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THEODORE THOMAS PUCK
1916—2005

A Biographical Memoir by
DAVID PATTERSON

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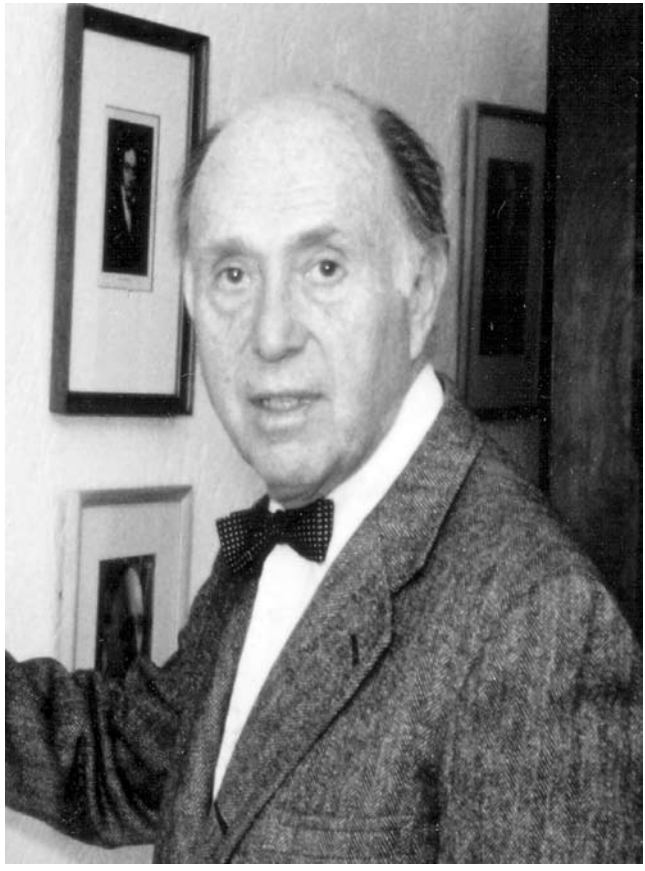
Biographical Memoir



Theodore T. Huck

THEODORE THOMAS PUCK

September 24, 1916–November 6, 2005

BY DAVID PATTERSON

THEODORE PUCK WAS ONE of those rare scientists who essentially created a new discipline, somatic cell genetics. His work made possible much of modern mammalian cell molecular genetics. He devised the first practical method to accomplish single-cell plating of mammalian cells with a high (indistinguishable from 100 percent in some cases) plating efficiency (1955). What is not so widely recognized are his contributions to the more technical aspects of this discipline; for example, he and his colleagues designed and built the first really practical CO_2 incubators for growing mammalian cells as individual colonies (1962,2). The incubators we all currently use, although technologically much different from Ted's original design, are based on the principles that he established.

Ted's lab was still building incubators when I arrived in 1971, and in my experience these incubators worked better than anything available to this day. He recognized early on the importance of devising well-defined, and hopefully completely defined, growth media for mammalian cells. He was certainly not the first to come to this realization, but he and his colleagues, especially Richard Ham and Gordon Sato, were among the most successful (Ham 1965; Barnes and Sato, 1980). One result of these studies was Ham's F10

and later Ham's F12 media, which are still widely used. He established and characterized the Chinese hamster ovary cell line K1 (CHO-K1), which remains a mainstay of modern mammalian cell genetics and is widely used in academic labs and in many biotechnology companies because of its favorable growth characteristics and ease of use for many different kinds of experiments (Puck, 1985). These innovations were critical for the success of somatic cell genetics.

Shortly after devising the single-cell plating technique, Ted and his colleagues determined the mean lethal dose of X irradiation required to kill mammalian cells (1956,2). This experiment is widely recognized as one that revolutionized the field of radiation biology. It is also recognized as having a revolutionary effect on the use of radiation to treat cancer. Another early contribution involved the definitive proof that humans have 46 chromosomes. Clearly this was first shown by Tjio and Levan, but their results were not easily accepted (Tjio and Levan, 1956); for example, in 1958 a suggestion was made that humans could have 46, 47, or 48 chromosomes, and that Caucasians and Japanese might differ in this regard (Kodani, 1958). Ted's immediate recognition of the outstanding nature of Tjio and Levan's cytogenetic work led him to invite Tjio to join the laboratory, where they made important contributions firmly demonstrating that 46 is indeed the correct number of human chromosomes (1958,1). He organized a seminal meeting in 1960 in Denver that established the Denver system of chromosome classification that is the basis for the methods still used today (1960,2).

Ted and his colleagues developed the first practical method for isolating auxotrophic mutants of CHO-K1 cells (1967,2; 1968). His laboratory was one of the first to use somatic cell hybridization to map genes onto human chromosomes and the first to identify different complementation groups among auxotrophic mutants with the same

nutritional requirements (glycine in this case) (1969,1,2). His laboratory was also one of the first to apply techniques of molecular biology to extend the resolution of mapping human chromosomes theoretically to any degree of resolution desired (1982). He was one of the first to recognize the relationship between structural components of the cell and regulation of gene activity, a phenomenon he called "gene exposure" (Ashall et al., 1988). He also devised what may be the most sensitive assay for mutation using mammalian cells in existence (1997, 2002). He looked upon this as one of his most important scientific endeavors, one that he continued to pursue until his death.

Ted was elected to the National Academy of Sciences in 1960 and the Institute of Medicine in 1974. He garnered numerous awards in his life, including the Lasker Award in Health Science in 1958, a Distinguished Professorship of the American Cancer Society in 1966, the E. B. Wilson Medal of the American Society for Cell Biology in 1984, the Bonfils-Stanton Foundation Award in Science in 1984, and many others. Unfortunately he was never awarded the Nobel Prize, which I and many others are convinced he deserved.

Ted was born in 1916 in Chicago. He remained in Chicago—with the exception of a one-year stay in Gary, Indiana, during his childhood—throughout his education, including his Ph.D. training with James Franck, a Nobel laureate in physics, at the University of Chicago. Early in his life he and his brother Bernard helped their father install asbestos insulation. At that time the dangers of asbestos were not known. Tragically his brother died of mesothelioma, a form of lung cancer provoked by exposure to asbestos fibers. Ted credits his brother's death, which occurred after he started working on cancer, with giving him a more personal stake in his research. This experience probably also contributed to Ted's lifelong interest in environmental mutagens. Indeed,

he was working on methods to detect environmental mutagens until he died. His goal was to develop a rapid, accurate, inexpensive, and simple method for detecting environmental mutagens so that exposure to them could be eliminated or minimized.

Ted was a dedicated family man who was extremely proud of the accomplishments of his wife, Mary, who coauthored many publications on sex chromosome disorders with Arthur Robinson. They were married at the Taos Pueblo in New Mexico, and had a home in Santa Fe, where his wife now resides. He was especially proud, and rightly so, of his three daughters, all M.D.s: Jennifer, Stirling, and Laurel. He died of complications from a fall on November 6, 2005.

James Franck had a major influence on Ted's career. Ted used to tell us that during World War II, he had been recruited (it seemed more like drafted to him at the time) to work on the Manhattan Project and that Professor Franck not only advised against it but made sure that Ted was not forced to work on the project. Franck, who was involved in the Manhattan Project, eventually chaired a committee that issued what became known as the Franck Report, the official title being "Report of the Committee on Political and Social Problems Manhattan Project 'Metallurgical Laboratory' University of Chicago, June 11, 1945" (http://www.dannen.com/decision/franck.html). In this report the committee, which also included Leo Szilard (see below), urged the demonstration of the atom bomb at an uninhabited site rather than its use against Japan and predicted the arms race that later occurred. Since this was a classified report, it is not likely that Ted knew about it until later, but one cannot help but speculate that Ted's relationship with Franck helped shape his lifelong interest in the role of science in human society.

During World War II, Ted stayed at the University of Chicago, where he worked in the laboratory of O. H. Robertson in the Department of Medicine on problems related to aerosols and the spread of bacterial and viral infections through the air and on dust particles. He was also a member of the Commission on Air-borne Infections, Army Epidemiological Board, Office of the Surgeon General, and his work had relevance to the war effort. In this capacity he was remarkably productive, publishing over 30 manuscripts. This period heightened his interest in biological sciences, and he applied for and obtained a postdoctoral fellowship in the laboratory of Max Delbruck at the California Institute of Technology, where he developed his interest in genetics and in the application of physical principles to biological problems. He remained in Delbruck's lab for only one year. At that point he was successfully recruited to establish and chair the Department of Biophysics at the University of Colorado Medical School. He remained affiliated with the University of Colorado for the rest of his life. He continued his work on bacteriophage until 1954, publishing 14 papers, many of which made important contributions to understanding of phage-host interactions. At that point his career shifted into mammalian cell tissue culture and somatic cell genetics.

At this point I would like to comment on Ted's relationship to Leo Szilard because this is a matter of some sensitivity. It is true that the nature of Szilard's involvement in the development of the feeder layer technology for single-cell growth of mammalian cells is a matter of some discussion, with the exact nature of the contribution being somewhat unclear (1994; Marcus et al., 2006). What is often overlooked in these discussions of events in and around 1954 and 1955 is that the evidence shows that Ted retained a deep respect and admiration for Szilard; for example, Szilard won the 1960 award as Humanist of the Year from the American Humanist

Association. Ted presented the award to Szilard on behalf of the association and wrote an eloquent article extolling Szilard's scientific accomplishments as well as his accomplishments as a humanitarian (1960,1). This piece closes with the statement, "If humanity is to survive this most threatening crisis of its history, something of Szilard's philosophy will have to become an accepted part of the universal attitude of mankind." It is also a matter of public record that Ted campaigned for Szilard to receive the Fermi Award, a presidential award for lifetime achievement in science.

In 1967 and 1968 Ted and his colleague Fa-Ten ("Louie") Kao published their classic method for isolating auxotrophic mutants of Chinese hamster ovary (CHO-K1) (1967,2; 1968). David Gillespie, my Ph.D. thesis adviser at Brandeis University, thought that these were seminal papers in genetics and insisted that his students read them. Shortly after this, Ted gave a seminar at Harvard that I attended. Ted's way of thinking about somatic cell genetics, his enthusiasm for science, and his optimism about the role of science in human society were incredibly impressive. David Gillespie strongly urged me to write to Ted about the possibility of joining his laboratory as a postdoctoral colleague, which I did.

A few weeks later Ted called me on the telephone and said he would like to meet with me. When I asked him where he was, he said, "I'm in a Radcliffe dormitory room." At the time I didn't know, of course, that one of his daughters was attending Radcliffe, and I was a little taken aback by this response. It was my first encounter with Ted's remarkable sense of humor. He was in town to give a talk at MIT. We met before his seminar and discussed possible projects.

We agreed that my project would be to isolate temperature-sensitive mutants of CHO-K1 cells, in the end a successful but somewhat limited accomplishment since at that time it was exceedingly difficult to determine the functional defects in

such mutants (Patterson et al., 1976). Meanwhile, Ted and his colleagues Louie Kao, Larry Chasin, Bob Johnson, and others were developing crucial genetic methods of somatic cell genetics, most notably the use of various mutagens to induce mutations, somatic cell hybridization for complementation analysis of mutants defective in the same biochemical pathway, and mapping genes to human chromosomes (1969,2; Kao and Puck, 1971). Ted encouraged me to take part in this ongoing endeavor, which was a turning point in my career (1974).

Ted suggested that I should study purine-requiring auxotrophs of CHO-K1, a suggestion which in hindsight was a remarkably good one. This pathway had been well defined enzymatically largely by James Buchanan, Joseph Gots, and their colleagues, and consisted of 10 enzymatic steps. Ted and his colleagues had isolated two complementation groups of CHO-K1 purine auxotrophs, named AdeA and AdeB. Following the general strategy for somatic cell genetics defined by Ted and his colleagues, I set out to isolate additional complementation groups and to characterize the biochemical nature of the defects in the mutants. Ted and I had numerous discussions about this project, often on Saturday mornings, a time during which the distractions of the week were markedly reduced and a really good time to engage Ted in scientific discussions. One particular experiment was to determine which intermediates in the purine biosynthetic pathway accumulated in mutants representative of each complementation group by separating radioactively labeled intermediates using thin-layer chromatography. This experiment resulted in unambiguous ability to discriminate each complementation group biochemically, except ones so early in the pathway that they did not accumulate intermediates.

On the Saturday morning after I had obtained this result I brought it to Ted, who instantly not only grasped its scientific significance, but also its significance for my career. One comment he made was, "This experiment can make your career." In many ways he was absolutely right. He suggested several additional experiments before believing that the results were suitable for publication, for example, inclusion of additional mutants that required a purine, a pyrimidine, and glycine (GAT^- mutants) or that required a purine and a pyrimidine (AT^-). While this was frustrating at the time, it proved to be excellent advice, and greatly improved the resulting manuscripts.

The first manuscript was published in the *Proceedings of the National Academy of Sciences* with Ted and Louie Kao as coauthors (1974). After this publication, Ted insisted that I publish on my own or with students and postdocs from my own laboratory or other faculty members, even though including him as an author would have been clearly justified. Ted's action allowed me to establish my scientific independence, an especially difficult task since Ted offered me a position at the University of Colorado, which I accepted.

Ted saw that my interests were becoming biochemical and introduced me to some of his colleagues in that area, including Seymour Cohen and Ernest Borek, both of whom had distinguished careers studying aspects of purine metabolism. Seymour Cohen introduced me to HPLC, which at that time stood for "high pressure liquid chromatography," but now stands for "high performance liquid chromatography." It was quite a new technique at the time, and remains a mainstay of modern biochemistry.

Ted also insisted that I audit a medical genetics course taught by Arthur Robinson to medical students at the University of Colorado. Arthur was a pediatrician in private practice in Denver in the 1950s who took care of Ted's

daughters. Soon Ted had him working in the lab one day a week, and then giving up private practice to join the faculty of the Department of Biophysics (Robinson, 1990). Shortly after joining Ted's department, Ted, Jo Hin Tjio, and Arthur published one of the first manuscripts describing a sex chromosome abnormality in humans (1959). In 1964 Ted and Arthur published a method for sex chromatin determination in newborns (Robinson and Puck, 1964). These publications enabled Arthur to undertake a long-term analysis of the effects of sex chromosome anomalies on human development. Arthur's collaborator on 10 of these manuscripts was Ted's wife, Mary Puck. As Ted often did, he chose not to coauthor these manuscripts, although it would have been well justified. This project continued until 1998, just two years before Arthur's death in 2000. Ted and Arthur published numerous manuscripts together and were colleagues and friends for almost 50 years.

Auditing Arthur's class was an incredibly valuable experience as I got to know Arthur. We remained close friends until his death. Scientifically, these lectures led to another major change in my career. As part of my studies on purine synthesis, I undertook to map each of the genes encoding enzymes of the pathway to human chromosomes using somatic cell hybridization. One of these turned out to be on human chromosome 21. Through Arthur's course I had become familiar with Down syndrome, or trisomy 21, and it became clear that the mapping of one of the complementation groups, AdeC, to chromosome 21, offered a major opportunity to attempt to define the genetic content of chromosome 21 and to try to understand Down syndrome. Ted, who had published work on Down syndrome in 1965, enthusiastically supported this effort. In the early 1980s I applied for a project grant on Down syndrome and was successful. However, the site visit report recommended that Ted's component be deleted. Though I

dreaded the unpleasant task of telling Ted the news, he took the news with equanimity and promised to remain available as an adviser to the project, which he did.

Ted assigned me to run the Eleanor Roosevelt Institute Seminar Series. This became one of the premier seminar series at the medical school, largely because most of the speakers were Ted's friends and included many of the luminaries in molecular biology and biomedical research, including Max Perutz, Fred Sanger, Francis Crick, Marshall Nirenberg, Paul Berg, Ruth Sager, Lou Siminovitch, Phil Marcus, and others of that stature. Ted insisted that I act as their host, so I had many private interactions with them, much to my benefit and inspiration. Importantly, Ted also encouraged me to invite some of my scientific colleagues to visit. One in particular stands out, and that was David Housman, a colleague of mine in graduate school. This visit turned out to be quite significant. It led to a collaboration between Ted and David resulting in a series of three publications establishing methods to extend the resolution of somatic cell hybrid mapping to the molecular level and for isolation of clones of human DNA from human and hamster hybrid cells (1979, 1980, 1982). This method was widely used by many others, notably Carol Jones, who continued a fruitful collaboration with David that lasted until 1993. Again, Ted chose not to be a coauthor after the first publications even though it would have been appropriate—to help Carol establish her own independent laboratory.

For his entire career Ted believed that what we do as scientists is central to the human endeavor. Not only did he believe this, he acted upon his beliefs in countless ways, sometimes at considerable risk to his career and reputation; for example, in 1955 Ted along with Ray Lanier issued a public statement stating that aboveground radioactive testing being carried out at that time in Nevada was resulting in radioactive

fallout in Colorado that posed a health hazard. At this time Ted had funding from the Atomic Energy Commission, which rejected his claims about the dangers of radiation. A telling quote from Ted was, "The trouble with airborne radioactive dust is that we breathe it into the lungs, where it may lodge in direct contact with living tissue." (*Los Angeles Times,* Mar. 13, 1955, p. 20). Lanier, then director of the University of Colorado's radiology department, pointed out the absence of any "safe minimum below which danger to individuals or their unborn descendants disappears." This statement is often credited with introducing the concept that there is no safe minimal dose of radiation. It was a prescient one, for decades later Ted worked on this exact question, namely, demonstration that extremely small doses of X irradiation, perhaps only one or two times above the dose all of us receive from background radiation, can cause mutations (1997). At the time this controversy was occurring the debate focused on X rays or gamma rays. Ted stressed that alpha and beta rays, especially from inhaled particles, might also cause health problems. This was another prescient statement. It is interesting that at that time Ted was most likely working on the experiments resulting in his publication with Philip Marcus of the true lethal dose of X rays. Many of Ted's early publications had dealt with aerosols, the spread of infections through the air and in dust, and ways to prevent these. He knew what he was talking about.

The governor of Colorado, Edwin C. Johnson, responded by saying that Puck and Lanier "should be arrested" and that "the statements are part of an organized fright campaign" (Miller, 1991). The Atomic Energy Commission also weighed in, claiming that there was no cause for concern from fallout. Of course, this position later changed, and atmospheric testing was stopped.

Later it became clear that even low doses of alpha radiation, the form released by radon, are causal for human cancers. Almost 50 years later Puck and his colleagues published a paper in the *Proceedings of the National Academy of Sciences* demonstrating the detection of mutations by extremely low doses of alpha radiation (2002). This manuscript also engendered some public response, although not nearly so strident, and much of the response had to do with the demonstration in this manuscript that caffeine inhibited repair of alpha-radiation-induced DNA damage. In this manuscript Ted warned against caffeine ingestion. Personally, Ted acted upon his findings and curtailed his intake of caffeine, something that he tried to convince me to do without any success. In that manuscript he also expressed his concept that mutation screening at low doses could be used to screen the environment for mutagenic agents, which then could be removed from the environment or protected against. He compared this to the use of sanitation to prevent infectious disease. He was fond of pointing out that sanitation was more important in reducing infectious disease deaths than the use of antibiotics.

Ted, as founder and chair of the Department of Biophysics at the University of Colorado Medical Center, instituted as one of the requirements of the Ph.D. degree that students demonstrate "some appreciation of the social, humanistic, and philosophical implications of the scientific and technological explosions which are occurring in our time" (Doctoral and Postdoctoral Training in Biophysics, University of Colorado Medical Center). This requirement was certainly still in force for many years after I arrived in Denver, and was taken quite seriously. If anything, Ted's belief in the crucial role of science in human history deepened as he grew older. He believed that the developed countries had an obligation to share the results of their scientific, and especially medi-

cal, research with emerging countries and that this would be a powerful force for world peace. Some considered this sentiment to be a bit of an overstatement, but not all. In an article in the *Economist* in 2002, "Sustaining the Poor's Development," the argument was put forward that Western leaders could contribute to helping developing countries by focusing their aid on "the issue that is still most difficult for poor countries to deal with themselves, disease" (*Economist,* Aug. 31, 2002, p. 11).

In the late 1950s and early 1960s Ted spearheaded the formation of the Eleanor Roosevelt Institute for Cancer Research. The concept was that to understand and eventually cure cancer would require a multidisciplinary approach not constrained along disciplinary lines. In this endeavor he was aided immensely by the support of Matthew Rosenhaus, president and chair of J. B. Williams Company. The name came about because the Rosenhaus and Roosevelt families had been acquainted for many years, and Matthew asked for and received Mrs. Roosevelt's permission to use her name. For many years the institute consisted of a single laboratory, Ted's. By the early 1970s Ted's success and changing conditions allowed the expansion of the institute to include other laboratories. I was one of the first of the new faculty members of the institute.

With Ted's support I also became an assistant professor in the Department of Biophysics and Genetics. As new faculty we were expected to apply for and obtain grants to fund our work, although initially we were all funded from Ted's resources. Ted suggested that I should apply for an R01 from the National Institute on Aging, which was formed in 1974. I was successful in this and received what I believe to be one of the first grants awarded by the NIA. Ted also urged me to apply for a Research Career Development Award, which was also successful. He suggested that I apply

for a Basil O'Connor starter grant from the March of Dimes. I applied for this award and was invited for an interview in Chicago. At that time I had never flown and was terrified of the prospect. At the interview I was told that I was ineligible for the award because my salary came from Ted's grant funds. I remember the flight back and landing in a raging thunderstorm at 10 at night being sure that I was going to die. I went to Ted the next day and told him about my experience, and after some thought, his solution was that I should convert the Basil O'Connor grant to an investigator-initiated research grant from the March of Dimes. I was really skeptical of this approach but went ahead, and was successful with this application as well. This would not have happened without Ted's encouragement and sage advice. So by 1974 because of Ted's encouragement and advice, I had my own well-funded laboratory at the Eleanor Roosevelt Institute and the Department of Biophysics and Genetics at the University of Colorado Medical School.

Funding was not always so abundant. I remember well Ted's attitude when the young (or sometimes not so young) faculty of the institute or department would complain about lack of funds. He consistently had two comments: "Anyone can do science with money" and "When all else fails, the Lord will provide." After hearing the first comment for several years, I finally responded, "I would like to try it that way." As I recall, I never heard that comment again. With regard to the second comment, it was usually not the Lord that provided funding when times were tight, but Ted.

Ted gave his students and fellows a remarkable degree of freedom. Some interpreted this as disinterest in their work, but my own experience was much different. Ted always had not only sage advice regarding research directions but also insights into experimental details and interpretation. Even before I had faculty status, I essentially had my own laboratory,

with a great deal of freedom. Having my own lab brought some interesting responsibilities. One day in the spring of 1973 Ted introduced me to a young medical student and asked me to discuss with him the possibility of his spending a summer doing research in my lab. I thought he was very bright and so he joined the laboratory. The young man was Bob Nussbaum. Bob learned the basic methods of tissue culture and somatic cell genetics during that summer and fall. Later he described to me a lunch with Ted at Hoover's restaurant, then across the street from the lab, at which Ted explained to Bob how to derive kill curves of cultured cells based on the Poisson distribution. Bob remembers Ted saying, "You know what that is, don't you?" As Bob told me, "Of course the entire episode was rendered even more exciting by the fact that I ultimately intended to make him (Ted) my father-in-law and I realized quite early that if I flunked the Poisson distribution test, I was very likely never to attain that goal." Bob is now Holly Smith Distinguished Professor in Medicine and chief of medical genetics at the University of California, San Francisco, and the husband of Jennifer Puck, M.D., Professor, Department of Pediatrics and Institute for Human Genetics, UCSF. That summer in my lab was Bob's first experience in biomedical research, but at least as influential were his interactions with Ted, even discounting the role of future father-in-law. Incidentally, Ted was the only person I knew who could sign for lunch at Hoover's, a restaurant where we often had lunch to discuss science, education, politics, and basically any topic. Unfortunately Hoover's, long a landmark in the medical school area of Denver, no longer exists.

I certainly resonated with Bob's experience. On one of my first days in Ted's laboratory he took another postdoc and me to coffee, not at Hoover's but in the University of Colorado Medical School cafeteria. As soon as we sat down

after getting our coffee, Ted started the discussion by asking, as far as I could tell out of the blue, "Do either of you know how a microwave works?" Fortunately the other postdoc answered immediately and correctly, because I had no idea. Of course, I was not courting one of Ted's daughters, so perhaps the stakes weren't so high for me.

As Ted and I grew closer I was able more and more to observe his administrative and development skills as director of the institute. It was fascinating to learn from Ted about scientific administration, leadership, and fund raising, until one day in 1978 Ted asked me to assume the responsibility of the associate directorship of the Eleanor Roosevelt Institute. I was somewhat shocked at this, having had absolutely no formal training as an administrator or fund raiser; nevertheless, I accepted, feeling that it would be an honor and privilege to work with Ted in this capacity. It was another turning point in my career. Ted arranged for me to meet many of his friends from outside the world of science, including the Roosevelts and other members of the board of the institute, including Matthew Rosenhaus, Emmett Heitler, at that time CEO of Samsonite, and others. I still maintain contacts with the Roosevelt family members, two of whom are now on the board of the institute, and with Bruce Heitler and Mattie's son Albie, although not as frequently as I would like. By 1984 I had assumed the position of president of the institute, succeeding Ted, and before him, James Roosevelt Sr., the oldest son of Eleanor and Franklin Roosevelt. In 1988 I became scientific director of the institute as well. I like to think that my assumption of these duties allowed Ted to devote himself more completely to his first love, biomedical research.

As chair of the new Department of Biophysics at the University of Colorado Medical School, one of Ted's responsibilities was teaching. As usual he threw himself into this effort and was very successful. To this day I run into people, often

physicians who graduated from the medical school decades ago and who, when they learn of my relationship with Ted, comment with great enthusiasm that he was revered and inspiring as a teacher. Some of them were in Ted's first class of medical students.

Ted thought deeply about education throughout his life, both in medical schools and in other venues. In 1962 he published an article entitled "Special Responsibilities of the Medical School in View of the Biological Revolution" (Puck, 1962). The current dean of the University of Colorado at Denver School of Medicine credited Ted with helping to inspire a revision of the medical school curriculum in the early 1990s. He was deeply concerned about the teaching of science, and indeed of teaching in general, from elementary school to the postgraduate level. He was a member of the Paideia Group, organized by philosopher Mortimer Adler, which considered the state of primary (kindergarten through high school) education in the United States, and in 1984 published *The Paideia Program,* an educational syllabus in which Ted in collaboration with Donald Cowan published an essay on the teaching of science in primary and secondary school (Cowan and Puck, 1984). The ideas expressed by this group are still influential in education today. He was a member of the Editorial Board of the *Encyclopedia Britannica.* Ted continued to develop his new ideas on the state of science and medical education, and general education in the weeks before his death.

Ted loved the outdoors and the mountains of Colorado, and often spent many weeks during the summer in Aspen, where he played an active role in the Aspen Institute, originally known as the Aspen Institute for Humanistic Studies. Ted helped establish the Given Institute, originally the Given Institute for Pathobiology, a conference center in Aspen, Colorado, in 1972. It was originally dedicated to biomedical

science conferences, although its mission has expanded since then. Ted organized some of the first scientific meetings at the Given Institute in Aspen and made sure that no scientific sessions were scheduled in the afternoons. During this "free" time, he organized hikes in the mountains around Aspen for the conference participants and their families. Many of the world's most renowned scientists took advantage of Ted's abilities as a hiking guide. Often the most advanced scientific ideas and hypotheses of the day were discussed and refined on these hikes. I had the good fortune to participate in many of these activities, and they were a great inspiration.

At my very first Aspen Conference, however, the tone was actually very depressing. Many of the speakers, renowned experts in their fields, seemed almost burned out, not knowing where their field was headed. Ted's response was "be bold, creative, think more broadly. This is the most exciting time in science." He never lost this attitude of infectious optimism about science. He worked with unflagging enthusiasm until the very end of his life. Only a few days before his death Ted, Sharon Graw, and I began a new collaboration based on his method to detect extremely low doses of environmental agents that can cause mutations leading to cancer. This project is completely consistent with his early, successful efforts to find the true lethal dose of radiation and to warn of its harmful effects. Ted's thoughts on this new collaboration were representative of the way he lived his entire scientific life of over 60 years: "This is the most exciting time in science. There is so much to do!"

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