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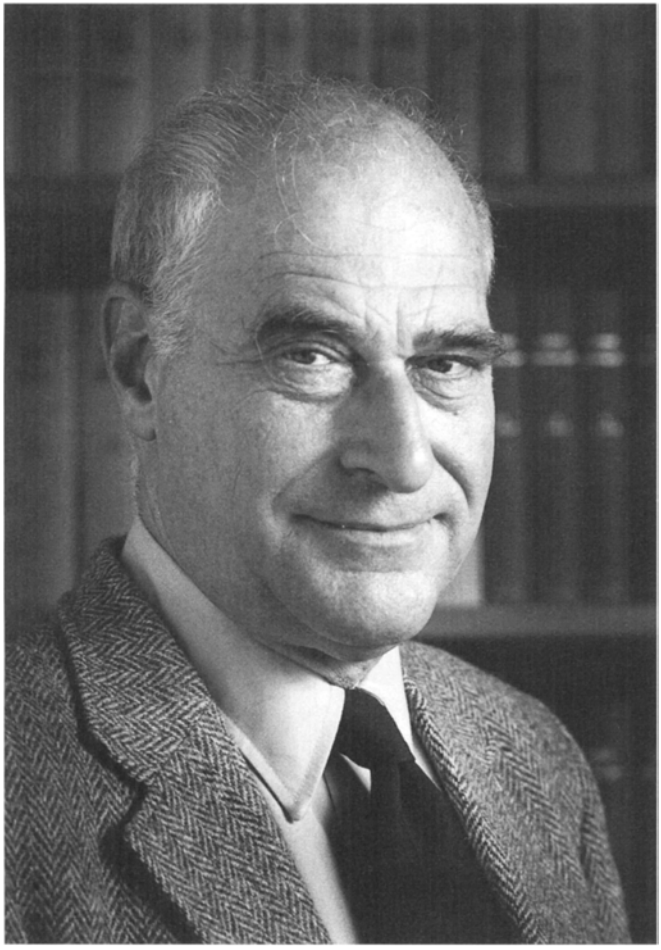

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University of Illinois, B.S. (1945)
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California Institute of Technology (1948)
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American Academy of Arts and Sciences (1968)
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Gunther Stent was trained in physical chemistry and initially studied DNA replication and expression. Moving in midcareer to neurobiology, he worked out the neural control of swimming and heartbeat in the leech. He also pioneered developmental studies of the leech, which resulted in a comprehensive description of cell lineage. He has written many philosophical essays on the epistemology and sociology of science.

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Gunther Stent

Childhood

Few Jews lived in Treptow, the unfashionable suburb of Greater Berlin where I was born. Its anti-Semitic, petty-bourgeois milieu was light years distant from the avant-garde—the Albert Einsteins, the Max Reinhardts, the Marlene Dietrichs, the Bertolt Brechts—to whom the Berlin of the Weimar Republic owed its cultural glamour. My religious upbringing, insofar as I had any, took place in the context of anti-Zionist, self-hating Germano-Christianized Reform Judaism. There were no observances of Hebrew ritual in my home: no Sabbath candles, no Passover seder, no matzoth. Judaism only became a major factor in my life when I was 9, Hitler came to power, and I began to fear for my life as I watched Nazi storm troopers march through the Berlin streets bawling: "When Jew-blood spurts from our knives, we'll all have twice-better lives."

My father, Georg Stensch, a native of Berlin, owned one of the largest bronze statuary and light fixture factories in Germany. My mother, Elli, came from a family of well-to-do, assimilated Jews in the Silesian city of Breslau. In 1933, shortly after the Nazi takeover, she was confined in a psychiatric sanatarium, and my teen-age elder sister, Claire, took charge of my upbringing until, newly wed, she emigrated with her husband to Chicago in 1937. By then, my mother had died. A year later, my sister sent me the affidavit of support I needed to apply for my U.S. immigration visa. I was wildly enthusiastic about starting a new life in the glamorous New World, led by the great president to whom that Nazi monster, Joseph Goebbels, habitually referred as "Crypto-Jew Fraenkel Rosenfeld." As I knew from poring over back issues of the *National Geographic* magazine I had come across in a resort hotel, America had the prettiest girls, the tallest buildings, and the most cars. I was crushed when the U.S. consulate in Berlin informed me that because of the sudden rush of German-Jewish visa applicants, it would be a few months until I could expect to get my papers. As it turned out, I had to cool my heels for 18 long months.

My father barely avoided being sent to Sachsenhausen concentration camp in the roundup of moneyed Jews during the *Kristallnacht* pogrom of November 10, 1938. Because he had connections with the Berlin police and a valid passport, he managed to escape to London, where my elder brother, Ronald, was living. Since neither my recently acquired stepmother nor I

had a passport, we decided to join my father in London illegally. We had heard that the most promising route was across the "Green Frontier" between Germany and Holland or Belgium, which meant stealing over the border in open country, avoiding not only the German but also the Dutch or Belgian frontier patrols who were handing the Jewish refugees they intercepted back to the Germans. To cut down the risk, it was advisable to engage the expensive services of a guide. Our first guide was arrested by the police on his way to meeting us at Aachen station. Our second attempt, which involved traipsing through the snow-covered Ardennes forest on New Year's eve, succeeded, but only after our second guide had led us directly to a German frontier police post. The post's chief, who was probably cut in on the exorbitant tour fee, let us go after checking the Gestapo's list of wanted persons and strip-searching us for contraband. We made it to Antwerp on New Year's Day 1939, physically safe but destitute.

We had to wait four months in Antwerp for our British visa before my stepmother and I managed to reach London. After hanging around London for another 11 months, I finally received my U.S. immigration papers and, in March 1940, sailed alone for the States from Liverpool in the third-class bowels of an ancient Cunard steamer. By then, the Second World War had begun, and I was lucky that my ship was not torpedoed by a German U-boat before it docked in New York harbor.

I moved in with my sister. Chicago's Hyde Park district had turned into one of the "Fourth Reich" settlements of German and Austrian Jewish refugees—like Washington Heights in Manhattan and Swiss Cottage in London—and she enrolled me at Hyde Park High School. Concealing my long absence from schooling, I struck the vice-principal as an upper-level junior, or maybe even as a senior (hadn't I enjoyed the benefits of the world-renowned German secondary education?) until he gave me a few tests. I couldn't do fractions, let alone geometry or science. Although I was almost 16, he made me start as a freshman, the graduating class of 1944.

Miss Rubovits, my English composition teacher at Hyde Park, demanded clarity as well as grammatical perfection. The weekly themes she assigned had to be written again and again, until her exacting literary standards were met. Imitating Miss Rubovits earned me much ill-will in my later professional life from scientific colleagues whose work, including feature articles I commissioned for the *Journal of Neuroscience* during the last few years of my career, I took the liberty of rewriting to Miss Rubovits' standards.

To make up time, I signed on for extra courses, went to summer school, and obtained credit for knowing French (but not for knowing German, because it was my mother tongue). Accumulating credits at a furious rate, I made it through Hyde Park High in 21 months, still appallingly ignorant of most academic subjects. In the fall of 1942, I moved to Champaign, to enter the University of Illinois.

Synthetic Rubber

I had never heard of chemical engineering when I chose it as my major at Illinois. Its name suggested something brand new, something futuristic. "Gunther Stent, Chemical Engineer," had a nice ring to it, and I figured it would set me apart from your run-of-the-mill college graduate. As it turned out, I didn't care for chemistry in college any more than I had in high school until, in my junior year, I took my first course in physical chemistry. Professor Frederick T. Wall's lectures were dynamic, lucid, and well prepared, and his presentation of chemical thermodynamics was captivating. In contrast to inchoate inorganic or organic chemistry,—not to speak of the boring engineering courses—physical chemistry appealed to me as a logically coherent discipline, whose theories are expressible as mathematical relations. I switched my major to physical chemistry.

Upon graduating from Illinois in January 1945, I applied to California Institute of Technology for a Ph.D. in physical chemistry under Linus Pauling, my scientific hero because his *The Nature of the Chemical Bond* was the first textbook that I actually enjoyed reading in all my 13 years of doing time in German and American schools. But Caltech turned me down and I resigned myself to staying at Illinois.

I accepted Prof. Wall's offer to do a Ph.D. under his direction as a research assistant on the War Production Board's (WPBs) synthetic rubber research program. The mission was to develop a process that would make synthetic rubber tires as good as, or even better than, tires made from natural rubber. Natural rubber consists of a homopolymer in which hundreds of isoprene monomers are linked end-to-end, whereas synthetic rubber (Buna-S) is a copolymer of equal proportions of butadiene and styrene monomers. One of the flaws of Buna-S that impaired its elastic properties was that, whereas natural isoprene homopolymer molecules are of uniform length, synthetic butadiene–styrene copolymer molecules are not. Wall assigned me to work out a method by which Buna-S could be resolved into a series of fractions, each of which would contain copolymer molecules of uniform length. I decided to try a modification of the thermal diffusion column invented by K. Clusius and G. Dickel in 1938 for resolving gaseous mixtures of atomic isotopes, such as $^{12}CO_2$ and $^{13}CO_2$.

I built a column, 2 m tall, of two concentric steel tubes separated by a narrow, 1-m gap which was filled with a toluene solution of the synthetic copolymer; the outer tube was cooled by cold water and the inner tube was heated by hot water. It worked as I had hoped. After letting the column run for 2 days, downward from the top, the gap contained Buna-S molecules of ever-greater chain length. Mathematical analysis of these data then gave me an entirely novel way of determining the molecular length distribution among the original synthetic copolymer molecules.

I was jubilant: It was my first success as an experimental scientist. I had finessed Mother Nature and made her do my bidding! Perhaps my

device would become known as the "Stent column." When people would congratulate me, I would feign modesty and point out that the idea was actually pretty obvious.

I proudly presented my findings at a national meeting of all WPB rubber research groups in the spring of 1946. There was no need for me to feign modesty. My talk aroused only mild interest; my colleagues thought that my method would never provide a practical way of producing Buna-S molecules of uniform chain length on an industrial scale. My results were never published, and my liquid-phase thermal diffusion method for resolving polymer molecules of different lengths vanished without trace from the corpus of science. This was a pity, because, unknown to me, biochemists studying proteins and nucleic acids in the 1940s were in great need of techniques for separating different size molecules in extracts from living cells. My thermal diffusion column could have served beautifully. In retrospect, I have no doubt that it would have made a stir among biochemists had I indeed adapted it for their purposes. But by the 1950s, when I finally became aware of the opportunity I had missed, much better molecular separation methods had been invented.

This proved to be only the first of several instances in my career when I hit on a good thing that could have gained me substantial fame—but didn't. Many scientists try to sell sour grapes by claiming that one of their brilliant original ideas was stolen by someone who claimed credit. Such thefts do occur, but not often. The more banal cause for the failure to get due credit for one's discovery is, as in my case, the lack of personal qualities needed to have it make an impact. Originality and inventiveness, though necessary, are not sufficient for making a mark in science: one also has to have intuition, stamina, and, above all, self-confidence to exploit one's inventions and present them as a salable package.

What Is Life?

In my second year of graduate studies, my friend and mentor Martha Baylor, a postdoctoral research biologist in charge of the Illinois Chemistry Department's electron microscope, suggested that I read *What Is Life?,* a recently published tract by the famous Austrian physicist Erwin Schrödinger. She thought that I would be interested in what the codiscoverer of quantum mechanics had to say about the connection between thermodynamics and biology. I had always found botany and zoology terminally boring, but I took her advice.

Schrödinger announced that a new era was dawning for the study of heredity, thanks to some novel ideas put forward by Max Delbrück, whom he identified as "a young German physicist." How, Schrödinger asked, do genes manage to preserve their hereditary information over the generations? Following Delbrück's then 10-year-old proposal that this stability derives from the atoms of the gene molecule staying put in "energy wells,"

Schrödinger proposed that the gene-molecule is an aperiodic crystal, composed of a long sequence of a few different basic elements, repeated over and over. The exact sequence pattern of these elements would represent a "code" by means of which the hereditary information is encrypted. Thus, Schrödinger was the first to put forward the concept of the genetic code, one of the most important life sciences ideas of the 20th century. Schrödinger had no idea of the atomic nature of this code and thought that "from Delbrück's general picture of the hereditary substance it emerges that living matter, while not eluding the laws of physics as established up to date, is likely to involve hitherto unknown 'other laws of physics,' which, however, once they have been revealed will form just as integral a part of this science as the former" (Schrödinger, 1946).

In posing the question "What is life?" Schrödinger confronted physical scientists with a fundamental scientific problem worthy of their mettle, at a time when many of them were suffering from a professional malaise in the immediate postwar period. In stirring up the passions of its impressionable readers, *What Is Life?* became a kind of *Uncle Tom's Cabin* of the revolution in biology that eventually left molecular biology as its legacy.

As a mere Ph.D. candidate of 22, I was too green to be suffering from anything as blasé as the professional malaise of my elder colleagues. Yet I was so captivated by the fabulous prospect that by studying genes I might turn up "other laws of physics" that I resolved to join the search for the aperiodic crystal of heredity. I thought that Delbrück, the young German physicist, had probably been drafted into the *Wehrmacht* and been killed during the war. But perhaps there were people in the States working along these lines.

Good news reached me in the summer of 1947. Delbrück was not only still alive, but he had just been appointed professor of biophysics at Caltech—my academic dream place, home of my hero, Linus Pauling. I wrote to Delbrück to ask if I could work under his direction in Pasadena. I was thinking of applying for a new type of National Research Council (NRC) postdoctoral fellowship sponsored by the Merck Chemical Company, whose purpose, according to an announcement in *Science* magazine, was "to provide special training and experience to young men and women trained in chemical or biological science who wish to broaden their fields of investigational activity." What sort of biophysical problem could I be working on in his laboratory if I were awarded a Merck Fellowship? Delbrück replied that he was not in a position to state in any detail the type of problems he was going to work on next year, but he was thinking of doing some experiments on phototaxis in purple bacteria, which might be a good opening for the study of excitatory processes.

At least Delbrück's response wasn't an outright rejection. I didn't know the meaning of phototaxis or excitatory processes, had never heard of purple bacteria, and was totally in the dark about what all this might have

to do with genes and leading me to the discovery of "other laws of physics." But I figured that there would be plenty of time to find out what Delbrück's proposed project was all about, in the unlikely event that my fellowship request would be granted. In my application I declared that I hoped to apply my knowledge of physical chemistry to the study of biophysical problems, with special emphasis on the investigation of life processes from the point of view of thermodynamics and reaction kinetics. To that end, I intended to study the general nature of excitory [sic] processes under the direction of Prof. Max Delbrück at the California Institute of Technology. I had the good sense not to let on in my application that I had a hidden agenda, namely, looking for other laws of physics.

Many months later, I received a telegram asking me to come to New York—all expenses paid by the NRC—for an interview with the Merck Fellowship Board. My sky-high exultation over this marvelous news subsided as soon as I began to think about the interview. It wouldn't take more than one or two incisive questions by the Board to reveal that I knew nothing about the "excitory" processes on which I was proposing to carry out advanced postdoctoral research by studying the phototaxis of purple bacteria and had no idea how all this was going to lead me to novel insights about life processes from the point of view of thermodynamics and reaction kinetics.

My fears were not unfounded. The Merck Fellowship Board comprised six formidably distinguished, awe-inspiring senior scientists: Chairman A.N. Richards, President of the National Academy of Sciences and ex officio High Priest of American science; the geneticist and future Noble laureate, George W. Beadle, Chairman of the Caltech Biology Division; Detlev W. Bronk, professor of biophysics at the University of Pennsylvania and President of the NRC; Hans T. Clarke, professor and Chairman of Biological Chemistry at the College of Physicians and Surgeons of Columbia University; George O. Curme, Director of Research of the Carbide and Carbon Chemicals Corporation; and René Dubos, the famous bacteriologist at the Rockefeller Institute for Medical Research. I was in deep trouble as soon as Chairman Richards asked his first question.

"So you want to go into biology; what do you plan to do?"

"I want to study excitory processes to test whether the Second Law of Thermodynamics applies to living systems."

"You mean ecitatory processes, don't you?"

"Yes, Sir. I think so. Yes, I do."

"How are you going to do it?"

"I'm going to study the phototaxis of purple bacteria."

"How? And how's this going to tell you something about the applicability of the Second Law?"

"I'm not exactly sure. Professor Delbrück suggested that this would be a good experimental material for my project."

At this answer, the Board members frowned and shook their heads in disbelief. After I proffered a few more obviously unsatisfactory responses to the questions of other Board members, René Dubos finally asked me sarcastically:

"Then, if I understood you correctly, your proposed postdoctoral studies in biology at Caltech would have to be at the—(pause and emphasis)—*undergraduate* level. Isn't that so?"

"Yes, Sir. I guess so."

After this response, I was dismissed summarily. As I shuffled out, totally humiliated, I noticed, to my astonishment, that Beadle winked at me. Three days after I got back to Champaign, a telegram came that said that they had given me the NRC Merck Fellowship, as one of only seven awardees among a total of 46 applicants. I could only conclude that the unsuccessful 39 were even more appalling phonies than I.

Delbrück asked me to meet him in Chicago in early May. He would be stopping in the City for a day on his way from Pasadena to Indiana University, where he was going to visit "Luria." I had never heard that name before, but savvy friends at Illinois explained to me that Delbrück was referring to his collaborator, Salvador Luria, with whom he had published an important paper in 1943.

I was enchanted by Delbrück—lightening-quick on the uptake, funny, and amazingly well-informed on a wide range of subjects. He seemed to know everybody, especially the all-time greats of quantum physics, such as Max Planck, Niels Bohr, Werner Heisenberg, Wolfgang Pauli, and Paul Dirac. When the time finally came to discuss my future projects, Delbrück didn't mention phototaxis of purple bacteria or sensory excitation at all.

"I take it that you want to work on phage?"

"Yes sir, that's exactly what I want to work on. But could you refresh my memory as to what "phage" is actually all about?"

"No need for that now. You'll find out what it's all about soon enough at Cold Spring Harbor Laboratory. You're going to spend the summer there and take the phage course. In early September, we'll all head out west, to Pasadena."

Contrary to the almost universally shared opinion that writing your thesis is a big pain in the butt—the worst part of getting a Ph.D.—I enjoyed writing mine. Thus, I became aware of my bizarre preference for writing about my scientific findings over making them in the first place. This gave me my first inkling that there seemed to be something odd about my motivation for doing science.

Scientists are supposed to be driven by a thirst for understanding the natural world. Their major reward for slaving away in the lab day and night is supposed to be a joy of discovery—the elation that attends reaching a novel insight into nature, as well as satisfying one's innate curiosity. This can't be the whole story, of course. Oddly enough, the satisfaction of a scientist's curiosity about nature provided by a competitor's discovery is cause,

more often than not, for disappointment rather than joy. My curiosity about the workings of nature was not all that fervid, anyhow; what attracted me to science was the life style that came with it. I found it hugely satisfying to work in a lab, to make good conversation—scientific or otherwise—with intelligent colleagues, to travel all over the world, finding friends everywhere. Whenever I did manage to find something new—which didn't happen often in my career—I too felt elated, of course. But my satisfaction came not from a joy of discovery, but from a joy of telling. What excited me most was the thought that, thanks to my discovery, I would have something to say next time I met a colleague or went to a conference.

That is why publishing papers was what I liked best about science. No sooner had I started a research project, than I was thinking about the paper that I would write about it. Long before I had found anything worth reporting, I was already composing the opening paragraph of the report. I thought of publishing as a way to start conversation. Compared to the joy of telling, the joy of discovery played such a minor role in my motivation that I don't believe I would have done science if I had been Robinson Crusoe. Isolated, out of my colleagues' earshot, I wouldn't have made experiments, even if there happened to be a fully equipped lab on the island, with Man Friday available as a postdoc.

Phage

When I got to Cold Spring Harbor in June 1948, Max (which is what everybody there called Delbrück) introduced me to James Watson, a 20-year-old graduate student, who had also been fascinated by Schrödinger's *What Is Life?*. Watson was working for his Ph.D. at Indiana University, doing research on the effects of X rays on phage with Luria, whom he had chosen as his mentor because Luria was a collaborator of Delbrück's. Jim was my junior by 4 years and a mere graduate student. I didn't like him at first because he treated me as an equal, as if his opinions were just as good as mine. But before long, I came to terms with the sobering fact that whenever we disagreed about some scientific proposition, his opinions were almost always right and mine almost always wrong. We became lifelong friends.

By the time the phage course was over, I felt I had become an expert phagologist. I had imbibed the conceit of Max's Phage Group that there was no point in paying any attention to the work of our predecessors or of contemporaries external to the "Church," as the French microbiologist, André Lwoff, referred to the coterie of Max's disciples. Reading publications lacking the Church's imprimatur was worse than a waste of time: The unsubstantiated claims based on poorly designed experiments presented by such confused heathen outsiders would just put wrong ideas in your head.

Besides the Phage Group votaries, other people with biological or biochemical interests were also summering at Cold Spring Harbor. Many presented seminars on their current work, most totally beyond my ken. But I

was impressed by Rollin Hotchkiss from the Rockefeller Institute in Manhattan, who spoke on the DNA-mediated hereditary transformation of bacteria, by means of which Hotchkiss' teacher, Oswald Avery, had shown in the early 1940s that DNA is the genetic material. There had been very little mention of DNA-mediated bacterial transformation in any of the other seminars, even though the physical and chemical nature of the gene was of capital interest not only to the members of the Phage Group, but also to most of the other people at Cold Spring Harbor.

Why had Avery's discovery, though known to everyone at the lab, made so little impact on the very people interested in the nature of the gene in the summer of 1948? Because the view, then generally held, of DNA as a monotonous molecule that is always the same no matter what its biological source made it impossible to imagine how DNA could be the carrier of hereditary information. By 1952, however, it had been shown that the composition of DNA does vary according to its biological source. Now it could be readily imagined that genes are inscribed in DNA as a specific sequence of the four kinds of iterated building blocks, whose long string makes up the giant DNA molecule. In other words, DNA turned out to be Schrödinger's "aperiodic crystal" composed of a succession of a small number of different elements, the exact nature of their succession representing a "hereditary code."

Caltech lived up to my fantasy of a palm-tree studded academic nirvana: a double tier of adobe-colored California mission-style laboratory buildings facing a subtropically landscaped central mall, stretching for a half mile between two Pasadena streets, set off against the sunlit San Gabriel mountains peaked by 10,000-foot Mt. Baldy and peopled with brilliant minds, like Pauling, Beadle, and Max.

My research project was one of the few Max could have picked for which my training as a physical chemist happened to have eminently qualified me. One of the phage strains we studied in the Phage Group fails to attach to its bacterial host cell unless it has been previously "activated" by contact with the amino acid tryptophan. Max suspected (or maybe hoped) that the hitherto known facts about this activation process were not compatible with ordinary physicochemical principles. So maybe there was a paradox hidden here which might lead us to one of those "other laws of physics."

Much as I was hoping to run into a biological system manifesting an "other law," I feared that this was not one of them. I thought that I wouldn't have much trouble coming up with an explanation of the seemingly bizarre tryptophan activation phenomenon within the framework of house-and-garden theories of physical chemistry. Max informed me that I would have a partner in my research project, Élie Wollman, a French bacteriologist from André Lwoff's Department of Microbial Physiology at the Institut Pasteur in Paris. According to Max, Wollman and I were going to complement each other like liverwurst and rye bread. He had the bacteriology, of which

I didn't know from beans, and I had the math and physics, of which he was largely innocent. Together, we would make the perfect phageology sandwich.

By fall 1949, there were six research fellows working in Max's lab—Élie Wollman, Jean Weigle, Wolfhard Weidel, Renato Dulbecco, Seymour Benzer, and me—a population explosion since I showed up as Max's first Caltech postdoctoral fellow a year before. We formed a close-knit sib, with Max as our *spiritus rector.* Dulbecco would presently succeed in extending the method of plaque assay we used in phage work to animal viruses, which would set the stage for quantitative studies on animal viruses to fathom their intracellular reproductive cycle. He also opened the era of animal virus genetics by isolating virus mutants and developing techniques for mixed infection of single animal cells with two or more genetically different mutant viruses. For these contributions Dulbecco would be awarded the 1975 Nobel Prize in Physiology or Medicine.

Benzer, who had received his Ph.D. in solid state physics from Purdue University, was my classmate in the 1948 Cold Spring Harbor phage course. He, too, had been seduced by Schrödinger's *What Is Life?* and hoped to get started on finding the aperiodic crystal of heredity in the Caltech lab of the protagonist of Schrödinger's book. Within a few years, Benzer would convert the fuzzy concept of the Mendelian gene of classical genetics into its precisely defined, latter-day molecular-genetic version. I will always believe it a shame that Benzer was not included in the set of Nobel laureates honored for laying the foundations of molecular biology.

In Max's research group, there was no clear separation between our professional and our private lives, because Max's benevolent (or in New Age California-speak "caring") interest in his disciples was all-inclusive. He not only guided our scientific work in the lab, but also supervised, not to say intruded in, what would normally be considered one's private, after-hours activities, such as dating, partying, concerts, plays, movies, dinner, and camping. As our *pater familias,* Max considered it his business—if not actually his duty—to inform himself about all facets of our lives. The concept of privacy was not known to him.

Exchanging my anxiety-ridden sovereignty for an insouciant thralldom under which I could leave decisions about my professional and private activities in Max's hands appealed to me. To give up all that freedom and personal responsibility for making choices with which I had been saddled was a relief. It was like being in the Army, where every soldier, downward from the Chairman of the Joint Chiefs of Staff, takes orders from a superior authority figure, who is held accountable for the commands one obeys.

It took Wollman and me most of our second year at Caltech to write three papers presenting the results of our experiments on the tryptophan activation and to hone our theory to account for them. I would never again devote as much effort and care to any of the couple hundred other papers and essays I eventually published, and I consider those three papers with

Wollman as my best. Max predicted that one day they would be famous classics. Alas, only a few people read them when they came out—we did get one fan letter from an immunologist in Australia—and they have long since been forgotten.

As I had feared, there was no need to invoke "other laws of physics" to explain the seemingly bizarre dynamics of the tryptophan activation phenomenon. We managed to devise a model based on conventional physicochemical principles that accounted for all the data. It was a forerunner of the "cooperative" models of the complex interactions of small molecules with enzymes and other protein molecules put forward a few years after our papers, which have formed the basis for understanding the regulation of protein function ever since. As far as I know, no contributor to the vast literature of cooperative protein interactions ever cited our tryptophan activation model.

DNA Replication

My Merck Fellowship was to end in June 1950, and Max suggested that I go to Copenhagen to work in the lab of the Danish biochemist Herman Kalckar. He made the same proposal to Jim Watson, who was finishing his Ph.D. dissertation with Luria at Indiana University. Max told us that it might do us good to learn something about DNA chemistry from Kalckar. Max had begun to think that DNA did have something to do with genetic self-replication, although he had not yet cottoned to the idea that DNA was the genetic material of the phage—Schrödinger's aperiodic crystal of heredity.

What he didn't realize was that Kalckar knew very little about DNA. His specialty was adenosine triphosphate (ATP) and its provision of free energy for driving biochemical reactions. Maybe Max thought that DNA, being composed of ATP-like nucleotides, provided the free energy for driving self-replication of proteinaceous genes, in chromosomes as well as in phage. Within a couple of weeks after Jim and I showed up in Kalckar's lab at the University of Copenhagen in September 1950, we realized that we weren't going to learn anything about DNA from him, and so we moved over to Ole Maaløe's lab at the Danish State Serum Institute. There we carried out radioactive tracer studies on the fate of the parental phage DNA and the synthesis of the progeny phage DNA in the infected bacterial host cell.

One of our labmates at the Serum Institute was Niels Jerne, who was studying the increase in antibody–antigen avidity during the immune response. We found his results only mildly interesting, not realizing that we were attending the gestation of his selective theory of antibody formation, which would revolutionize immunology in the late 1950s and bring Jerne the 1984 Nobel Prize in Physiology or Medicine. Our own results were not exactly world-shaking, but they helped to define the problem of DNA replication that had to be solved. At the end of our Copenhagen year, Jim Watson

moved to Cambridge to learn how to do X-ray crystallography on DNA. There he met Francis Crick, to whom it had also occurred that knowing the three-dimensional structure of DNA would be likely to provide important insights into the nature of the gene. The result of their collaboration—the discovery of the DNA double helix—is history.

Meanwhile, I went to Paris to spend the last of my postdoctoral *Wanderjahre* in André Lwoff's Department of Mircobial Physiology at the Institut Pasteur. I didn't accomplish much in the way of research results there, but my intellectual development profited enormously from my close contacts with the brilliant crowd hanging out in the "Attic of Monsieur Lwoff" at Pasteur, such as Jacques Monod, Roger Stanier, and François Jacob, in addition to *le grand patron* himself and my old Caltech *copains,* Élie Wollman and Seymour Benzer.

My main accomplishment in Paris was getting married. I had met my future wife, Inga Loftsdottir, in Copenhagen at the boardinghouse where Jim Watson and I took our evening meals. She was Jim's table partner, and he introduced her to me as the Herring Princess of Reykjavik. I was in thrall of the stupendous romance associated with Iceland under the Teutonic mystique of an Ultima Thule. Stark glaciers, volcanoes, and geysers; handsome, tall, invincible men and beautiful women with long, braided blond hair, in colorful medieval costumes. I was captivated by Inga's good looks, quite apart from the built-in glamour that came with her being a Viking maiden. Moreover, I was enchanted by her professional-level piano playing on her huge grand, which took up almost all the space in her room at the boardinghouse. In the fall of 1951, we went to Paris together, where she studied piano with Reine Gianoli at the École Normale de Musique.

Just before leaving Copenhagen for Paris, I managed to line up a stateside job to which I could return with my bride in the fall of 1952. At a dinner that Niels Bohr gave for the galaxy of star-virologists who had come to Copenhagen to attend the International Poliomyelitis Congress (to which Bohr had invited me as his sole scientific grandson, via Max, in virus research.) I happened to be seated next to Nobel laureate Wendell Stanley. Having heard that he was recruiting people for his Virus Laboratory in Berkeley, I asked him whether there might be an opening; his offer of a research position in Berkeley equivalent to the rock-bottom academic rank of Instructor reached me a few weeks later in Paris. Eventually, I learned that although a Nobel laureate, Stanley never missed a chance to add yet another feather to his cap—however tiny a feather—and he fancied the idea of having on his staff someone he imagined was a young intimate of Niels Bohr's.

I spent my entire academic career as a member of the Berkeley faculty, eventually becoming founding chairman of a mega-Department of Molecular and Cell Biology with a faculty of 90 professors and, as Stanley's successor-twice-removed, the Director of the Virus Lab.

A few months before I left Paris, Alfred Hershey and his young assistant, Martha Chase, had shown that when the phage infects its bacterial host, only its DNA enters the cell while its protein stays behind at the gate, devoid of any further function in the reproductive drama about to ensue within. Thus the genes of the parent phage that are responsible for directing the synthesis of progeny phages reside in its DNA. Inspired by the Hershey-Chase results, on setting up shop in the Berkeley Virus Laboratory I resumed the studies on the replication of phage DNA I had begun in Copenhagen, but now using the "suicide" of ^{32}P-labeled phages recently discovered by Hershey, Martin Kamen, J.W. Kennedy, and Howard Gest. This suicide arises from the lethal cut of both polynucletide strands of the double helix by 1 out of 10 decays of a radioactive ^{32}P atom incorporated in the phage DNA. Nine out of 10 decays, however, cut only the single polynucleotide strand in which it occurs and leave intact the reproductive potential of the phage. The suicide method allowed us, i.e., my first graduate students and postdoctoral associates (among them Clarence Fuerst, Gordon Sato, Hisao Uchida, and Niels Jerne), to follow the fate of the DNA of the infecting phage after its entrance into the bacterial host cell. The results of our experiments indicated that in the course of its replication, the parental phage DNA is broken into several variously sized chunks, of which about a third reappear in the DNA of the progeny phage, and that this breakup is associated with genetic recombination. But contrary to my hope, we were not able to demonstrate by use of ^{32}P decay suicide the semiconservative mode of the DNA replication process predicted by the Watson–Crick model.

It was after I bewailed our failure to Matthew Meselson on his visit to my laboratory that he devised his ingenious differential density labeling method by which he and Franklin Stahl managed to deliver their justly celebrated proof that had eluded me. A year after the Meselson–Stahl experiment, my postdoc, David Pratt, and I provided an independent, genetic proof of the semiconservative mode of phage DNA replication. We showed that most (base-analog-induced) phage mutants arise as heterozygotes, which carry the mutant allele in only the most recently replicated of the two strands of the double helix, while the strand that served as the template in the last replication round still carries the nonmutated allele. But by then it was too late; hardly anyone paid any attention to our frightfully clever paper.

DNA Expression

Eight years after the discovery of the DNA double helix, a new chapter began in the history of molecular biology. The formerly paramount problem of gene replication had been solved, at least in its broad outlines, and the focus of interest had shifted to the puzzle of how genes manage to express

the hereditary information they encode in their DNA. This problem was solved, also at least in its broad outlines, by 1961, by the formulation of two great theories. One, the Central Dogma, in whose development and eventual validation Watson and Crick also played a leading role, asserted that gene expression is a two-stage process. In the first stage, the nucleotide sequence inscribed into DNA is transcribed onto RNA, and in the second stage the RNA transcipt is translated into its specifically encoded polypeptide chain by the cellular machinery for protein synthesis.

The other great theory, the operon model of regulation of gene expression developed by François Jacob and Jacques Monod, asserted that the Central Dogma's DNA transcipt is an ephemeral, short-lived messenger RNA (mRNA) molecule, which is picked up by a ribosome on whose surface it is translated into the encoded polypetide chain. The operon model also asserted that the rate at which a given polypeptide chain is produced in the cell relative to all other genetically encoded polypeptide chains is determined by the rate at which its mRNA template is transcribed relative to all other mRNA species. The relative rate of mRNA transcription is, in turn, controlled by the interaction between an operator locus encoded in the DNA near the origin of mRNA transcription and a repressor molecule, whose affinity for the operator locus depends, in turn, on its own intraction with an inducer molecule.

So in the early 1960s, I switched my focus of interest from DNA replication to the exploration of the mechanism and control of DNA expression, guided in my thinking by the Central Dogma and the operon model. I began my new line of research during a sabbatical at the Cavendish Laboratory of the University of Cambridge, where Watson and Crick had discovered the DNA double helix. There, in collaboration with Sydney Brenner, I studied the regulation of transcription of ribosomal RNA (rRNA), which, being a stable part of the machinery of translation, is not itself translated into polypeptide chains and composes the bulk of cellular RNA. Brenner and I were able to identify a genetic locus, which we designated RC, that regulates the differential rate of rRNA transcription in accord with the availability of amino acids for protein synthesis. The mechanism by which this cell-physiologically critical gene implements its control turned out to be an enormously complex instantiation of the operon model which took about 10 years to work out and gave rise to a minor cottage industry.

On my return to Berkeley from Cambridge, I assembled a new crew of graduate students and postdoctoral associates for the study of DNA expression. Before long, two members of that crew, Hans Bremer and Michael Konrad, showed that in the DNA–RNA hybrid molecule which arises in the transcription process, only the most recently assembled RNA nucleotides are still in contact with their DNA template, while the older parts of the polynucleotide transcript have already dissociated from it. This finding suggested to me that in bacteria (if not in eukaryotes) mRNA tran-

scription and translation are dynamically coupled processes. Thus I envisaged that a ribosome picks up a nascent mRNA molecule from its DNA template and starts translating it before transcription of the whole messenger molecule is even complete.

According to Karl Popper's demand for "falsifiability" of scientific theories (which I don't accept), my hypothesis of dynamic coupling of transcription and translation had the merit of being falsified if any one of three conditions failed to obtain. First, there should arise an *in vivo* complex of template DNA, nascent mRNA, and ribosomes. Second, the chemical direction in which mRNA is synthesized must be the same as the chemical direction in which it is translated. Third, because of the triplet nature of the genetic code *in vivo,* the rate of chain growth of mRNA (i.e., the number of nucleotides added per unit of time) must be three times the rate of polypeptide chain growth (i.e., the number of amino acid residues added per unit of time).

Being actual people rather than Popperian logical robots, we set out to verify rather than falsify these conditions. As for the first condition, Bremer and Konrad showed that it is met, by isolating the conceptually obligate DNA–mRNA–ribosome complex from phage-infected bacteria. The second condition was met as well. Bremer and Konrad showed that the synthesis of mRNA proceeds from the 5' phosphate end of the molecule toward its 3' hydroxyl end, while a group working in the laboratory of Severo Ochoa studying the synthesis of oligopeptides directed by synthetic oligonucleotide templates showed that mRNA translation proceeds in the same direction, as did also George Streisinger's analysis of the effects of frameshift mutants in phage DNA on amino acid sequence in phage proteins. Finally, the third condition is met too. One of my postdoctoral associates, François Lacroute, found that at 37° C, the *in vivo* peptide chain growth rate of the bacterial enzyme, β-galactosidase is 15 amino acid residues per second, while another postdoc, Haim Manor, found that the average chain growth rate of bacterial mRNA under the same conditions is just about three times as great, namely 43 nucleotides per second.

I consider my validated hypothesis of dynamic coupling of transcription and translation as my most significant contribution to molecular biology.

A Prenatal Forecast of the Death of Molecular Biology

At one of our lab lunches at Caltech in fall 1949, when the birth of molecular biology fathered by the discovery of the DNA double helix still lay 4 years in the future, Max intimated to us that he was beginning to lose interest in the gene. He thought that phage research was bound to lead to an understanding of biological self-replication before long. But, he said, Mind you!—Once the self-replication riddle has been solved, there would still remain an even harder problem posed by living creatures—the function of the

brain—for which reasonable, physical mechanisms couldn't even be imagined. Max ventured that some "other laws of physics" were still needed to explain the function of this most mysterious ensemble of atoms in the universe and to explain how mind arose from matter.

To prepare us for our post-molecular–biological future in brain research, Max made us present a series of seminars on sensory neurophysiology. He drew up a list of publications, divided into chunks of three or four papers. Each of us had to pick one chunk for presentation, which, so Max promised us, would turn us all into brain experts by the next spring. Four of the chunks he selected comprised papers on vision, and they were quickly snapped up by the others. The fifth chunk was devoted to hearing, which my false friends left for poor, ignorant me. As I soon realized, my buddies already knew enough about sensory neurophysiology to stay away from hearing, compared to which vision, however complex its function may seem, is a breeze.

My chunk consisted of three papers published in the late 1920s in the *Physikalische Zeitschrift* under the title "Zur Theorie des Hörens" by the future (1961) Nobel laureate, Georg von Békésy, then at the Royal Hungarian Telegraph Research Laboratory in Budapest. My reading bogged down as soon as I got beyond the first sentence of Békésy's first paper, which declared grandly that "the treatment of a series of problems in telephone technology is greatly impeded by the lack of a theory of hearing." The papers were full of complex equations and circuit diagrams relating to hydrodynamics, resonance, and mechanical and electrical oscillators, while the text was couched in esoteric anatomical and physiological parlance, completely beyond my ken.

This, my first encounter with the literature of neurobiology, was counterproductive to Max's missionary goal of arousing our interest in brain research. Maybe there were some "other laws" that could be revealed by studying hearing, but there was no way in which I could possibly find them. No Sir, I was going to stick with simple research on phage and bacteria. I was not alone among Max's early disciples in refusing to switch to brain research at that time. Only Max himself stopped working on phage in the 1950s and took up sensory physiology, selecting as his experimental paradigm the growth response to light of the fungus *Phycomyces.*

It was not until the late 1960s that Seymour Benzer and I, and a few other romantics who had once been seduced by Schrödinger's *What Is Life?,* realized the truth of Max's prophecy that the brain would be the last exciting frontier of biological inquiry. By then, our kind of molecular biology—the avant garde discipline practiced by a closely knit coterie of aficionados of heredity and self-reproduction—no longer existed. Killed by success, romantic molecular biology had transformed into a mainstream academic and industrial mass movement in which there was no place for Max's snobby little Phage Church.

The Hebb Synapse

Seymour told me that the best place for me to take my orders in brain research was Steven Kuffler's Department of Neurobiology at Harvard Medical School, whose staff included his famous students, David Hubel and Torsten Wiesel, the Watson and Crick of neurobiology. Seymour recommended me to Kuffler, whom he had met at Woods Hole, as being serious in wanting to become a neurobiologist, rather than intending to do molecular biological schnapps experiments to decide whether memory resides in RNA, DNA, or protein molecules. In view of the dire shortage of electrophysiological setups in his department, it seemed to border on irresponsibility for Kuffler to waste any of them on a total ignoramus like me. But, in an uncharacteristically softheaded move, he agreed to take me on anyhow for my sabbatical year.

On my arrival in Boston in fall 1969, Kuffler's very first piece of advice turned out to be the best counsel he ever gave me. He suggested that I, his eldest postdoc, work with his youngest faculty member, John Nicholls, who turned out to be a perfect teacher. Moreover, Nicholls also happened to be working on the leech, whose simplicity and experimental accessibility seemed like God's gift to a hacker like me who lacked all surgical or electrophysiological skills. The central nervous system of this wonderful, unjustly maligned annelid worm consists of a chain of 32 iterated segmental ganglia linked by a longitudinal connective nerve. Each of these ganglia contains the somata of about 400 bilaterally paired and a few unpaired neurons, which project their axons to peripheral targets via segmental nerves, to targets in anterior or posterior segments via the connective nerve. By the time I joined him, Nicholls had already identified many leech neurons, with respect to their function and connectivity. It took me the whole year to acquire the bare minimum level of skills needed for neurophysiological experimentation, and I hadn't contributed anything of value to my teacher's research project when the time came for me to go home to Berkeley.

There was a tradition in the Kuffler department of a weekly lunch seminar at which the graduate students, postdocs, and faculty members reported their recent research results. When my turn came and I had no research results to report, I decided to present the results of my recent reading of a brilliant paper by the young English mathematician, David Marr, on the cerebellar cortex as a learning machine. The feature of Marr's paper that interested me most was his idea that the cerebellum can learn to perform complex motor routines thanks to modifiable synapses that link parallel fibers and Purkinje cells. Marr proposed that these synapses have the property first put forward by Donald Hebb in 1949 to account for classical conditioning, namely that their activation or inactivation in a plastic neural network rises or falls with the synchronicity of the impulse activity of pre- and postsynaptic neurons.

I closed my seminar with a theory I had devised for a physiological mechanism by which the postulated property of the Hebb synapses could be instantiated at the subcellular level. I proposed that the receptors for the synaptic neurotransmitter are eliminated from the postsynaptic membrane by the transient reversals of membrane polarization that occur during action potentials in the postsynaptic cell. This would lead to inactivation of the synapse. But because the release of neurotransmitter by the presynaptic cell anchors the membrane potential of the subsynaptic region of the postsynaptic cell at a level about half-way between the negative-inside resting potential and the positive-inside action potential, the membrane patches surrounding the receptors of a synapse, whose activity has contributed to setting off the postsynaptic impulse, would be spared the full extent of the noxious polarity reversal. Thus only synchronous, but not asynchronous, activity of pre- and postsynaptic cells would preserve the existing strength of the synapse.

My seminar was not appreciated by my Harvard colleagues, who regarded neurobiological theorizing as snake oil selling. They didn't conceal their exasperation over my wasting their time, especially when it came to my own proposal of a mechanism for the, in any case wholly fictive, Hebb synapse. Despite the disdain of my Harvard colleagues, I wrote a paper on my proposed Hebb synapse mechanism and asked a distinguished Berkeley physicist to communicate it to the *Proceedings of the National Academy of Sciences,* which did not then (as it does now) require an expert peer review, or my paper certainly would have flunked. Of the more than 100 neurobiological papers that I would eventually publish, this, my first, turned out to be the most successful; it was the only one of them anointed by the Institute of Scientific Information's *Citation Index* as a "Citation Classic."

Leech Swimming and Heartbeat

In making my mid-career switch to neurobiology, I had been strongly influenced by my friend Werner Reichardt, the founder–director of the Max Planck Institute for Biological Cybernetics in Tübingen. His studies of visually controlled locomotion of insects represented a close dialectic between elegant, nonlinear mathematical theories and brilliant quantitative experimental tests of their predictions at the behavioral, anatomical, and cellular level. During the 1950s, Reichardt solved the problem of how moving patterns are perceived by motion detectors of the insect visual system. In the 1960s, he showed how the neural circuitry he unraveled in the insect brain accounts also for perceptual tasks higher than simple motion detection, such as tracking an object in front of a textured background.

On my return to Berkeley in the fall of 1970, I decided to follow Reichardt's lead and set out to study the visually controlled locomotory behavior of leeches. I thought that because of the simplicity and easy experimental

accessibility of the leech nervous system I would soon have the advantage over my friend and beat him at his own game. Unfortunately, I didn't know then that vision plays only a minor role, if any, in leech locomotion, and so I never posed any real threat to Werner's primacy. But in the end I did find a few things about the neural control of rhythmic movements that Werner hadn't worked out.

Of the two locomotory modes of leeches, swimming and inchworm crawling, I decided to study swimming. My predecessor in this investigation, Leonardo da Vinci, had shown in the quattrocento that leeches swim by undulating their flattened body in the dorso-ventral plane, forming a wave which travels from head to tail. The moving crests of the body wave are produced by progressively delayed contractile rhythms of the ventral body wall and the moving troughs by similar, but antiphasic, contractile rhythms of the dorsal body wall. The forces exerted against the water by these changes in body form provide the propulsion that drives the leech forward.

In getting started on this project, I had the luck to acquire an outstandingly competent young neurobiologist as a postdoctoral associate, William B. Kristan. He helped me set up my laboratory for this new line of work and develop a semi-intact leech preparation which carries out the swimming rhythm while permitting intracellular recordings from its central nervous system. We were soon joined by my first neurobiological graduate student, Carol Ort, and within about 3 years we had identified an ensemble of segmentally iterated motor neurons (some of which had been previously identified by Nicholls and Ann Stuart). The rhythmic impulse activity of these motor neurons—some excitatory and others inhibitory—drives the antiphasic local contraction and distension of the longitudinal muscles embedded in the segmental dorsal and ventral body walls. We found, moreover, that the rearward travel of the body wave is attributable to the impulse burst phase of each motor neuron leading that of its serial homolog in the next posterior ganglion by a phase angle of about 20°.

Kristan presently discovered that the motor neurons of a completely isolated leech nerve cord, deprived of all sensory input from the body wall, can exhibit sustained episodes of rhythmic activity. Hence, we could infer that the basic swimming rhythm is produced by a central rhythm generator, whose oscillatory activity pattern is generated independently of any proprioceptive feedback. In collaboration with my second, highly competent neurobiology postdoctoral associate, W. Otto Friesen, we then identified a network of bilaterally paired, rhythmically active interneurons as components of the central swimming rhythm generator. The interneurons of this generator owe their rhythmic impulse burst activity to their being linked into an intrinsically unstable oscillatory network, whose periodic activity pattern arises from the principle of *recurrent cyclic inhibition,* first proposed in 1967 by the Hungarian neuroanatomist G. Szekely. The central generator imposes the swimming rhythm on the motor neurons via a set

of identified excitatory and inhibitory synaptic connections. Kristan and Friesen eventually established their own laboratories, where they continued the study of leech swimming with their students and brought its understanding to progressively higher levels.

When I acquired my second neurobiology graduate student, Wesley Thompson, I made him an uninspired research proposal, namely that he survey the leech ganglion in search of other rhythmically active neurons that might take part in swimming. Before long, Thompson identified two hitherto unknown pairs of oscillatory neurons. Their long cycle period indicated, however, that they had obviously nothing to do with swimming. On pursuing their function, Thompson discovered that they control the beat of the leech "heart," which consists of two contractile lateral vessels, or heart tubes, that form part of a closed circulatory system. The walls of the heart tubes are ringed by heart muscles, whose periodic contraction and distension, or heartbeat, circulates the blood through this vascular system. Thompson found that the heartbeat pattern is not bilaterally symmetric. On the *peristaltic* body side, the segmental heart-tube sections constrict in a rear-to-front pattern, producing frontward peristalsis. On the *synchronic* body side, the sections constrict almost simultaneously. Peristaltic and synchronic heart beat modes are not permanent features of right and left sides, however. Every few minutes, the peristaltic side switches to the synchronic mode and the synchronic side switches to the peristaltic mode.

One of the rhythmically neuronal pairs discovered by Thompson, designated *heart excitors,* innervates the circular muscles of the ipsilateral segmental heart tube. The heart excitor activity cycles, in which impulse bursts alternate with bursts of inhibitory synaptic potentials, are phase-locked in a manner that corresponds to the segmental heart-tube constriction pattern. The other pair, designated as *heart interneurons,* is the source of the periodic bursts of inhibitory synaptic potentials in the heart excitors and part of a central heartbeat rhythm generator that does not require peripheral sensory input for its patterned output. Unlike the swim oscillator interneurons, however, the heart interneurons do possess an endogenous polarization rhythm, as indicated by their maintaining a periodic impulse burst activity while deprived of inhibitory synaptic input. Thompson's pioneering work on the leech heartbeat system was continued by my later postdoctoral associate, Ronald Calabrese.

Cell Lineage in Leech Development

In the late 1970s, my research interests shifted from the functional organization of the adult leech nervous system to its genesis in embryonic development. Two veteran, card-carrying leech biologists, Roy Sawyer and Juan Fernandez, had joined my laboratory and drawn my attention to the stereotyped sequence of cell divisions which, onward from the fertilized leech egg,

gives rise to an embryo with individually identifiable cells. As early as the 1870s, Charles Whitman, the American founder of experimental embryology, had ascertained by direct microscopic observation of the early leech embryo that a definite developmental fate could be assigned to each of its blastomeres and inferred that the differentiated properties that characterize a given cell in the mature animal are causally linked to its developmental line of descent. Despite these highly promising beginnings, the study of developmental cell lineage went into decline at the turn of the 20th century, until it was revived in the 1970s, when novel techniques capable of revealing cell lineage became available.

One of these novel techniques—intracellular lineage tracers—was developed in my laboratory by my postdoctoral associate, David Weisblat. It consists of microinjecting into an identified embryonic cell a tracer molecule that is passed on to all, and only to, the lineal descendants of the injected cell. These descendants can then be identified at a later developmental stage by observing the distribution pattern of the tracer within the embryonic or postembryonic tissues. The first tracer molecule used by Weisblat was the enzyme horseradish peroxidase, whose intracellular presence can be detected by treatment of the labeled tissues with a histochemical agent that causes formation of a black precipitate in any cell containing the enzyme. Later we developed lineage tracers consisting of an adduct of a fluorescent dye, such as fluorescein or rhodamine, and an inert carrier molecule, such as dextran. The cellular distribution of fluorescent tracers can be observed in living tissues under the fluorescence microscope, in contrast to horseradish peroxidase, which can be detected only in dead tissues killed by the reagent treatment.

By use of the cell lineage tracer technique, we managed to identify the ensemble of founder cells of each of the leech's 32 body segments, trace the individual lines of descent of the identified components of its nervous system and musculature, clarify the process of neuroblast commitment to a particular developmental cell fate, and chart the pattern of postmitotic neuronal migration and axon outgrowth. The members of my laboratory engaged in this work at various times during the next decade included also Jochen Braun, Siegward Elsas, Lydia Glazer, Andrew Kramer, Martin Shankland, Duncan Stuart, Steven Torrence, and Saul Zackson. Eventually, Weisblat and Shankland each established his own highly productive laboratory and became an internationally renowned leader in the developmental biology of the leech.

Neurophilosophy

In my junior year at Illinois I had chosen philosophy as a secondary major because a fraternity brother had advised me that philosophy was a cinch. To get started, I signed up for a course with the seemingly weird title "Phi-

losophy of Science," taught by Max Black, the Russian-born, British-trained analytic philosopher. "What's philosophy got to do with science?" I wondered. As I eventually found out, you don't need to study philosophy to do good science. But, contrary to the opinion of many eminent scientists, you do need to study it if you want to participate in philosophical discourse without making a fool of yourself. Philosophy became my "secondary major" also in my professional career.

I made my debut as a philosopher when I published *The Coming of the Golden Age: A View of the End of Progress,* lectures I gave under my special appointment as Professor of Arts and Sciences for the 1967–1968 academic year, during the Free Speech Movement student revolt on the Berkeley campus. In these lectures, I tried to persuade my faculty colleagues and the few students who came to hear me that the Free Speech Movement was just one more omen of the end of the 10,000-year-long historical era of progress. Progress, which brought mankind ever-greater dominion over Nature, started with the neolithic agricultural–urban revolution and, so I declared, is ending in our time because its inherent self-limitations are now being reached. In successive lectures, I presented a set of diverse arguments in support of my thesis, drawn from epistemology, psychology, economics, and sociology, and applied them to the end of science and the arts which we are witnessing in the latter, postmodern half of the 20th century. Only a few thousand copies of my *Golden Age* book were sold and, except for a brief, favorable review in *The New Yorker* and a Marxist panning in the Moscow *Literaturnaya Gazeta,* it did not attract much critical notice. Nevertheless, my announcement of the end of science and the arts made me enough enemies to last a lifetime.

In later years I published philosophical essays on other topics, such as "Prematurity and Uniqueness in Scientific Discovery" (1972), "The Dilemma of Science and Morals" (1974), "Limits to the Scientific Understanding of Man" (1975), "The Poverty of Scientism" (1975), "Morality as a Scientific Phenomenon" (1978), and, in collaboration with Judith Martin, "A Philosophy of Etiquette" (1990).

My philosophical sensibilities were shocked when, in 1986, I read Patricia Churchland's *Neurophilosophy,* which *Science* magazine had asked me to review. According to Churchland, the agenda of neurophilosophy is to produce, by means of an interaction among philosophy, psychology, and neuroscience, a uniform theory that explains what she calls the "the mind brain." I too, like almost every other author who writes on the subject, have always advocated an interaction among these three disciplines to advance our understanding of mental processes. But, as I pointed out in my review, I doubt that what Churchland called her "cardinal hunch," namely "that to discover our nature, we must see ourselves as organisms in Nature, to be understood by scientific methods and means," can fathom the depth of the ancient mind–body problem. There are compelling metaphysical reasons

why that problem has persisted ever since there have been philosophers and biologists, onward from Plato and Aristotle, and why dualist solutions that are contrary to "scientific methods and means" keep on being put forward by people who know all about the brain. The reason for the perennial persistence of dualism is simply that hardly anybody actually shares Churchland's cardinal hunch and that, instead, nearly everybody is beholden, willy-nilly, to the ancient—possibly categorically innate—paradoxical theory of our being half beast, half divine, whose explicit Judeo–Christian version was first published in *Genesis.*

In my most recent philosophical essay I pointed out that a satisfactory solution to the mind–body problem has actually been available since the latter part of the 18th century, when Immanuel Kant put forward the idea that we live in two metaphysically distinct worlds, both constructed by our mind, whose architecture each of us shares with our fellow humans. One of these worlds is constructed by our faculty of *theoretical reason* whose natural objects are governed by the laws of causal determination that science tries to fathom. The other world is that constructed by our faculty of *practical reason* whose supernatural, rational human subjects are governed by laws of freedom that ethics tries to fathom. Thus, according to practical reason, the notion of free will—nonsensical from the viewpoint of theoretical reason—is a rationally necessary constituent of the metaphysical concept of personhood that governs interpersonal human relations. And that is why, to discover our nature, we must see ourselves as organisms in, as well as out of Nature, to be understood by scientific as well as metaphysical methods and means.

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