heart and the head. Our whole society exhibits a similar antinomy as it struggles to deal with the explosive growth of our scientific knowledge and powers.

Personal Background

I was born in 1916 in Franklin, Massachusetts, a town of about 7000 located 30 miles from Boston. My parents had met in this country after coming from Lithuania in their late teens. The first immigrant from a region usually was followed by neighbors, and the first generation from a given shtetl usually arranged to end up in the same burial ground. Boston became a center for people from the Vilna province. In the U.S., our not-very-Jewish family name, Davis, was created from the middle name David by an immigration officer because he found the surname on the passport, Borukhovitch, too difficult to Anglicize.

I heard little from my parents about their earlier life in Europe. They focused instead on the remarkable opportunities afforded by this country, on the long and peculiar history of the Jewish people, and on the difficulty of maintaining the religious bonds that had held this people together for so long.

My parents could not arrange for me to learn the Hebrew that had contributed so much to this continuity, so they adopted a widespread American compromise: for instance, I was tutored to enunciate, without understanding the language, the long prayer that is required for Bar Mitzvah. This irrational solution so disturbed me that many years later, on a sabbatical in Israel, I found myself reacting equally irrationally: trying to learn Hebrew proved too unpleasant, though I had learned several other languages with pleasure.

Another experience turned me against religion very early. My maternal grandmother came as a dowry with her youngest daughter, my mother. She never learned English, though our town had only half a dozen Jewish families. Her main concern was strict adherence to religious rituals (including peasant superstitions that she thought were religious). She would not turn on the electric light on the Sabbath, because it was equivalent to making a fire and therefore was forbidden work. But she allowed us children to turn lights on for her convenience. I recall vividly my hand on the switch at the stairway, at the age of perhaps 12, thinking that if this system would help her to get into Heaven I wanted none of it. Thus began, however primitively, my shift to atheism, which I later decided not to soften with the euphemism "agnosticism."

Much has been written about the Jews of the lower East side in New York and their intense political, religious, and literary conflicts, but a second form of the Diaspora, scattered in small towns, has been neglected. As was typical, my father learned English at night school, was lent enough capital for a peddler's pack, and was helped to find a town that did not yet have a peddler. He eventually came to own a retail store—a mode of assimilation that became widespread in the small towns of America.

These scattered Jewish families lacked the social solidarity of those in the urban community, and so they were inevitably more alienated from their earlier culture. We children certainly suffered a good deal of teasing for our differences, but it was a pretty mild anti-Semitism. On the other hand, the relative isolation in small towns also provided direct benefits, by diluting competition. Arthur Kornberg's autobiography describes his bitter experience at City College in New York, where only one out of 200 Jewish premedical students got into any medical school. My experience at Franklin was quite different. The principal of the high school followed up my application to Harvard by taking me to visit the director of admissions and describing me as a promising student. This seemed to assure my admission. My subsequent record in the college made admission to Harvard Medical School seem almost automatic.

My father was intensely dedicated to providing the best educational opportunities for his children. He succeeded, but at great personal cost. He had built a flourishing store, but it was destroyed by a fire, with little insurance, in

1928; he borrowed to rebuild, and in 1929 came the depression. My brother, the valedictorian of his high-school class, had just started at Harvard. We three younger children also all became valedictorians, and my father took on the expense of sending us all through Harvard or Radcliffe—and then me through medical school. After his death a decade later, the family was moved by the vivid evidence of what sustained him: the first item in each of his account books was a report on some child's academic achievement.

I later felt guilty for not appreciating his sacrifices—and at having criticized his preoccupation with the perpetual problem of money. (I found asking for money very uncomfortable; later every grant application was a burden.) As high-school students, we children clerked in the store. I recall the agony of adult customers, in the depression years, deciding whether to spend ten cents or fifteen cents on a Christmas present. My father honed our skills in arithmetic by practicing sums during our family's Sunday drives. After I entered Harvard, I proudly demonstrated the slide rule to him that I had had to buy for a course. "You set 2 here, and 3 there, and here you see the answer, 6." I will never forget his expression as he asked, "For this you paid $2.00?"

While my mother encouraged pleasant relations with non-Jewish neighbors, she also emphasized that for real trust "your own is your own." But many years later, when she was more assimilated, and also desperate that I was not yet married at 39, she wholeheartedly accepted a non-Jewish daughter-in-law.

My father tried to persuade my mother to work in the store, but she insisted on caring for the children full time. I also chose a wife whose primary aim was raising a family, and I followed my father's pattern of being excessively preoccupied by work. Although I felt that time spent in scholarly activities was more justified than time spent making money, the result was similar: less time spent with the growing children, which I now regret.

Premature death of my grandparents in the old country, followed by remarriage, led to my having a number of half-aunts and half-uncles. As a child, I noticed that the set who shared a particular stepmother were kindly, sweet people, while the direct children of that mother all had difficult personalities. I cannot help wondering whether these striking differences might not have initiated a sensitivity to the role of genes in behavior.

For some years, my brother aspired to a career as a violin virtuoso. I played piano, less well, and chamber music became a major avocation, shared with my brother and later with my wife and son (a professional cellist). I was a poor athlete, and withdrawal from competition with my skillful older brother probably helped drive me to the excellent town library. The science teacher in our high school was hardly inspiring, and so medicine seemed the natural outlet for my curiosity about how things work.

I began school in a one-room schoolhouse that served both the first grade

(which stayed until lunch) and the second grade (which left earlier and returned after lunch). One day, in the first grade, the teacher asked me to return after lunch—and so I had skipped a grade and was a young member of my classes thereafter. (That school was recently reported to be the oldest functioning one-room schoolhouse in this country.)

An interest in language showed up early in my life, along with stubborn independence and excessive confidence in the power of logic. I learned to read before I began school, and when my mother helped me take out my first book from the library, I had great difficulty with the beginning—realizing only years later that I had struggled with the introduction for teachers. Also, I can still picture my nose pressed against a window pane, staring at "Union" on the sign at the street corner, knowing how the letter U is pronounced, and trying to figure out by logic how one could spell the word for onion if not with a "u."

In graduating from high school, I learned a lesson in future grantsmanship. The topic I chose for my valedictory address was Creative Chemistry, but the teacher insisted that all the essays have a central theme: the bicentenary, that year, of the birth of George Washington. Linking these two themes seemed impossible, until inspiration struck: "Little did George Washington dream that chemistry. . . ." The teacher was satisfied with this opening sentence, and the audience received a buoyant 1930s message on progress through chemistry.

College: Medicine, Chemistry, Biology

On entering college in 1932, I planned to seek a broad education in history and literature before moving on into a career in medicine. But I soon switched to concentration in biochemistry, for I had no difficulty in obtaining a grade of A in courses in science, mathematics, or language, but I could not get a better grade than C in the introductory history course, with its relatively large volume of reading matter, no matter how I tried.

In a curious episode connected with that switch, a brilliant upperclassman concentrating in history, who had just been elected to Phi Beta Kappa as one of the top eight in the class, had decided to go to medical school, and so he was taking the introductory physics course. He was having difficulty with the material and he asked me to study with him to help get him oriented. It soon became clear that one of us could assimilate the content of science easily, while for the other it had a different Gestalt. He returned to history (and particularly the history of discovery); years later he became Librarian of Congress. It seems to me that each of us develops early a few key ideas that spring up repeatedly in our subsequent intellectual life. It therefore may not be too farfetched to suggest that this episode, like that involving my aunts, further encouraged my later growing interest in the importance of genetic differences for our behavior.

Another theme, prominent in much of my scientific life, turned up in my undergraduate honors thesis: an interest in interactions of proteins more complex than the Michaelis-Menten relation between enzyme and substrate. This field became much more important later, when the atypical functional interactions could be correlated with shifts in shape (i.e. allostery). My research in this area, on the hemoglobin of a species of fish, was guided by a very kindly and encouraging teacher, D. Bruce Dill.

The oxygen dissociation curve of most hemoglobins, measured by equilibration with the gas at various tensions, has a sigmoid curve rather than the hyperbolic one predicted for a first-order reversible association. This property greatly increases the amount of oxygen that the hemoglobin transports between the lungs and the tissues in each round of circulation, and physiologists had long regarded it as a triumph of evolution in making circulatory systems efficient. Many years later, at the Cold Spring Harbor Symposium in 1961, an allosteric enzyme within the bacterial cell was shown to have a similar sigmoid relation between concentration of substrate and the amount bound (which in turn regulates the catalytic activity of the enzyme). Jacques Monod emphasized the physiological value of this mechanism for amplifying the sensitivity of the regulatory response. Having benefited from the breadth provided by a medical education, I was delighted to be able to point out the close parallel between the already well-explored hemoglobin system and the newly discovered allosteric regulation of an enzyme.

I was particularly interested in this parallel because it is striking how often the specialized products required for the physiology of higher organisms are not new in the sense of a fundamental new property of a molecule: the three billion years of prokaryotic evolution provided a wide array of nuts and bolts, which the additional 600 million years of evolution of multicellular organisms could then combine and permutate. Their novelty lies in the variety of ecological niches that they allow organisms to fill, and the mechanisms evolved for these purposes, more than in unusual features of the molecules. Moreover, I am amused by my own sense of gratification when one of the presumably late marvels of evolution is found to have originated in bacteria—"we" got there first. This identification with one's material is probably widespread among scientists, defining their turf.

At the same time, it is humbling to realize that the biomedical sciences have generated a rather constricted notion of the range of properties of living matter. If the familiar forms of life at the earth's surface should disappear, evolution would not necessarily start from scratch again, at the prebiotic stage. Some remnants of the DNA pool could still be maintained in what we regard as "peculiar" organisms: for example, those that thrive at the pressures encountered at the deep-sea bottom, and at temperatures above 100°C.

Clearly, our notion of the normal range of properties of living matter tends

to be anthropocentric. But it is broadening now, as an interest in the whole panorama of evolution, starting from its prebiotic phase (the "origin of life"), increasingly replaces medicine's domination of the life sciences. But an evolutionary perspective came to me much later. When I was an undergraduate, the curriculum paid little attention to genetics and evolutionary biology compared with physiology.

I did my thesis research in the Fatigue Laboratory, a curious organization where Dill had done most of the experimental work underlying L. J. Henderson's theoretical studies on blood as a physiological system. Henderson's search for broad principles fascinated me, especially as synthesized in his imaginative book on *The Fitness of the Environment*. But by that time he had become infatuated with the scientism of Pareto, whom he saw as creating a scientifically rigorous sociology. Henderson therefore had less influence on my intellectual development than one might have expected. Nevertheless, I certainly absorbed from him the principle that one should seek reciprocal interactions of multiple components—a system—rather than simply linear causal relationships. Also, his views might have contributed, subliminally, to my own later interest in interactions of science and society.

During college, I spent a summer at Woods Hole with my biochemistry tutor, Ancel Keys, doing analyses of sea water. This experience began a life-long association with that unusual community. I taught in the Marine Biological Laboratory, wrote for many summers in its library, and enjoyed activities, as a regular summer resident, that have greatly enriched the lives of my family members.

By the end of college I had difficulty deciding whether to go on to medical school or to seek a PhD in chemistry instead. I was attracted by the intellectual elegance of physical chemistry, which extracted general principles from empirical details. I also had been inspired by George Kistiakowsky's graduate course in physical chemistry. The deciding factor for me was probably the realization that chemistry then offered very limited career opportunities for a Jew, while a medical degree provided a broader set of options—including that of going into business for oneself if necessary. In those days, virtually no one sought the double MD/PhD degree, and I finally pursued the MD.

In making this choice, I was excessively confident that a good grounding in the powerful tools of physical chemistry, which I had formally mastered in Kistiakowsky's course, virtually guaranteed success in solving the presumably easier problems of medicine. I did not conceal this overconfidence, and it resulted in a painful comeuppance. I had the impression that I was expected to end up with highest honors. But having read every paper on hemoglobin, I incorrectly assumed that my thesis should correct the many errors that I found in that literature. The chairman of the oral examination, Professor Edwin J.

Cohn from the medical school, was neither impressed nor amused, and he had strong views on how people should behave. Hence, I ended up with a disappointing magna cum laude rather than a summa.

My interest in music came alive in college. Previously I had dutifully taken piano lessons, but teachers in that era discouraged sight reading. Now, playing piano again for pleasure, and without a teacher, I found that reading at sight came easily to me. For a long period I studied until midnight and then climbed seven flights of stairs to a room in the tower of Eliot House, where there was a Steinway that one could play at any hour.

To round out the description of my college experience: I was shy, and awkward with girls, and I did not take much advantage of the opportunities for social development. Of course I had a circle of friends, but with little money to spend we focused more on serious discussions than on seeking fun.

I was indeed a very earnest student. Perhaps I was responding to my father's hopes and sacrifices more than I realized. In 1936, I moved on to Harvard Medical School, dreaming that I could become a scientist, but also with a sense of obligation to help patients directly.

Medical School and Internship

Fairly soon after entering medical school, I arranged for part-time research, pushed by a fatherly upperclassman. He pointed out that E. J. Cohn had one of the few laboratories that was studying proteins in depth and that if he got to know me better he would surely overcome his unfavorable reaction to my smart-aleck thesis. My friend suggested that I should therefore try to work directly under him. That is what I did.

I spent a great deal of time in Cohn's laboratory throughout medical school, almost like a graduate student. At that time Cohn and some other investigators were struggling to move the study of proteins from the morass of colloid chemistry into the world of definite chemical structures. Cohn believed that study of the electrical properties of the whole molecules, correlated with similar studies on peptides, was the most rewarding feature to pursue at that time.

The studies of Cohn and John T. Edsall in this area did indeed add a great deal of useful knowledge. However, it seems clear now (though it may not have been so clear to me then) that Cohn's forceful direction of all the efforts of his highly coordinated laboratory along one line caused him to miss a more fruitful approach that emerged later: the development by Stein & Moore, and by Sanger and others, of the analytical tools for studying a purified protein as an organic molecule with a definable sequence.

Cohn set me to work studying the electrophoretic mobility of hemoglobin with the traditional cylindrical U-tube, using the color of the protein to locate the boundary. Electrophoresis had not then been used much as a tool for

studying proteins. Tiselius in Sweden scooped us by introducing sophisticated new technical developments, including an optical system that depended on refractive index and hence could be used to analyze mixtures of any proteins.

What Cohn and I reported, in my first publication (how important to the budding scientist!), now seems very obvious: electrophoretic mobility varies not only with pH (as was already known) but also with ionic strength (23). Developing the theory that would explain the quantitative features of this effect was beyond me, and so I was not unhappy to drop the problem at that stage—the beginning of my shift of interest from the chemical toward the biological aspects of biochemistry. I did not foresee how powerful electrophoresis would subsequently become as an analytical and preparative tool.

Cohn had an extraordinary personality, and the members of his laboratory competed with anecdotes about his harshness—yet with appreciation for his intellectual standards. As an example of his need to control, he renamed me "Ben," and others in the laboratory followed his lead. But they also depended on him for a job, while as a medical student I was more independent. When we finally sent off a joint manuscript he said "Ben, you've fought me every step of the way, and I respect you for it." Moreover, I am sure he had a hand in the decision to award me highest honors on graduation from medical school.

Cohn shrewdly foresaw that World War II would bring in our country, and that it would create valuable opportunities for research. He built up perhaps the first sizable research program in the basic biomedical sciences to be funded by the government: fractionation of bovine plasma. During my last year of medical school (1939–1940) I participated in this project with enthusiasm, under the guidance of Thomas McMeekin. The project did not succeed, for it was based on the false assumption that purified albumin might serve as a blood substitute without causing the immunological reactions encountered with whole foreign plasma. But Cohn showed his usual capacity for extracting valuable dividends from a bold and even perhaps rash program, and the fractionation of blood that he began has continued to be a fruitful enterprise.

I learned a good deal from E. J. Cohn about how to direct a laboratory—including more than I realized about why one should not direct people too closely. My success in standing up to him no doubt reinforced my tendency to rebel against authority.

Of course many other activities in medical school aroused my interest, and they had a strong enough attraction to keep me in clinical work a bit longer. Many scientists have proceeded directly from medical school into research without an internship, but I did not lose easily the sense of obligation to try to be a warm physician as well as a scientist.

The choice of hospital was easy. The chairman of the Department of

Medicine at Johns Hopkins Hospital, learning that the Tiselius apparatus was a powerful new tool for analyzing proteins, offered a fellowship, combined with a part-time internship, so that I could build such an apparatus and use it to seek novel abnormalities in plasma proteins. Unfortunately, despite my substantial laboratory experience, I did not have the maturity to make the most of the opportunity. I had a technician who analyzed a random plasma from the clinical laboratory each day, and we encountered many new patterns; but I did not follow through with most of them. For example, buried among them are the first agammaglobulinemia and the extraordinarily high concentrations of a novel protein in multiple myeloma. But evidently such descriptive findings, however novel, did not seize my interest, probably because they lacked an accompanying mechanistic explanation.

Meanwhile, I made my first discovery that seemed to me quite original. The sulfonamide drugs were receiving a great deal of attention at Johns Hopkins, and at a department meeting someone reported that sulfathiazole, unlike sulfanilamide, did not reach nearly as high levels in the cerebrospinal fluid (CSF) as in the plasma. The accepted explanation was a limited ability of sulfathiazole to penetrate into the CSF. But it seemed to me that the problem was one in the physical chemistry of a distribution at equilibrium: both drugs might penetrate freely, yielding the same concentration of free compound in the two fluids, but additional sulfathiazole might bind to something in plasma (very likely a protein). To test this hypothesis, as an intern without a laboratory, I equilibrated plasma in a cellophane bag against buffer containing either drug and then sent the samples to the clinical laboratory as though they came from a patient. Sure enough, sulfathiazole was extensively bound to plasma proteins but sulfanilamide was not (3).

This finding led me to add to a small literature that demonstrated the ability of serum albumin to bind a remarkable variety of compounds. I published a review, of which I was quite proud (4), emphasizing the physiological importance of this binding—not only in influencing the distribution of drugs in the body, but even more in protecting cells from many toxic compounds, both endogenous and foreign.

As an intern, I was conscientious but bored by many details, except for those patients whose problems suggested an interesting scientific challenge. The bulk of medical practice does not fit this bill. So I was not a very good intern, and I was not invited to continue into a residency.

In addition, the social attitude toward African Americans in Baltimore, and at Johns Hopkins Hospital, disturbed me. The white and the "colored" patients, though receiving identical care, had separate wards, blood banks, and toilets. I was shocked to learn that a nurse was not allowed to take orders on a colored patient if the intern referred to him as Mister rather than by his first name. I have been pleased to see how well Hopkins now deals with the

problems of integration and of recruiting black students—perhaps with more balance than my own school.

At the end of my internship, I entered the U.S. Public Health Service. I might not have known about this relatively obscure alternative to the regular armed forces, except that the wife of the Surgeon-General had been my patient. Also my part-time internship included routine duties on the metabolic ward at Hopkins, a research unit that was concentrating on study of the newly available adrenal steroids, and on the basis of rumors that German aviators were using these hormones to increase altitude tolerance, the Hopkins unit had initiated a cooperative research with a small aviation medicine facility at the NIH in nearby Bethesda. On entering the USPHS I joined that unit, where I completed a study begun by another research fellow. The results did indeed show that rats given deoxycorticosterone survived a higher simulated altitude.

I might note an additional interest that arose during medical school: the study of foreign languages. Leaving dormitory life, I moved to a rooming house run by an impecunious Boston dowager, in which most of the other tenants were German refugees. I enjoyed the chance to learn conversational German, and in later years, I created a similar opportunity to learn Russian.

U.S. Public Health Service; Tuberculosis

After I spent a brief period in aviation medicine, the USPHS assigned me to set up a study of biological false-positive serological tests for syphilis, which were exempting significant numbers from the military draft. The Service hoped that I could discover some properties of the serum proteins that would distinguish the false reactions. I felt that I needed guidance in immunology, which I was fortunately able to obtain in the laboratory of Elvin Kabat, at Columbia University College of Physicians and Surgeons. Thus began a long friendship, as well as the first of a series of appointments in various research institutions of New York City.

This research failed to solve the problem, but it taught me a good deal. Elvin handled his part of the arrangement very conscientiously and modestly, but I must confess that I, being accustomed to being on top of my problem, found it uncomfortable at times to be working with a master of the field who was always one jump ahead of me. Among our findings we obtained and characterized a pure solution of the Wassermann antibody (at a time when any pure antibody was hard to obtain) by simple ether extraction of the antigen (cardiolipin) from the precipitate that it formed with positive sera (29). The antibody turned out to be a larger molecule than most antibodies, and it was later identified as IgM. We also found that the pure antibody (or any isolated gamma globulin fraction) destroyed the activity of complement in the complement fixation test, and the effect was prevented by restoring the albumin that would normally be present in the serum in the test (27). I am not sure that this interaction has yet been explained.

I was also invited to review the literature on biological false-positive tests for syphilis, and in the medical-student tradition of being thorough and dutiful, I took pride in tracking down every referencc. I later lost interest in erudition as a goal, compared with the discovery of significant novelty. But respect for historical continuity is another matter: I still enjoy introducing material within a historical framework, and I have regretted the need to cut down the history in the succcssive editions of a textbook.

Though the Heidelberger-Kabat school of quantitative immunochemistry was then at the leading edge of immunology, I did not enjoy doing repetitious nitrogen analyses. After this project, the USPHS offered another opportunity in immunology, which might have fit my interests better, in the laboratory of Jules Freund (at the Public Health Research Institute of New York City). His war project aimed at using his powerful new immuno-adjuvant technique to try to develop a vaccine against malaria. My assignment was to develop a complement fixation diagnostic test based on fractions of the blood of our infected ducks and monkeys (6). But my stay was short because I found it difficult to accept Freund's insistence on secrecy. My position was very uncomfortable, but I fortunately received strong support from Robert Loeb, a forthright person whom I had come to admire while at Columbia.

Meanwhile, World War II drew to a close. I had expected to return to academia, but I had already seen that one could achieve great flexibility and independence, and excellent facilities for research, within the theoretically bureaucratic confines of government. The USPHS created a Tuberculosis Control Division at the end of the war, and the director of its research program, Carroll Palmer, invited me to set up a basic science research laboratory, at whatever site I thought most suitable. This opportunity seemed too good to pass up. Cohn, however, was furious, professing that his training had not been designed to be wasted in a second-rate institution. In fact, even though Carroll Palmer was disappointed that he could not arouse in me a deep interest in the intellectual challenges of his field, epidemiology, he provided a budget for my research on virtually no basis except personal confidence, and he gave me extraordinary freedom to pursue any leads.

To direct a tuberculosis research laboratory effectively, I needed a background in bacteriology. In medical school, this subject had been largely descriptive. Moreover, research on tuberculosis was carricd out mostly by convalescents in sanatoria and in general was not very exciting. But Rene Dubos was then enthusiastically describing a new approach to tuberculosis, in an outstanding institution, the Rockefeller Institute. I therefore sought training in his laboratory.

My interactions with Dubos were a very important part of my development. It was an intellectually and culturally inspiring period for me—even though the science was not as rigorous, in retrospect, as what I had encountered with Cohn and with Kabat. As I have already described this experience in some

detail, in a book celebrating Dubos' contributions to the development of antibiotics (19), I cover it here only very briefly.

Reminiscing about the contrast between Dubos and his teacher Selman Waksman encouraged me, belatedly, to rethink a rather snobbish attitude of admiring only those scientists with brilliant, often romanticized, ideas, while undervaluing those whose systematic, persistent, and even pedestrian approach laid solid foundations or provided practical benefits. Today, the growth of biotechnology has broken down the earlier barrier between biologists in academia and in industry. Though this development has created conflicts of interest, the benefits, including faster discovery and marketing of useful products, seem to be far outweighing the costs.

It further struck me that even though Waksman received his Nobel Prize for the discovery of the first effective drug against tuberculosis, his most valuable discovery was the principle that a persistent search for useful antibiotics will pay off. Dubos, in contrast, was too impatient to continue the search when his early antibiotic proved to be too toxic. His charismatic style subsequently led him increasingly to activities with wide public appeal, especially in the environmentalist movement, so we regrettably lost contact.

Incidentally, Dubos immensely admired the very different, profound style of Oswald Avery, and I am sorry that he did not introduce us while I was at Rockefeller. Among the friendships that I did develop there, I particularly treasure that with the highly original Rollin Hotchkiss, who was continuing the Avery work on genetic transformation.

My main discovery during the period with Dubos stemmed logically from my earlier work. By adding both a nonionic detergent and Cohn's Fraction V (albumin), Dubos developed culture media that provided somewhat faster and more dispersed cultivation of *Mycobacterium tuberculosis*. I found that the detergent was slowly hydrolyzed, and the released free fatty acids were very toxic to mycobacteria. The albumin neutralized that toxicity by its tight binding of the fatty acid (24). This finding solidly established the scavenging property of albumin that I had discussed earlier, and also the principle of a nonnutrient, protective growth factor for bacteria.

In this work, I further noted that normal serum contains a low concentration of free fatty acid—but as a few sentences inserted in a paper on methods, this finding was buried. Later, other workers rediscovered this fraction and showed that despite its small size its rapid turnover gives it an important role in lipid metabolism.

The period with Dubos had an additional, unexpected impact on my life: infection with the tubercle bacillus, with a minimal surface lesion that caused a persistent pneumothorax. Perhaps persons who were tuberculin-negative (as I was), and hence lacked the partial immunity of those with a positive test, should not have undertaken work with virulent tubercle bacilli. And we

certainly should not have employed careless techniques, as we did in a macho manner, proud of the medical tradition of taking risks for the benefit of others.

Physicians were then unwilling to use the toxic drug streptomycin on minimal cases, and the pinhole of my pneumothorax finally required surgery. Meanwhile, the traditional treatment, prolonged rest, gave me a sort of early sabbatical for more than a year. I think it was very valuable, at a time when I was ruminating about the program that I expected to launch on recovery. Much romantic literature has been written about the predilection of tuberculosis for people of talent and even genius; but I suspect that if there is any correlation it is because the prolonged rest gave the victims the chance to meditate about what they really valued.

My reading during this period turned more to philosophy than to current science, and I read Bertrand Russell's *History of Western Philosophy* twice, marveling at the clarity of his style. I intended to continue to read philosophy after recovery, but that interest did not persist. Philosophy has increasingly struck me as mostly an intellectual game, enjoyable for those who choose it but of declining importance in an age of science.

The scientific reading that most fascinated me was a review by George Beadle on the use of biochemical mutants of the mold *Neurospora* (i.e. those blocked in a biosynthetic step) as tools for genetic and biochemical studies. It seemed to me that such work, on universally distributed biosynthetic pathways, should be deeply satisfying because it was near the trunk of the evolutionary tree, while attempts to grow bigger and better tubercle bacilli were only twigs.

In developing the new tuberculosis laboratory, I was probably reluctant to expose persons without any immunity to virulent tubercle bacilli. So we launched a Tuberculosis Research Laboratory without any tubercle bacilli! It was located in a New York City health facility near the Rockefeller. The city lent the space to the Department of Preventive Medicine at nearby Cornell, and in turn, the chairman, an epidemiologist with no use for labs, lent them to us.

Bacterial Genetics and Amino Acid Biosynthesis; New York University Medical School

At first I floundered in searching for a focus for our new laboratory. But Beadle's review had already planted a seed in my mind, and it suddenly germinated during a seminar, when the speaker noted that biochemical mutants of *Escherichia coli* had technical advantages over those of *Neurospora* but were more difficult to isolate. Recalling that penicillin kills bacterial cells only when they are growing, I realized that in a culture growing in minimal medium it should kill off the wild-type *E. coli* while allowing any rare mutants with an additional growth requirement to survive.

The same idea occurred to Lederberg & Zinder, who submitted a letter to the *Journal of Biological Chemistry*. Lederberg generously offered to ask the journal to hold up their manuscript if I wished to send one immediately. The journal rejected both papers, on grounds of insufficient biochemical interest. We demonstrated our annoyance by publishing the two short papers in a chemical journal (5), but they really were papers on a bacteriological method. I am more pleased to recall the spirit that led us to have the two reprints bound under a single cover. Because independent discoveries in science do not represent a zero sum game, it does not seem to me that simultaneous announcement diminishes credit to either party.

I soon had a more extensive collection of mutants than the *Neurospora* group had accumulated in years (7). I named this class "auxotrophic" (for the additional nutritional requirement). I also introduced the terms "phenome" and "phenomic lag" to explain why my initial experiments, in which cells were exposed to penicillin immediately after mutagenic irradiation, had failed: any alteration in the genome would not yet have been expressed in the phenome. The cells required some growth after the irradiation, to allow phenotypic expression, before killing by penicillin could be selective.

Because I had never studied genetics, I arranged to give a summer course in Beadle's department at Caltech, as a way to learn some genetics and to become acquainted with that outstanding group, as well as to tout the virtues of bacteria. I also discussed with Lederberg a variety of challenging problems that I had thought of in the wide-open new field of bacterial genetics. But almost invariably he had already ruled out the value of each or already done it. I decided that competition with him in genetics would be much less profitable than mining the intermediates in biosynthesis, which auxotrophic mutants accumulated in large quantities.

Succumbing to the easy prosperity afforded by this field was probably a mistake for me, in the light of my later interest in more complex biological mechanisms. This was all the more true because I depended on associates for the chemical identification of our novel intermediates. And though I took the phage course at the Cold Spring Harbor Laboratory—which initiated a treasured friendship with Max Delbruck—I still did not get deeply into bacterial genetics itself. Van Niel's famous summer course at Pacific Grove on general microbiology, which I audited, had a stronger influence on my interests and my approach to problems.

Nevertheless, it seems to me that the role of the explosive advances in bacterial genetics, as a major foundation for much of the early work in molecular genetics, was taken for granted all too quickly. I made one contribution to the early phase of bacterial genetics: use of a U-tube with a sintered glass barrier to separate two of Lederberg's conjugating strains but allow the surrounding medium to be pumped back and forth. The results

showed that conjugation requires cell contact and hence is not a process of transformation by a labile substance in the medium (9).

In studying biosynthesis, I did undertake one prolonged program: working out many of the steps in a common pathway of aromatic biosynthesis, leading to tyrosine, phenylalanine, tryptophan, and *p*-aminobenzoate. This path also led to a previously unknown growth factor, *p*-hydroxybenzoate (8), which others later found to be a precursor of a quinone cofactor. The first intermediate that we identified in the common pathway was an already known but obscure natural plant product, shikimic acid. This intermediate was accumulated by mutants blocked immediately after its production, and it supported the growth of those blocked earlier (10). It is gratifying that the shikimic pathway has given rise to several books and to a review of the past decade with over 500 references.

I will not dwell on my early contributions to this pathway, but I would like to acknowledge my debt to Roger Stanier. He was studying the breakdown of aromatic compounds by soil bacteria, and he suggested, and supplied, the shikimic acid that turned out to be an intermediate in my pathway (but not in his). The sample was prepared for him by H. O. L. Fischer from the dried fruit of the shikimi tree, obtained from a Chinese pharmacist. The fruit, which contains an alkaloid as well as shikimic acid, is used as a laxative, and the pharmacist originally pretended not to know of it. Stanier fortunately learned why and persisted: the fruit is apparently also used traditionally, in larger doses, to poison one's mother-in-law (11).

My associates identified many intermediates and enzymes in the aromatic pathway, as well as in pathways to several other amino acids. These investigators included Ulrich Weiss, Ivan Salamon, Susumu Mitsuhashi, Charles Gilvarg, Elijah Adams, Edwin Kalan, and Henry Vogel. Our approach could not tell us how the aromatic pathway branched off from the central metabolic pathways (which I named amphibolic, for both catabolic and anabolic). To solve this problem, David Sprinson at Columbia College of Physicians & Surgeons initiated a long, enjoyable collaboration. Using precursors radioactively labeled in specific atoms (some at 5 counts per minute above background!), and then enzymes, he showed that three of the atoms of shikimic acid come from phosphoenolpyruvate and the other four from erythrose-4-phosphate to yield 3-deoxyarabinoheptulosonic acid-7-P (37). I admired his patient and thorough approach, as an organic biochemist, because I tended to seek problems with intellectual challenges but easy technical solutions.

Identifying the sequence of a pathway opens up the possibility of studying its regulatory mechanisms. Mitsuhashi worked on this problem, but we used bioassays that were not very satisfactory and we did not publish the results. I was deeply interested in problems of regulation (14), but I failed to follow

through and clearly establish the role of feedback in repressing as well as in inducing enzyme synthesis (which Vogel and I did note in an abstract). This was probably the largest mistake in my choice of directions. One factor may have been my propensity to intermittent depression at that stage in my life.

My group also made interesting contributions in some other areas. The role of the tricarboxylic acid (TCA) cycle in *E. coli* was then very much in dispute because the organism could not metabolize citrate, supplied exogenously, and yet it could oxidize acetate. Gilvarg settled the matter by showing that a glutamate auxotroph lacked citrate synthase, and it could not oxidize acetate (31); hence the oxidation in the wild-type proceeds via endogenous citrate. This is an excellent example of the sharp tools provided by mutants.

Carl Hirsch, Hans Kornberg, and Chandra Amarasingham further pursued work on the TCA cycle in the lab to which I subsequently moved. The results included the finding that succinate dehydrogenase is distinct from the anaerobically induced fumarate reductase. Chandra encountered something quite surprising. Under anaerobic conditions, the organism does not oxidize acetate, and as we expected, it does not make the superfluous α-ketoglutarate dehydrogenase. But the enzyme was also absent from aerobic cells growing happily on glucose. Instead the acetate accumulates until it reaches a critical, quite high concentration of free acetic acid, which induces formation of α-ketoglutarate dehydrogenase and thus completes the cycle (1). Thus, under optimal conditions, the culture initially extracts only one-third of the available energy from glucose and stores the remainder in the medium. The teleonomic significance of this regulatory response is not clear. Unfortunately Chandra died prematurely, and this finding has not been pursued by students of the cycle, though it seems to me quite fundamental.

At NYU, Werner Maas was primarily responsible for the first strong evidence that a gene can affect the structure, rather than only the quantity, of its product. He showed that a temperature-sensitive pantothenate auxotroph formed a temperature-sensitive enzyme (34). We often discussed ways of generalizing this finding, but we failed to formulate clearly the later concept of conditionally lethal mutants. Any scientist can look back and see boats he should not have missed, but this was a large one!

My chief in the USPHS finally decided that he could not justify my work in his tuberculosis program. At the same time I was offered chairmanship of the Department of Pharmacology at New York University Medical School, a school that was more willing than most to make unorthodox appointments based on future promise. I knew little pharmacology, and I have been amused to meet former students who recall with pleasure that I emphasized principles. They did not know that I had little else to offer!

Just when I was moving from the USPHS to academia, in 1954, FBI agents

visited me and unsuccessfully pressed me to identify Communists whom I might have met as a moderately radical student. The experience was frightening, and it sensitized me to the heavy hand of government. My flirtation with a communist cell in New York reflects the astounding success of the Party in securing converts among people distressed by the economic injustices so prominent in depression years, but the secrecy and deception required by this approach to politics made me very uncomfortable. My experience with committed Marxists also sensitized me to their frequently tricky techniques in academic disputes.

Before starting at New York University, I spent two months in the laboratory of Jacques Monod in Paris. It was an exciting period there; the work on gene regulation was gathering momentum. But I was an observer more than a participant, and I failed to build on this exposure. I think my research has been limited by a conservative reluctance to use new techniques.

I enjoyed very much becoming a teacher at NYU, though more in the theatrical role of the lecturer than that of a teacher relating to individual students or small groups. But I am impressed by how much a teacher can influence students, even as a lecturer, if he is willing to go beyond conveying facts and offer guidance on principles and values.

My research during the three years at NYU wound up our contributions on biosynthesis. I enjoyed extracting from the wealth of detail a broad generalization about intermediary metabolism: "On the Importance of Being Ionized" (13).

I also discovered the first specific transport system in a bacterial membrane and its inducibility (12). *E. coli* ordinarily cannot use citrate as a carbon source, but we had shown that it does metabolize endogenous citrate via the TCA cycle within the cells. The block therefore had to result from impermeability. Hence, when we encountered conditions that permitted the cell to use exogenous citrate, without any general increase in permeability, I had to conclude that we were inducing a specific transport system for uptake of the compound.

At that time, the idea of adaptively changing the composition of a morphological unit such as a membrane, and even more the idea that the tiny bacterium could have a wide variety of specific transport systems, seemed wild. Indeed, in publishing this work (13), I could only credit with a footnote some important data produced by a subsequently very distinguished postdoctoral fellow, Howard Green, who feared that such a claim might destroy his reputation. I also had difficulty persuading Monod, who had just discovered accumulation of nonmetabolized β-galactosides in bacteria, that he must be dealing with specific active transport rather than with binding to intracellular constituents. Monod soon went on to develop the "permease" as a major contribution, while my further studies on citrate were not fruitful. But I

thought he was excessively ungenerous in utterly ignoring the logic of my pioneer finding.

In moving from Paris to NYU, I invited Luigi Gorini, who had encountered an undefined aromatic growth factor, to join us. A collaboration between him and Werner Maas led to an important contribution to our understanding of regulation: feedback in the arginine pathway not only provides economy in response to an exogenous supply of arginine, but it ensures a proper level of endogenous synthesis, over a wide range of conditions. In steady-state growth, this level is usually far below the cell's capacity, but the reserve capacity allows a rapid adaptation to shifts in the supply of nutrients.

I saw a good deal of Leo Szilard, whose main interest had moved from physics to microbial genetics. He lived in a hotel in New York and circulated through nearby laboratories, critically evaluating their latest experiments and generously offering ideas that led to many valuable publications. He was the cleverest and most cerebral person I have ever met, and like his other young friends, I was overawed by him. But his character could present problems. He applied to the National Science Foundation for a lifetime salary, with no restrictions. As a member of the Committee that ruled on the application, I supported it as an appropriate way for society to recognize and assist this genius. But I failed to persuade the Committee to approve the grant—I believe because I had failed to persuade Szilard to make even a token commitment to the several sponsoring institutions. Our contacts subsequently evaporated.

Szilard had an extraordinary capacity for realistic and farsighted analysis of political as well as scientific issues. But his behavior sometimes reflected an insensitivity to the rules of behavior expected by others—which may help to explain why he was excluded from development of the atomic bomb after he had done much to initiate the program.

While at NYU, I married Elizabeth Menzel, who has brought a great deal of balance to my life. We had our first child in New York and then moved to Boston, where we both had roots and where it would be easier to raise a family. We had two more children in Boston, and the three have added a great deal to life's pleasures. Their striking differences in temperament, apparent from the moment of birth, reinforced my ideas about the importance of genetic diversity. It has been very gratifying to watch their progress, as a computer software engineer, an independent filmmaker, and a graduate student working on protein structure (and also conducting an orchestra). I am strongly dedicated to the nuclear family as the most natural pattern for our species.

Though I admired the spirit at NYU, and what it has been able to accomplish with limited resources, I could not resist an invitation to return to my alma mater, to a more comfortable city for raising a family, and to chairing a department in my field, microbiology.

Aminoglycosides and the Ribosome; Harvard

The move back to Boston in 1957 renewed ties with the university where I had studied for eight years, and it shifted my teaching from pharmacology to microbiology. The Dean at Harvard, George Berry, was intensely dedicated to the school. I tended to rebel at his forceful, authoritarian style, but I recognized that he, like E. J. Cohn, also could respect independence and put talent to good use.

Our microbiology department was then responsible for teaching immunology. A decade had passed since I had worked in that field, but it still looked to me like only a minor branch on the tree of science. The introduction of molecular genetics, which made immunology such a powerful model system to cell biology, was still a few years off.

In my new role, I took the teaching and administrative duties too seriously and delegated too little. Hence I became increasingly distanced from the details of my research, a common problem for senior scientists. Nevertheless, several excellent associates were highly productive, focusing mostly on the interactions of the ribosome with antibiotics and on the mechanisms of drug resistance. I viewed these as challenging problems in their own right and also as useful tools for studying ribosomal function.

During that period a leading microbiologist, W. Barry Wood, Jr., invited me to join him, along with Renato Dulbecco, Herman Eisen, and Harold Ginsberg, in writing a new kind of microbiology text for medical students (25). We proposed that in order to prepare students for the future advances in medical science microbiologists should now emphasize much more the use bacteria as model cells in the new genetic and molecular biology. This view was quite different from the widespread belief that microbiology was no longer an exciting area of medical research because the empirical triumphs of antibiotics had eliminated many of the challenges of infectious disease.

In fact, it was a great time for a microbiology department with the new orientation. Faculty from other departments would come to the lectures to learn about the latest developments at the Pasteur Institute. Later, I noted that at the 25th reunion of a medical class of that era the customary symposium on research by its members was devoted entirely to molecular studies of microbial pathogenesis. It struck me as being no coincidence that our earlier teaching about exciting scientific advances, even though not close to medicine, had stimulated some medical students to apply the same approach later to pathogenic microbes.

My role in the book gradually expanded because I turned out to be more interested than the other coauthors in its style. As a young student I disliked writing, partly because teachers then emphasized belles lettres rather than expository prose. But the final product of a scientist is usually a paper, and so I was a professional writer willy-nilly. I therefore decided to undertake a

course in self-improvement, primarily by reading Fowler's *Modern English Usage* from A to Z. Precision in communication then became almost as interesting a challenge for me as precision in the data.

In fact, I may have developed a time-wasting habit of reading scientific papers with too much attention to the language. But it seems to me unfortunate that current pressures encourage fast publication, for as the literature grows it seems ever more important that it be made more accessible by being well written. Dubos told me that Avery stored each of his manuscripts (a few per year) in a drawer for a month or more before final revision—a difficult model to follow today.

The five coauthors of the text discussed drafts of their chapters in great detail during two summers at Woods Hole. Because my comments on style were so extensive the others began to comment only on the content. In addition, Barry Wood developed a health problem and so I became director of the project. I then found myself trying to achieve a homogeneous style in a book by five independent senior scientists. Their reactions to my heavy editing were often not happy, but we remained good friends and ended up agreeing that the final product benefited. I regard my work on this book, through four editions and 25 years, as one of my most important contributions to microbiology.

At one stage of work on the first edition, I took off two months for full-time writing, in a colonial town in Mexico, San Miguel Allende. It was the most idyllic period in our family life. We had no contact with phone, radio, or periodicals, but we did not feel bored, even though our news was mostly about such matters as the foaling of our neighbor's burro. When we returned to Boston, I found that what I had missed in world affairs could be assimilated in an hour or so, yet I resumed the lifelong habit of compulsive reading of the trivia that form so much of our news.

From the start of my connection with tuberculosis research, I had tried, intermittently, to understand the action of streptomycin. I did not recognize that I was making one of the commonest and most serious mistakes in scientific investigation: choosing a problem that was not ripe for solution. Streptomycin and the other aminoglycoside antibiotics irreversibly block protein synthesis; the nonviable cell remains grossly intact, and almost anything that one can measure then changes. It was, therefore, difficult to decide which effects were important.

Our first breakthrough came from the work of Nitya Anand, a exceptionally idealistic person and excellent pharmaceutical chemist from India who joined us for a year to broaden his background for drug development. He subsequently became Director of the Central Drug Research Institute, responsible for virtually all drug development in India. In our lab, he discovered an effect of streptomycin that was quite unexpected, because it was not obviously con-

nected to the inhibition of protein synthesis: bacteria growing in its presence become permeable, in both directions, to a variety of small molecules, including increased uptake of streptomycin itself. Moreover, the effect is prevented when protein synthesis is reversibly inhibited by chloramphenicol (2). We inferred that streptomycin acts directly on the growing cytoplasmic membrane, causing nonspecific damage, and we suggested that this effect, rather than the block in protein synthesis, might be the lethal step. Donald Dubin added detailed data on its kinetics that seemed to support this hypothesis.

However, the mechanism of protein synthesis was just then beginning to open up, and Roger Stanier suggested, on the basis of indirect evidence, that streptomycin blocks protein synthesis by binding to the ribosome. This conclusion was soon directly confirmed by others. But Stanier's intellectually powerful paper also had an unfortunate influence on the field, for he emphasized the importance of separating the key step in streptomycin action from the epiphenomena. Only 25 years later did we realize that there is no key step. Moreover, his paper caused all workers in the field to neglect, for decades, the membrane damage. I in particular was embarrased at having overinterpreted this effect as the cause of cell death.

Building on Anand's discovery, Paul Plotz, then a medical student and now a distinguished immunologist at the NIH, explained the known synergism in the bactericidal action of a β-lactam plus an aminoglycoside—an effect of considerable clinical value. By exposing the cells sequentially to sublethal concentrations of the two antibiotics, he showed that pretreatment of growing cells with penicillin, which distorted cell-wall synthesis, evidently induced membrane damage, because it increased sensitivity to subsequent killing by streptomycin. In the reverse order, the two agents were not synergistic. Others later confirmed the sensitization by penicillin directly by measuring uptake of radioactively labeled aminoglycosides. The brutally direct approach to most problems with labeled reagents generally enables deeper analysis, but I have always had sympathy for the biologist who makes the initial discovery by a primitive but ingenious experiment and then is quickly forgotten.

Meanwhile, Luigi Gorini, whom I had brought from NYU to Harvard, discovered that in the cell streptomycin at sublethal levels causes misreading, rather than blockage, in protein synthesis. This discovery was independent of my program, except that Julian Davies in my group, working with Walter Gilbert, confirmed the misreading in vitro, and he later defined some of the specific misreadings of one base as another.

Unfortunately, as Gorini acquired fame for this important discovery he grew increasingly resentful of our relationship, and then he began to compete directly with a post-doc of mine, Fred Sparling, who was well along in a study of the ribosomes in cells heterozygous for streptomycin sensitivity and resis-

tance (36). Gorini's insistence on continuing the competition destroyed our friendship, and it brought to a head tensions in the department. I can recognize now that the egalitarian revolt against authority in 1968 was only part of the reason for the tensions, since I had failed to change the style of strong administration of the department that the school had initially encouraged. I withdrew from administration and set up a small, independent unit. While the result was painful, the change greatly improved my research.

Studies by Juan Modelell (from Spain), though very carful, failed to identify the links between the ribosome and other chages in streptomycin-killed cells. In a later major advance P.-C Tai and Brian Wallace (from Australia) solved one mystery: how the ribosome can have two different, mutually exclusive responses, blockade or misreading, though it binds tightly only one molecule of streptomycin. These investigators separated initiating free ribosomes from chain-elongation polysomes, which lack initiation factors and hence can only complete the already growing chains. They found that several classes of antiribosomal antibiotics (including aminoglycosides) block further synthesis only when they bind to an initiating ribosome. However, on chain-elongating ribosomes aminoglycosides have a unique effect: they cause misreading and slowing but not blockade, while the other classes (such as spectinomycin) do not cause misreading and some indeed have no apparent effect (29b). Since inhibition of growth is reversible with the latter classes and irreversible (i.e. lethal) with the aminoglycosides, it appeared that the characteristic misreading effect of the aminoglycosides is probably involved in their lethal action.

The nature of this involvement, as well as the mechanism of the membrane damage and its relation to the ribosomes, remained unexplained. Accordingly, when I retired I felt that I had lost the battle with streptomycin. However, an invitation to review antibiotic actions on the ribosome, at a meeting of the Society of General Microbiology in England, led to the answer—which could have been recognized many years earlier. I brought some reprints with me to study before the meeting. Assimilating a bundle of facts at such a time is quite different from more or less remembering them over the years, and doing so in a new atmosphere may encourage new associations. Sitting in a London hotel room, I suddenly had a Eureka: if misreading affects all proteins being synthesized, it would include those that will be incorporated in the membrane. An abnormal protein there might create nonspecific leakiness, thus providing the missing link between ribosome and membrane.

With this link we only needed to recognize that killing depends not on one key step but on a cycle of multiple steps, each equally important (17). First, a few molecules of antibiotic stray into the essentially impermeable cell, perhaps through transient imperfections in the growing membrane. Because they first encounter mostly chain-elongating ribosomes, which predominate in growing cells, they cause misreading. This causes membrane damage, which

results in increased uptake of antibiotic—far beyond the amount needed to saturate the ribosome population. All the ribosomes are thus fixed in initiation complexes, blocking protein synthesis. Recent work has confirmed this mechanism, and it has also explained why the block is irreversible: the abnormal membrane protein is rapidly destroyed, thus caging the antibiotic in the cells (2a).

Additional, particularly strong evidence for the proposed bactericidal mechanism is its ability to explain a remarkable paradoxical effect observed earlier by others: low concentrations of puromycin accelerate killing by streptomycin, while high concentrations block it. Because puromycin releases incomplete chains, which is a form of misreading, membrane damage provides an obvious explanation. At low puromycin concentrations, the released chains would be long enough to cause such damage, while at high concentrations, they would be too short (17).

The extensive literature on the action of aminoglycosides in recent years has focused mostly on quantitating their uptake. But the final uptake of streptomycin may reach 100 times the molar concentration of ribosomes in the cell. Because the cell has already been killed by uptake too low to be detected against the background of surface adsorption, the measured uptake may be irrelevant, except as an extrapolation revealing membrane damage.

Among the other problems taken up by my graduate students or post-docs at Harvard, Loretta Leive studied the competition between exogenous and endogenous sources of diaminopimelate, which we had shown to be a precursor of lysine. It is also a component of the peptidoglycan of *E. coli.* She demonstrated that, in these incorporations, the two corresponding diaminopimelate sources, differentially labeled, exhibit a gradient or compartmentalization (32). This problem is still not well understood and does not fit the picture of the cytoplasm as a homogeneous solution.

David Smith discovered that novobiocin interferes with DNA metabolism—an effect that became useful when others later identified the enzyme on which it acts, DNA gyrase. Eliora Ron, from Israel, found that growth at elevated temperatures is limited not by melting of the membrane, which is what we expected, but by reversible inactivation of the first enzyme in the biosynthesis of methionine. She has since found this curious property in all the bacterial species tested.

Porter Anderson found that inosine can pair with adenosine in the translation of polyinosinic acid as an artificial messenger, and I suggested that this fit of two purines in a double helix, and in Crick's wobble hypothesis, could best be explained if one of the purines was in the *syn* rather than the usual *anti* configuration (22). This was one more bright idea, subsequently established by others, that gave me pleasure but had no visible impact as an isolated contribution based on indirect evidence.

Elizabeth Mingioli was a most effective technician and my virtual right

hand for many years. Unfortunately, having such an effective assistant accelerated my withdrawal from doing experiments myself. Among many contributions, she showed that vitamin B_{12} could replace methionine in certain mutants blocked in its methylation step.

I also became involved with the ribosome cycle, at a time when there was much controversy over the distribution of the ribosomal particles (polysomes, single ribosomes, and native 30S and 50S subunits) in the lysates of *E. coli* prepared in different ways. We distinguished initiating monosomes from free ribosomes, which accumulate after polysome runoff, by their difference in dissociability at low Mg^{2+}. Others had shown that the three initiation factors (IF1,2,3) are not free in the lysates but are bound to 30S ribosomal subunits. It seemed to me logical to conclude that one or more of the attached IFs must serve as a dissociation factor, preventing the 30S and 50S subunits from pairing and thus stabilizing them as a reservoir awaiting initiation.

This idea came shortly after I began a wonderful half-year sabbatical actually working in the lab with Pnina Elson at the Weitzmann Institute in Israel. I instructed Eliora Ron and Robert Kohler, back at home, to prepare a mixture of IFs and see whether it would cause purified free ribosomes to dissociate. It failed, so I cabled to ask them to try 10 times as much. They thought I had been touched by the hot sun in Israel—but the experiment worked. A. R. Subramanian identified the dissociation factor as IF3 (38).

Subramanian further found, unexpectedly, that at the end of translation the ribosome is released as a 70S particle rather than as subunits. Tai later showed (as did Kaji elsewhere) that this release is accelerated by a protein ribosome-release factor, whose significance is still not clear. The ribosome cycle was now quite complete. Michael Gottlieb, Robert Beller, and S. Ramagopal further added to our understanding of the ribosome, and Nicolette Lubsen, a graduate student from the Netherlands, studied the complex initiation factors of rabbit reticulocytes.

In one of our most important contributions, Robert Thompson provided the first experimental confirmation of Hopfield's suggestion that the recognition step in protein synthesis involves proofreading, which greatly increases its accuracy (39). Our approach was very direct: forming ternary aa-tRNA-EFTu complexes and showing that the ratio of GTP hydrolyzed to the amount of incorporated amino acid varied as predicted for a cognate, near-cognate, or distant tRNA.

We also became interested in a different and neglected aspect of the ribosome: its possible role in cell death. The reported extensive loss of total RNA in starving cells suggested to me that in starved *E. coli* cultures the breakdown of ribosomes might proceed to the stage where death could result from complete loss of ribosomes. An undergraduate, Selina Luger, showed that this was indeed true (28), though others have obtained quite different results under other conditions.

Our findings support what seems to me an interesting theoretical generalization: in a starving cell, complete elimination of any species of protein is not lethal if the cell retains or can restore the capacity to transcribe and translate its messenger when supplied with the necessary building blocks and energy; but if any protein required for protein synthesis (including ribosomes) is exhausted, it cannot be regenerated. I am glad to see breakdown of ribosomes during starvation now being studied in depth in other laboratories, because in the cycles in nature bacteria face famine much more often than feasting.

My last major area of research was protein transport across cell membranes. In a dense, short paper, Cesar Milstein, at Cambridge, England, had shown that a special, cleavable sequence, which he called a signal sequence, initiates transfer of an immunoglobulin chain across the membrane of a lymphoid cell. Walter Smith in our laboratory demonstrated such cotranslational transfer in bacteria more directly: chains protruding from the surface could be chemically labeled or enzymatically cleaved, with the inner terminus still attached to membrane-bound ribosomes in the cell (35). Milstein did not continue work on this problem, having meanwhile discovered how to grow monoclonal antibodies in hybridomas, and he seemed to be losing credit for the work on secretion. I wrote with Tai a review that was aimed in part at straightening out the history of the signal sequence (29a) for it seems to me important to assign credit properly for original discoveries, both to satisfy a sense of fairness and to provide motivation for investigators.

Further pursuing protein transport, David Rhoads showed that incorporation of protein into membrane vesicles in vitro requires a membrane potential. Seikoh Horiuchi & Michael Caulfield, using the gram-positive *Bacillus subtilis* to avoid outer membrane fragments, isolated a complex of four proteins, attached to cytoplasmic membrane or to ribosomes, that appear to be involved in protein secretion (2b). Others have identified this complex (also in another gram-positive organism, *Staphylococcus aureus*) as pyruvate dehydrogenase, and so its function in secretion is not certain.

We also examined the problem of how gram-negative bacteria excrete proteins to the exterior even though they lack any evident source of energy for moving them from the periplasm across the outer membrane. Stephen Lory showed that when this excretion is inhibited by ethanol, which distorts membrane organization, the protein flows through the junctions between the inner and outer membranes and is then held up on the external surface of the outer membrane; none is found in the periplasm. If the ethanol is removed, the bound protein can be released to the exterior by cleavage of its signal sequence (33). More recent work, however, on other systems, as well as by Lory using a mutation to block the pathway, has made it uncertain that the normal pathway bypasses the periplasm.

One of my last scientific papers, far from microbiology, was on what seems

to me a major mystery in biology: the function of sleep, during which the brain is about as active as during waking hours. Francis Crick published in *Nature* a theory that all this work serves primarily to correct errors encoded in memory during that day. I offered an opposite view, based on the theory that memories are encoded by changes in proteins that occur when synapses are fired. Since these proteins inevitably fade, through the normal process of turnover, I suggested that during sleep we consolidate waning memories by firing sets of neurons in a process that systematically scans the brain (15). This mechanism does not seem to me to bear on the separate problem of why we dream, and it would not be surprising if a process of scanning memories were influenced by the cognitive and emotional content of the most recently recorded items. My paper was rejected by *Nature* and appeared in a less prominent journal. But it is gratifying to see that in the currently expanding research on sleep, the idea of consolidation of memories seems to be acquiring increasing acceptance.

Another speculative publication was stimulated by a paper by John Cairns, who found that a substrate, lactose, increased the rate of mutation from lac^- to lac^+. He offered a provocative Lamarckian interpretation that challenged a fundamental principle in genetics and evolutionary biology: that mutations occur in nature at random rather than being directed. I suggested an alternative mechanism that did not contradict this principle. In my mechanism, the mutagenic effect of the substrate depends on induction of transcription of its operon, which creates a short region of single-stranded DNA. This region, moving along the operon, is more mutable than double-stranded DNA, and so it would introduce a bias in the mutation rate—but a bias is not a directed mutation (18).

On retirement in 1984, I turned over my laboratory to P.-C. Tai, who had worked with me for over 15 years, and I have been delighted to see his success in further dissecting the problems of protein export. I subsequently enjoyed periods of teaching at the University of Tel Aviv and at the National Taiwan University Medical School. In addition, Carlos Chagas of Brazil had converted the ancient Pontifical Academy of Sciences into a useful advisory group to the Pope, and at a workshop on genetics I predicted that the Church would find it increasingly difficult to refuse to use our growing knowledge of genetics to prevent human misery by prenatal diagnosis and elective abortion. I was encouraged by the free and open discussion with the bishop in charge of family policy, but the response at other levels remains to be seen.

I often felt that I might not be guiding my students and fellows in enough detail. However, I have been pleased to see that nearly all of them have found new and interesting directions in their later careers, rather than remaining specialists building on their earlier training. This flexibility may have been

encouraged by the freedom to pursue their problems with a good deal of independence in my laboratory.

To try to encapsulate the portrait of me as a scientist: I clearly have "internalized the canons of science," emphasizing rationality and reality, more than most. I think my strongest suit in science has been critical, logical analysis, leading to a simple but decisive experiment. And although a systematic program, pursuing the shikimate pathway, has probably contributed most to my scientific reputation, I have tended not to pursue programs at length but to skim the cream from a variety of problems. My greatest satisfaction in science has come from unexpected associations, such as those leading to the penicillin method, the ribosome dissociation factor, or the multistep action of streptomycin. I have perhaps been more willing than most serious scientists to publish ideas that seemed bright and even playful but lacked proof. But my predictions on genetic engineering have been too conservative.

In dealing with social issues I have focused on defects in current policies and in the underlying assumptions, rather than on supporting laudable aims and achievements that are already widely accepted. I have functioned more as a Socratic gadfly than as a member of committees or an active participant in political organizations.

Science and Society: the Genetic Revolution

Virtually a second career, in science and society, began in 1969, quite unexpectedly.

The Biology Department at Boston University was sponsoring a symposium, at a national meeting, where Peter Medawar was to discuss the ethical impacts of molecular genetics, but meanwhile he suffered a stroke. With great diffidence I filled the breach. I then spent a sabbatical year, as already noted, at the Center for Advanced Study of the Behavioral Sciences. This rather deep involvement in an unfamiliar subject was stimulated in part by my reaction to what seemed to me irresponsible attacks on behavioral genetics by a group called Science for the People, and particularly by a brilliant population geneticist in my university, Richard Lewontin. After he had made some especially outrageous statements on a television program, I enjoyed challenging him to a formal debate, like Thomas Huxley debating Bishop Wilberforce in the 19th Century.

Soon I was publishing on various aspects of science and society, and in 1986 I collected the articles in a book, *Storm Over Biology* (16). Its topics included evolution and sociobiology, genetics and racism, and genetic engineering. I summarize here two additional items from the book.

The first, a guest editorial in the *New England Journal of Medicine,*

applauded efforts to increase the number of minority physicians but emphasized that especially in medical education we must not sacrifice standards, because lives are at stake. A very similar statement that I had drafted had been favorably received by the administration in my school, and because other medical schools also had problems with affirmative action, it seemed useful to publish the piece in a professional journal. I did not anticipate how the news media would portray me as a racist, with the result that students picketed me and Dean Robert Ebert denounced me in a letter to all other medical deans. My colleagues offered no public support, though I suspect that most of them agreed with me. Many years later, I received an unexpected rehabilitation when an annual report of the next Dean, Daniel Tosteson, commended *Storm Over Biology*. But the charge of racism has undoubtedly influenced the reception of my subsequent publications.

I determined to avoid further involvement with the topic. However, when the suit by Bakke over racial preference in medical school admissions subsequently reached the Supreme Court, the extensive public discussion all supported one or the other of the two extremes: de facto quotas or color-blind admission. I finally felt obligated to call attention to a third possibility: that we stretch standards but reject quotas, in order to increase numbers but still have some control over the cutoff. The court adopted this position, though on different, legal grounds.

The second piece in *Storm Over Biology,* on objectivity in science, emphasizes that the word science is used with three different meanings in different contexts: a methodology, the activities of people using that methodology, and the resulting body of knowledge. Because the results are tested against nature, they can be objective even though the activities are highly subjective. A great deal of confused criticism of science seems to me to have arisen from failure to distinguish these three meanings of the word.

The areas of my interest in the interactions of science and society continued to include public ambivalence about genetic engineering. I edited a book for a general audience, *The Genetic Revolution* (20), by a group of experts on scientific and social issues.

I have also become concerned by the increasing politicization of science. An early example was the attack on human behavioral genetics. More recently, the Human Genome Project has thrust on biomedical research (21) the precedent of a centralized, large-scale organization. A third example, with much greater menace, has arisen from outside our community: increasing public ambivalence about science, and increasing intrusion of government in the style of research, as a consequence of exaggeration of the problem of misconduct.

It is particularly challenging to try to foresee the future impacts of the genetic revolution. Current discussion focuses mostly on hazards and prob-

lems arising from our increased power to manipulate DNA. However, I suspect that our greatest problems will arise from our increased insights into our genetic diversity. These insights not only may give us more prognostic information than we can handle comfortably, they will surely have major implications before long for social policy, including education, the distribution of jobs and of rewards, and the definition of racial justice. And perhaps the more distant future will bring an irresistible pressure to guide human evolution.

Finally, my interest in social implications of evolutionary biology has led me to defend sociobiology, which focuses on cooperative instincts as well as on the competitive drives that dominated early evolutionary thinking. Moreover, while premature or grossly distorted applications of genetics and evolutionary biology were often used in the past to rationalize conservative and even racist political views, modern genetics has had the opposite effect, for it has replaced the false typological notion of races with a populational view, which recognizes races as groups in which prolonged reproductive separation has inevitably led to different, but overlapping, gene pools. But a review of my thoughts and writings on the aspects of science and society that I have listed would take us too far from the central theme of this autobiography.

We scientists are probably more idiosyncratic than we realize in viewing the search for truth as a paramount human goal. Most people prefer a belief because it is expected to make them, or others, feel or act better, rather than because it is based on evidence. But with the mounting global crises, an effective set of responses would have to be anchored in the reality that science elucidates. So we come back to the antinomy of the heart and the head—and the hope that we will be guided by each only in its proper realm.

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