Chapter 3: Purity 1958-1962*

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 questions 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 promotion and tenure, mainly the size of grants obtained and the number

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

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 Institutes' 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 be 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 without the need for any specific congressional authorization because the Congress had already authorized the Institutes to fund any 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 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 as provided in the law that created the Institutes. The Leaders 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.

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.
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> 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 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 sake.

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 at 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 U.S. 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 make 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.
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> 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 research grants to everyone. Handler confronted the issue of surplus biochemists by promising to institute a system of rigid competition that would force 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 than it did on the merits of the proposal. Indeed, human nature being what it is, no other decisional basis could be expected because every Panel member effectively wore a Ring of Gyges that gifted them with invisibility to public scrutiny. No one had benefited more from the Ring than Handler himself. His first Institutes grant 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 similarly tainted by the cronyism facilitated by the Ring. Handler mastered the system for judging grant applications and used it to advance his interests, those on the faculty of his biochemistry department at Duke and, as his circle of influence expand nationally, to a larger group of his friends. 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 world of science. The committee members 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 creation of a new Institute; they were especially supportive of its purpose — free unencumbered money that could pay salaries and research expenses at their universities while they pursued research that interested them. Their attitude was that whatever the research rules were — reductive, integrative,

cybernetic, epidemiological, clinical, or anything else — money was better than no money. The medical and clinical societies mostly remained aloof regarding the wisdom of creating a new Institute. 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 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 existing 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 that 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 is 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.
>
> A 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.

According to Handler, "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 "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 the oxymoronic name was created and a budget that pleased Handler was authorized to support biochemical research and train new biochemists.

DURING HIS SERVICE ON THE Leadership Panel, Handler framed biomedical research as a combination of applied biochemical research, performed by grantees of the existing Institutes, and pure biochemical research, also supported by the existing Institutes but only if the grantees lied and said their studies were applied research. Handler worked diligently to teach the Congress about the difference between the two kinds of research and about the need for a new Institute dedicated to pure research without the necessity of lying about the objective. In the course of his efforts, Handler became the first witness in American history to repeatedly testify before congressional budget committees as an advocate for a specific science policy. The lack of knowledge about biochemistry by the committee members and the absence of witnesses who held opinions that differed from those of Handler afforded him the latitude and longitude he needed to praise the methods and motives and accomplishments of pure biochemistry with an impressive crisp technical sufficiency, which he did like a Pinocchio. Each year he appealed for ever 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. Handler had already succeeded in defining what biochemistry was — an exclusively reductive chemical enterprise that produced pointillist knowledge of living things. He had also created an educational system that produced biochemists and instantiated reductionism as the exclusive basis for funding applied biochemical research by the Institutes. He lacked only the achievement of his deepest desire — what he regarded as a properly purposed Institute. All the existing Institutes had the limited mission of applied research for curing disease. Handler sought creation of an Institute whose single mission was the advancement of biochemistry for its own sake, irrespective of its relation to disease or any other practical objective. He wanted the mission statement incorporated into the founding legislation of the Institute so as to guarantee stability in the Institute's annual budget. Handler unabashedly admitted that he and himself and other biochemists would be the primary beneficiaries of the new Institute, but argued that taxpayer funding of pure biochemical research and education of new biochemists was appropriate because the public would ultimately benefit.

After numerous testimonies, Handler finally achieved his goal when the Congress created the single-purposed Institute he sought and provided a generous start-up budget. His professional achievements — biochemistry department chairman, board member of the Biochemical Society, consultant to the Institutes — clearly impressed the congressmen before whom he testified, as did his persona. 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 individual congressmen, especially budget-committee chairmen, all fused to create a witness perfectly matched to his forum.

By force of his will and with the benefit of propitious historical timing, Handler had catalyzed creation of an Institute exclusively dedicated to biochemical research into the ramifications of his conception of life 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.

Handler contemporaries recognized that only he could have secured creation of the new Institute — no one else had his stature, silver tongue, and ability to project wisdom to laymen. He presented scant evidence to supported his opinions, mostly just naked averments, but his effort was sufficient to sustain his assertion that the federal government had a moral obligation to fund pure biochemical research. The members of the congressional committees that heard Handler speak had as much resistance to his charm as the Incas did to the diseases brought by the Spanish.

Handler regarded creation of the new Institute as the government's acceptance of the principle that pure biochemical knowledge was needed by the existing Institutes to "discover knowledge needed to cure disease and help understand how the body works." He anticipated the new Institute would be a warm and welcoming home for funds to explore his reductive principle that diseases do not have causes but rather what he called "biochemical mechanisms," and regarded as the fundamental explanatory factor in biochemistry for disease — like force was used in physics to explain motion. Handler had identified three classes of such mechanisms: those arising from toxic chemicals, bad genes, and proteins that allowed infectious agents to enter the body, and asserted

they explained all disease. He expected the new Institute to underwrite never-ending searches for the chimeric biochemical mechanisms.

For a brief period, Handler experienced professional contentment, a rare emotion for him. He thought he had fulfilled his deepest desire. Very soon after the new Institute was created, however, 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 or state a foreseeable public benefit. The new Institute 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 thrust into scientism was blocked and a new policy directive required that the mission of *all* Institutes was to advance biomedicine, not biochemistry itself. Handler had sold the Congress blue sky — that Handlerian reductionism, enforced by the new Institute, would produce world-class pure biochemical research which would facilitate discovery of cures for diseases by the other Institutes. But his achievement was transient; there would be no authorized pure biochemical research paid for by the Institutes. Unofficially, however, the new policy could easily be undercut 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 had long been the practice in the Institutes.

Although Handler failed in his attempt to establish 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 didn't. Handlerian reductionism continued to adversely affect the evolution of biomedical research — like the cloud from an asteroid strike that blocked the sun and killed the dinosaurs. His method prevailed over deserving biomedical research initiatives which he strangled by using his influence to block their financial support, like a lion killing the progeny of other males. Pursuant to their policy, the Institutes implemented reductionism while simultaneously refusing to fund all competing research methods. Handler was forced to rest contented with that level of achievement because he recognized that biochemical research was resource-intensive, and could survive only by depending heavily on the government for money, which effectively made biochemical research a federal activity. Handler accepted government control of biochemistry in return for generous public funding of applied biochemical research and the education of more biochemists. At least some biochemists could expect research support for a lifetime, so Handler gave up on his idea that government should pay the piper but the piper should call the tune.

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 ones 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, 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 ensured Selye went unfunded. Nevertheless, Selye persisted and made consistent progress in explaining the clinical reality faced by physicians. His continuing progress 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 promoted 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 serious allergies that developed after he began his experiments with animals. He worked long hours, had few friends, was a heavy smoker, followed an idiosyncratic diet heavily reliant on food supplements, was prone to occasional fits of unprovoked anger, and 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 that 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 kept 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: the signal had to exhibit two cycles each 24-hour period at every location on earth; it had to easily pass through the walls of a laboratory; and it had to 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. He 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 regarded 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 one of Handler's biochemical colleagues, 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. 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 Becker found 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, a matter that was not mentioned in the biochemistry textbook he studied in medical school. 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 for biochemical and microscopic analyses of excised tissues. Becker thought the methods lacked the potential to facilitate an understanding of growth and healing — that relying only on them was like diagnosing patients by analyzing their footprints.

Becker was chief of orthopedics at a federal hospital for military veterans operated by the Veterans Administration, and a professor at an affiliated medical school. He accepted the hospital position the same month he finished his orthopedic residency because the agency promised him an opportunity to do biomedical research. After studying the publications of Burr, Szent-Gyorgyi, Brown, Morgan, Singer, and Bullock, Becker speculated that electromagnetic energy was somehow fundamentally important in controlling growth and healing, and he tested the idea in a related series of animal experiments. Becker measured the slowly varying electromagnetic signals on the skin of salamanders to discern where the signals came from and found they followed a pattern that corresponded to the anatomical organization of the salamander's nervous system. At the time, Becker was working inside the cognitive box of Handlerian reductionism which did not countenance

the study of growth and regulation, denied the possibility that electromagnetic energy could have biological or biomedical significance, and demanded that all forms of biomedical experimentation be based on biochemical hypotheses. On all three counts, however, he demurred to Handler's ideas. Becker envisioned the signals he measured 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, and he believed an understanding of the growth-control system was a central issue in clinical medicine.

Becker theorized that a general level of supervisory control over growth was located in the brain, that it transmitted information-containing electromagnetic energy through nerves, and that the information governed the local processes which mediated growth. He conceived of the relation between the brain and local growth phenomena as a closed-loop negative feedback system in which the local process furnished what amounted to information regarding growth status, and the brain sent messages that effectively downregulated the healing rate as the process neared completion. In Beckerian biocybernics, biochemistry was the raw material of growth and healing, a necessary ingredient but not the whole story and, at least in his eyes, a relatively uninteresting aspect. He once told me, "If there is control, there must be a controller; identifying the biochemicals involved is only stamp-collecting, identifying the controller requires ingenuity."

For Becker, archetypes of growth were the automatic healing of a bone fracture in humans and the innate ability of salamanders to regenerate an entire limb. He tested his idea of information flow by observing the effect of cutting the animal's spinal cord at the level of the brain stem on the measured signals and found that they disappeared, as expected under his theory. In animals with an intact spinal cord, he sectioned the nerves where they exited from the cord into the limbs, and the signals on the skin of the limbs disappeared, again consistent with his theory. In amputation experiments, Becker tested the aspect of the theory that an energy flow mediated healing. Knowing that salamanders had the ability to regenerate a lost limb but frogs did not, he predicted that the post-amputation signal from the injury site would differ between the two species. He amputated a hind limb in animals of both species, measured the injury-site signal daily, and observed that the temporal patterns of change differed, consistent with existence of an electromagnetic data transmission and control system that regulated regeneration.

In his injury-response model, 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. He viewed the localized regeneration as a complex self-organizing system, and distinguished it from the stimulus-response system consisting of the local site and the brain which eventually ended the response by means of negative feedback. Similar feedback information was absent in the frog which, compared with the salamander, was a slightly more advanced species on the evolutionary scale. Becker believed the frog probably had the cells necessary to regenerate a limb and lacked only the necessary encoded information. Inasmuch as frogs and even humans had the same cells, the difference in regeneration response he observed in the laboratory 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.

In an experiment that had significant implications for Becker, he observed that magnetic fields affected the neural flow of electromagnetic energy in salamanders. The conditions of the experiment insured that energy flow involved the motion of electrons not ions — a revolutionary idea in biology at the time. Further, the result raised the possibility that earth's magnetic field might also be able to cause a similar effect, thereby suggesting that the data control system he intuited might be able to serve as a link between living organisms and the environment. After Becker presented his research 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 budget than had been provided by the local hospital where he worked. 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 based on biochemical hypotheses. Becker was awarded a grant by the his agency's central office, but his application to the Institutes for additional support to expand his laboratory was rejected.

In 1961, at a national symposium on magnetic fields, Becker delivered an invited presentation and summarized the results of his experiments. He said he and his colleagues observed that slowly varying electromagnetic signals could also be measured on the skin of animals and humans, and that in both species the measurements changed in characteristic ways during sleep and anesthesia. His research team correlated daily fluctuations in the earth's magnetic field with the daily rate of admissions to two local hospitals over a four-year period, suggesting a relationship between instances of psychiatric disturbances and changes in the geomagnetic field. Becker described further experiments he thought revealed the physical basis of the relationship. He told the audience that limb-regeneration studies in animals led him to suspect that the nervous system was involved and, seeking supporting evidence, he anesthetized animals and measured the flow of electromagnetic energy transported by the nerves. He observed that in the nerve fibers which transmitted sensory information, the energy moved in one direction, and that in the nerves that commanded 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.

Becker concluded the measured flow of energy, which varied with time at any given point on the skin, was an electromagnetic phenomenon that was fundamentally different from the well-known sensory and motor nerve impulses. He speculated that mankind's most primitive regulatory system had been discovered — a system by means of which the environment originally informed mankind's ancestors regarding the optimal behaviors for survival. As evolution progressed, he further speculated, 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 that the ancient data transmission system continues to function, at least as regards the flow of information that controls growth and healing.

Perhaps the most important research results Becker described at the conference were those related to his attempt to understand the physical mechanism by which the electromagnetic control signal moved through the body. At that time, according to physicists, electromagnetic energy could move through the body only via motion of ions in the body's watery milieu. Becker, however, described experiments he believed indicated that electrons were also carriers of information. He

observed that freezing tissue increased the energy flow, as would be expected if the flow were carried by electrons rather than ions, suggesting that 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 biochemical research as the driving engine for what he viewed as the applied biochemistry physicians needed to cure disease. 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, and for their exclusion of all competition to his ideas about biomedical research. 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 a lie. Historically, the advances in biomedicine that occurred weren't dependent only on biochemistry or on the freedom of biochemists to spend the government's money as they saw fit. Nevertheless Handler repeated the lie incessantly and labored to ensure that academic biochemists received robust government funding for their research and —notwithstanding what the law required — were not shackled by the principle that their work should be primarily concentrated on meeting the needs of for society. According to the gospel he continued to preach, biochemical research would ultimately yield the basic knowledge needed to ensure the health of the nation. He seductively capitalized on the then widely held beliefs of 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. For a while, politicians responded by delivering generous levels of taxpayer funds to biochemists, allowing only them, in secret, to both choose the research they did and evaluate its value. At budget hearings, Handler continued to argue that allowing biochemists to make their decisions in secret was necessary to ensure that decisions of whom and what to fund were not influenced by laymen or political pressure. In all his stories of past successes, however, the research he described was successful because it was influenced by laymen or political pressure in the sense that laymen shaped the objectives and decided whether the results were worthwhile. Even though influences from outside the biochemical establishment were the driving force behind the successes, Handler falsely intimated otherwise to the budget committees.

Handler had persuaded the Congress to create a new Institute dedicated to pure biochemical research, but the decision was quickly reversed, not because Handler's arguments were recognized as based on casuistry but because the new Institute's mission was illegal — giving away public money for the private purpose of personal edification. Although the reversal enraged Handler, in the end he decided it wasn't the hill he would die on. One reason was that the work-around he had perfected when he first joined the Institutes — the transparently contrived lie by which a grant applicant's true

objective was obscured — remained a viable option for grant applicants. Another reason involved his success in obscuring the Institutes' policy of forgoing any attempts to discover the causes of disease. Handler recognized that openly challenging the Congress on the issue of personal freedom for biochemists would illuminate 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.

Handler's lie led to the corruption of the Institutes. In actual practice, when research was prioritized by an advisory panel, biochemists were awarded money and essentially 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. Thus, funded investigators were free to proceed according to their own lights. Handler claimed 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 one another but had no utility in the world, like developments in abstract mathematics. 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 stunning 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 pointillist biochemical studies, which 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 cooperated. They channeled money into the willy-nilly production of unverifiable facts that were mostly 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 cures for cancer and other diseases 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.

In the face of the evidence that confronted him, Handler continued to believe that 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 a Kafkaesque enterprise. One indication was their treatment of the ideas and work of numerous contemporary non-Handlerian investigators including but not limited to Dubos, Wolff, Szent-Gyorgyi, Burr, Wiener, Shannon, Prigogine, Selye, Brown, and Becker. Another indication of the descent of the Institutes was the cut-throat competition it inspired among establishment biochemists, who essentially went to war with each other in order to obtain grants so that they could produce the pointillist publications needed for promotion and tenure. But Handler could not bring federal money into the system fast enough to feed all the PhDs his policies produced, and consequently there ensued ruthless competition for grant funds and professional recognition, resulting in chronic internecine warfare among biochemists. 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 Handler tried to paint as something good saying, "The system insured that only the best survived."

Competition among biochemists became progressively more desperate after Handler began losing his budget fights with the Congress, with the result that the Institutes were no longer flush with money. Grant applicants began routinely making outlandish claims they were doing novel, path-breaking work, and had found a new positive result, something different, eye-catching, and transformational that merited receiving a grant. In short order, every grant was touted as 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 1930s, as was obvious to anyone who had a basic understanding of human nature.

The merger of Handler's idea of freedom of research choice for biochemists with Handlerian reductionism resulted in a uniquely modern form of scientific corruption — production of inherently useless mega-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 systems, 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 specific objectives 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 advancing understanding. The lie led to a culture among biochemists that primarily incentivized the pursuit of pointillist megadata rather than the solution of biomedical problems.