Chapter 3: Purity1958-1962*

LEGAL RESPONSIBILITY FOR THE policies and research strategy of the Institutes rested with the members of its Leadership Panel. In several ways, the Panel members indicated their gratification with Handler's guidance of the Biochemical Advisory Panel and his public activities on behalf of the interests of Institutes. Clear evidence of his positive impact on the Leaders was their adoption of his reductionist philosophy as the sole scientific basis for the research sponsored by the Institutes — they made it de rigueur guidance for all advisory panels. The Leaders also engaged Handler as their agent and advocate; he spoke on their behalf during meetings with congressmen and traveled nationally to give speeches that boosted the importance of the Institutes' sponsored research. The Institutes generously financed Handler's research activities at Duke and paid his salary through grants to the university. He continued to hold the title of chairman even though he spent so much time working for the Institutes that his first-author publication rate dropped to near zero, indicating his co-authors were primarily responsible for his pointillist publications. The largess of the Institutes also extended to Handler's departmental faculty, who were hugely successful in securing grants from the Biochemical Advisory Panel; his faculty outcompeted more productive but less politically connected biochemical faculties.

Handler's attitude toward the job of chair of biochemistry at Duke changed as he came to recognize that he was not in the same intellectual class as the chairmen at the prestigious universities. They were men whose quality of research provided intellectual leadership for their departments by conducting systematic purposeful high-level research that yielded major biochemical breakthroughs — a standard of excellence to which their faculties might aspire. The scientific skills and insights into nature of the famous chairmen far exceeded those possessed by Handler and he recognized that reality, calling himself a good biochemist perhaps, but nothing more. Just as soberly, however, he felt he had strengths that gave him the potential to be a highly successful chairman and have a positive national effect on biochemical research. He described himself as "an entrepreneur or operator," someone who "knows the important people in his discipline, knows where to find bright and talented young people, knows where to find the funds to support the activities of a growing department." Those abilities together with his talent for public speaking made him unique among his biochemical contemporaries, and his connection with the Biochemical Advisory Panel made it financially possible to build his department.

Handler received many grants, the management and execution of which the Institutes allowed him to assign to subordinates at Duke so that he could maintain his heavy schedule of service to the Institutes. He hired many new faculty members and required them to be self-sustaining independent investigators who obtained grants, managed their own laboratories, determined the question they would pose to nature, and designed the experimental approach they would follow. Handler's substantive biochemical thinking had minimal influence on their work because he had few ideas for new lines of research, but he rigorously enforced the productivity standards for his faculty's

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

promotion and tenure, mainly the size of grants obtained and the number of publications in biochemical journals. In Handler's value system, the highest and best research objective of an academic biochemist was the production of pointillist knowledge that passed peer review by a journal. He had no standards related to the scientific merit of a publication or to its benefit to society. In less than a decade after becoming chairman, Handler built his department into the richest and most politically powerful biochemistry department in the country, many times larger than when he first became chairman. He indisputably had far more clout in the national politics of biochemistry than any other biochemist, even those who had won Nobel Prizes.

WHEN AN OPENING OCCURRED ON the Leadership Panel, the Leaders offered the position to Handler which, although unsalaried, was an opportunity to directly influence national biomedical research policy. The offer crystallized his ambition concerning a higher calling than managing a biochemical department. He thought he was capable of much more, and he saw a promotion to the Leadership Panel of the Institutes as the next level, where the large ideas he had developed concerning national biomedical policy could implemented. Handler accepted the offer and moved further along the arc of his professional career, but technically he remained a full-time employee of Duke because his entire salary was paid by research grants from the Institutes. He kept the title of chairman but delegated most responsibilities and shifted his professional focus from North Carolina to Washington, DC.

From the outset of his time on the Leadership Panel, Handler assumed a central role in dealing with the scope of the mission of the Institutes and the size of its budget, which were the major issues confronting the Leaders. He thought the Institutes should position themselves as dedicated to the study of the biochemical intricacies of the human body, but not to determining what caused disease. He argued that causes of medical diseases were medical questions, and therefore not resolvable experimentally in the laboratory using the methods of science, but rather should be studied by physicians in the clinic. After Handler solved the Institutes' smoking-cancer problem, the Leaders recognized that a strict focus on treatment and cures, while avoiding causes, provided a firm and noncontroversial foundation for growth of the Institutes. The strategy obviated the need to address future questions concerning links between environmental factors and diseases by placing the questions outside the jurisdiction of the Institutes. The Leaders adopted Handler's position and decided it could be implemented automatically because the Congress had agreed that the Institutes could spend public funds on *any* kind of biomedical research approved by its advisory panels.

Handler reconceptualized the meaning of "biochemical research," as applied to the activities of the Institutes, and the Leaders again followed Handler's lead. Traditionally, the term had been understood the term to mean "applied biochemical research" — an activity motivated and guided by a useful societal purpose like finding a cause or treatment or cure for disease — which was the reason the Congress created the Institutes. For purposes of increasing congressional funding for the Institutes, Handler invented the term "pure biochemical research" to describe pointillist research motivated by the intellectual curiosity of the investigator, irrespective of whether the results had a

foreseeable use. Money budgeted for pure biochemical research, he said, would be used to satisfy any biochemically meaningful curiosity that arose as a result of the free play of the investigator's intellect. His metaphor for its effect on applied biochemical research was a tide that raised all ships. Handler also wanted congressional budgetary approval for what he called "biochemical education," which would allow the Institutes to indirectly support biochemical research in any way deemed appropriate by the Leaders. He envisioned the budget category as broad and multi-faceted; his examples included training new PhD biochemists and post-doctoral fellows, purchasing major scientific equipment, constructing research buildings, and paying university overhead expenses.

The Leaders agreed to ask the Congress to fund "pure biochemical research" and biochemical education, in addition to funding "applied biochemical research," the mission the Congress had specified when the Institutes were created. Left undisclosed by the Leaders was their intention to eschew research involving the causes of diseases and to seek only the treatment and cure of disease. Their intention to support only proposals based on the use of Handlerian reductive research methods was similarly undisclosed because the Leaders believed doing so was their prerogative. They depended on Handler's oratorical ability to argue their case before the congressional budget committees, and to overcome the unflattering image of biochemists as hogs rooting in the public trough — a metaphor that appeared in the conservative press after word of Handler's plan to seek funds for pure research leaked out. Handler's personal agenda was to establish pure biochemical research as the path leading to the recognition of biochemistry as the queen of bioscience — the fundamental aspiration of his career. He believed applied research was useful and popular, but that only pure research was intellectually ennobling and capable of achieving his career goal for biochemistry.

IN THE SPRING OF 1958, HANDLER testified before the senate appropriations committee as an expert biochemist in support of proposed expenditures for pure biochemistry research and for a national education program to produce more biochemists. The Institutes were forbidden by law from directly lobbying Congress for money, so Handler appeared in his capacity as a member of the governing board of the Biochemical Society. He said:

> Gentlemen, I have been sent by the members of the Biochemistry Society to discuss with you what we consider to be our most urgent and critical needs. The present request does not represent a reaction to sputniks. Let me explain. The clinician — the practitioner of medicine or surgery — is engaged in the practical application of that body of knowledge produced by biochemistry. Just as the engineer must utilize the fundamental information obtained by physicists and chemists, the clinician applies the information and techniques provided by biochemistry. Biochemists spend their lives seeking knowledge that is fundamental to an understanding of the normal human, and of those aberrations from the norm which we call disease. Let me illustrate. It was biochemists who discovered and identified the vitamins, discovered viruses, cortisone, antibiotics, insulin, drugs, and the link between fatty materials deposit on the walls of arteries and heart disease. Biochemists discovered the difference between a cancer cell and a normal cell — our hope of ultimately finding a rational basis for cancer chemotherapy. The request we make is that you provide funds to support pure biochemical research that simply seeks knowledge irrespective of the foreseeability of its relationship to health or disease. Future progress is utterly dependent upon increasing the level of this pure research activity.

Handler also wanted the Congress to allow the Institutes to pay PhD students who would actually do the pure basic research, so he sought funding for what he called "training grants." His idea was that established biochemists on university faculties who had Institutes' grants for biochemical research could seek additional money from the Institutes for salary, tuition, and laboratory expenses of post-graduate students who would work in the laboratories of biochemistry professors as apprentices. Handler said:

> The supply of young investigators is inadequate. The result of their probing curiosity is the very knowledge we need to understand and combat disease. It was Faraday's curiosity about the nature of electricity that ultimately made electricity our everyday servant. Carother's curiosity about certain organic compounds gave us nylon, the curiosity of Einstein, Bohr, Fermi, and Meitner about the nature of the universe which gave us atomic energy. Unfortunately, curiosity is not enough. As a research tool, curiosity must be sharpened, focused by long years of rigid training. At this time, it appears to be the supply of young investigators so trained in biochemistry which limits the rate of progress in pure biochemical research. If we, as a Nation, fail to recruit and train a sufficient proportion of our best young brains in biochemistry and to support their research activity, then your future appropriation of funds for research in the dread diseases will be in vain. Accordingly, I come before you to ask that appropriations for the Institutes for 1959 include at least $20 million to support pure biochemical research, that is, research which seeks only fundamental knowledge irrespective of a foreseeable relation to health and disease, and at least $10 million to support programs for training future biochemists to perform such research.

Handler testified that the country had only about five thousand biochemists and many more were urgently needed, but that the training was expensive. So, to complete their course of study the students needed to be paid. Doing so, he said, would have the added benefit of stimulating the growth of a new industry that manufactured special scientific equipment the students would need. He argued it would be pointless to authorize funds for research to cure disease if there were no biochemists to do the applied biochemical research to find cures and warned:

> If we, as a Nation, fail to recruit and train a sufficient proportion of our best young brains in basic research, then your future appropriation of funds for research in the dread diseases or for construction of medical research laboratories will be in vain.

One of the committee members was skeptical about Handler's budget requests and questioned Handler:

> Q: How much of the requested money would go to you?
> A: It would be between a quarter of one percent and two percent
>
> Q: Why complain? Apparently, your applications at Duke have been fulfilled.
> A: In the main, sir, yes. We have competed favorably for funds. This is based on the quality of our staff.
>
> Q: Is this the first time you have appeared?
> .A: Yes sir. This is the first time I have appeared. It is the first time anyone appeared.
>
> Q: How did this item get in the budget in the first place?

A: I don't really know this.

Congress approved only part of what Handler sought, but that meant the Institutes got millions of dollars it would not have received but for Handler's testimony. It only remained for the Institutes to systematically increase the size of the research-funding beachhead that allowed them to concentrate on pure basic biochemical research.

Handler returned to the congressional budget committees the following year, seeking more money for pure biochemical research. Testifying before a senate committee, he conceded he could not be objectively define what pure research was but asserted he knew it when he saw it:

> Defining pure biochemical research would be misleading because a definition neglects the forces that produce it, the training, discipline, values, way of life, and system of social control that motivate men to advance knowledge for its own sakes."

Instead, he told stories about past research including the recent award of a Nobel Prize to three American biochemical geneticists, intimating that what they did was pure research and not principally motivated by a desire to produce a public benefit. Handler promised that if he and other biochemists who shared his outlook regarding the prime importance of pure biochemical research were given more money for their experiments, they too would make great discoveries on behalf of mankind. "Please understand," he said, "this request does not merely reflect the vested interests of a group desiring to enlarge or embellish its own activities." When Handler encountered an assertion by a committee member that spending for pure biochemical research was mainly intended to fulfill the personal aspirations of biochemists, Handler replied:

> The fact that the prime motivation of those engaged in pure biochemical research is their own curiosity and, perhaps, only secondarily a desire to benefit their fellow men does not militate against support of their research. On the contrary, it serves only to assure us that such investigators will extend their utmost efforts in seeking to find answers to the questions which they have raised.

He acknowledged that his proposal could be called a give-away program for which biochemists could qualify formulaically, claiming "I have an idea, send money" and countered:

> I do not for a moment condone any unwise expenditure of funds. The Institutes' advisory panels pledged never knowingly to support the projects which seemed ill advised or improperly founded or investigators who are inadequately trained and incompetent. The people who sit on the advisory panels are honest scientists of great moral integrity. It would be repugnant to them to take any other course of action. I am quite serious about this. It might appear that I represent a vested interest, that I am a biochemist and I am talking about other biochemists, but the proposals claimed broad support within the biochemistry industry. We are hardly alone. As hardheaded and as practical a group as the board of directors of the Pharmaceutical Manufacturers Association believes exactly the same thing.

Handler reiterated his point that the direct beneficiary of pure biochemical research ultimately would be physicians, and he painted a picture of a physician as "nothing more than

someone who applies its results to the diagnosis and treatment of human ailments." Handler consistently drew a bright line between a biochemist, whom he characterized as a basic scientist, and a physician, whom he styled as a kind of clinical-oriented engineer who applied the knowledge generated by the biochemist in the same way ordinary engineers applied the knowledge generated by physicists. He said:

> May I remind you once again that pure biochemical research is fundamental to medicine and feeds information and techniques to clinicians and to investigators whose research is supported through the various categorical Institutes.

In further testimony before a House committee, Handler reiterated his notion that pure biochemical research was whatever the grant applicant proposed, as long as the research addressed the problem of understanding living things and was approved by the Biochemical Advisory Panel. He continued his rhetorical approach, offering heroic stories of scientific discovery as a rationale for giving the Institutes the freedom to fund biochemists to produce knowledge that might someday rationally guide the activity of clinicians — his pointillist philosophy of biochemistry writ large.

> It has been the result of pure biochemical research over the years which has taken medicine out of the Dark Ages. It has been this increased understanding of the nature of the human body, and its functioning which makes possible intelligent application of these findings and this is called the practice of medicine."

Handler sought more money for biochemists on university faculties so that they could train new PhDs — the principle he gained approval for the previous year. He said the plan was a feeder program to provide biochemists who would perform the pure biochemical research for which he was seeking funds as well as the applied biochemical research normally sponsored by the Institutes. Handler told the committee that "letting the well go dry" would be absurd and that the Congress was ethically obliged to fund biochemists:

> You cannot undertake biochemical research projects without the sheer necessity for undertaking biochemical education. If you believe, as I do, that the health of our population is our paramount concern, we have a moral obligation to do what we can.

Further, he said the Congress had a responsibility to underwrite biochemical education not only at the graduate level but also undergraduate and post-graduate levels, and at the post-MD level so that physicians could learn how to do biochemical research.

For two years, Handler had prepared and presented testimony in support of funding for biochemical research and education not necessarily related to health or disease. His actions were historically unprecedented in the history of US science policy; a private citizen, ostensibly unpaid, formally acting on behalf of a professional society and informally representing a federal agency, had never previously pled for money for the personal edification of the society's members, who were also the clients of the agency. Each year Handler was successful, and during his third year of testimony he took his boldest step. He asked the appropriations committees not only for approval of pure biochemical research that had no necessary instrumental objective, and for additional

funding for education to produce more investigators dedicated to performing such research, but also for the creation of a new Institute whose actual mission was to achieve exactly those objectives. He said:

> I urge that the Congress consider at this time the creation of an Institute whose exclusive purpose would be to fund "pure biochemical research," by which I mean biochemical research performed for the principle purpose of increasing human knowledge irrespective of any link to health or disease, and to train new biochemists.

He requested $40 million for the new Institute and explained it was needed because the existing Institutes were funding applied biochemical research related to specific disease. Those Institutes were doomed to fail, he said, unless their investigators were given the results of pure biochemical research so that cures could be found.

Handler carefully avoided tasking the new Institute he sought with the performance of pure biochemical research that could be used to find causes, and no committee member had the presence of mind to raise that glaring omission from the mission statement of the government's only agency devoted to biomedical research. Instead, Handler concentrated on making predictions of momentous discoveries the new Institute would make:

> All sophisticated scientists understand that it is only from pure biochemical research that we can obtain the information necessary to guide the disease-oriented research which, we hope, one day will alleviate the physical ills which beset mankind. This has been the entire history of medical progress in the past, and we are confident that it is in pure biochemical research that our hopes for the future must lie. We can hope, although we cannot promise, that pure biochemical research of genetic mechanisms will one day provide us with the means of treating and perhaps even of preventing the problems of cancer, heart disease, arthritis, and diabetes, all of which arise because cells have escaped from the normal genetic control of their metabolic activities. No true understanding of these problems is possible until we have a clearer picture of the mechanisms whereby the information coded into DNA is utilized by the cell in the normal regulation of its metabolic activities.

Prior to Handler's bold predictions, the Leaders expressed their concern that he was making promises — that the new Institute would make discoveries as significant as the discovery of genes and DNA — that were not credible. They also worried that trying to obtain money for an open-ended commitment to pure biochemical research without indicating what actual beneficial results might be expected would be difficult. When he testified, Handler adjusted his story rhetorically to made his inability to promise anything worthwhile sound like a benefit while simultaneously emphasizing the necessity of pure biochemical research:

> I must emphasize that it is not possible presently to foresee the practical application in clinical medicine of the results of pure biochemical research. In fact, quite the contrary is the case. None of us has a crystal ball sufficiently clear to reveal which of the fundamental studies of the structure and function of living things supported by the new Institute will provide the information which will underlie some great advance in tomorrow's medicine. The history of medicine is replete with examples of instances in which an unheralded fundamental investigation serves, years later, as the basis for an important advance in medical practice.

Handler addressed committee concerns about the cost of his proposed open-ended commitments to pure biochemical research by asserting that the Congress had a moral obligation to protect the health of the public, and that doing so would be cost-effective.

> It has been argued that the requested budget is too high. I disagree because I cannot regard the health of the people of the United States as a problem which you solve by balancing budgets. I recognize the need for financial responsibility on the part of the Congress, but the population of the United States is expanding very rapidly. Medicine has improved enormously during our lifetime, but it has a long way to go. The ill are still with us, our mental institutions are crowded, our hospitals are crowded. We are aware of the fact that the improved health conditions in our civilization are filling the population with people at the aging end of the spectrum and people who are a drain on society because they are incapacitated by illness. I submit that if pure biochemical research accomplishes nothing more than adding one more year of useful life to the life of every American, a year in which he contributed to society rather than as a drain on society, the economic gain would be simply enormous by contrast to the cost. We can't wait.
>
> In the long run, the proposal is a good investment. If General Electric didn't invest in the future, its competitors would drive them out of business. I don't believe as a nation we can afford to disregard what General Electric could not. If our research budget remains too low, research in other areas of the world would continue to be supported and we will be outpaced. We should do like DuPont during the depression when they increased their research and it created an enormous pool of scientific advancement. I believe a dollar invested in health research will do the same thing. It is very foolish to look at just the costs today and not at the long run.

Handler was the first on the Leadership panel to recognize that the jurisdiction and budget of the new Institute would be greatly expanded if aging were defined as an area of pure biochemical research, so that was what he did:

> The proposed Institute will support studies of aging, seeking to understand why and how we age and why and how the aging process renders us ever more susceptible to the ravages of disease with the passage of time. We are all aware of the rapid growth of our population with its skewed distribution in the upper age bracket. If pure biochemical research of aging can succeed in adding but one more year of useful, active life for each of us, a year in which we can contribute to society rather than be supported thereby, the economic gain for our nation will be enormous.

The Congress increased the Institutes' budget for applied biomedical research but did not authorize the creation of a new Institute, more or less as the Leaders had expected because on its face the idea seemed preposterous — the use of public money primarily for the avowedly private purpose of the personal edification of biochemists. Nevertheless, Handler had struck a responsive chord among biomedicine advocates on the committees', and during the ensuing months the Leaders received reports that his proposal had political legs, especially after the Biochemical Society lobbied heavily in its support.

A year later, Handler returned again to testify before the appropriations committees of both houses:

> Work to create the new Institute should be continued with the maximum of effort because the ultimate alleviation of disease is in the national interest. Anything we can do about it is worth doing, and the best place to begin was at the beginning, by funding pure biomedical research.

He continued to style the new Institute he sought as a feeder resource for all the other Institutes because it would produce the knowledge that grant applicants to the other Institutes needed to successfully perform applied biochemical research. The new Institute would also educate the new biochemists who would join the faculties of the nation's universities from where they would apply for grants seeking to perform applied biomedical research concerning specific diseases. Thus, according to Handler, from the new Institute "would come the information and the trained scientists necessary for the existing Institutes to vigorously pursue our national programs for the understanding and eradication of disease," by which he meant Handlerian reductive data, not the causes of diseases. "Eradication of disease" was Handler's code for curing disease. In other words, the new Institute would eradicate disease after it occurred as opposed to preventing it from occurring in the first instance.

The committees expressed concern that too many biochemists would be produced for whom there would be no available jobs, and that the government couldn't award a research grant to everyone. Handler confronted the issue of surplus biochemists by promising to institute a system of rigid competition that forced applicants to compete against one another, like hungry dogs fighting for a piece of meat. He said the new biochemists would participate in "a competitive national marketplace" for money from the new Institute which would be awarded strictly on the basis of scientific merit, as assessed by the Biochemical Advisory Panel, which he depicted as scrupulously honest and objective.

But Handler's testimony about the Panel's peer-review process was misleading, as anyone knows who has ever applied to the Institutes for a grant or witnessed the star-chamber process by which the Panel formed its decisions. In reality, its decisions depended much more on the biases, backgrounds, and beliefs of the panel members as it did on the merits of the proposal. Indeed, human nature being what it is, no other process could be expected because every Panel member effectively wore a Ring of Gyges that gifted them with invisibility to public scrutiny. No one benefited more from the Ring than Handler himself, beginning with his first Institutes grant which was authorized by a Panel that included his mentor when Handler was at Illinois, as well as friends from the Biochemical Society. All his subsequent grants were tainted by the cronyism facilitated by the Ring. Handler mastered the system for judging grant applications and used it to advance his interests and those of his university. During his testimonies , when he characterized how the Panel functioned, Handler belied reality, conjuring up an ethically perfect and reliable process that objectively assessed the difference between good and poor science. He never hinted that the Panel adjudicatory process was even slightly impacted by self-interest, a condition that was certainly not novel in the congressional world. The committee members, however, would probably have been shocked had they learned biochemists were no more honest than politicians because, in those days, that was simply not the way scientists were perceived by laymen.

Handler had strong backing from the organized biochemistry societies for the new Institute, all of which supported his goal of free unencumbered money that could pay salaries and research expenses at universities. Their attitude was that whatever the research rules were — reductive, integrative, cybernetic, epidemiological, clinical, or anything else — money was better than no money and they could learn to compete for and spend it. The medical and clinical societies mostly remained aloof and disinterested regarding the wisdom of a creating a new Institute, backing no particular dog in Handler's hunt for money. They used their political clout to prod the Congress to spend whatever money was necessary for whatever research was needed to find the causes and cures of cancer and other serious diseases.

The political climate was conducive to large anti-disease spending programs, but the Congress had no will to hold the Institutes accountable for how they went about their business producing their results. Mostly, the Congress simply accepted upbeat summary evaluations and lofty language from the administration of the Institutes about progress made against each disease. Handler anticipated that the new Institute would be expected to identify some questions or issues that it would resolve, paralleling the claims of the exiting Institutes that cures and treatments for each of the diseases were being sought. During his testimony, Handler listed some of the questions he said a new Institute would answer. "How does a nerve transmit its impulse?" was one such question, but the answer had already been provided by Hodgken several years before Handler testified. He promised an answer to "How does an electrical signal transmitted by a nerve make a muscle contract?," but Szent Gyorgyi had provided the answer a decade earlier. "How does the 'information' encoded in DNA direct the synthesis of proteins ?" Handler asked during his testimony, but the question had been answered by Watson almost a decade earlier. "How do cells convert food into energy?" had been answered By Krebs when Handler was still in college. The committee members were astute politicians, but quite naïve in matters of science, and neither Handler nor the other Leaders who were present during his testimony explained that they were faux questions because the answers were already in textbooks.

Handler similarly misled the committees by promising that the new Institute would answer the central unanswered questions in biomedical science that existed at the time, which he enumerated like a child's Christmas list:

> What is memory?
> What is learning?
> What controls appetite?
> What is aging?
> What regulates differentiation of embryo cells into the many cell types in the adult?
> What controls the reaction between an antibody and an antigen?
> How does the brain integrate and extract information from nerve signals?
> How are the metabolic reactions in a cell harmoniously integrated?
> How do bone-forming cells make bone?
> How does the body regulate the composition and volume of blood plasma?
> How do hormones cause their specific actions on their target cells?
> How do cells regulate their interior composition despite wide external variations

But the Institutes had already funded relevant research by the existing Institutes. Answers had not been found, but not because the questions were unconsidered. They were not found because the research methodology was limited by the Institutes to Handlerian reductionism, and the questions were unanswerable when the methodology was so severely restricted. When Handler said the questions would be studied for the first time and would be answered by his methodology, he lied twice.

When Handler appeared before the budget committees in 1962, the political decision to create the new Institute had already been made, and only the financial details remained to be decided. The Leaders recommended $192 million be added to the overall Institutes' budget for the new Institute, the President recommended $143 million, and the appropriations committees recommended $122 million. Regardless of the final amount, halcyon days for academic biochemistry appeared to lay immediately ahead, and Handler was ebullient, not an emotion he exhibited often. He told the senate committee:

> On Saturday morning last, it was my pleasure to serve as chairman and presiding officer over one of the largest biochemical meetings ever conducted in this country. It was in Atlantic City. The huge Convention Hall was filled. There were some 9,000 biochemists in the room. I consider it absolutely imperative that members of the Congress and all of the American people somehow develop an understanding of the bubbling contagion of excitement that now pervades biochemistry. We have come remarkably close to understanding what life is, perhaps as close as man is likely to come. These are the kinds of programs of research which are in being and will be continued by the new Institute. They could not possibly be more important. Nothing could possibly contribute more to our understanding of what man is and what his potential might be. If you gentlemen can see to it that we do not engage in some nuclear holocaust, if you can see to it that the population of this earth does not run riot, if you can see to it that we do not squander our natural resources but manage to conserve them in order to achieve a better life for our population, then the kind of information which biochemistry is now bringing to the American people will truly help us to achieve a better life in the future.

Later in the year, on the eve of final approval of the new Institute, Handler again appeared again before a committee, this time as conquering hero, like Julius Caesar returning to Rome after the Gallic wars, and he made one last attempt to gin up the size of the budget that would be authorized:

> I come before you specifically to discuss those provisions of the current bill which would create a full-fledged Institute to advance pure biochemistry research and education. I do so in the conviction that its programs, compared with the programs of all other Institutes will be, perhaps, the most important. All of the research supported by the other Institutes is focused on specific diseases and is derivative or applied in nature. That research assumes there exists a sufficient body of knowledge concerning the normal functioning of the human body so as to permit studying diseases. In other words, the research supported through the categorical Institutes is very largely derivative or applied in the sense that it addresses specific diseases of the human body. If one is to do so successfully it must be assumed that there already exists a sufficient body of knowledge concerning normal physiological function is perfectly understood. If this premise is not correct it is highly unlikely that research

> specifically addressed to those disease processes will likely be successful. The new Institute will have two purposes. One is to produce information and concepts and understanding of the human body. It is this body of information which will be made available to all others who seek to understand the problems of disease. The second to feed the categorical Institutes trained investigators. It is these two programs upon which all other programs at the Institutes must rest. These, I think, are the cogent and, I hope, compelling reasons for creating the Institute.

The Congress chose "The Institute of General Medical Sciences" as the name of the agency it was creating. Handler objected furiously. He thought the Medical Science was an oxymoron, like gay death, and would be an impediment to what he was trying to accomplish because, he testified, the name commingled two very different things — medicine and science. He said there was a bright line, between pure biochemical research and applied biochemical research which he called "technology," and that medicine was a form of technology. He emphasized his point by telling a story about Einstein:

> Although knowledge generated by both pure biochemical research and applied biochemical research is important, knowledge from pure biochemical research is seminal and hence more important.
>
> An event from physics shows this to be true. Only after Einstein, performing pure physics research, had shown $E=mc^2$, the equivalence of mass and energy, could the applied physics research that yielded nuclear weapons have been performed. Just as there could be no nuclear weapons until the knowledge generated by pure research was first discovered, so too there could be no medicine until biochemistry produced the basic knowledge on which it is based. The analogy is completely apt.

Handler emphasized the depth of his belief in the primacy of pure biochemical research and its separateness from clinical medicine by telling a personal story about his wife, who he said was "one of the half million people who have multiple sclerosis," and was "just about ready for the wheelchair stage." Nevertheless, Handler said, "I wouldn't myself today attack the problem of multiple sclerosis." He said he would first conduct pure biochemical research on "the cells responsible for making myelin which disappears in patches along the spinal cord of people with this disease." If that process were understood, he said, understanding multiple sclerosis deductively, from a hypothesis, might be possible.

In the end, a new Institute with oxymoronic name was created. A budget of several hundred million dollars was authorized to support biochemical research and train new biochemists.

DURING HIS SERVICE ON THE Leadership Panel, Handler reconceived biomedical research as a combination of applied biochemical research performed by grantees of the existing Institutes and pure biochemical research performed by grantees of a new Institute, and he constantly struggled to teach the Congress about the difference between the two kinds of research. He envisioned the new Institute as the government's continuous source of the pure biochemical knowledge that was needed by the existing Institutes to "discover knowledge needed to cure disease and help understand how the body works." In the course of his efforts to strengthen the Institutes and the Biochemical Society, Handler became the first scientist in history to repeatedly testify about science before

congressional budget committees, most of whose members knew little about science, a lack of knowledge that afforded Handler the latitude and longitude he needed to testify like a Pinocchio, which he did with impressive technical sufficiency. His habit, prior to appearing before any committee, was to send a meticulously prepared written statement of his opinions, and during oral testimony he showed himself able to precisely identify the location of a particular point without fumbling to find it, a skill that greatly impressed the committee members. There were no rules governing the content or validity of his testimony, and no witnesses who presented differing viewpoints or gave testimony that moderated his flights of language that excessively lauded the methods and motives and accomplishments of science. Each year he appealed for even more money to fund pure biochemical research and for the professional freedom of biochemists to perform any research they thought best, irrespective of foreseeable social benefits. Unabashedly, Handler identified himself and other biochemists as the primary beneficiaries of the requested largess, but argued that taxpayer funding of pure biochemical research and education was appropriate because the public would ultimately benefit.

After more than four years and numerous testimonies, Handler thought he had achieved his goal, and for a brief period he experienced what for him was a rare emotion — professional contentment. He recognized that modern biochemical research was resource-intensive, and could survive only by depending heavily on the government for money. The law requiring the traditional Institutes to sponsor only applied biochemical research effectively made biochemistry a department of the federal government. However, Handler accepted government control of biochemistry in return for generous public funding of biochemical research and education, and creation of the new Institute where biochemists would be free of government instruction regarding their work. Handler believed that, because of his efforts, at least some biochemists could expect grant support for a lifetime for research they found worthwhile, irrespective of whether the results had any societal benefit. What he thought he had achieved was a situation wherein the government would pay the piper but the piper would call the tune.

Handler was recognized as the only biochemist who could have secured creation of the new Institute because no one else had his stature, silver tongue, and ability to project wisdom to laymen. His status as the chairman of the biochemistry department at Duke, head of the Biochemical Society, and an expert consultant to the Institutes had clearly impressed the members of the budget committees. His life-long practice of reading avidly, his photographic memory which enabled him to recall verbatim what he had previously said or written, his instinct as a good storyteller, and his ability to accommodate the interests and sensibilities of the committee chairmen all fused to create a witness perfectly matched to his forum. He presented scant evidence to supported his opinions, offering only naked averments, and constantly argued that the federal government had a moral obligation to fund both forms of biochemical research. But he did it all extremely well. The committees had as much resistance to Handler's charm as the Incas did to the diseases brought by the Spanish.

Handler thought he had fulfilled his deepest desire, but he was wrong. Very soon after the new Institute was created, strong political pressure required the Leadership panel to promulgate an

official policy that every grant funded by any Institute or approved by any Advisory Panel must serve an identifiable public purpose state a foreseeable public benefit. Handler had sold blue sky to the Congress, that Handlerian reductionism enforced by a new Institute dedicated to personal biochemistry would mass-produce world-class pure biochemical research that would elevate biomedicine to great heights. But his achievement was transient. Formally at least, there would be no authorized pure biochemical research paid for by the Institutes. Informally, however, the new official policy was undercutable by skilled grant writers, a fact that partially cushioned Handler's disappointment; grant applicants could continue to tell transparently contrived lies that satisfied the legal requirement of a foreseeable application to human health, as was the practice in all the other Institutes.

THE NEW INSTITUTE QUICKLY became perceived as an undemocratic development because the Institutes' budget came from taxpayers but its mission was elitist — the personal edification of biochemists. Handler's initial thrust into scientism, consequently, was soon blocked — new policy directives dedicated *all* Institutes to advancing biomedicine, not biochemistry itself. Although Handler failed in his attempt to create an Institute dedicated to advancing biochemistry, he succeeded in other areas of biomedicine where the democratic outcome would have been for him to similarly fail. But he didn't. By succeeding in his mission, Handler adversely altered the evolution of biomedical research during the last century — like the cloud from an asteroid strike that blocked the sun and killed the dinosaurs .

By force of his will, with the benefit of propitious historical timing, Handler established the policy of the Institutes that both pure and applied biomedical research were activities founded on the conception of the human body as a collection of independently observable biochemical parts governed solely by chemical laws. From his perspective, biochemistry had been raised to the intellectual plane of physics. His achievement was real but inherently impermanent because physics has four sets of laws that predict everything about inanimate matter, whereas Handlerian reductionism had no cognitive basis and predicts nothing. Nevertheless, pursuant to their policy, implementation of his biomedical principle was heavily financed by the Institutes, which simultaneously refused to fund all competing principles. The situation was avidly supported by multifarious biochemical societies for whose members Handler always made money. Handlerian reductionism prevailed — at least up to now — over deserving but seriously underfunded biomedical principles that he strangled by blocking their financial support, like a lion killing the progeny of other males.

Handler employed "biochemical mechanisms" as a term of art in pure biochemistry to describe its fundamental concept of what caused disease, its fundamental fact — like physics employed "force" to explain motion. A corollary he deduced from his reductive principle was the proposition that diseases do not have causes, they have "biochemical mechanisms." He identified three classes of biochemical mechanisms — those arising from toxic chemicals, bad genes, and proteins that allowed infectious agents to enter the body — and asserted that their respective mechanisms explained all disease. Handler's corollary yielded no benefit for biomedicine, but it benefited the Institutes by stabilizing their existence as a vehicle for giving grants, and biochemists

who earned enough grant money to feed their families by conducting never-ending searches for the chimeric biochemical mechanisms.

Important developments in biomedical research occurred outside the orbit of Handler, the Institutes, and the biochemical societies. The work of HANS SELYE, a physician and probably the most important biochemist of the last century who did not receive a Nobel Prize, was one such instance. Selye took seriously the obvious fact that the numerous types of tissues in the body communicated with one another by means of chemical and electromagnetic energy, and in his laboratory and clinical experiments he asked how the interactions were related to health and disease. His experiments, which were funded by private philanthropies, were of the type that allowed direct study of the interactions among the tissues, as distinguished from the single-tissue studies Handler advocated but Selye regarded as inadequate for answering the most important biomedical questions — the only one that interested him.

When Selye began practicing medicine, his observations of patients led him to question an aspect of the method of diagnosis and treatment of disease that was based on the identification of clinical signs observed by the physician and the description of symptoms by the patient which, taken together, were assumed to be specific for each disease. Selye asked why patients with widely different diseases exhibited a common set of signs and symptoms that included musculoskeletal pain, headache, temperature, changes in blood cells and metabolites, listlessness, and insomnia. Motivated by the idea that answering the question might improve clinical treatment, he used laboratory animals to study the essential aspect of what he observed — that different diseases could cause the same clinical responses. Selye exposed animals to different physical agents, which he called "stressors," that were known to cause physiological changes; the stressors included heat or cold, toxic chemicals, trauma, food or water deprivation, housing in crowded conditions, and too much or too little exercise. He found that the stressors caused a common response pattern that encompassed pain, changes in tissue anatomy, alterations in particular blood metabolites and cells, and specific effects on heart activity, kidney and lung function, and body temperature. In his experiments, he identified the particular biochemical agents that moved among different tissues throughout the body to cooperatively bring about the system-level responses. Selye's research was highly disfavored by biochemical orthodoxy — Handler, the Institutes, and the biochemical societies — which generally regarded his work as unimportant and useless, like studying the effects of dirt. Nevertheless, he had discovered the extraordinary fact that the effects of a diverse range of stressors were mediated by a cascade of specific biochemical and electromagnetic interactions among hormonal, immune and neural tissues. Contrary to orthodox dicta, no single biochemical agent was solely responsible for any specific effect. Selye's observation that a group of interacting biochemical agents were cooperative causes of system-level effects contradicted Handler's theory that disease causation was a simple mechanistic process.

During further experimentation, Selye discovered that psychological factors could also be stressors. He found that fear, anger, and anxiety elicited a biochemical response pattern similar to that triggered by non-psychological stressors like heat, cold, toxic chemicals, and trauma. The ability of both somatic and neurogenic stressors to elicit the same internal signals led Selye to develop a

theoretical framework for explicating the biomedical significance of the stress-response system. He hypothesized that evolution had conferred on humans the ability to defend against harmful agents and influences in many different ways, and that any factor which weakened one of the body's defenses could, depending on the circumstances, be a contributing cause of any harm that subsequently developed, including but not limited to disease. In effect, according to Selye, disease could have multiple causes in the sense that it wouldn't have developed when it did but for the presence of a particular cause. In the vocabulary he developed to communicate his framework, a "stressor" was a physical or psychological factor that initiated a physiological response consisting of a change in the homeostatic levels of one or more biochemical agents, and "stress," which was related to the strength of the changes, described their cumulative internal force that drove the response. Selye used "resistance" to describe the body's ability to oppose changes in homeostatic levels of biochemical agents, and "adaption" to describe the process of accommodating changes in the levels initiated by a stress that successfully avoided occurrence of harm or disease. Thus, using Selye's terms, a stressor caused stress which initiated resistance, resulting in either adaption — the teleological process for maintaining homeostasis which was the condition of health — or disease if homeostasis were sufficiently disturbed.

Selye showed that adaption was a continuous process that maintained homeostasis by initiating and controlling appropriate responses to stressors. In his experiments, a cold stressor initiated a shiver response and a heat stressor initiated perspiration. According to Selye, the unique set of stressors in the external environment combined with those in an individual's internal environment that reflected past behavior including food, drugs, and previous diseases, all taken together, determined whether homeostasis was successfully maintained. By continuous changes in the balance of a range of biochemical and electromagnetic signals, the adaptive process mitigated damage from the totality of the stressors to which a subject was exposed. If a maladapted state developed, the unique mix of stressors would determine the particular pathological result. In other words, according to Selye, Handler's mechanistic theory of disease causation was a gross and misleading oversimplification.

Stress was a qualitative factor that affected the dynamic balance of the body's tissues — a system-level phenomenon rather than a simple parameter like the level of a biochemical agent. Study of stress perforce required system-level experiments. Handler, however, who did not recognize the validity of non-reductive experiments and particularly disapproved of Selye's research, surveilled grant applications to the Institutes and insured Selye went unfunded. Nevertheless he persisted. Selye's consistent progress in explaining the clinical reality faced by physicians further angered Handler, who regarded Selye's work as a marginalization of the importance of pure biochemical research and an elevation of teleology and other nonbiochemical principles. Handler and the academic biochemists who followed his lead took overt acts to marginalize the biomedical significance of Selye's concept of stress. Their opposition restricted Selye's access to research funds and denied him recognition in their textbooks, which promoted Handler's theories and his perspective on the purpose of biomedical research. The unremitting antagonism of the biochemical orthodoxers slowed but did not stop development of Selye's stress concept and its recognition as a seminal principle in clinical medicine. Selye published many papers and books and vigorously

promote medical and popular awareness of stress, and managed to survive, although he could not prevail in Handler's purely reductive world of biomedicine.

Ironically, Selye, who operated a clinic for treating patients suffering from stress, was probably one of the few physicians then who could have treated the medical problems Handler had developed. He had neurological symptoms since college and serous allergies that developed after he began his experiments with animals. He worked long hours, had few friends, followed an idiosyncratic diet that left him rail thin, and manifested occasional fits of unprovoked anger, but he self-medicated for all his ailments because he distrusted physicians.

FRANK BROWN was a biology professor who sought to understand the natural behavior of animals that lived in the intertidal zone of the northeast seacoast. His research asked questions and used methods that Handler highly disfavored and ultimately succeeded in thwarting. Brown observed the Fiddler crabs could change their skin color and discovered they did so by means of hormones rather than neural regulation, as had been supposed. He then studied what regulated the rhythm of the change in color, which changed from dark to light in synchrony with the 24-hour cycle caused by the earth's rotation. What particularly interested Brown was that the clock hours when the skin was the darkest and lightest advanced fifty minutes each day, matching the rhythm of the tides. The crabs also displayed a tidal rhythm in activity; at each low tide they scuttled from their burrows onto the beach that had been exposed by the receding tide and then returned as high tide approached even though they could not see the ebb and flow of the sea.

Funded by his university and the U.S. Navy, Brown found that the color rhythms persisted after the crabs were housed in his laboratory under constant illumination, indicating that they could keep track of time even without environmental light signals. The rhythms in the laboratory were no longer precisely 24 hours but rather a few minutes longer or shorter depending on the animal. Brown hypothesized that crabs had a genetically-determined clock that measured time, and also genetically-determined rhythms of approximately 24 hours whose precise timing was determined by natural signals in the environment. He verified his discovery of an animal clock when he flew some crabs from the east to the west coast and showed that their rhythms remained the same as those of crabs on the east coast, meaning that the ability of the crabs to measure time did not depend on the rotation of the earth.

Light was the obvious timing signal for hormonal regulation of the skin-color rhythm, ensuring that it was exactly 24 hours, but the timing signal for the activity rhythm was unobvious because the crabs could not see when high and low tides occurred. Based on experiments, Brown eliminated the possibility than any natural geophysical signals known capable of affecting animals could be responsible for synchronizing their innate activity rhythm with the local 24-hour clock. He recognized that the putative signal had to have unique physical properties: exhibit two cycles each 24-hour period at every location on earth; easily pass through the walls of a laboratory; exist during the evolution of life, allowing ample opportunity for the rhythm to become encoded in the genes of the crabs. Brown rejected advice of biochemists that he concentrate on the problem of identifying the biochemical oscillators that created the genetic clock which the crabs used to measure time.

Instead, he asked a question that had broader implications — the nature of the environmental signal that allowed the crabs to synchronize their rhythms with the cycle of the tides.

Brown speculated that electromagnetic energy provided by the geomagnetic field was the timing signal because it alone had the necessary physical properties and tested the theory using oysters, which also exhibited an activity rhythm in synchrony with the tides. Brown confirmed that when housed in a laboratory under constant illumination, the oysters maintained the rhythm of opening and closing their shells in synchrony with the local tides. He then flew oysters from the east coast a thousand miles westerly and observed that they gradually adjusted their open-close cycle to coincide with the tidal pattern that would exist if their location were a seacoast, supporting his hypothesis that the local geomagnetic field was the timing signal. In actuality, Brown had uncovered the first evidence that animals had a sensory system in addition to the eye for detecting natural electromagnetic energy and transferring information in the detected signal to the brain, permitting it to orchestrate appropriate behavioral responses. Unfortunately for Brown, the scientific environment in which he worked was strictly oriented toward biochemistry and not receptive to the pursuit of questions framed in other scientific specialties.

Using snails from the intertidal zone, Brown directly tested the theory that animals could detect changes in the electromagnetic energy contained in the earth's magnetic field. He placed snails in a box with an exit facing magnetic south and verified that they displayed a tidal activity rhythm identical to that of the free-living snails, turning westward early in the morning as they came out of the exit, eastward at noon, and then westward again in the early evening. When Brown positioned a bar magnet beneath the exit and oriented the magnet to increase the natural field, the angle of the snails' turned increased. Rotating the magnet, which had the effect of altering the extent to which the natural magnetic field was changed, also changed the angle at which the snails exited the box, showing that that the snails had the capability of detecting electromagnetic energy, as Brown had supposed.

In further studies of the effects of electromagnetic energy on the responsiveness of animals, Brown proved that snails, flatworms, and Paramecium were extraordinarily sensitive to natural levels of the energy, as evidenced by changes in their behavior in response to small changes he made in their local electromagnetic environment. Characteristically, the animals did not respond until enough time had elapsed to allow them to accommodate to the new energy level that he imposed on them in the laboratory; when he made unnaturally large changes in the in the energy level, the organisms did not respond at all. He found that animals could differentiate the natural periods of change of electromagnetic energy in the atmosphere from the small fluctuations that occurred in association with changes in in longitude and latitude, an ability that could enable organisms to use the earth's field as a compass.

Brown's research showed that animals had inborn clocks, inborn rhythms, and inborn sensory systems, three related but different things, and that the sensory systems detected not only light but also natural and man-made electromagnetic energy. His discovery of an animal electromagnetic sense had a dramatic effect on natural biologists, resulting in field and laboratory studies by many investigators that showed birds, insects, fish, bacteria, and even the platypus, a

mammal, were sensitive to environmental electromagnetic energy, and employed the information in the detected signal for purposes of migration, orientation, and prey-location. However, from among the multiplicity of questions that Brown's novel insight raised, the only question that seriously interested Handler and other biochemists involved the biochemical nature of the clock and the rhythm, which they mistakenly assumed were the same thing. The biochemists embraced the existence of biochemical clocks but fanatically denied the possibility that external information other than light signals was needed for the clock to function as a physiological regulator. A heritable system of biochemical oscillators that measures time and facilitates rhythmic physiological activity was eventually discovered in the brain, but otherwise, Brown's work had nil effect on reductive biochemists. From their viewpoint, whatever a living organism did was determined solely by its chemical properties, not something in the environment; electromagnetic energy was especially objectionable for reasons of historical bias and because there was no proven detecting organ except in the platypus, fish, and bacteria, which the orthodoxers regarding as irrelevant to human biology.

No contemporary biochemist made an attempt to repeat Brown's experiments involving electromagnetic energy, apparently believing that the experiments were wrong on their face because electromagnetic energy was biologically insignificant. Brown's most vociferous critic was a friend of Handler's, J. Woodland Hastings. He regarded the clock and the rhythm as the same thing, and argued that the clock was a completely self-contained timer, not a forced response to a geophysical agent but a self-regulating property of the biochemical activity inside animals and humans, plants, and plankton. Repeatedly, in print and at meetings, Hastings claimed that Brown's work on energy biosensitivity was unsound and that "the property of being sensitive to a hypothesized exogenous geophysical cue whose putative effect is that of providing time information of some sort is not supported by evidence." Hastings faulted Brown for failing to explain the biophysical nature of the clock mechanism that was sensitive to geophysical factors, and urged that "the hypothesis should be viewed with the greatest skepticism."

ROBERT BECKER was the son of a Lutheran minister who grew up a few miles from where Handler lived and achieved a national reputation for nonbiochemical biomedical research. After serving in the Army during the Second World War, he married a woman he met while they were in medical school and became an orthopedic surgeon. The work of Dubos and Selye and Szent Gyorgyi impressed him greatly because of its science and humanism, factors that seemed to him to be directly relevant to the welfare of his patients. By the end of his formal training, Becker had become deeply interested in the scientific basis of the healing process itself. He wondered how the body knew a fracture had occurred, what initiated the healing response, how it was controlled, how the body knew to grow arm bone in the arm and leg bone in the leg and not the other way around, and what ended the process after healing was complete. He considered the final result amazing, the growth of new bone that was indistinguishable from uninjured bone, the exact replacement of what was lost, true regeneration. The questions that occurred to him were unstudied except by biochemical and microscopic analyses, but he considered attempts to understand growth and healing using only those methods to be like diagnosing patients by analyzing their footprints.

Becker worked his entire career as chief of orthopedics at a hospital in Syracuse operated by a federal agency that provided medical care for military veterans, and at an affiliated medical school where he was a professor. He accepted the position the same month he finished his orthopedic residency because the agency promised to provide him the opportunity to do research. After studying the publications of Burr, Szent-Gyorgyi, Brown, Morgan, Singer, and Bullock, Becker speculated that electromagnetic energy, independent of the neural activity responsible for sensory perception and muscle action, was fundamentally important in controlling growth and healing, and he conducted experiments accordingly. He measured slowly varying electromagnetic signals that occurred on the skin of salamanders, as Burr had done but, with the intention of understanding where the signals came from. Becker showed they were not located randomly but rather followed a pattern that corresponded to the anatomical organization of the salamander's nervous system. He envisioned the signals as somehow originating in nerves and forming the working part of a control system that shuffled regulatory information around the body by means of a flow of electromagnetic energy. He believed the system was centered in the brain, where control algorithms were located, and that it was connected by the energy flow to regional processes that mediated growth, the prototypes of which for him were the automatic healing of a bone fracture in humans and the innate ability of salamanders to regenerate an entire limb.

Becker's first observations in experiments designed to test his idea were that the signals on the skin disappeared after he cut the animal's spinal cord at the level of the brain stem, as expected under his theory. Leaving the spinal cord intact but sectioning the nerves at the point they exited from the cord and passed into the limbs caused the signals on the skin of the limbs to drop to near zero within a few seconds, again, consistent with his theory. He next tested the aspect of the theory that an energy flow mediated healing. Knowing that salamanders and frogs reacted differently to the loss of a limb, Becker amputated a hind limb in animals of both species and measured the injury-site signal that occurred daily as healing ensued after amputation. Post-amputation healing differed significantly between the species, as expected — a stump in the frogs and a new limb in the salamanders. The post-amputation flow of electromagnetic energy also differed significantly between the species, as Becker predicted under his theory. He interpreted that observation as evidence that the signals in the nervous system were an integral part of a data transmission and control system that regulated regeneration. His basic idea was that information carried by electromagnetic energy transmitted by nerves occurred as a consequence of the amputation injury triggering accumulation of cell types capable of organizing into a new limb in salamanders. In this fashion, brain-sourced electromagnetic energy was linked to cells in the limbs in a closed loop that fed information back to the brain during the healing process, thereby progressively blunting the effect of the initial stimulus produced by the injury. But similar information was absent from the signal in the frog, which was slightly more advanced on the evolutionary scale compared with the salamander. From Becker's perspective, the frog had the cells necessary to regenerate a limb but lacked only the necessary encoded information. Inasmuch as frogs and even humans had the same cells, the difference in response he saw meant to him that someday humans might be able to grow new limbs, if the necessary signal could be introduced as a form of treatment to compensate for the tradeoff

mammals made as they evolved, developing larger brains but losing some primitive healing properties.

Becker and his colleagues observed that slowly varying electromagnetic signals could also be measured on the skin of humans, and that the measurements changed in characteristic ways during sleep and anesthesia, just as they had observed in animals. He published a study in *Science* showing that strong magnetic fields affected the flow of electromagnetic energy in salamanders, an observation that had two implications for him. First, that the energy flow involved the motion of electrons not ions — a revolutionary idea in biology at the time. Second, that earth's magnetic field might also be able to cause a similar effect, thereby serving as a link between living organisms and the environment.

Becker's research had been supported by the local hospital where he worked. But after he presented his results at national conferences and published them in prominent journals, he was invited by his agency's research officials in Washington to submit a research proposal with a far larger proposed budget. At the time Handler was a consultant to the agency for biomedical research, but he was not asked to review Becker's proposal because it was nonbiochemical, and Becker was awarded the grant.

In 1961, at a national symposium on magnetic fields, Becker delivered an invited presentation and summarized the experiments he and his colleagues had done. They correlated fluctuations in the earth's daily magnetic intensity with the daily rate of admissions to two Syracuse hospitals, over a period of four years, and concluded the results suggested there was a relationship between the instances of psychiatric disturbances in the human population and changes in the geomagnetic field. Becker described experiments he thought revealed the physical basis of the relationship. He told the audience he suspected the nervous system was involved, and described the results of experiments on salamanders and frogs as supporting evidence. He anesthetized the animals and measured the flow of electromagnetic energy transported by the nerve fibers. Along the nerve fibers that transmit sensory information, the energy moved in one direction. Along the nerves that command the muscles to move, the energy flowed in the opposite direction — apparently the complementary half of the complete circuit that could react to magnetic change. It was undoubtedly true that the flow of energy Becker measured, which varied at any given point on the skin very slowly with time, was a fundamentally different electromagnetic phenomenon compared with the well-known sensory and motor nerve impulses. He and his colleagues believed they had discovered mankind's most primitive regulatory system — the system that was the means by which the environment originally instructed mankind's ancestors regarding which behaviors were optimal for survival. As evolution progressed, living systems grew more sophisticated, and the faster impulse system that makes man rational, reflective, and resourceful gradually took over the body's controls systems. But beneath the surface the ancient data transmission system continues to direct man, particularly as regards the flow of information that controlled growth and healing.

Perhaps the most important aspect of the research Becker described was its implication regarding how electromagnetic energy moved through the body. It had been believed that any electromagnetic energy moved through the body did so via motion of ions in the body's watery milieu. If so, freezing a section of the nerve would be expected to stop the motion of the ions,

thereby creating an open circuit in the energy flow. But Becker found that freezing actually increased the energy flow, as it would if the flow were carried by electrons rather than ions. Therefore, the evidence suggested, Becker said, the ancient electromagnetic regulatory system worked through a tissue analogue of the transistor.

Handler saw himself as the capstone of a century-long process that established the specialty of biochemistry as the sole source of objective biomedical knowledge. He had no illusions that he contributed meaningfully to the process of knowledge generation. He did imagine, however, that he was responsible for establishing the definition of biomedical knowledge and the financial system of governmental support which ensured continuation of biochemical research. Handler viewed pure biochemical research as the driving engine for the applied biochemistry physicians needed to cure disease based on scientific principles. He used his rhetorical skill and political clout to surround his beliefs with a defensive wall of hype, myth, denial, and aggression toward those who had a different perspective, and he was largely responsible for the meteoric budget growth of the Institutes. He repeatedly told the Congress that progress in solving the mysteries of health and disease was completely dependent on the freedom of biochemists to choose what research should be done. On two levels, however, what he said was the greatest lie in the history of biomedical research because the solutions weren't dependent only on biochemistry or on the freedom of biochemists. But he repeated the lie incessantly and it worked.

Handler labored to ensure that academic biochemists received robust government funding for their research but were not shackled by the principle that their work be primarily concentrated on meeting the needs of society. According to the gospel he preached, pursuit of research in the purest realms of biochemistry would ultimately yield the basic knowledge needed to ensure the health of the nation. He seductively manipulated then widely held beliefs by the public about the integrity of science, asserting that "the free play of free intellects" of biochemists would provide the knowledge that the nation needed to confront the challenges of the future. The politicians responded by delivered generous levels of taxpayer funds to biochemists, allowing only them to choose the research they did and evaluate its value. Any governmental efforts to guide the course of biochemical research, the Institutes told congressional budget committees, would interfere with its free and unpredictable advance.

During his testimonies, Handler frequently pointed to historical successes of biochemical research, and used the stories to bolster his position that biochemists should be left alone to decide what research should be done. Allowing them to make their decisions in secret was necessary, he argued, to ensure there was no outside influence. In all his stories of past successes, however, the research was successful because it had a specific public benefit as its objective, which channeled and shaped the activities of the investigators, not because they were free to do what they thought best, as Handler falsely intimated to the budget committees. So, outside influence was the driving force behind the success.

Initially, Handler persuaded the Congress to create a new Institute dedicated to pure biochemical research, chosen solely by biochemists for the purpose of generating basic knowledge they thought was most desirable. The decision was quickly reversed, however, not because the

Congress recognized Handler's argument was based on casuistry but because its decision was bad politics — giving away public money for the private purpose of personal edification. Although the reversal enraged Handler, he decided it wasn't the hill he would die on. He had successfully hidden from the Congress the changed policy of the Institutes to forgo all attempts to understand the causes of disease, and he recognized that openly challenging the Congress on the personal-freedom issue would shine light on the Institutes' covert decision to avoid causal research, a potential public-relations disaster for continued stable governmental funding of biochemical research. Consequently, although he demurred, Handler went on to other policy issues.

Prior to Handler, discovering new knowledge pertinent to particular human needs was the motivation for all biochemical research concerning human health and disease. During his time at the Institutes, human need also set the agenda for all biomedical research, but only formally and superficially. In reality, the situation was complex. For most Institutes-funded research, if approved by an advisory panel, biochemists were given the money they requested and left undisturbed, unsupervised, and unmonitored in their university laboratories to do whatever research they thought best, irrespective of whatever they initially told the Institutes they would do. The rationale for permitting investigators to change the research objectives at will was that such flexibility was needed to respond to latest results obtained by the investigators. Thus, even when the investigator employed the naked-lie gambit to get a grant, effectively, they were free to proceed according to their own lights. Handler believed that the system of effective intellectual freedom of grantees would inexorably produce what society needed — but it didn't In the absence of connection with and direction by the public, biochemists began mass production and publication of abstractions, that were entertaining for the biochemists but of no necessary purpose or utility in the world, like developments in mathematics. Handler's lie went unrecognized and, as a consequence, the biomedical research sponsored by the Institutes was corrupted.

Corrupted in what way? To a preponderantly large and undemocratic extent, Handler's maneuvering gave biochemists a free rein to do whatever research they wanted to do for whatever reason they wanted to do it. They had carte blanche to define what progress was with reference only to other biochemists and without considering its impact on the world beyond themselves. Inasmuch as there was no measure for progress outside biochemistry itself, objective assessment of whether biomedical knowledge was advancing or standing still was not possible. Handler exploited this corrupting consequence of his great lie to tell his stories and, unsurprisingly, he always concluded that biochemists had made progress. In his eyes, every experimental initiative supported by the Institutes was a success, and every resulting peer-reviewed publication was a positive contribution to human knowledge. He never critically analyzed any publications but rather only sought more money for more such publications and pointillist biochemical studies flooded the scientific literature. He believed that more pointillist research and more peer-reviewed publications and more funding were always steps in the right direction, and the Institutes channeled money into the willy-nilly production of unverifiable facts that were irrelevant to any meaningful unanswered biomedical questions. The pointillist biochemical research system Handler built, with its emphasis on the "free play of free intellects," didn't help alleviate human suffering, at least not in any way that was objectively measurable. The promised cure for cancer never materialized. Rather than producing the biomedical

knowledge that would allow physicians to control and treat disease, what developed was a pattern in which almost every pointillist publication was opposed or contradicted by another publication, rendering their totality dubious or worse, like a circular firing squad. His lie resulted mostly in an aporia not in progress.

Handler believed the organizational structure of biomedical research he created at the Institutes was self-correcting and inexorably led to permanent truth. Actually, the system had many limitations and was as much self-destructive as self-correcting, mostly because he systematically opposed and silenced voices of criticism and complaint. The upshot was that the Institutes turned biochemical research into an Kafkaesque enterprise, as shown by their treatment of the ideas and work of numerous investigators including but not limited to the work of Dubos, Wolff, Szent-Gyorgyi, Burr, Wiener, Shannon, Prigogine, Selye, Brown, and Becker.

Handler's political base consisted of university biochemists, whose professional goals were promotion and tenure, which depended on obtaining grants from the Institutes that, in turn depended on publishing pointillist studies. But Handler could not bring federal money into the system fast enough to feed all the PhDs his policies produced. There ensued ruthless competition among biochemists for funds and professional recognition, resulting in chronic low-level internecine warfare within the specialty. The only biochemists assured of survival were those on the Biochemical Advisory Panel and journal editorial boards, and their colleagues and former graduate students. To get research done, the privileged biochemists needed graduate students and postdoctoral fellows to help perform experiments and collect data; consequently, the biochemists competed against one another for the best students as well as for Institutes funding. The overall system of biochemical research that resulted favored aggression and disfavored collegiality, which pleased Handler. During his testimony he boasted it was advantageous for science because, "The system ensured that only the best survived."

When competition among biochemists became desperate after Handler began losing his budget fights with the Congress, one of the ancient vices of scientists reared up, the belief that one's work was greater than that of any other scientist. To elevate their competitive position in the eyes of the Biochemical Advisory Panel, applicants routinely claimed they were doing novel, path-breaking work, and had found a new positive result, something different, eye-catching, and transformational which merited receiving a grant. In short order, every grant became a new research initiative so, even in principle, the resulting pointillist publications could not coalesce into a biomedically meaningful outcome and simply remained as isolated points in an incompletable landscape of knowledge. The basic reason for this pervasive bias toward the novel result was Handler's successful detachment of biochemical research from its historical goal of achieving something useful to society, a goal that gave research its focus and discipline and identified its value. Nothing was left to keep research honest except for the internal norms of the professional, peer-review system itself, which itself was highly conflicted from the moment the system was first created in the 1930s, as was obvious to anyone who had a basic understanding of human nature.

When Handler's idea of furthering the free play of the intellects of biochemists who were free to do the research of their choice was combined with Handlerian reductionism, a uniquely modern form of scientific corruption developed — production of inherently useless

megadata. To obtain preliminary data for a grant proposal — an absolutely necessary requirement— biochemists used hundreds of different strains of rats and mice for reductive biochemical experiments and obtained unprecedentedly large volumes of data. The idea of using rodents as simplified and convenient models of human physiology originated in the early studies of food-energy conversion, muscle contraction, and genes. Reductionism succeeded in those cases for two reasons: because the phenomena studied could easily be isolated in simple system, the chemical reaction of a protein in the stomach was the same as in a test-tube containing fluid removed from the animal's stomach, as an example; and because the investigators had a specific objective that would benefit the public. However, when Handler extrapolated the use of reductionism to biochemical research regarding every biomedical issue, the use of rodent models resulted in the production of massive amounts of conflicting data because different animal strains routinely yielded different results. Extraction of meaning regarding biochemical mechanisms and extrapolation to human physiology became an arbitrary and capricious process — the exact opposite of the intended result of biochemical research. Handler was a central influence in bringing about the development of the system for producing massive amounts of data obtained from rodent models which, when published, created the false appearance that useful knowledge had been gained. The effort was akin to looking for lost keys under the streetlight only because that's where the light was.

Handler's paradigm dominated biomedical research and hogged most of the resources the federal government set aside for that purpose, but it never delivered any transformational biomedical breakthrough or even any important results that could be objectively justified as such. The advances that occurred came from outside Handler's orbit and that of the Institutes and the Foundation. Handler's great lie — that allowing biochemists to be accountable only to themselves was best for the nation — essentially guaranteed they would wind up serving only themselves, because the experimental questions asked differ profoundly when the goal is to solve a problem compared with the goal of advance understanding. His lie led to a culture among biochemists that primarily incentivized the pursuit of pointillist megadata rather than the solution of biomedical problems.