Chapter 2: Pointillism 1953-1958*

WHEN HANDLER JOINED THE BIOCHEMICAL ADVISORY PANEL, the panel system for choosing grant recipients was on the cusp of a major increase in importance. The first panels of biochemistry experts were created by private philanthropic trusts to decide who deserved financial support. The panels were intentionally biased toward famous biochemists at prestigious universities because they were presumed to be the best judges of good science. Panel decisions, made by a process called "peer review," were almost never rejected by the trust managers, who assumed biochemists were objective and uniquely intelligent, and therefore not appropriately amenable to oversight by laymen. The first-generation panelists heavily favored biochemists who were their colleagues, friends, former students, or who shared the ideas of the panel members regarding what questions to ask of nature.

Following the end of World War II, as a consequence of a huge increase in government spending for biomedical research, the trusts largely disappeared and a group of quasi-independent federal agencies, the National Institutes of Health, were created to support biochemical research. The Institutes, employing the same biases and presumptions as the trust managers, jointly created the Biochemical Advisory Panel to choose what experiments would be done and who would do them. Despite the intrinsic weaknesses of the panel process of peer review, it became the canonical method for retail distribution of federal grant money to academic biochemists in the U.S. The Leadership Panel of the Institutes retained legal authority to modify Panel decisions, but did so only in rare instances that involved politically sensitive issues.

The Panel routinely received more grant proposals than could be read and evaluated individually by each Panel member, who were uncompensated for time lost from university tasks, and there was never enough money in the Institutes' budget to fund all the proposals the Panel found worthy of financial support. The Institutes remedied the problems by requiring each Panel member to evaluate and grade only an assigned fraction of the applications; the other members then voted on the recommendations rather than directly on the merits on the applications. A low grade or rejection of an application typically occurred in the context of professional or personal grudges, or when the theory behind the design of a proposed experiment was inconsistent with the theories of someone on the Panel. The Panel's power to define biomedical orthodoxy was essentially absolute because there was no other significant source of money for biomedical research in the US.

Some in Congress objected to reliance on the Panel for dispensing federal funds. They distinguished between biomedical validity and social utility and complained that a panel of biochemists might be the worst judges of what research the nation needed, because the primary objectives of biochemists usually was not social utility but rather personal edification and academic advancement. The operational secrecy of the Panel obscured public determination of whether the Institutes were funding investigators who asked the right questions. But after repeatedly telling the Congress that only biochemists could judge the merits of a research project proposed by other biochemists, and arguing that the process of peer review inherently guaranteed the money budgeted for research to treat and cure disease would be spent wisely, the Institutes overcame the congressional concerns.

The Panel's composition, procedural practices, and control over the disposition of a large annually-increasing budget was fertile ground for the evolution of a powerful autocratic chairman. A series of clever men helped prepare Handler to gain a position on the Panel. One was Handler's former mentor, who had secured Handler's initial funding by the Institutes. Another was the author of a biochemical textbook whose offer to Handler to become a co-author elevated his stature within

* This is a preprint of a manuscript that will undergo copyediting and review before publication in final form.

the Biochemical Society. A third was a politically savvy board member of the Society who arranged for it to support Handler's candidacy to become chairman at Duke and then later negotiated the deal for him to take over the leadership of the Society. However, Handler alone, by the force of his personality and the accident of fortuitous historical timing, after he became Panel chairman expanded the authority of the office and made himself the nation's most economically powerful voice in biomedical research — the Congress provided the money but it was Handler who determined how it was spent. The evolution of an autocratic chairman culminated in Handler, providing him the opportunity to utilize the power of the federal government to shape U.S. biomedical research according to his image.

HANDLER USED HIS TIME on the Panel to advance and establish his concepts of biochemical research and how it was related to biomedicine. In the process, he developed into a shrewd politician with an understanding of the motivating force of the fear biochemists seeking grants had about their employment future. He became the most powerful force on the Panel, someone whose opinions other Panel members rarely opposed.

The foundation of Handler's concept of biochemistry was the lawful structure of physics, which he praised frequently but understood only superficially because he did not speak its language — mathematics. Physics regarded lumps of inanimate matter that had the same chemical composition as identical, and its experimentally-proven laws required every lump to react exactly the same in a given circumstance. Early in his career, Handler adopted a mirror version of the lawful organization of physics to explain his biochemical experiments on nutrition in rats. He conjured the existence of a gedanken law that predicted all the rats in a test group must react identically in a given circumstance. They never did, of course, a problem he overcame by arbitrarily defining the average response of the group as the true response of each animal. In this manner, Handler believed, he had established biochemistry as a law-governed science, like physics. Further, he invoked the physicist's reductionist model of inanimate matter to explain animate matter. Physics regarded every lump of inanimate matter as composed of parts and, based on its proven laws, explained the behavior of a lump in a given circumstance in terms of the behavior of its parts. Handler aped the reductionist model of physics and applied it to biochemistry. In Handlerian biochemical reductionism, a gedanken rat, and by extension, a gedanken human, was composed of biochemical parts whose individual behavior could be summed to account for every observable biological phenomenon. He revealed the depth of his faith in Handlerian reductionism when he predicted that biochemical research would ultimately show how life could be created in a bottle by mixing biochemicals in proper proportions in accordance with the chemical doctrine of mass action.

In Handler's perspective, experimental evidence supporting reductionism came from pointillist laboratory studies like those he performed before he got sick and stopped working in the laboratory. He had measured biochemical levels in homogenized tissues from rats and used average values to characterize the values in the tissue of an imaginary living rat. In this manner, Handler made biomedical meaning from the pointillist results, which he called "biochemical facts" and which, in his mind, summed to biomedical understanding in the Seurat sense of a whole composed of parts. Proposed biochemical experiments that did not promise to seek such pointillist evidence invariably failed to gain the approval of his Panel for funding.

Handler believed that the points collected by an army of Institutes-funded biochemists would ultimately coalesce into the biomedical knowledge that explained human health and disease. In speeches, newspaper interviews, and published opinion pieces, he argued that the government had a moral responsibility to sustain such an army by increasing the budget of the Institutes, thereby allowing his Panel to fund more research. He further argued that the government had a moral obligation to support the education of more PhD biochemists, whom he depicted in congressional testimony as starving while they were being trained, a notion he supported using a personal story. During congressional testimony, he said that when he was in graduate school had to eat the livers of the rats in his experiments to survive.

Handlerian reductionism was adopted by the Biochemical Advisory Panel as the guiding principle for determining which grants should be funded. Adoption of the principle effectively transformed the mission of the Institutes from determining the "causes, treatment and cure" of disease to elucidating the biochemical mechanisms involved in disease treatments and cures — a towering perversion of the original congressionally assigned mission of the Institutes. Nevertheless, Handler relentlessly advanced his concept of reductionism, seemingly oblivious to its consequences and limitations. Early in his career at Duke, buoyed by the results of reductive biochemical studies that led to important discoveries concerning metabolism, vitamins, and proteins, Handler had tried to find a biochemical basis for the signs and symptoms of pellagra. He believed that a biochemical explanation for the disease would have been one more success — his success. After he failed, he drew the wrong lesson from his experience. Rather than recognizing his own research naïveté in undertaking a Sisyphean task — explaining signs and symptoms purely on the basis of test-tube biochemistry — he blamed the government for not providing him the requisite financial support. The truth was that Handler's reductive version of biomedicine had not succeeded in providing a biochemical explanation of *any* disease, or for biomedical phenomenon except for extracting energy from food, but Handler did not see the truth.

The Handlerian reductionist paradigm for biomedicine retarded the development of American biomedicine, paralleling the damage Lysenko caused to Soviet agriculture. The demand that biomedical inquiry rely exclusively on reductive experimentation especially devastated the research of scientists who were studying the biological role of electromagnetic energy, which was present in the brain, the peripheral nervous system, and in every living cell, but was absent in the blended soup Handler viewed as the source of all points of biomedical knowledge. He believed all biomedical phenomena ultimately could be reduced to parts and explained with physics-like accuracy based on biochemical measurements of cellular detritus. That belief led him to consciously disregard any possible explanatory significance of the unique properties of living systems — complex hierarchical organization, appearance of purpose, and time irreversibility, which does not exist in physics but that invariably results in the death of every biological organism. Ignoring these properties enabled Handler to ignore every difficult question in biology. His philosophy provided no starting point from which to understand the origin of life, the development of a vast number of species, the range of different behaviors of different organisms within the same species, why every organism in each species changes so drastically with the passage of time and ultimately dies, the interactions that occur between living systems from different levels of organization, and how organisms grow, heal, age, and get and cope with diseases. Handler summarily dismissed the most important questions in biology and medicine that mankind could ask, as if he were the head of an autocratic regime, like Augustus. Handler saw biochemistry as the sole science of life, and regarded direct study of the properties of living systems as unscientific because, reasoning circularly, they were not describable in biochemical terms. It was as if the child prodigy and PhD at the age of twenty-one actually had only a walnut-sized brain that could not simultaneously hold the ideas of biochemical and non-biochemical approaches to the elaboration of biomedical knowledge.

In his leadership role on the Panel, Handler systematically advocated funding only those experiments that matched his idea of what biomedical research ought to be. He was hugely antagonistic to non-reductive research proposals designed to explore the explanatory role of electromagnetic, mechanical, kinetic, gravitational, or thermal energy in biomedicine. He also reflexively opposed a galaxy of types of biomedical studies: cause-effect studies that were not based on a biochemical hypothesis; studies of the role of biological cybernetics in health and disease; almost all clinical research whose objective was to test a clinical hypotheses such as the safety and efficacy of drugs rather than a biochemical hypothesis; epidemiological studies aimed at providing initial information regarding the determinants of disease; research proposals related to the study of how tissues and organs functioned and reacted to changes in the body's internal environment or to man-made changes in the external environment. He regarded any methodological paradigm or scientific specialty that differed in any material respect from Handlerian reductionism as perforce antiscientific, a category in which he placed a variety of sciences and clinical specialties including psychiatry, psychology, and the social sciences. Instead, he exploited his dominant position on the Panel, and its procedural rules, to chisel in stone his cognitive structure of biomedicine. He approved only purely reductive studies of the biochemical properties of tissue debris, especially studies related to food metabolism, genes, and the biochemical machinery for synthesizing proteins, effectively blind to the limits of a purely biochemical approach to the study of biomedicine. Handler recognized no legal or ethical obligation to create a written record justifying any of his decisions regarding the disposition of grant funds. The other members of the Panel, mindful of Handler's clout within the Institutes, his anger when it flared, and his role as a determinative voter on their own grant applications when they came before the panel, were no brake on his excesses.

During Handler's time on the Biochemical Advisory Panel, so-called "biochemical mechanism" proposals became the sole experimental design that was allowed to compete for research support by the Institutes; proposals based on any differing scientific approach were more or less automatically eliminated from consideration. The effect of the Institutes' adoption of Handlerian reductionism was to instantiate biomedical research as a strictly biochemical endeavor. By excluding system-level biomedical studies from possible funding, Handler financially choked off the careers of scientists dedicated to the pursuit of novel paths to understanding the dynamics of processes manifested by living systems. His antagonism toward any form of biomedical research that differed from that of his biochemical hero in *Arrowsmith* corrupted the mission of the Institutes and prevented studies of innumerable biomedical phenomena, including but not limited to growth, development, healing, memory, consciousness, health, and the occurrence and prognosis of chronic and infectious diseases. Studies of these phenomena could not be supported by the Institutes because Handlerian reductionism recognized no valid method for such, and it is axiomatic in science that knowledge is the product of method.

THE READER SHOULD NOT UNDERSTAND that Handler completely arrested the occurrence of new insights into biology and biomedicine, the development of new methods for conducting biomedical studies, or the growth of a practical and useful biomedicine. Advancement in these areas continued, but at a muted level and outside the domain of biomedical orthodoxy that the federal government had established, however unwittingly, when it created the Institutes and gave it the freedom to spend the pot of money the government had set aside for biomedical research. Scientists who ignored the Dicta of the Institutes, Handler, and the Biochemical Society had only limited access to federal research grants , a burden that limited their upward mobility in scientific society, like Jim Crow laws. Despite being intentionally discouraged and seriously underfunded, heterodoxers were active in diverse areas of science. The defining aspect of their work — what they had in common — was its potential, whether implicit or explicit, to transform biomedical research into an activity primarily geared to benefit human health and welfare rather than the employment and edification of biochemists. They showed how the limitations on biomedicine embodied in the

Dicta, especially Handlerian reductionism and its doppelganger, the methodological impossibility for biochemistry alone to explain health and disease, could be overcome.

RENE DOBOS was such a heterodoxer. He was a biochemist who worked at the Rockefeller University, and perhaps the first to recognize that Handler's dream of proportionate mixing of chemicals together in a beaker to make life was just that — a dream. Dubos' research was funded by a private philanthropy and resulted in significant biochemical advances including the discovery of antibiotics , far outstripping what Handler accomplished. When they both attended the annual meetings of the Biochemistry Society, Dubos was royalty and Handler was a backbencher. Dubos was elected to the National Academy of Sciences, a rare event because the Academy was composed almost entirely of physicists, who generally had a dim view of the validity of biomedical research. During the 1940s and 1950s, while Handler was looking down into the biochemical parts of rats, Dubos shifted his focus upward from test-tube biochemistry to system-level experiments. He theorized that infectious disease was not solely a result of a particular pathological microbe, but a consequence of a complex interacting series of various types of signals occurring in the body — the microbe alone was no sufficient explanation. He tested his theory in animal experiments designed to show that susceptibility to infection was influenced by the effects of metabolic products and environmental factors on the host's natural resistance to infection. Dubos' experiments demonstrated that biochemistry alone was inherently insufficient to answer questions regarding when and why and in whom infectious disease developed — exactly the kinds of questions Handler despised. During his entire tenure on the Biochemical Advisory Panel, Handler opposed funding grant applications from Dubos and others like him who asked such questions.

Dubos differed starkly from Handler in many respects. Handler never wrote a book or other publication in which he rationalized Handlerian reductionism or explained why he regarded Dubos' questions about nature as nonquestions. Dubos, in contrast, believed that the states of health or disease were not biochemical constructs but rather adaptive responses of organisms to environmental challenges, and he gave detailed explanations of his opinion in a series of books. He saw life not as a collection of molecules, as did Handler, but rather in terms of organization and the ability to adapt to change — the fundamental basis of evolution. Dubos rejected Handler's belief that biochemistry alone would someday lead to an understanding of all features of the living state, calling it a "dream of reason." The better view of living organisms, according to Dubos, was not as biochemical machines but rather as systems in unstable dynamic equilibrium with their environment — kinetic, not static as Handler demanded.

Handler's vision of a society in which biochemistry could make everyone healthy and banish disease was, in Dubos' perspective, an unattainable medical utopia. He believed disease would constantly assume new forms thereby presenting new challenges to physicians and to society, challenges not amenable to a biochemical approach alone because the challenges existed above the level of atoms. Dubos argued that every civilization creates its own diseases, that the continuing advance of medicine produces more problems than it solves, and that the oversimplified mechanistic theory of life entertained by Handler and those like him was an illusion. Dubos reasoned that "some unknown principle runs like a continuous thread through all living forms and governs the organization of their physicochemical properties." Only later was the principle identified by others as information carried by electromagnetic and biochemical energy. Dubos pinpointed the necessity for biological cybernetics, presaged its development, and recognized the need for understanding the feedback relationship between the organism and its environment. He explicitly identified the painful mistake of Handlerian reductionism — always depending upon the analytical method and never attempting a synthesis of biomedical information.

Ethical considerations powered Dubos' work. For Handler, ethics and values had only a minimalist role in science. They were similarly trained biochemists when their careers began, but Dubos came to see biomedicine as more than biochemical facts, as Handler argued. Dubos envisioned biomedicine as an activity that involved human judgment regarding the collective values of society — what we want life to be. He made seminal contributions to biochemistry, served for decades as the editor of a journal devoted to experimental medicine, and explained his scientific and ethical reasoning with unprecedented clarity in many journal articles and books. Handler, in contrast, did no worthwhile biochemical research and never explained his reasoning in any publication, most of which were only naked unchallenged opinions. Dubos argued, "It is essential that scientists discuss more thoroughly in public the implications of their findings with regard not only to the practical applications of science but also to its influence on the concepts of man's place in the order of things." And he famously said, "A society that blindly accepts the decisions of experts is a sick society." Handler disagreed. He opined that society should trust and accept the opinion of its scientists in all matters touching on science and should regard their views as objective and value-free. He called scientists who spoke publicly on matters of health risks "prophets of doom" and condemned their "overly emotional and irrational imaginings of future catastrophe." His opinions on abortion, eugenics, and human experimentation were all on the historically wrong side of the public debates regarding those issues. Handler never spoke publicly about Dubos nor accepted invitations to review his books, remaining aloof, as if on a throne.

THE WORK OF HAROLD WOLFF, a neurologist, showed him to be another prominent heterodoxer. He brought to biomedical research the component of human compassion that is unique to those who treat the sick and see their suffering first-hand, but alien to those who never leave the laboratory and pursue knowledge for knowledge's sake. Wolff's research, which was funded by private philanthropies and his university, focused on the nervous system, which he viewed as the master organizer of the complex reactions inside a human being that occur in connection with changes in the internal and external environments.

Wolff presented extensive evidence from clinical studies of his patients that showed an unidentified but indubitably real regulatory system protected the individual despite continuous changes occurring inside the body and the presence of diverse time-dependent factors in the environment. The external stimuli consisted of infectious agents and chemicals, and also of neurogenic factors resulting from involvement with other people that resulted in fear, anger, or threat. When the limits of the body's normal adaptive reactions, which were under the control of the neural regulatory system were exceeded, the body responded with a reaction that was self-destructive, with manifestations that included common maladies such as peptic ulcer, hypertension, colitis, and migraine headaches. Wolff saw the human pathologies as a failure of biological regulation, and recognized a clinical responsibility to treat the dysregulation and a scientific obligation to identify its causes with the aim of preventing it. The concept that both somatic and neurogenic stresses of life incited bodily disease, Wolff's best-known contribution to clinical medicine, unified human pathology by revealing that pathological reactions occurring in the body depended on personal goals, purposes, aspirations, and values, as well as on physical agents — Handler's biochemical model of pathology was far too simplistic and had nil clinical usefulness.

Wolff studied headache pain and developed a theory that the primary source of the pain was a disturbance in the brain's regulation of cerebral blood vessels — tension caused vasoconstriction and fatigue caused vasodilation — as a reaction to the inability of the patient's body to cope with the stresses of life. His clinical investigations of the relationship between the stresses encountered in life and bodily disease that developed profoundly influenced the modern concept of diseases, and helped explain them as outcomes of attempts at adaptation. Reductionist biochemists had no explanation whatever for headaches, and could offer nothing but promises that their approach to biomedicine would ultimately provide the answers. Wolff, who had no interest in waiting for them, developed research methods based on statistical evaluation of cause-effect associations manifested at the system level — a method perfectly suited to his objective, treating patients. In Handler's perspective, Wolff's research was inferior because it was not reductive and was motivated by teleological principles, which Handler furiously opposed. Handler believed Wolff did not merit financial support from the Institutes for his research because he did not propose experiments whose objectives were production of specific points of biochemical knowledge, and Wolff received no Institutes support. When private philanthropies ceased funding biomedical research , Wolff's research funding ended. In effect, Handler defeated Wolff not on the merits, but rather by controlling the national purse-strings for biomedical research.

ALBERT SZENT-GYORGYI was a biochemist and a physician who made seminal discoveries concerning the biochemical reactions in cells that extract energy from food — the reactions that had so impressed Handler when he learned about them in college — and won a Nobel Prize for the work. He next sought sought to understand how living things moved, and won acclaim for explaining the biochemical basis of muscle action. But muscles obviously facilitated motion and just as obviously there had to be a biochemical basis, so its discovery was just a matter of time. Although intellectually satisfying, in the larger picture of health and disease or life and death, the discovery was relatively unimportant, a fact that Szent-Gyorgyi recognized and saw as only a facet of a far larger problem.

At this point in his career, Szent-Gyorgyi was probably the most famous biochemist in the world. After reflecting on what he and other biochemists had accomplished, he concluded that the approach of biochemistry to biomedicine was deeply flawed because it had utterly failed to explain what life is. Handler believed that not doing so was right and proper, not a failure, because life was not a biochemical question. Szent-Gyorgyi was a visionary who was often wrong, but when right, his work changed the world of science; he thought oppositely and persisted in his quest to understand life. One evening near the end of his life he poignantly described to me his view of the fatal flaw in Handler's conception of the relation between biochemistry and biomedicine. He held his hands palms up and said I should imagine he was holding a live rat in one hand and a dead rat in the other, and then he asked what the difference was between the two rats. When I told him I didn't know, he said it couldn't be biochemical agents because they were the same in the two rats, so it had to be some form of electromagnetic energy — a point of view that constituted mortal sin in Handler's religion.

Handler resented Szent-Gyorgyi's international stature and thought him well past his prime. Under pressure from many biochemists, however, Handler approved a grant request from Szent-Gyorgyi that dealt with muscle biochemistry. But he rejected a proposal to study the link between electromagnetic energy and life, and pointedly told Szent-Gyorgyi that any future proposals to study electromagnetic energy would be similarly treated. Szent-Gyorgyi's research activities survived for a while only because some laymen formed a publicly supported private philanthropy, and raised the money he needed to continue the work of the world's greatest living biochemist, as well as that of a handful of other scientists who sought to help him establish his ideas. But the effort ultimately failed because the orthodoxing power of the Institutes colored the work as a fringe activity, and the group could not survive the stigma.

HAROLD BURR , a biology professor at Yale, was he first investigator who systematically addressed the possibility that electromagnetic energy might be an intrinsic explanatory element for how living systems functioned. His interest in the biology of electromagnetic energy began with the question of how a salamander egg developed into a fully formed salamander. At that time, Handler and his colleagues in the Biochemical Society viewed questions regarding biological control or regulation as essentially philosophic or religious rather than scientific. According to their wisdom, embryonic development was simply a condition of the world, like gravity, not something to be investigated beyond resolving the problem of identifying the relevant biochemical entities. Burr sought a scientific explanation for a specific aspect of salamander development — his observation that the rates of cell division in one area of the embryo were always temporally coordinated with the growth of specific nerves in another area of the embryo. Recognizing that causal behavior occurring at a distance was an inherent property of electromagnetic energy, he developed the theory that electromagnetic energy was present in the embryo and somehow coordinated the two processes. With financial support from private philanthropic foundations and his University, but none from the Institutes, Burr invented instruments capable of measuring the extraordinarily small levels of energy that he supposed existed, and he discovered that they were present everywhere in the embryo throughout the entire period of its development, as he had supposed.

During a long series of published experiments, he generalized his idea, speculating that the energy controlled the entire process of embryonic growth so that the successive developmental stages followed each other in regular order. According to his theory, each stage was guided by, contributed to, and modified the flow of the electromagnetic energy, which he regarded as the unifying principle responsible for integrating myriad local biochemical processes that produced regulated growth and development, resulting in new animals that always looked more or less as expected. Burr then discovered that the electromagnetic energy was also present everywhere on the skin of the salamanders and mammals, including humans. He conducted many animal and human experiments aimed at understanding where the electromagnetic energy came from, its function, how measurements of the energy levels could be used for diagnostic purposes, and how desirable processes such as healing could be trigged by the application of man-made electromagnetic energy. He proved that the energy levels changed in relation to growth and after pharmacologic or surgical interventions, as would be expected if the electromagnetic energy were part of a control system. In Handler's perspective, however, Burr was little more than a charlatan, someone like Descartes who believed that it was a soul that made the human machine move. Neither Burr nor any other scientist interested in exploring the limits of the electromagnetic energy hypothesis received a grant from the Institutes during the time Handler was in charge of the Biochemical Advisory Panel, or for many years thereafter.

In so far as I could determine, I was the first investigator to receive an Institutes grant for the purpose of conducting experiments of the type and for the purpose Burr envisioned. The award was made more than a decade after Handler left the Institutes, during a brief period in history when the Institutes were under political pressure to approve proposed experiments involving electromagnetic energy that were not based on Handlerian reductionism. But the window of opportunity did not last. My grant was terminated after only two years, and during the following half century no grant with a similar purpose was awarded by the Institute.

NORBERT WIENER was a mathematician who fathered cybernetics, the study of the processes that govern control and communications in complex systems, whether man or machine. He sought to identify the principles that govern how complex systems transmit information, respond to stimuli, and adapt to changes. Cybernetics was pregnant with importance for biomedicine because movement of information inside the body was what permitted it to adapt to environmental changes and modify itself in myriad different circumstances, which were the central issues in the research of Dubos, Wolff, Szent-Gyorgyi, and Burr. Wiener conceived of a system not in terms of the atoms of biochemicals that constituted the system, but rather as a three-dimensional dynamically changing structure that hosted the flow of information. For him, dynamical changes and information flow weren't parts of a system, they *were* the system.

The physical basis of information could be electromagnetic or chemical energy, however information itself was not energy but rather a third fundamental scientific entity, in addition to energy and matter. Wiener's objectification of information had profound implications for biomedicine. The mysterious stuff that moved through nerves, reverberated in the brain, produced homeostasis, regulated growth, and mediated health and disease became legitimate subjects for study. Biocybernetics promised to occupy some of the explanatory space Handler had reserved for biochemistry. He began referring to "information" in his speeches after the genetic structure of DNA was discovered, but only to emphasize the importance of biochemistry, arguing that explaining heredity in terms of the static atomic structure of DNA proved biochemistry's explanatory power. "Why do horses give birth to horses and not pigs?" he asked, and answered, "Because the information in the genes of a horse's DNA specifies a horse, not a pig." He opposed the use of government funds to explore the implications of Wiener's work, that biochemistry and information, although related in the sense that neither could exist without the other, were actually two distinct indispensable but incommensurate ideas.

Wiener recognized that if information regulated structure and function, as he supposed, then information must in some sense be a scalable variable capable of specifying this or that structure or function, or no structure or function. He identified the lack of information as a kind of randomness akin to static or noise in a telephone signal, and assumed that all non-random signals contained some information. He introduced the cybernetic concept of circular causality — when communicated information produced a change in structure or function, the resulting change itself became a source of information that modified the consequences of the earlier informational signal. No idea could be more antithetical to the basis of Handlerian reductionism — linear causality. Wiener and co-workers-built machines that modeled living systems wherein a cause produced an effect that, in turn, became the cause of an information-bearing signal that modified the original effect.

Because of Wiener's work, the central nervous system was no longer conceived as a self-contained organ receiving signals from the senses and activating muscles. Some of its most characteristic activities became seen as explainable only as circular processes in which information travels throughout the body in a continuous cycle of cause and effect that never ceases until death. In a biocybernetics approach, human beings were viewed as integrated wholes that functioned by means of the constant flow of information-bearing electromagnetic and chemical energy. Biocybernetics was quite irreconcilable with Handler's exclusively biochemical vision of biomedicine, but the two ideas did not compete on a level playing field. Handlerian reductionism grew exponentially in importance during the 1950s because it had the financial backing of the Institutes, whereas Wiener's vision of cybernetics as applied to biomedicine faded into the background because his funding from philanthropies ended after they died away and the Institutes denied financial support for all research proposals designed to explore biomedical cybernetics.

One of the members in the informal group of scientists that was created cybernetics was an engineer named CLAUDE SHANNON. A main reason, besides Handler's influence, that biocybernetics was stillborn even though it was a conceptual advance, stemmed from the perception that its core variable, information, apparently could not be measured. In contrast to matter and energy, there was no information meter, information scale, or information standard in a vault in Paris by which information could be quantified. No one could specify, for example, the exact number of informational units contained in an electrical signal in the brain. Shannon invented a method for measuring information at least in some situations — telephone messages and storage devices on a computer as examples. He called his measurement unit a "bit" and proved that the number of bits was a reliable measure of the amount of information in the message. Bits were not directly applicable for quantifying biomedical cybernetic information such as the signals that regulated homeostasis, or communicated the stress response, or provided feedback control of bone growth, or carried information to the brain from receptors in the body that electromagnetic energy had been detected. Even so, the idea of measuring information was revolutionary. Before Shannon, the term "information" had been used in science only metaphorically, as when Handler asserted that DNA contained "genetic information." Shannon showed that information was a measurable scientific construct, like matter and energy.

The lack of a biological-information meter that could measure biological information in standardized units was an existential limitation on the development of the post-reductive biomedical research that would hasten the death of Handlerian reductionism. But the limitation was only an empirical problem that could be overcome by future investigators. What was certain, because of the work of Wiener and Shannon, was that there were three measurable entities in science: matter, energy, and information. In a biological context, information was fundamentally and indubitably a post-reductive entity — a sobering and disappointing development for Handler and his supporters which they never ceased opposing.

ILYA PRIGOGINE was a chemist whose research was supported by the Department of Defense. His work undercut the credibility of Handlerian reductionism from a direction quite distinct from that of the other investigators whose work had a similar effect. Prigogine's initial objective was to understand the behavior of a prosaic model laboratory system consisting of heated water in a jar. The water normally bubbled in a random pattern and rose to the top of the jar, but under special conditions the random bubbling ceased and standing columns of water appeared spontaneously, showing the creation of order from disorder. A necessary condition for the order to emerge in Prigogine's jar was that the system had to be "far from energy equilibrium," meaning that the creation of the order was completely dependent on a continuous supply of heat energy to the system — when the energy flow ceased the order disappeared. A salient aspect of the occurrence of order was that it was not composed of independent parts that could be studied separately. There were no individual parts whose behaviors could be added to produce standing columns of water, indicating that column formation was a true system-level effect, not understandable in reductive terms. After many other investigators verified his observations, Prigogine created a novel mathematical theory in which the appearance of order from randomness — a new phenomenon not previously observed in nonliving matter — was a deductive consequence, and was rewarded with a Nobel Prize.

Prigogine encountered opposition from physicists, who had interpreted the Second Law of Thermodynamics to say that the appearance of order from disorder was impossible. Nevertheless, his results were validated and explained with mathematical rigor, and were recognized internationally. Therefore, according to the established understanding of the cognitive structure of physics, the objections he encountered were baseless and improper. Prigogine legalized his observations by changing the way the Second Law should be understood, a process which always happens when valid observations are inconsistent with established theory.

Prior to Prigogine's work, physicists opposed Darwin's theory of biological evolution on the basis that it violated the Second Law of Thermodynamics as they then understood it, because the Law said life turned into dust whereas the theory of evolution said dust turned into life. The opinion pf physicists concerning evolution had nil significance for biologists, who universally regarded evolution as the seminal principle of biology. But the difference in attitude concerning evolution created a mutual distrust and disdain between physicists and biologists — physicists tended to consider biologists as unscientific, and biologists saw physicists as irrelevant in the real world, particularly after physics birthed technology. When Handlerian reductionism emerged, biomedicine, the primary experimental part of biology, physicists — who at that time controlled the national policy and purse strings of science in the U.S. — viewed the emergence as a maturation of biology, in other words, a movement toward the adoption of pure physical principles and away from the theory of evolution. The antagonism of physicists toward biology lessened somewhat, at least in the area of biomedicine. but Prigogine's work quickly changed the dynamic of dawning acceptance of Handlerian reductionism, and left physicists more confused than ever regarding how they should regard biology. Why? Because nothing in the universe is farther from energy equilibrium than humans. Yet, Prigogine legalized — in the physics sense of law — the possibility that humans could have evolved from dust. It appeared, for the first time in modernity, that biology was arguably the greatest science invented by mankind, at least in the sense of most inclusive of all reality. Biology included all of the laws of physics as well as something physics didn't encompass — life, the concept of which is totally absent within physics. Physics was a distant second in stature because a science that can't rationalize life is something puny compared with a science that can. Handlerian biochemistry, which was a pale cognitive version of physics was still lower.

As measured by political power over national science policy, however, at the time Handler was entrenching his model of biomedicine, the ruling authority of physicists was decreasing precipitously, and ranked no more than third, behind technology and biomedicine. Handler's problem therefore wasn't with physicists, but rather with Prigogine's work. Handler rejected the idea that Prigogine's work might explain evolution by showing that the purposes and consequences of food energy went beyond metabolism, and actually facilitated the ordered development of life. Instead, he demanded that what biologists called life and Wiener called system behavior be regarded solely as the consequence of test-tube-type biochemical reactions, not as an emergent property of an organized system. Handler implemented his position, by denying grant support to Prigogine and all other investigators who sought kinds of biomedical information other than the test-tube kind. Prigogine survived because his work was important to the Defense Department, but investigators who wanted to directly study the biomedical implications of far-from-equilibrium living systems never received any financial support from the Institutes.

Handlerian biochemists had not contributed any useful information toward understanding evolution, a situation that undercut Handler's claim that biochemistry was the basic science of biology. In what seemed to be a desperate attempt to rehabilitate the status of biochemistry as regards evolution, Handler approved a grant from his own Panel to workers in his own laboratory at Duke to find biochemical evidence that proved the validity of evolution. Biochemists working at his behest performed test-tube reactions on cells from many different species of plant and animal life and found a specific protein in each species examined. On that basis, in a nationally syndicated newspaper article, Handler claimed he had biochemically proved the theory of evolution, because his findings meant there had to be one common ancestor for all the plants and animals on earth. After his claim was widely mocked he withdrew it, leaving the situation as it had stood, that biochemistry contributed no insight toward understanding evolution.

Despite Handler, Prigogine's work demonstrated that systemic studies of living systems were legitimate scientific activities, and thus that Handlers' characterization of living systems as completely deterministic at the molecular level — an unforced error on his part brought about solely by his blind love of biochemistry — was insufficient to explain biophenomena. Handler's second and even more serious error was his diligent effort to stop others from remedying his first error.

WHEN HANDLER JOINED THE BIOCHEMICAL ADVISORY PANEL, most grant applications to the Institutes involved proposed studies of cancer, and consequently it was the predominant topic of the applications Handler reviewed for scientific worthiness. They contained averments of relevance to cancer that sometimes were sincere and other times were transparently contrived lies that satisfied the legal requirement of a foreseeable application to the disease. Most grant swingers were sufficiently skilled in grantsmanship to characterize any experiment that appealed to them as foreseeably relevant to cancer. The field of play for the swingers increased after the structure of DNA was discovered, which established that genes had a biochemical basis. The Institutes received applications promising foreseeable results related to heritable diseases, and defective genes responsible for some rare heritable diseases were biochemically identified. The defects were truly causal because every person who had the defective gene developed the disease, and it never developed in someone who lacked the defect. Handler construed the fruits of gene research as strong evidence of the importance of biochemistry for biomedicine, and told the Congress that biochemists would eventually find a way to repair gene defects and then show clinicians how to correct the human gene pool. He increased the prestige profile of biochemistry before the Congress when he testified that he thought cancer also was a result of mutated genes in the sense that each kind of cancer was caused by a different defective gene and only those who had the gene got cancer.

Handler believed biochemistry deserved to be regarded by the government, for funding purposes, as the preeminent science of biomedicine, but biochemistry was only a subspeciality within chemistry. To foster elimination of biochemistry's subordinate status, which he felt interfered with his attempts to promote biochemistry as the science of biomedicine, Handler originated the notion that biochemistry and chemistry were actually different specialties. He styled chemistry — a specialty in which he had no political constituency — as only applied physics because all chemical phenomena were explained by the laws of physics — there was no such thing as a law in chemistry that didn't come from physics. Since physics couldn't explain biology or biomedicine, Handler argued, obviously chemistry couldn't, only biochemistry could.

Handler sustained his story by originating a foundational principle that ran from biochemical reactions to system-level biophenomena like growth and healing — a principle that played the same role in biochemistry as did laws in physics. The closest thing biology itself had to a law was the theory of evolution, but it was unacceptable to Handler as an foundational principle because it did not demand a causal chain that ran from the parts to the whole. With the support of the Institutes, Handler provided the foundational principle by propounding a myth of a universal biochemical theory of disease causation, a myth that putatively explained all human disease. According to the myth, disease was caused by three types of malevolent biochemicals: special protein molecules that allowed infectious agents to enter the body, environmental chemicals that became toxic biochemicals inside the body, and defective genes. The protein molecules were present on the surface of a virus and bacteria that had evolved to facilitate infectious disease by enabling the entry of pathogens into the body. The toxic chemicals, some natural and some man-made, entered the body and disrupted normal biochemical activity. Defective genes were caused by toxic chemicals, heredity, or fate. He envisioned a deterministic world of disease that operated probabilistically, like quantum mechanics in physics.

Handler promoted the myth in speeches at Biochemical Society meetings, talks at universities he visited on behalf of the Institutes, and congressional testimonies, but never explained it in detail in a scientific article or book. He inculcated his opinions into the culture of the Institutes, and advocated for pointillist research to find the biochemical causes he imagined existed for diseases. Handler repeatedly made bold promises to the Congress that, if enough biochemists were produced and given government grants with the freedom to plan their own experiment objectives, the malevolent biochemical responsible for each disease, even aging, would eventually be discovered.

The myth of a causal link between malevolent biochemicals and disease was supported by the Leaders of the Institutes during their annual testimony before congressional budget committees.

The gist of their testimony was that disease was a biochemical process caused by specific abnormal or toxic agents, which logically meant there existed chemicals capable of interrupting the process, resulting in treatments and cures that could be could be identified more quickly if the research budget were increased. Although Handler's testimony was same as that of the Leaders, his motives differed from theirs. He actually believed the myth and sought to establish it as reliable truth. The Leaders, in contrast, after they were confronted with the issue of a link between smoking and cancer, learned they could use the myth as the basis of a strategic response to an existential problem caused by tobacco issue.

The motives and strategy of the Institutes sharpened after the possibility of a relationship between the habit of smoking and the occurrence of cancer was suggested by nonbiochemical scientists, both epidemiologists and medical investigators. During nonreductionist biomedical research supported by their universities, the scientists analyzed clinical and government health data and found that smoking and cancer were statically related, suggesting the possibility of a causal link. Handler, whose home state was the largest producer of tobacco in the country and whose university was founded and funded by the man who started the U.S. cigarette industry, was keenly interested in the issue. Influenced by his argument that if smoking caused cancer, there had to be a causative chemical constituent in the inhaled smoke, the Institutes funded pointillist biochemical studies that promised to find the causative chemical. But none was found; not even one of the several thousand chemicals in cigarette smoke was proven to be a biochemical cause of cancer. Despite the failure of the Institutes to find a biochemical cause, epidemiological and clinical studies continued to yield strong evidence of a correlation between smoking and cancer, particularly lung cancer. The Leaders recognized that the inability to identify a putative toxic agent in smoke, despite the persuasive evidence published by epidemiologists and clinicians that smoking caused cancer, had dire implications for the Institutes. The story the Leaders told the Congress — that malevolent biochemicals directly caused diseases — was apparently untrue because there obviously was a link but the Institutes couldn't find it. Additionally, the Institutes might *never* learn how to prevent cancer by identifying its causes because they apparently weren't biochemical — a politically embarrassing limitation on what the Institutes could hope to accomplish

The tobacco companies and their supporters in the Congress criticized the Institutes for funding studies looking for the toxic chemical in smoke that caused cancer. The critics argued that the Institutes should not use taxpayer money to study a possible link between smoking and cancer because the studies were a threat to the livelihood of small tobacco farmers, and because the claim that tobacco caused cancer was a hoax. The epidemiological and medical studies were dismissed as non-scientific and inconsistent with the opinions of biochemists and physicians who denied the existence of a link. Further, biochemical researchers who worked for the tobacco companies interpreted their results as meaning that tobacco was completely safe. The resulting adverse publicity threatened the budget of the Institutes and even their existence as government agencies

Handler remained firmly committed to the myth he created, and believed there was no public-health reason for the government to interfere with the tobacco industry because, he said, there was no compelling evidence that smoking caused cancer. His recommended solution to the Institutes' problem was that, on a principled basis, all funding of biochemical studies intended to identify the biochemical cause of cancer immediately cease. He reasoned that "system-level causality," his euphemism for cancer, wasn't a biochemical question and had no meaning at the biochemical level. Consequently, he advised, the Institutes should decline to fund research designed to prevent cancer by discovering its causes, and instead concentrate on treating and curing cancer, objectives that could be achieved by means of biochemical research. The Leaders accepted and adopted Handler's advice although they never formally disclosed to the Congress what they had done. That subterfuge was possible in those days because the Congress had not yet recognized that biochemists were not a special class of humans, but rather were as value-laden, self-interested, and greedy as any other group of people. After the Institutes ceased funding studies of whether cigarettes cause cancer, the criticism they received abated and shifted to the epidemiologists and medical investigators. The new strategy also immunized the Institutes against adverse publicity generated by future cancer scares associated with other toxic agents because, on principle, the Institutes would not begin to seek finding the cause. The high regard the Leaders had for Handler increased even further.

HANDLER WAS STRONGLY BIASED AGAINST grant proposals involving electromagnetic energy which, in his eyes, had no more credibility as a biomedical hypothesis than did the hypothesis of a heavenly spirit. In the mid-1950s, he and others at the Institutes were approached by agents from the Department of Defense regarding a problem then occurring at the U.S. Embassy building in Moscow. They were told that Russia was aiming a beam of microwave electromagnetic energy at the building, and that Embassy personnel had complained of various nonspecific illnesses. When the agents sought Handler's advice and that of others at the Institutes regarding the biomedical significance of the energy beam, they were told that there was none.

At the same time, the Defense Department funded an analysis of the biological effects of microwaves by a physicist, Herman Schwan, who had worked in a Nazi laboratory during World War II and studied the potential use of microwaves for cooking the food of the crews on German U-boats. The Defense Department sponsored Schwan for U.S. citizenship because of his experience with the effect of microwaves and supported his research into safety levels for human exposure. In his concluding report he wrote, "Assume a human being is shaped like a sphere made of copper or muscle tissue," and then evaluated the application of microwaves to his reconceptualization of a human as a simple, inert sphere. After he also reconceptualized "safety" to mean the absence of harm caused by heating, Schwan reached the same conclusion of complete safety of microwaves that Handler and others at the Institutes had reached, but with added precision — a mathematically exact determination of the dividing point between cooking and no effects at all — 10 milliwatts.

The Russians, however, based on animal and human experimentation, rather than calculations involving humans modeled as metal balls, had arrived at safety level ten thousand times smaller. The energy level in their Moscow beam was slightly above the Russian safety level but far below the Defense Department's safety level. Handler completely discounted the Russian safety level because, he told the Defense Department, Russian biological research was far inferior to that in the U.S. Handler supported Schwan's calculated safety level because it was based on what Handler called "general biological principles," by which he meant that a very small amount of anything is presumably safe unless proven otherwise.

The Defense Department began a series of secret animal and human studies in various government and university laboratories, including those at the University of Rochester and Veterans Administration Hospitals in California and Kansas, but the results were classified. Throughout the duration of the secret program, and thereafter, Handler and the Institutes maintained a strict ban on funding biomedical studies of the health and safety aspects of exposure to electromagnetic energy. There were no exceptions. Consequently, because of government secrecy policies and the absence of any source of funding, progress in the area was significantly impeded.

THE 1950S WAS A RIPE PERIOD FOR HANDLER'S aggressively narrow vision of biomedicine. The metabolism and protein paradigms of biochemistry had been successful and the concept of DNA as a master molecule was developing. Handler believed he was on the cusp of establishing biochemistry as a free-standing science whose mission was the production of pointillist facts that, he believed, would govern clinical medicine. The Congress had tasked the Institutes to develop a comprehensive science of biomedicine as a rational basis for clinical medicine, and Handler worked diligently to make his objectives and methods the definition of that science. He established the Institutes' cognitive priorities and formed a formidable political alliance with numerous biochemical societies, which had multiplied like rabbits beyond his Biochemical Society and organized into a super-society to best further the interests of the member societies. The framework of the Institutes' research agenda was developed by consensus with the academic elite — the leaders of the societies and the heads of the university laboratories where the research took place. In the process of forming an agenda, the Institutes and the academicians reinforced each other's interests, and their representation of life in terms of biochemistry supplied an instrumental rationality that legitimized and empowered both groups.

Handler's biochemical vision of biomedicine had dramatic intellectual and social consequences. He effectively created a national industry dedicated to biochemical research that was financed by grants from the Institutes and housed in university laboratories, especially those at prestigious universities. Universities benefited greatly from the influx of federal research money. The biochemical research also created a strong demand for expensive scientific equipment, which helped the emergence of a scientific-equipment industry. Handler had a key role in choosing and promoting the issues and problems that were important in biomedicine, and therefore fundable by the Institutes. The harmful aspect of his program was the absence of financial support for biomedical research that wasn't strictly biochemical in design. The Institutes targeted their resources at select areas thereby accelerating their development and creating a congressional sense of rapid progress which elevated the prestige and budget of the Institutes. They purposely avoided funding research into numerous critical problems that required novel methodological approaches, with the result that workers in the neglected areas faced enormous financial obstacles trying to establish those areas as true sources of biomedical knowledge. Study of the role of electromagnetic energy and the cybernetic processes of regulation and control was especially marginalized, despite their intellectual validity.

Measured against his objective, Handler was successful during the 1950s because he was able to define what questions were important in biomedicine, establish Handlerian reductionism as the monochromatic method of biomedicine, and gain prodigious support within the biochemical community by virtue of his ability to generate government money the biochemists needed. From the beginning, however, the effectiveness of Handlerian reductionism in biomedical research was severely limited because it hindered and sometime explicitly forbade other methods that were often far more appropriate for studying biophenomena that were critically important in clinical medicine. There were numerous questions in biomedicine to be explored, many possible representations of life that merited consideration , and alternative visions of nature and nurture. But the Institutes aimed their money only at the narrowest targets — those amenable to study by resort to reductive biochemistry. The projects funded by the Institutes exclusively favored upward causation by biochemical mechanisms, and regarded them as the only path to understanding health and disease. Handler's assertion that they could be understood within the framework of metabolism and proteins and genetic determinism essentially obviated the possibility of non-reductionistic explanations and resulted in the neglect of all other perspectives on biomedicine. He was like a lion that kills the cubs of other males so his progeny will survive. The faith of the Institutes in the power of reductive biochemistry led to enormous investments in drugs designed to block unwanted biochemical mechanisms — a dialectical process in which reductive biochemistry and the drug industry justified each other.

During his time on the Biochemical Advisory Panel, Handler became a fully-fledged autocrat, imperious and domineering, someone people didn't argue with unless they were courageous. He achieved widespread support among biochemically orientated researchers, who benefited significantly from his success. Handle recognized "biochemistry was an old-fashioned word that was in the process of passing away," and used a plethora of synonyms during his speeches to characterize its practitioners — molecular biologists, physiologists, pharmacologists, microbiologists, immunologists, embryologists, geneticists, among others. In that way he broadened his base of political support to include the numerous groups of biochemical subspecialties that had arisen. Handler became their hero because they were competitive for the additional research money he secured from the Congress, and their professional societies lobbied Congress incessantly in favor of whatever Handler favored, like the followers of a cult leader. He shaped biomedical research, as if it were wet concrete and he were the mold into which it was poured and hardened. By the time Handler's tenure as chairman of the Biochemical Advisory Panel ended near the end of the 1950s, Handlerian reductionism was firmly established at the Institutes and dominated the funding marketplace, and he had successfully blocked or impeded development of many new alternative ideas concerning biomedical research that deserved consideration but were anathema to him.