Chapter 1: Deconstruction 1917-1939*

PHILIP HANDLER was born in 1917 and brought up in Brooklyn, New York, the oldest of three children of an unsynagogued Jewish immigrant from Russia. His father faced many difficulties but learned to speak English and eventually owned his own business. He impressed on his son the necessity of making his way in the world by using his mind not his back. Philip had a lonely childhood and mostly home-schooled himself, reading many books and spending much of his time at the library. While working part-time in a gas station, he first met people who didn't live in his ethnic neighborhood They struck him as simplistic, with little prospect for a good future, a fate he resolved to avoid by obtaining an education. His family doctor, who was respected and lived in a big house, was the only educated person Philip knew and he resolved to become a doctor. At age 15 he graduated from high school and entered Columbia University as a pre-med student. His family's dire financial situation soon forced him switch to the City College of New York, which offered a free education to the children of immigrants, and whose student body was mostly Jewish.

Handler found it difficult to participate meaningfully in the social life of the other students. He joined the college boxing team, not because he liked boxing but to counteract the feeling of awkwardness he felt as the youngest student in his classes and to cultivate a feeling of belonging. After losing all his bouts and sustaining a head injury, he quit the team, still an outsider, suffering from headaches. Later in life he reflected on his boxing experience: "Perhaps, in the long run it was a boon since I was thrown back on my own resources and those of the library."

During his second year in college, while entertaining uncertainties about his future, he read *Arrowsmith* and was impressed by the world view of one of the characters, a biochemist named Gottleib who believed living things were biochemical machines and that becoming a biochemical scientist devoted to studying human biochemistry was the highest calling in life. Gottleib regarded being a biochemist not just as a job but rather something intensely religious that prevented acceptance of half-truths because they would be insults to his faith in pure science. For him, a true scientist lives in a world of facts and knows how much remains to be known and spends his life in an uncompromising search for facts; he has disdain for physicians who treat people with methods that aren't proved beneficial by laboratory studies. Gottlieb's gospel bowled over Handler, then an emotionally pliable seventeen-year-old who had nothing else large to believe in.

Soon after reading *Arrowsmith*, Handler heard enthusiastic lectures by his biochemistry professor about newly discovered biochemical reactions that produced the chemical energy necessary for life. The professor described how food was converted into pyruvic acid and how the energy it contained was transferred in the Krebs cycle to molecules that fueled cellular activity. Handler later described the professor in exuberant terms. "He was an exciting, vibrant lecturer, he made it plain that although biochemistry was but a rudimentary science which had scarcely learned what questions to ask if life was to be understood, it must be in the language of chemistry. And I was converted." Handler decided to become a biochemist even though he was uncertain how that would lead to respect and a big house.

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

AT THE TIME Handler made his plans, the subspeciality of biochemistry was early in the process of emerging from chemistry, an applied science that had developed from physics about a century earlier. Physics, in the sense of a science of nonliving matter, began about two centuries earlier when humans conceived the straightforward idea of mass and the more abstract idea of energy. In the period between the birth of physics and Handler's eureka moment at City College, physicists used the ideas, and the assumption that nonliving matter was composed of parts, to invent a small set of equations to produce the understanding of nonliving matter that still prevails. From their perspective, everything that happens in nonliving nature is explainable using the equations. Biology, the science of living matter, effectively began during the Renaissance, particularly after Descartes defined a human being as a machine energized by a soul. The biologists never explained what life was or how the machine could move itself. They knew it was composed of organs and specialized tissues but never localized life in any part smaller than a cell, an understanding about living organisms that still prevails. In contrast to physicists, who regarded nothing as not composed of parts, biologists regarded the cell as an absolute lower limit of life.

BY THE TIME Handler appeared, chemists interested in biology had organized into a society dedicated to exploring the chemical basis of the myriad behaviors exhibited by the different forms of life. From the beginning of their laboratory investigations, the biochemists viewed a cell as merely an anatomical structure composed of independent biochemical substructures, like the electron, proton, and neutron structure of an atom in physics. They equated life not with the organization of the cell but rather with the biochemistry of its substructures. Biologists, in contrast, universally conceived of the cell as a fundamental unitary structure, because life didn't reside in any of its parts, only in their sum. But biochemists, who disdained biologists as merely catalogers and classifiers rather than true scientists like themselves and physicists, ignored the biological perspective and the evidence on which it was based. The belief that life could ultimately be understood in terms of the biochemistry of parts of cells became the bedrock of their specialty. And as personified by Gottlieb, biochemists had even less respect for physicians, whom they regarded as technicians, not scientists.

Like other chemists, biochemists based their research methods on those of physics, but the biochemists went further. They focused so heavily on the role of chemical energy, the effect was to essentially exclude a meaningful role for electromagnetic, mechanical, kinetic, gravitational, and thermal energy in explanations of the behavior of living matter. By the time Handler embraced biochemistry, biochemists, especially his teachers, had come to believe that their perspective and methods formed the canonical basis for explaining all phenomena manifested by living organisms. In principle, according to their single-energy stance, phenomena that occurred at the system level including growth, development, healing, memory, consciousness, health, and the occurrence and prognosis of chronic diseases were somehow amenable to biochemical explanations. How that could happen was a mystery, especially considering that biochemists had no methods to study system-level phenomena, but they had faith that the biomedical questions would ultimately be solved. Biochemists made progress in explaining pure chemical phenomena, especially the process that turned food into chemical energy. Handler believed the developments in nutrition were a harbinger of what was to come and set sail to become a biochemist.

HANDLER GRADUATED from City College at age 18 and enrolled at the University of Illinois to begin postgraduate studies, expecting to study under a famous nutritionist. But he lost his financial support for tuition and living expenses when the nutritionist declined to be his mentor. Another biochemistry professor accepted Handler as a student and arranged for him to work half-time as a chemist in a government agriculture research laboratory to support himself. None of the other graduate students faced the degree of economic and social difficulties that confronted Handler. Later, he told a group of senators that he literally had to eat the livers of rats from his experiments to survive.

HE TOOK COURSES in general chemistry, organic chemistry, and biological chemistry, but avoided physical chemistry because it involved concepts from physics including motion, energy, force, thermodynamics, and electromagnetic energy that were not part of his prior training. In his mentor's laboratory, Handler learned how to extract biochemicals from animal tissues, and his attitude about biochemistry solidified. The perspective of a physician, which had appealed to him when he started college, and the wonder he felt about the complexity of living things when he studied biology receded in importance to him, replaced by a purely biochemical perspective.

Handler's dissertation research dealt with the biochemistry of proteins in rats. Proteins had recently been discovered to be composed of fewer than two dozen building blocks called "amino acids," some of which were synthesized in the body and others that, although essential for health, could not be made in the body and had to be ingested in the diet. For reasons he never explained, Handler's research focused on whether artificially modified versions of some essential amino acids could be unmodified by the body and used metabolically to make proteins. He fed rats a controlled diet of carbohydrates, fats, salts, and vitamins, but with an essential amino acid replaced by a modified version. He studied the effects of the diet on body growth, and found that some of the modified amino acids retarded it to varying degrees while others had no effect. After homogenizing the rats' livers and kidneys in a blender to make them amenable to test-rube biochemical analyses, he saw that some of the modified amino acids were metabolically unmodified by the body in various ways to varying degrees, while others remained chemically identical to what they had been when he added them to the rats' diet.

Handler could not come to any defensible generalizations, so the meaning of his work remained obscure and was unpublished except in his dissertation. Later in life, he thought there was merit in his work that others just hadn't recognized. He wrote: "All of the experiments proved successful, although their interpretation remains difficult." His explanation for the failure of his research to gain recognition was that his results conflicted with the then-prevailing biochemical orthodoxy, and he described the lesson he drew from the experience: "That taught me experimental observation, judiciously and honestly conducted, is the first obligation of the experimental scientist, and that theory must be compatible with observation, not the reverse."

HANDLER ACQUIRED a reputation in graduate school for talking down to his peers. They called him a "storyteller" which meant, depending on who described him, someone who spoke paternalistically or someone who talked but didn't listen. He motivated others to do what he wanted by giving them what they wanted in return—a characteristic that became his trademark and was particularly perceived by those who spoke highly of him. He developed an idiosyncratic speaking and writing style that included poetic, historical and rhetorical flourishes, injection of sideways comments, use of alternating long and short sentences, and particularly characteristic, statements of opinions cast as facts. Depending on who was opining, Handler had an incomparable mastery of language or was a pompous blowhard.

Handler embraced the outlook that the behavior of living things was determined by heredity and diet and would ultimately be shown to be explainable in biochemical terms if a sufficient amount of research were done. He didn't appear to recognize any limitations entailed by a strictly biochemical conception of life or by the classic biochemical method for studying life—destroying its complex structure in blenders and analyzing the debris. Contrarywise, he appeared to believe that biochemical reactions in test-tubes were identical to those in the body. He gave no indication of any effort to consider a possible role of non-chemical energy in biological function, and he was conspicuously silent regarding the role of electromagnetic energy in the brain, the peripheral nervous system, and in every living cell—a form of energy that was absent in blended tissue soup, which was the only place he ever looked for answers concerning biology. Later in his career, he succinctly explained the concept of biochemistry he had adopted when he predicted that biochemical research would ultimately show how life could be created in a bottle by mixing biochemicals in proper portions in accordance with the chemical doctrine of mass action. By the time he completed his doctoral training, he had great confidence in the validity of his opinions, and a remarkable ability to deliver them by telling stories in which the opinions were couched as seemingly value-free facts.

AFTER ONLY THREE YEARS at Illinois, in 1939, at age 21, Handler received a PhD in nutritional biochemistry and accepted an offer from Duke University to teach biochemistry to first-year students in its medical school. Duke was less than a decade old and located in the tobacco-growing area of North Carolina. His annual salary was less than what he earned working in the government laboratory in Illinois. Thirty years later he described what Duke was like when he arrived:

> Desolate. I came from the University of Illinois which was one of the largest universities in the country. I really didn't know much about Duke. I was aware that Duke's football team lost in the Rose Bowl. I knew about the experiments here on extrasensory perception. I was aware of the fact that it had been stated that Mr. Duke had founded a country club college here on Methodists Flats, but I didn't know much about it. When I came, I found a somewhat overgrown college with an upstart medical school in a sleepy southern town, the social center of which was Walgreen's drugstore. Well, it was here and real, but it had no style. It had not developed any kind of academic zeitgeist. You couldn't tell where you were, really.

Handler married a girl he met in Illinois and adjusted to the cultural shock of life in the south. His formal education, from the beginning of high school to beginning at Duke, lasted only nine years and was heavily focused on biochemistry with nil exposure to the social sciences or humanities. He had never been in the south, where social attitudes were quite different from those in Illinois and Brooklyn, and he had no life experiences that deepened or added nuance to his cultural perspective and opinions. Methodist Flats was predominantly Southern Baptist and operated under a racial caste system. The medical school had no black faculty, students, or employees except for the maids and janitors. Handler, in contradistinction, was a socially liberal agnostic—biochemistry was the closest thing he had to a religion. He had opinions about almost everything, and the attitudes and customs where he lived were no exceptions. On the other hand, the freedom and security of the academic life, and the sense of safety it provided in a world where the storm clouds of war were gathering, became extremely important to him and his new family. The "upstart medical school in a sleepy southern town" gave him a career path, the opportunity to teach the subject he loved, and an environment within he could do any kind of research that interested him. He wanted to protect his comfortable situation and he realized that voicing his personal and political opinions would play directly into the locally perceived stereotypical behavior of an aggressive loud-mouthed Yankee who came to the south and tried to tell everyone how things ought to be done. He developed the discipline of keeping his opinions about race and politics to himself, and thereby avoided conflicts that might jeopardize his reputation in the eyes of the administration, faculty, or the people who were the bedrock of the local community. He told the strained story that he had always been a southerner because he was born in a part of New Jersey that was below the Mason-Dixon line if it were extended easterly. He knew his conscientious efforts to fit into the local culture had succeeded when longtime southerners began using language and expressing ideas about race and religion in his presence that they would feel comfortable doing only in the company of family or friends.

HANDLER WAS an excellent classroom lecturer. He spoke slowly and clearly, with a strong voice, a deliberate demeanor, and a passion for biochemistry. His descriptions of the biochemical reactions of metabolism were readily understood by the medical students, although they didn't manifest the same enthusiasm he felt when he first learned them. The difference troubled Handler. He believed what he taught was important and reliable scientific knowledge. But the medical students were mostly interested only in memorizing the details, regurgitating them on exams, and then moving on to medical tasks which, from the students' perspective, had little to do with what Handler was teaching. They were also taught anatomy and physiology, which Handler recognized had foundational value for future physicians, but he regarded the subjects as unscientific because they were based on observation, not experimentation. His dismay about medical education only increased after he saw the medical curriculum for the clinical years, which was when the students observed physicians demonstrate traditional methods of diagnosis and treatment and were taught to express empathy for the distress experienced by the patients to help improve outcome. Handler believed there were no scientific studies that validated the traditional methods or the biochemical basis of an empathetic effect. His mindset led him to conclude that physicians were teaching therapeutic methods they did not understand, and that physician influence on healing was at best anecdotal and at worst a myth.

He thought the murk of clinical medicine would be dispelled if medical practice were based on biochemical research. He envisioned physicians as scientists whose clinical decisions were determined by factual evidence provided by biochemists.

Handler proposed to modify the curriculum so that MD students would be educated like PhD students, and trained to base their clinical decisions on biochemical facts, but the university administration declined

HANDLER OBTAINED deferments from the national military draft because of the head injury he incurred as a college boxer and because his university certified to the local draft board that he was an essential employee under the federal rule that "the expanding Army will eventually require doctors in numbers heretofore unknown." The deferments afforded Handler the opportunity to do laboratory research throughout the war years. He obtained the necessary financial support from a private philanthropy that promoted research likely to lead to discovery of useful knowledge about nutrition and health. His initial experiments were of the type he had done at Illinois, and he presented the results at annual meetings of the Biochemical Society. Even though he was the youngest speaker, he acquitted himself well and the Society published his results in its journal. Officials at the philanthropy, however, were dissatisfied with Handler's work, having expected that their support would lead to more useful insights into nutrition and health than appeared in the society journal.

His next experiments were not substantially different. He fed animals a controlled diet, removed and homogenized their livers, and analyzed the liquid to learn something about the intermediate metabolism of dietary fats. Again, he presented the results at Society meetings and published them in its journal; the academic successes earned him election to membership in the Society and promotion by his university to assistant professor, but did not quiet the concerns of his funder. He changed his experiments and began seeking useful information about a dietary vitamin, nicotinic acid. Pellagra was a common disease among farmhands where he lived, and its cause had recently been shown to be a diet deficient in nicotinic acid. Handler's research objective was to discover the biochemical reactions that connected the fact of the vitamin deficiency with the symptoms of the disease—diarrhea, muscle weakness, pain in abdomen, inflamed mucous membrane, skin sores, delusions. He also sought biochemical evidence that could explain why there were no symptoms when the vitamin was in the diet. He fed rats a controlled diet deficient in the vitamin, believing he could achieve his objectives by analyzing their homogenized tissues. But his experimental approach hopelessly confounded biochemical measurements in test tubes with clinical symptoms and he made no meaningful progress, producing only impenetrably dense prose. In "The Biochemical Defect in Nicotinic Acid Deficiency," an experiment whose problematical objective was to ascertain why all the dogs in a prior experiment died when they were fed a diet that contained no nicotinic acid, Handler concluded:

> The findings presented here have served to clarify somewhat the chain of events leading to death in nicotinic acid deficiency. However, at present, it is not possible to state the underlying factor which is responsible for the dehydration and electrolyte imbalance. The fluid loss is not solely due to the bloody diarrhea, since many dogs never do exhibit it. Nor can the dehydration or electrolyte imbalance be ascribed simply to the prolonged period of anorexia, since quite frequently dogs have been observed to die within 24 hours of the time when they first refused to eat or drink. The lack of appetite and thirst, however, may be associated simply with the pain occasioned by the severe necrosis of the oral mucosa. On the other hand, the possibility must be borne in mind that these animals do not feel thirsty. The effect

> of the administration of salt solutions and of salt itself, the decreased blood chloride and glucose, the renal impairment, suggest a dysfunction of the adrenal cortex attendant upon a deficiency of nicotinic acid or its physiological derivatives. These findings lend support to the conclusion that death in canine pellagra is not due to a deficiency of the pyridine nucleotides with consequent failure of tissue respiration in the organs studied. They do not, however, suggest the exact nature of the relationship between nicotinic acid and the normal functioning of the adrenal cortex.

Handler's abstruse publications were not what his funder wanted, and it ended its grant. Handler obtained a grant from another philanthropy which supported research aimed at improving health care.

Handler undertook experiments on an eclectic series of topics that yielded a hodge-podge of findings: lethal doses of cyanide and other tissue poisons produced essentially the same biochemical changes in the body; addition of the vitamin inositol to the diet as a supplement might have had health benefits; animals fed a diet abnormally high in fats and low in protein developed liver disease that could be treated by adding more protein; anorexia in dogs treated with a sulfa antibiotic for severe rashes due to their vitamin-deficient diet probably developed the anorexia because of the sulfa not the vitamin deficiency. The research was personally satisfying to Handler, far more so than lecturing medical students who seemed not to appreciate the importance of biochemistry, and further raised his profile within the Society. He was recognized as an excellent presenter at its annual meetings, and his research generated the qualifying number of publications for promotion to associate professor with tenure—one of the few such promotions that took place in the US during the war.

Handler's speaking skills and academic recognition did not gainsay the fact that the body of his research was unfocused, of only average quality, and not remotely suggestive that he was on the path to meaningful discoveries. His publications characteristically consisted of descriptive language without any conclusions. His report, "Factors affecting the occurrence of hemorrhagic kidneys due to choline deficiency," demonstrated the aporetic character of his work, what he called "the need for further study."

> Rats fed a diet deficient in the vitamin choline and housed in group cages failed to develop the hemorrhagic kidneys that routinely occur in rats in single cages. The addition of the vitamin nicotinamide to this diet resulted in hemorrhagic kidneys even in the rats housed in group cages. The vitamin inositol appeared to increase slightly the incidence of hemorrhagic kidneys due to choline deficiency. A combination of inositol and the vitamin tocopherol significantly decreased the incidence of hemorrhagic kidneys while the vitamins biotin and folic acid were without effect. Weanling rats on a diet containing 6% casein milk proteins did not develop hemorrhagic kidneys until after 35 to 45 days, in contrast to rats receiving diets of higher protein concentration which develop that condition in 6 to 10 days. While few adult rats developed hemorrhagic kidneys on choline-deficient rations, choline-deficient adult rats subjected to removal of a kidney uniformly showed hemorrhaging after 10 to 14 days, the period during which the remaining kidney became enlarged. When adult rats with one kidney were placed on a choline-deficient regime 2 weeks after the operation, hemorrhagic kidneys were observed in only one of 12 animals although they were continued on the diet for 6 weeks.

HANDLER HAD NO research plan to seek improved health care or any other useful objective, but rather continued to pursue whatever unrelated questions interested him. At first he did so by instinct, as if conducting research in that manner were a natural thing to do. But then he developed a more conscious sense of intent after reading about a vision of science by the President's science advisor, who was the architect of the nation's research effort during the war and delivered crucial technologies including the atomic bomb and radar. The advisor argued that giving free play to the intellects of scientists and encouraging them to seek objectives they chose, guided only by "their curiosity for exploration of the unknown," was the best way to encourage scientific progress. He predicted that pure undirected basic research, motivated solely by a thirst for knowledge with no foreseeable societal benefit, would create the foundation for new products and methods, improve health care, produce full employment, and guarantee national security. Handler was greatly influenced, and decided mankind would be best served if biochemists followed their own lights and worked on topics of their own choice, with no requirement that something useful be produced and answerable only to other biochemists—just as his career had unfolded.

HANDLER LOST his external funding because his philanthropy had demanded useful research, which was exactly what he refused to do. To prevent closure of his laboratory, the school administration was forced to fund his research until he found other external support—an academically uncomfortable position for an associate professor with ambitions of becoming a full professor. Despite the financial pressure, Handler remained wedded to his formulaic research design. He created pathological conditions in laboratory animals using vitamin-deficient diets, surgery, toxic drugs or abnormal housing conditions to disrupt metabolism, and made measurements of some of the biochemical consequences that were sufficiently stable to be detected in homogenized liquified tissues. His research formula led to numerous publications: lethal doses of metabolic poisons injected into rabbits adversely affected their ability to metabolize carbohydrates; insulin prevented the rise in blood-sugar levels in rats fed lethal doses of metabolic poisons; bleeding kidneys and fat deposits in the liver occurred in rats whose diet did not contain the essential vitamin choline; liver damage induced by choline deficiency rapidly reduced the high blood pressure caused by surgical removal of the kidneys; altering dietary calories, protein or salt affected the blood pressure in rats; altering thyroid activity in rats altered fat levels in their liver and blood. In each publication, Handler described the results using a distinctive verbose syntactical structure that developed into his signature narrative style. It consisted of an assertion that previous experiments by himself and others had produced unclear results, an announced intention to explore the problem, and a description of his activities and observations, but no meaningful conclusion. In a typical publication he wrote:

> During the past 15 years there has accumulated a considerable body of literature describing the biochemical changes in the liver due to diets deficient in choline and cystine. Unfortunately, this literature has been complicated by the fact that the many investigators in this field have employed rats of different strains and ages as well as diets of quite different composition The present paper describes an attempt to determine the extent to which the initial age of the rat modifies the liver's response to choline and cystine deficiency in one strain of rats fed one variety of deficient diet. In this study, young rats died much more readily than did older rats due to the effects of dietary deficiencies in cystine or choline. While choline

deficiency almost invariably resulted in liver fibrosis in young rats, in older rats it frequently caused nothing but fatty livers, even after 8 months. The incidence of liver necrosis due to cystine deficiency in young rats was about the same as that observed in older rats but the young rats developed such lesions in one-third the time required in older rats. Many rats of all ages have been were observed to die of cystine deficiency with no detectable histological abnormalities in any of 19 organs examined. Young rats fed a diet deficient in both choline and cystine live somewhat longer than simply cystine-deficient animals but show no liver damage. Older rats on such rations develop livers which are were necrotic, fibrotic, and fatty despite a loss of as much as two-thirds of their initial body weight during the experimental period.

HANDLER'S STYLE of research design made drawing generalized conclusions or discovering cause-effect relationships impossible, and permitted only a descriptive narrative. In other words, Handler could tell a story but couldn't prove anything; his idiosyncratic combinations of numbers and words did not generalize to biological facts but rather produced only indeterminacy. Some biochemists at the Society meetings criticized Handler's work as sub-par because he had not provided information that could be verified by others—the inevitable result of work that lacks a proper experimental design and a well-formed hypothesis. But the majority at the meetings agreed with Handler's approach—not the famously successful biochemists like those who had won Nobel Prizes, but rather men with mediocre intellects and little sense of moral responsibility to help relieve mankind of the scourge of disease, men who were devoted to biochemistry because it was their job and fed their families.

Handler believed the endless production of narrative statements about diet, and about everything else related to the function of living systems, was exactly what biochemical research ought to be, at least at the level of the individual investigator. An infinite number of such experiments were possible and the narrative result of each, according to his view, was biochemical knowledge that would ultimately help frame the big picture concerning human health, like points in a painting by Seurat that reveal a landscape. Handler regarded an understanding of human health and disease as the ultimate goal of biochemical research, but rejected the view it should be the goal of individual biochemists, whom he believed were entitled to pursue pointillist knowledge, free from the burden of a utilitarian objective. On the contrary, he believed a biochemist was entitled to the opportunity of seeking untrammeled pursuit of biochemical truth for its own sake, aloof from any concern for its practical application.

AROUND 1947, Duke contracted with two industry organizations to provide financial support in return for Handler's research services. Handler was given the freedom to do any nutrition-related research he desired, and the funding levels were sufficiently high that the university administration reduced his teaching load in the medical school to near zero, allowing him increased time to do experiments. He continued his established pattern of disjointed experiments and aporic publications. In a study on rats that was prompted by reports of illness in infants fed milk containing artificially modified milk sugar, he opined that the illness was "not a qualitative idiopathic phenomenon but a quantitative exaggeration of events which can be elicited in a normal animal when the modified sugar intake is sufficiently high." In other words, be guessed that the illness occurred because the milk contained too much of the additive, not because the additive was inherently unsafe. He performed an experiment in which he removed one kidney and half of the second from rats, producing high blood pressure, which he claimed to have cured by means of a second biological insult, feeding the injured rats an abnormally low protein diet. In another study, he fed young rats a diet containing only 50% of the calories needed to sustain life and reached the unsurprising conclusion that their bones did not grow normally, an observation he characterized as additional knowledge in his pointillist concept of biochemical research.

His experiments were based on the assumption that knowledge regarding human nutrition could be inferred by studying the biochemical reactions of laboratory animals to changes in their diet. However, in his comparative study of choline metabolism in rats, guinea pigs, and hamsters, the different species responded differently to diets deficient in the vitamin. The study provided clear evidence of a limitation in the use of laboratory animals to study human nutrition, but Handler was blind to the implication and never considered the possibility that his assumption was problematical. His mind was closed to even the possibility that a reductive approach to nutrition utilizing animals as surrogates for humans—the foundation of all his research—could be unsuitable for explaining human nutrition.

HANDLER'S PROMINENCE within the Biochemical Society continually increased, as did the number of his publications in its journal, each written in the arcane language biochemists were developing to communicate with one another. During presentations at Society meetings, he projected an imperious but thoughtful demeanor and a fashionable appearance, thin and well-dressed, contrasting sharply with the popular image of a slovenly dressed professor. In his audience were Szent Gyorgyi, Dam, Doisy, Virtanen, Northrop, Stanley, Summer, Cori, Tiselius, Kendall, and Reichstein, all of whom had won Nobel Prizes and collectively driven the international rise in perceived importance of biochemistry; other biochemists in the audience were on the cusp of international recognition. Handler's research was trivial in comparison to their work, but he displayed strengths in other areas, suggesting to the Society leadership he might be good choice to represent the interests of the Society on the national stage.

During press interviews he demonstrated skill in morphing biochemical jargon into simplistic language that could impress laymen. When speaking to an audience at a Society meeting about his blood-pressure study, Handler said, "purified, synthetic diets altered blood pressure in rats rendered hypertensive by sub-total nephrectomy;" at a press interview, however, he characterized the work as "the first definitive study of the effects of diet on high blood pressure." The Biochemical Society was an elite scientific organization but had many business-related problems including housing and managing its journal, maintaining accurate records, locating a home for its headquarters, defining its membership criteria, and establishing relationships with the other US societies that were interested in biological research. After Handler was appointed to several committees that were addressing the problems, he showed an organizational ability to get things done, further enhancing his reputation in the society.

HANDLER WAS FREE to do whatever research he chose, but forming ideas of the type that launches a line of experiments leading ultimately to useful results , as opposed to his pattern of one-and-done experiments, continued to elude him. He was honest with himself in that regard. "I was a good biochemist but not a great biochemist," he later described himself. His self-assessment was not the recognition of a limitation but the formation of an aspiration. Mostly, he wanted biochemistry established as the science of living systems, akin to the role of physics as the science of non-living systems. The goal could be achieved, he believed, only by using his method, which was to give free play to the intellects of biochemists as a matter of government policy—not only Nobel-Prize winners but all biochemists.

Handler enjoyed having a laboratory with the latest equipment and a staff he could control, but was unenthusiastic about spending his career to personally generating pointillist publications. He believed he was capable of achieving more. While pondering his career plans, Handler's chronic health problems worsened. He had grown up in relative poverty, which contributed to his persistently poor diet during his youth. At Duke, he typically worked more than twelve hours a day facilitated, he believed, by daily doses of vitamins and other diet supplements. He projected a calm persona but was always on the verge of a bout of muted sarcastic anger. Working in the laboratory became progressively more difficult, producing a variety of sporadic clinical signs and symptoms, which he always treated himself because he had little confidence in physicians. Finally, over a short period in 1948, he became completely unable to do laboratory research and self-diagnosed himself as allergic to the rats in his experiments. He continued to treat himself but his condition didn't improve, and his industry funding was insufficient to support hiring the additional laboratory assistants he needed to compensate for his absence from the laboratory.

Handler also had other money problems. He couldn't afford the continuous stream of new equipment needed to maintain a national-level proficiency in biochemical measurements, which would be essential were he to shift his career goal from doing research to training students how to do research. Further, his research contracts did not provide meaningful payments to Duke for overhead costs—a practice that was developing nationally whereby federal agencies paid universities to allow their professors to accept research grants. Other professors at Duke were bringing in overhead funds, and Handler knew that his failure to do so would likely be a bar to promotion to full professor and, under university promotion policies, would require him to do more teaching, which he enjoyed but considered to be only a minor task.

HANDLER'S FINANCIAL PROBLEMS began to resolve after he was contacted by the Atomic Energy Commission, which was attracted by his high publishing rate of biochemical analyses. The Commission, which was promoting public acceptance of atomic energy by publicizing the use of radioactive chemicals for diagnostic and metabolic studies, hired Handler to teach courses on their use. To gain experience with side-effects of electromagnetic energy emitted by the radioactive chemicals, Handler was sent to Japan to observe the consequences of the radioactivity from atomic bombs. Handler saw overwhelming evidence that the radioactivity caused numerous types of cancer that developed at differing times following exposure to a large range of radioactivity levels. He told the Commission that his observations didn't reveal what levels or durations of exposure to the radioactivity from the radioactive chemicals would be safe. But, he said, whatever the safe levels were, exposure to radioactivity used for biomedical purposes was very low and therefore certainly safe. Handler's experience with radioactivity raised a question in his mind regarding how the electromagnetic energy emitted by radioactive chemicals could produce so many different kinds of cancer at so many different times of exposure, but he did not pursue the matter.

HANDLER'S CONNECTION with the Commission helped solve his financial difficulties, but the association he developed with the National Institutes of Health was far more significant. The Institutes had been created after the war to provide grants for research related to human health, and an advisory panel was created to decide who received the federal funds. The panel appointees were mostly academic biochemists because biochemistry was the only extant academic specialty then involved to any meaningful degree in biomedical research. Named the Biochemical Advisory Panel, it was given absolute authority to decide who received a research grant. Handler had been consistently unsuccessful in obtaining a grant from the Institute because they were legally obligated to fund only research that was linked to health or disease, and he was disinterested in applied biochemistry. But Handler's fortune improved. The composition of the Biochemical Advisory Panel changed to include Handler's former mentor at Illinois as well as others he knew personally. Additionally, Handler received effective advice from friends in the Biochemical Society about how to construct naked averments in his grant application to convey a false impression of its relevance to disease—transparently contrived lies that satisfied the legal requirement of a foreseeable application to human health. In 1948, the Panel approved a grant request by Handler for research on how rats metabolized amino acids, and over the next two years the Panel approved three additional grant requests for similar work.

HANDLER, WHO could not actually do the research himself because of his medical problems, presented a long-range plan to the administration regarding how he planned to manage his new financial resources. He envisioned that they would pay for all research expenses, institutional overhead, and the tuition and salary of post-graduate students, who would work in his laboratory while earning a PhD. The grant money would also pay his salary for the proportion of his time spent on the grants. Handler justified the use of public money on the basis that the public would be the ultimate beneficiary of the research.

IN LESS THAN TWO years Handler became the best-funded investigator in the biochemistry department, but he had no authority over departmental policy because was only an associate professor. As it turned out, however, the departmental situation was a ripe moment for him. The first and only chairman the department ever had died suddenly. The apparent choice for a successor was the department's only full professor, a respected protein biochemist whose research had been supported by the Institutes and major private philanthropies. Handler, however, very much wanted the job. He sought the support of friends in the Biochemical Society, where his notion of free play for the intellects of biochemists as a matter of government policy was a huge favorite of the membership. Prominent Society members wrote strong letters of support for Handler, emphasizing his leadership skills, as did the Board of the Society, which regarded Handler as an effective spokesman for the Society's interests. In the end, the administration chose Handler as chairman, and promoted him to full professor. He became the youngest professor ever at Duke and the youngest biochemistry chairman in the US.

Twenty years later, Handler answered questions regarding his appointment:

"You became chairman of the department in1950. What was the task of the chairman of the department?"

"The task, ultimately, of the department chairman is to plan the future. I've always had a little placard that said 'Think.' A department chairman's motto should be 'Connive.'"

"What did it seem to you to be like, to face all these administrative duties early in the morning, first thing, at 32 years of age? You had not been the chairman of a department before. What were your ambitions along this line?"

"I didn't really have any administrative ambitions. They didn't mean anything. But with the passage of time I developed some vision of what I would like to see for the biochemistry department and for the institution. I, as an administrator, if such I was, wasn't very much of an administrator. We didn't do much administration. We did sit around and dream, and I suppose I did my share of that. I began to have some vision of what I hoped the biochemistry department and the medical school would one day be."

HANDLER NOTIFIED the administration that he intended to expand the plan he had devised for his own laboratory and apply it to the entire department, which would focus heavily on research and make teaching PhD students how to do biochemical research its dominant mission. Teaching biochemistry to first-year medical students would become the secondary mission. He wrote that that the "task of developing researchers competent to investigate the edges of knowledge is a terribly expensive and complicated task, but it is imperative for the sake of both the present and future." To pay for the research and education initiatives, he said he would write grant proposals to the Institutes, similar to what he had already done, and that he expected to be even more successful in the future. He envisioned a much larger departmental faculty that would be supported completely by the Institutes, requiring no funds from the administration. He planned to recruit new faculty who were effective grant-writers and successful managers of their own laboratories. If they failed to live up to his expectations, they would not receive tenure.

HANDLER KNEW he could more efficiently obtain funds from the Institutes to fulfill his promises to grow his department if he were a member of the Biochemical Advisory Panel. His opportunity to secure an appointment to the Panel occurred in 1953, occasioned by a worsening of business and financial problems experienced by the Biochemical Society coupled with the lack of a candidate to replace the incumbent on its governing board who was responsible for solving the problems. Handler agreed to accept the position and, to lessen the financial pressure on the Society, he offered to house the Society at Duke and pay for the office rent and secretarial services. He also promised to work toward finding permanent locations for the Society and its journal. In return, Handler asked the Society to recommend to the Institutes that he be appointed to the Biochemical

Advisory Panel. Handler joined the Board and became the chief operating officer of the Society. Shortly thereafter he was appointed by the Institutes to its Biochemical Advisory Panel.

Handler systematically resolved the major problems that were in the queue when he took charge of the Society. He was instrumental in finding a permanent home in Bethesda for the Society and its journal; the location was near the Institutes and the offices of the congressmen who would decide the appropriations levels for biochemical research. He streamlined the member-selection process, successfully organized major national and international biochemistry meetings, appointed a new editor for the journal, and spoke at national forums where he aggressively advanced the Society's views regarding the importance of increased funding of biochemical research.

Handler skillfully ran the Society for the good of its members and demonstrated an ability to act quickly when it was threatened. At an annual meeting, he was unexpectedly confronted with a serious problem related to congressional concern about communists in the federal government. The Leaders of Institutes, under pressure from politicians, had begun denying research grants and positions on the Biochemical Advisory Panel to Society members who had secretly been accused of being communists; the blacklisted members were not afforded an opportunity to learn any details regarding the accusations or to rebut them. Society members raised the problem at the annual meeting, and Handler quickly organized a group that drafted a statement opposing the Institutes' practice of denying research funds to society members for reasons not related to scientific merit. A famous biochemist became the spokesman for the group and defended the statement in numerous public appearances, but Handler was the effective behind-the-scenes organizer and proponent. In the end, the statement was adopted as national policy by order of President Eisenhower. The episode dramatically elevated Handler's stature within the Society, and he became progressively emboldened to resolve issues unilaterally.

HANDLER'S ATTITUDE, at least in the eyes of his critics, became increasingly more imperious. In one instance, a senior biochemistry professor who was in the process of writing a biochemistry textbook invited Handler to write the portion of the book that dealt with proteins, which he did. When Handler received the galleys of the book from the publisher, he saw that a portion of what he had written had been changed. In a fit of temper, he shredded the galleys and sent the pieces to the senior author who reacted with anguish because his contractual obligations to the publisher were jeopardized by Hander's action. Handler's anger cooled after his original text was restored, but the episode served notice that, when he had power, he wouldn't shrink from using it aggressively to obtain his objective.

PANEL MEMBERSHIP and his position as managing officer of the Society gave Handler the opportunity to shape the evolution of US biomedical research according to his image. He later described the developments as pivotal in his career decision to devote his career to matters related tothe organization of science, its role in society, and its relationship to government.