

HISTORY OF THE
NATIONAL EYE INSTITUTE
1968–2000

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WITH NANCY BERLAGE

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Introduction

The creation of the National Eye Institute (NEI) by Congress in 1968 under the umbrella of the National Institutes of Health was a seminal event for vision research. It fully legitimized the field as a distinct and important component in advancing the health and welfare of the American public. It provided the foundation to build scientific and clinical infrastructure for an enduring enterprise that has made significant contributions in the treatment and prevention of eye disease. This act of Congress has yielded tremendous benefits to preserving vision for millions of Americans and countless millions more across the globe.

This book chronicles the first 30 years of the NEI and its programs. These first years were critical for the development and growth of the intramural research program; the strong commitment to investigator-initiated research; the creation of extramural program areas; and the inception of clinical trials for vision and eye disease.

Dr. Carl Kupfer served as the first director of the NEI and was instrumental in envisioning and creating the institute and its structure. His organizational prowess, and his ability to recruit talented staff and scientists, are an enduring legacy. Dr. Kupfer was aided in his quest to develop the NEI into a premiere institute by identifying and selecting Mr. Ed McManus in 1973 as the NEI Executive Officer and later as the Deputy Director. Mr. McManus brought management skills in planning, organization, developmental finance, and public policy, which greatly facilitated the rapid expansion of the NEI. The NEI grew from a budget of \$24 million in 1970 to in excess of \$500 million when Dr. Kupfer retired 30 years later in 2000.

The challenge of attracting this funding and spending these resources effectively is described in the pages that follow. There were many others who also took part in the development of NEI and the eye and vision research field, starting with Dr. Jules Stein, the president of the Music Corporation of America; David Weeks, the president of Research to Prevent Blindness; and especially Dr. Edward Maumenee, a giant in ophthalmology as the Chief of Ophthalmology at the Wilmer Eye Institute, Johns Hopkins Medical School. Other ophthalmologists, such as Dr. David Cogan and Dr. Bradley Straatsma, also need to be applauded as well for their contributions in founding the NEI and providing advice to the Institute leadership as it developed its programs. Finally, in the '80s and '90s, the political and scientific leadership of Dr. Stephen Ryan contributed greatly to the success of the NEI.

As the current director of the NEI, I read this book with a deep appreciation for the efforts that went into making the NEI and vision research the success that it is today. Under the leadership of these dedicated individuals, the eye health of the American public has flourished.

Paul A. Sieving M.D., Ph.D.

Prologue

The year was 1968. It was a typical hot, sunny day in Sarasota, Florida, quite characteristic for early May, the usual date for the annual meeting of the Association for Research in Vision and Ophthalmology. Sitting on the rooftop restaurant of the Azure Tides Motel on St. Armand's Key were three association members. They had taken a break from the lectures and presentations to meet and have a friendly conversation.

V. Everett Kinsey, Ph.D., was a senior researcher in the vision research community. He was at the pinnacle of his career, having just been appointed as the first director of the Eye Research Institute which he had co-founded that year at Oakland University, Michigan.¹ His outstanding laboratory research in the physiology of the cornea and lens were well known, and he had led a major clinical trial demonstrating that high concentrations of oxygen given to premature babies at birth caused the blinding disease known as retrolental fibroplasia. Always a leader and a visionary, he was now enthusiastically discussing rapidly progressing developments in the movement to create a national institute devoted solely to research on the eye, vision disorders, and blindness.

Dr. Kinsey had been involved in negotiations to establish an eye institute at the National Institutes of Health (NIH), and he now described the concept to his two younger visitors—Carl Kupfer, M.D., Chair of the Department of Ophthalmology, University of Washington School of Medicine, and Marvin Sears, M.D., who chaired the Ophthalmology Section of the Department of Surgery, Yale University School of Medicine.* The eye institute would be carved out of the National Institute of Neurological Diseases and Blindness (NINDB), where ophthalmology research was currently located at NIH, and that portion of the research portfolio devoted to vision would be transferred to a separate, independent research entity. Kinsey displayed great excitement about this proposition—and yet, his younger listeners could not quite understand why this was such an important issue.

To them, NINDB seemed to provide bountiful grant support for ophthalmic research and training. Both Sears and Kupfer had received research grants from NINDB; indeed, they often held more than one extramural grant simultaneously. NINDB extramural staff was solicitous of grantees, it was not unusual for them to visit researchers and inquire about the adequacy of grant support or ask if more was needed. Their staff also provided information on how to negotiate the arcane, complicated, and bureaucratic procedures for obtaining NIH

* Dr. Marvin Sears soon became the first chair of the new Department of Ophthalmology and Visual Science at the Yale School of Medicine, which was created in 1971.

research funds. All in all, NINDB appeared to be anxious to support vision research to its fullest capacity.

Kupfer, as a member of a study section that evaluated grants for NINDB, knew that the institute was giving high priority to particular types of grants (center and program project grants) that would help establish specific ophthalmology programs as “centers of excellence” in vision research. NINDB was even sponsoring a new initiative to fund outpatient department clinical center grants, specifically geared to the vision research community. Thus, Kupfer and Sears were uncertain as to why Kinsey saw the need to create a new institute. Instead, the old adage “If it ain’t broke, don’t fix it” came to mind.

Clearly, Kupfer and Sears—both early into their careers—had not experienced the frustration that older vision researchers had felt in seeking research support; a frustration fueling the drive for a separate institute. Now, as Kinsey discussed this dissatisfaction, he was very persuasive; marshalling facts and rationales that bolstered the case for a separate eye institute. The young listeners began to contemplate how vision research might expand in the future. For instance, Kinsey argued that the institutional origins of research funds impacted their availability; therefore, only an eye institute could be counted on to dedicate its funds to ophthalmic-related research. He pointed out that the vision research portion of the NINDB budget was artificially pegged at a limit of about 15 percent of whatever money Congress appropriated; this despite the fact that research opportunities in the vision field might be greater than those in neurology or neurosurgery fields.²

Moreover, academic institutions tended to relegate ophthalmology to a subordinate position, as a section within departments of surgery. Even if a university had a separate ophthalmology department, it was often regarded more as a clinical component than a research center. As a result, vision research had not expanded much by the 1960s. There had been little growth in the number of departments developing research programs, and only a few departments offered research training and support for staff. Instead, medical schools emphasized creating strong clinical departments and establishing collaborative arrangements with private practitioners, who in turn received privileges to treat patients in school facilities. Kinsey also pointed out that NINDB’s training program was geared toward preparing neurologists, neurosurgeons, and ophthalmologists for practice in their respective clinical specialty rather than in research. In the end, NINDB did not encourage the sort of research training for ophthalmologists that would result in the gradual growth of a vision research community large enough to take advantage of the many research opportunities present.

Sears and Kupfer found Kinsey’s arguments compelling; particularly the rationale that an institute dedicated to eye research would provide ophthalmology with a stronger research base. Both men were part of a new breed of ophthalmologist who believed that ad-

vances in eye care would pivot on both laboratory and clinical research, and not solely clinical experience. Sears and Kupfer themselves were heavily invested in the notion of research. Sears had received his medical degree from Columbia University College of Physicians and Surgery in 1953, and Kupfer had received his in 1952 from the Johns Hopkins University School of Medicine. These two institutions were known for advancing the research model in the United States, and Hopkins was also a pioneer in bringing clinical science to medical education. Both men had learned the value of scientific research for medical practice and had undergone extensive postgraduate research training and experience. After completing his medical residency at the Wilmer Eye Institute at Johns Hopkins, Sears spent over a year in Sweden on an NIH fellowship, doing research in the laboratory of Professor Ernst Barany. He continued his research with an NIH grant after joining the faculty of Yale Medical School in 1961. Kupfer had begun laboratory work as a post-doctoral fellow at Wilmer, and had then spent eight years with the Howe Laboratory at Harvard Medical School. At the latter, he received NIH grant support for his research on the control of intraocular pressure and the neuroanatomy of the optic nerve and visual pathways within the brain.

Sears and Kupfer believed that academic ophthalmologists needed to understand the techniques, methodologies, and epidemiological underpinnings of research, and be able to pass that knowledge on to their students. Both men thought that academic ophthalmologists could benefit from specialized research training, encompassing at least two to three years in the lab, which would allow them to acquire the skills and knowledge for developing hypotheses and designing and conducting experiments. They could then pass on to students an appreciation for research and its clinical uses. Eventually, through application of the scientific method, research would reveal new treatments for patients.

By no means was this thinking in concert with that of all visual specialists. The notion of laboratory research in ophthalmology—much less three years of training for it—was not yet fully accepted in the discipline. Thus, if a new institute dedicated to vision research could help convince naysayers of the importance of providing research training and supporting scientific investigation, then it would, in the long run, provide an important service to the general public, as well as to ophthalmologists in both universities and in private practice.

Sears and Kupfer left that Florida meeting with a new appreciation of why the creation of a separate institute to represent vision research was absolutely essential—if vision research as an enterprise was to grow, be productive, and stay engaged in the highest quality research. Little did they realize that forces at work in the community would soon turn the possibility of establishing an eye institute into reality. This new entity would have the personnel and budgetary resources to catalyze the growth of vision research, and ensure success in lessening the pain and suffering of millions of blind and visually impaired people, not only in the United States but worldwide.

Chapter 1

Beginnings

Introduction

The National Eye Institute (NEI) was created in 1968, some 38 years after the National Institute (singular) of Health was named in 1930. That is not to say that the “study of the eye”—the literal translation of ophthalmology—and interest in eye disease are only recent phenomena. Rather, for a thousand years and more, humans have been attempting to determine exactly how the eye functions and how to cure or prevent diseases that interfere with vision. Sight is precious to both man and animal, enhancing not only the ability to survive but also our perception of the world. Sight allows humans to derive a deep aesthetic pleasure from the physical beauty of the things they see. Through the ages, men and women motivated by intellectual curiosity and the desire to help have worked to improve knowledge of the visual system and unlock the secrets behind eyesight, our “first sense.”

The study of problems related to vision can be traced back to the ancient Egyptians who wrote about treatments for eye ailments in one of the oldest known medical works, the *Ebers Papyrus*, dating from circa 1550 B.C. Through the centuries, philosophers, medical practitioners, and dabblers in science attempted to gain a better understanding of the eye, with only a limited body of scientific knowledge at their disposal. Little by little, advances were made in the understanding of the physiology, anatomy, pathology, and treatment of the eye. Slowly, improvements in eye care began to ease the burden of those afflicted with poor eyesight. The thirteenth-century invention of eyeglasses and the development of bifocal lenses by Benjamin Franklin in the eighteenth century were important milestones. Eye care was then revolutionized when Hermann von Helmholtz, a distinguished German physician and scientist, invented the ophthalmoscope in 1851. Three decades later, in 1881, Carl S. F. Crede, M.D., a Leipzig gynecologist, made an important breakthrough when he discovered that silver nitrate drops could prevent blindness in newborns affected by ophthalmia neonatorum (conjunctivitis usually contracted through the infected birth canal of the mother), then a leading cause of blindness in children.³

The study of eye disease and treatments increasingly incorporated modern scientific techniques. Whereas vision was first conceived as a mysterious, almost magical process and treatment often focused on spiritual or religious practices, over many hundreds of years vision slowly came to be understood as a natural phenomenon. Consequently, there was increasing interest in the mechanical operations of the eye. As belief in the scientific method took hold, doctors began to emphasize more technical approaches to treating illnesses, including those affecting the eye. In the late nineteenth century, the notion of scientific research as an important component of clinical eye care began to gain acceptance. The institutionalization of graduate education and medical research in America, based on the German model, helped to legitimize this concept. Still, through the early part of the twentieth century, doctors relied on anecdotal evidence and their own personal experience in treating patients. By the latter half of the twentieth century, researchers increasingly believed that medical treatments should be scientifically verifiable through randomized controlled clinical trials. At the same time, researchers came to believe that blindness and other vision problems encompassed a discreet set of issues often distinct from those covered by surgical practice under which blindness had previously been subsumed. NEI was born at the intersection and culmination of these long-developing trends.

Momentum

The early twentieth-century public health movement in the United States brought increasing attention to a variety of health maladies and diseases such as tuberculosis, though little attention was paid to vision disorders. The numerous local and national voluntary and professional organizations that formed around specific health issues behaved in quasi-governmental fashion, organizing and implementing all sorts of health regulations and ameliorative activities. There were a few devoted to blindness: the National Society for the Prevention of Blindness (currently known as Prevent Blindness America) was organized in 1908 as a voluntary nonprofit agency to educate the public about preventing eye disease, and a few state and local organizations were organized around the same time. Most of these focused strictly on public health issues and disseminated information about eye disease and patient care. Still, despite this flurry of activity, only a scant amount of public and private resources was devoted to eye issues, especially compared to other disease fields. A few small studies were completed. The Public Health Service (PHS), a new agency authorized to conduct research on human diseases, undertook in 1912 the first U.S. government eye disease study. The PHS studied trachoma among Native Americans and residents of the eastern U.S. mountains. Additional PHS-supported studies considered the effects of venereal disease on the eye.⁴ It was only later, after the federal government became fully vested in supporting biomedical research, that eye study began to claim its share of attention and support.

Federally Funded Research and the National Institute of Health

The early actions taken by the federal government in support of biomedical research, culminating in the establishment of NIH, have been described elsewhere in great detail, so a brief description here will suffice. In short, Congress created in 1879 the National Board of Health, which gave grants to university scientists to carry out disease-oriented research. Research by government scientists started in earnest when J. J. Kinyoun, an officer in the Marine Health Service, started a small bacteriological laboratory in 1877. The Hygienic Laboratory, as Kinyoun's lab came to be called, made research advances in vaccines and antitoxin serums against infectious diseases.

The Ransdell Act of 1930, when it created NIH to replace the Hygienic Laboratory, also authorized research fellowships for the study of basic biological and medical problems. In 1937, the National Cancer Institute (NCI) was created as the first institute centered on a specific disease category. The founding legislation also authorized a research grants program, training and fellowships, intramural research, and a national advisory council. Subsequent institutes would follow that basic organizational template.⁵

Federal funding of biomedical research exploded during World War II under the guidance of the Office of Scientific Research and Development, which coordinated all scientific research for military purposes. The federal commitment to technological, scientific, and biomedical research continued after the war. NIH grew as an institution, and its functions and research scope expanded. The NIH budget increased dramatically from a total of \$8 million in 1947 to more than \$1 billion in 1966.⁶

Multiple interest groups promoted the continued expansion of NIH. By the 1940s, a web of voluntary medical advocacy groups had organized around a plethora of specific diseases and disorders; each group lobbied the government for increased research funding in support of its favored cause. Preeminent was the Lasker Foundation, founded in 1942 by Albert Lasker, a successful marketing executive, and his wife Mary, a Manhattan art dealer. Their efforts greatly boosted the federal role in biomedical research. The Laskers used new publicity techniques to transform the American Cancer Society into a fundraising powerhouse, which in turn became an effective advocate in the Laskers' campaign to increase federal funding for NCI. Although Albert died from cancer in 1952, Mary, aided by wealthy ally Florence Mahoney, continued the work and mobilized a powerful health lobby that brought together policymakers, donors, physicians, scientists, and the general public. The Lasker group deployed highly organized political lobbying techniques, including recruiting and preparing expert witnesses to testify at congressional hearings in support of increased federal funding for health research. As a friend to key legislators such as Senator Lister Hill (D-AL) and Representative John Fogarty (D-RI), and with access to presidents and large campaign contributors, Mary Lasker would wield a great deal of political clout for decades.⁷

In the late 1940s, voluntary health organizations spurred Congress to create three new institutes encompassing mental health (1946), the heart (1948), and dental research (1948), setting the precedent for future “categorical” institutes. NIH added an “s” to its name and became the National *Institutes* of Health.

No sooner was the National Institute for Mental Health (NIMH) up and running, when other groups began calling for a new neurology-oriented institute and separating out neurology research from NIMH where it was housed. Different advocacy groups simultaneously urged Congress to establish an institute focusing solely on a single neurological disease, such as Parkinson’s disease, multiple sclerosis, and others.

At the same time, groups began to agitate for an eye disease and blindness institute. Two laymen—Jacob C. Ulmer and Al Hirshberg—joined forces with Dr. Everett Kinsey to create in 1949 the National Foundation for Eye Research in Washington, D.C. With support from the Laskers and other lay groups, they lobbied Congress for legislation addressing research on blindness.⁸

In 1949, several bills for a neurology institute—of some sort—were introduced in the House and Senate. There was considerable resistance on the part of Executive Branch representatives and Bureau of the Budget* administrators who wanted to limit the creation of additional institutes. Some NIH administrative officials and scientists were also unhappy with this trend, believing that adding more institutes would be inefficient and expensive, and that it would undermine the effectiveness of the NIH research program as a whole.⁹ They disparaged such “disease-of-the-month-club” legislation, believing that research priorities should be chosen not by Congress and lay groups but by objective medical science experts.¹⁰ R.F. Rinehart, from the Research and Development Board oversight agency, also opposed the proliferation of new institutes. At the same time, though, he had the foresight to acknowledge that forming specific institutes might attract greater attention to particular fields of research, draw more eminent personnel to the national institutes, and capture additional support for diseases.¹¹

The hearings on creating a neurology institute proved consequential. In the end, the study of blindness and visual disorders was added almost as an afterthought to one of the neurology bills, a result of Mary Lasker’s influence with Congress and the White House. Apparently, Lasker had come to believe there was a dearth of federal funding for visual research, and she meant to have something done about it. The story goes that representatives from the National Foundation for Eye Research and other groups swayed Congress—through the power of their moving testimonies—on the need for additional eye research. Mildred Weisenfeld, the founder of “Fight for Sight!” and a patient of Dr. John McLean, was extraordinarily effective in her testimony. Young, vibrant, and attractive, Weisenfeld knew

* Today’s Office of Management and Budget (OMB).

how to generate publicity—and she was blind as a result of retinitis pigmentosa, a genetic eye disease. She testified that more funding was needed for research on blinding diseases, despite knowing that she herself could not be helped. Her pleas stirred the committee members. Unexpectedly, the committee added blindness to the specific mission of the proposed neurology institute, apparently partially motivated by the fact that Congressman Andrew Biemiller’s own mother was blind. This add-on did not sit well with the neurology community, which wanted to emphasize mainstream neurological diseases—not blindness—in the proposed institute. Nevertheless, the National Institute of Neurological Diseases and Blindness (NINDB) was created in 1950 when President Truman signed the Omnibus Medical Research Act (P.L. 81-692), which also set up the National Institute of Arthritis and Metabolic Diseases (NIAMD).¹²

NINDB and Ophthalmology

While NIAMD received \$578,000 for start-up costs, NINDB was allotted no funding at all for Fiscal Year 1951. It fell to the mental health institute, NINDB’s parent, to provide startup funds. Ironically, such a situation had happened before when the mental health institute itself was authorized in 1946; for its first year, Congress had failed to appropriate any funds. Luckily, the new NIMH director, Robert Felix, M.D., had received a donation from the small Greenwood Foundation to get mental health up and running. For NINDB, however, no such foundation stepped forward. Fortunately, the following year, Congress found funding for NINDB. Still, in those first years NINDB found it difficult going, especially with the budgetary demands imposed by the Korean War and other domestic policies taking their toll on government finances.¹³

NINDB was able to establish an Ophthalmology Branch with extramural and intramural components, but it functioned primarily as an ophthalmic consultation service for NIH’s new clinical center. The intramural program grew slowly despite having some clinical and laboratory research successes. The overall vision portion of intramural research reached \$2.6 million in 1966, “one-sixth of the total vision research grant appropriations” of NINDB, according to Ruth Harris’ brief history of NEI. The remainder of the vision budget was expended on extramural research grants.¹⁴

The NINDB extramural program in ophthalmology expanded at a slightly quicker pace than the intramural one but not nearly to the levels that vision researchers thought necessary. Extramural research only supported nine grants in 1951; this number jumped to 30 in 1952, and ultimately increased to 337 projects and almost \$10 million by Fiscal Year 1966.¹⁵ These expenditures generated new findings and the NINDB ophthalmology extramural program, like the intramural, did have its accomplishments. One grantee discovered a drug that was effective against ocular herpes simplex, the most common cause of corneal ulcers and

resulting blindness. Impressively, four grantees later received Nobel Prizes for eye research. Perhaps the extramural program's most significant accomplishment was in funding the study that solved the mystery of retrolental fibroplasia (RLF), the leading cause of blindness among children. Frank W. Newell, M.D., a renowned University of Chicago academic ophthalmologist, described this as one of the most outstanding discoveries made in ophthalmology during the 1950s.¹⁶

Unfulfilled Expectations

Still, despite these achievements, many thought the ophthalmic community could accomplish more and that additional grants funds needed to go toward eye and visual research. In financial terms, the 1950s and early 1960s were certainly better for eye research than ever before, even though the vision community for the most part did not acknowledge this at the time. The dollar amounts spent on ophthalmic research increased significantly at NINDB: expenditures increased from \$81,026 in 1951, to approximately \$12.4 million in 1965.¹⁷ Just as the overall NINDB budget increased, so too did the portion set aside for blindness, increasing from 7 percent in 1951 to 14 percent in 1966.¹⁸ To the neurological community, this probably seemed more than a fair slicing of the pie—but not so to the eye community. The scale of these efforts paled when compared to the growth of other NIH intramural programs, and academic ophthalmologists believed eye research should be greatly expanded.

Unsatisfied vision researchers thought that too many ophthalmic-related research proposals with merit went unfunded. There were also disciplinary considerations: ophthalmology was beginning to emerge as a discrete academic discipline, no longer subsumed under surgery. Many in the vision community believed that the discipline could now stand on its own, but generating further development required a great deal more financial and institutional support. For the discipline to advance, researchers needed to gain additional knowledge that would be useful to patients. Some academics were convinced that when the budget was tight, ophthalmic study was assigned a lesser priority for funding than neurology proposals. They believed that vision research proposals did not fare well during the review process and that NINDB's National Advisory Council and the relevant study sections were slanted toward neurology.¹⁹ Dr. Newell later recalled that members of the ophthalmic community had been unhappy because their grant applications had a hard time securing funding, for a variety of reasons.²⁰ In looking back from today's vantage point, Dr. Bernard Becker, a leader in the eye institute movement, thought that ophthalmologists in general had had a more difficult time getting funded than their neurology competitors. Becker remembered back when he was a member of NINDB's eye committee in the mid-1960s, "We had an enormous increase in applications for eye research and we were just swamped and there weren't enough funds."²¹

Still others point out that a number of important vision researchers received NINDB grants. John E. Dowling, Ph.D., thought the drive for a new institute came less from disgruntlement with funding than from a general belief among eye scientists that much more emphasis was needed on eye and vision research. Not only did they want more recognition of the importance of eye studies for basic science research, but also more emphasis on clinical research and application.²²

NINDB did launch a few funding and research initiatives to appease the blindness constituency. An epidemiological study of glaucoma, begun in 1957, proved successful. Less compelling was a new biometrics project that compiled statistics on the extent of eye disease instead of launching more useful epidemiological work, such as studying the risk factors underlying eye diseases.²³ NINDB also failed to recruit and retain highly trained research-oriented ophthalmologists with knowledge of epidemiology.

The Drive for a Separate Eye Institute

It was perceived that NINDB lacked leadership and interest in the vision field. Some influential members of the public, along with members of the vision research community, believed that the problems of blindness and visual disability deserved much greater attention from NINDB and NIH. They believed that ophthalmology was up to the task of launching a scaled-up research program at the institute level. By the mid-1960s it seemed clear that it was time to establish a separate national institute devoted solely to eye research.

Leaders in the Movement for a National Eye Institute

The drive for a separate institute came from both academic ophthalmology and advocacy groups. This was no surprise, given NIH's established pattern of giving support to academic departments for research and training. The leading academic ophthalmologists and vision community supporters of the day led the charge, including Bernard Becker, David Cogan, Edward Maumenee, Michael Hogan, John McLean, Frank Newell, Jules Stein, and Frank Winter.

Bernard Becker, M.D., was chair of ophthalmology at Washington University Medical School in St. Louis since 1953. For NINDB, he had served on its advisory council, the sensory disease study section, and its grants committee. He established *Investigative Ophthalmology* and was its first editor. Like so many leaders in ophthalmology, he had been a resident at the Wilmer Eye Institute at the Johns Hopkins University Medical School. His research interests were wide ranging and his publications voluminous.²⁴

Alfred Edward Maumenee, Jr., M.D., had been chair of the Department of Ophthalmology at Stanford University, before becoming ophthalmologist-in-chief in 1955 of the Wilmer Eye Institute. He was the acknowledged leader of the ophthalmic academic community. A colleague described Maumenee as a man with “enormous capacity of leadership in organization, teaching, research, surgical innovations, and patient care who kept the Wilmer [Eye] Institute at the cutting edge of ophthalmology. A superb clinician, his knowledge of ophthalmology was all-encompassing and his contributions to the literature legend.”²⁵ He was a member of NINDB’s Advisory Training Committee in the 1950s, served on NINDB’s Subcommittee on Impaired Vision and Blindness (1967-1969), and was active in several other prominent associations. He later served on NEI’s National Advisory Eye Council from 1969 through 1971, and from 1975 through 1981.

During this period, Maumenee exercised the necessary leadership to bridge the gap between the political and academic circles. He treated the eye needs of several congressmen, developing close personal relationships with some such as Senator Lister Hill.²⁶ According to Bernard Becker, of all the people in the small group working to establish an eye institute, “Ed Maumenee was the most effective politically.” He was “a great leader and a great administrator,” who easily got people to follow along.²⁷

David Glendenning Cogan, M.D., was preeminent in American ophthalmology as a researcher, teacher, diagnostician, and clinician. He had a grand vision for making ophthalmology a research-oriented discipline. Cogan held the position of director of the Howe Laboratory at Harvard Medical School for 33 years, and he was chairman of the Harvard Department of Ophthalmology from 1955 to 1972. During this time, he helped shape the direction of ophthalmic research and made significant contributions to the field of neuro-ophthalmology. He used his visionary talents to establish a vibrant vision research program at Harvard, training a generation of doctors who would become leaders in eye and vision research (including NEI’s own Carl Kupfer). Cogan stressed the “marrying of basic vision research disciplines of biochemistry and neuroscience with clinical research ophthalmology, and through his success at Harvard, demonstrated that the ophthalmology field was ready for the accelerated growth that the establishment of the NEI would surely bring.” His long and distinguished career is best summed up on the plaque that was unveiled during the dedication in 1985 of the David Cogan Library at NEI. It reads, “So great have been Dr. Cogan’s achievements in all three areas—research, patient care and education—that he more than anyone else, is credited with transforming the field of ophthalmology from a branch of surgery into medical specialty at the forefront of science.”²⁸

Frank Newell, M.D., was section chief of ophthalmology at the University of Chicago before becoming the first chairman of the school’s new department of ophthalmology when it separated from surgery in 1970. He was a leader of numerous ophthalmology associations,

author of multiple textbooks, and a leading clinician. Newall's passion was teaching, and he was known for enforcing high standards.

Michael J. Hogan, M.D., became chair of the Department of Ophthalmology at the University of California-San Francisco in 1959. Previously, he had been director of the Francis I. Proctor Foundation for Research in Ophthalmology, a privately endowed research unit. Hogan was one of the first investigators to utilize the electron microscope in studying the structure of the eye. According to Dr. Phillips Thygeson, "His work in ocular pathology and his study of the pathogenesis of serious ophthalmic disease are exemplary of much of his investigative work which bridged basic and clinical research." Uncle Mike, as everyone fondly knew him, died of cancer in 1975.²⁹

Frank C. Winter, M.D., had a long career at Stanford University, where he directed the Eye Pathology Laboratory (1955–1971) before becoming chief of the Ophthalmology Division (1959–1967). Devoted to international outreach, he would later establish eye clinics and provide eye care in Botswana, Ghana, Baja California, and Central America. He also founded the Christian Eye Ministry (now a division of International Aid Inc.).³⁰

John M. McLean, M.D., was a professor and distinguished surgeon in charge of the ophthalmic division at Cornell University and several New York hospitals. He had studied ophthalmology at the Wilmer Eye Institute and was well known for his clinical research in fungal eye infections, cataract surgery, and retinal detachment.³¹

Jules Stein, M.D., an entertainment business magnate, was the academic ophthalmologists' strongest ally, and he played a major role in the creation of NEI. Before leaving ophthalmology to start his own booking agent company, Stein had attended medical school at Rush University, been an ophthalmology resident at Cook County Hospital, and had worked in a leading Chicago ophthalmologist's office. Stein worked his way through medical school by booking music acts, and he parlayed this entrepreneurial skill into extraordinary success, creating one of the largest and most profitable entertainment companies in the world—the Music Corporation of America (MCA).³²

Research to Prevent Blindness

In 1960 Stein founded Research to Prevent Blindness (RPB) to generate support for eye research. He thought that "ophthalmology needed a businesslike approach to raise funds for research."³³ Stein created RPB after meeting Robert McCormick, a business executive whose cataract surgery had been unsuccessful. According to Frank Newell, McCormick's story motivated Stein to consult with ophthalmic circles about the status of eye research; he learned that it was not adequately supported. To rectify this situation, RPB made grants-in-aid to academic ophthalmology departments. During its first years RPB also focused on

securing increases for the eye programs of the NINDB, with Stein advocating for expansion before Congress. In 1962 Stein and his wife, Doris, established the Jules Stein Eye Institute at UCLA.³⁴

Dr. Bernard Becker recalled discussing eye research funding with Stein during those years. He remembered how the generous Stein set up RPB, which not only directly supported eye departments all over the country, but also provided support to assist in the fund-raising efforts of individual departments for building new facilities. Stein's contributions and grants had a multiplying effect and brought key people to eye departments through block grants. Becker recalled that his department at Washington University, for example, had "unfailingly" received "a chunk of money every year" from RPB.³⁵

In addition to providing grants-in-aid, RPB served as a platform for publicly discussing the great scope of blindness and the paucity of funding for eye research. It also served as an extremely effective lobbying base. To manage RPB, Stein assembled a powerhouse team that would be considered formidable even today in the high-octane lobbying world of Washington, D.C. Stein served as chairman, with Robert McCormick as president. Mary Lasker served as a vice-president, as did Lew Wasserman, a colleague of Stein's at MCA and a Hollywood power broker with political connections at the highest levels. David F. Weeks, who had extensive experience with the National Foundation for Infantile Paralysis and the March of Dimes, became executive director. C. J. Van Slyke, M.D., the former medical director of the U.S. Public Health Service and a retired NIH deputy director, was RPB's scientific director, and Colonel Luke C. Quinn, a health lobbyist who had a proven track record working with the Laskers, was hired to serve as congressional liaison.³⁶

From whence first came the notion of a separate eye institute is not known definitively, as is often the case with ideas that gain broad appeal. Nonetheless, support for the notion had certainly gained considerable strength by the mid 1960s. David Weeks credits Harvard's Dr. Cogan with the idea: "David Cogan had written to Jules Stein and indicated that he thought that we should try to get an eye institute. His suggestion interested Stein, but Dr. Maumenee was the key ophthalmologic player in seeking the establishment of NEI."³⁷ As momentum grew, RPB helped orchestrate a campaign whose end goal was legislation for creating a national eye institute.

Meanwhile, at NINDB, dissatisfaction was growing within the ophthalmology ranks for a variety of reasons. Bernard Becker, the scholarly, research-oriented academic, had become disillusioned with NINDB's neurology-dominated advisory council, of which he was a member. He had previously sat on an NINDB committee and a study section.³⁸ Many in the academic research community continued to believe that eye research grants fared worse than those directed at neurological diseases; whether this was because the ophthalmic researchers were less trained or were the victims of bias on the part of the dominant neuroscience group

was not certain.³⁹ Nevertheless, they thought the neurology-dominated council and study sections unfairly rated the vision applications, such that they were funded less than those in neurology. As a result, some researchers applied inordinate pressure on Becker to influence the council to obtain better outcomes for eye research grants.

Becker was between the proverbial “rock and a hard place.” He pleaded the case directly to NIH Director James A. Shannon, M.D., Ph.D., and NINDB Director Richard Masland, M.D. Shannon agreed with Becker that ophthalmic research needed more encouragement, direction, and a special position within the organizational structure of NIH. According to Murray Goldstein, D.O. (the neurology institute’s associate director for Extramural Programs, and later, the institute’s director), Masland too wanted to increase the scale and quality of NINDB ophthalmic research.⁴⁰ In a recent interview, Becker described how Shannon and Masland offered to make him director of a proposed Division of Vision Research to be created within NINDB. The division would have its own discrete funding resources at a level determined through negotiations between Becker and the NIH director. Becker thought about this offer long and hard, but he finally opted to stay in St. Louis and the academic milieu where he performed so well. He had seen enough bureaucratic intrigue and inertia in his years spent on NINDB committees to believe the job was not right for him.⁴¹ Shannon no doubt was aware of the forces being marshaled to initiate a new institute and understood the emotional appeal blindness had as a political issue—no one at NIH could easily forget the coup that had propelled blindness into sharing the neurology institute in the first place. It is doubtful that this counterstrategy to head off the movement for a new institute could have succeeded given the force of the momentum.

In 1964 NINDB formed the permanent Subcommittee on Impaired Vision and Blindness to make recommendations to the NINDB’s advisory council.⁴² Jay M. Enoch, Ph.D., who served as the subcommittee’s executive secretary, was assigned to assemble a comprehensive report on the state of eye research, consisting of topical sections written by specialists. Enoch, then a colleague of Becker’s at Washington University, remembers that no one ever explicitly stated that the purpose of the report was to bolster support for a new institute. Still, he was asked to compile information on the NINDB funding that went toward eye research. After two years, the committee presented a three-volume report to NINDB and its advisory council. According to Enoch, the committee was ordered to limit the public release of the report—the implication being that the report portrayed NINDB too unfavorably in regards to eye research.⁴³

Also in 1964, a group of eminent academics met in Chicago to discuss establishing the Association of University Professors of Ophthalmology (AUPO). Snowed in at the Chicago airport, Maumenee, McLean, Hogan, Becker, and Cogan discussed their vision for AUPO, which led to talk about a separate eye institute. Maumenee remembers that “The

question then came up: Shouldn't we see if we could get out from under the Institute of Neurological Diseases and Blindness and get a national eye institute started?" Subsequent to the Chicago meeting, Maumenee talked to an enthusiastic Jules Stein and Senator Lister Hill, long-time champion of the health research community. Hill warned of a tough battle because NIH Director James Shannon did not want to divide existing institutes or create additional ones. Maumenee also spoke with Representative Harley O. Staggers of West Virginia, the Democratic Chair of the House Committee on Interstate and Foreign Commerce.⁴⁴

Opposition and Progress

According to Maumenee, a number of ophthalmologists opposed the idea: "They said, 'We've got a good, secure thing [in NINDB]. The neurologists are taking care of us very well. You don't know if you are going to get any money. You don't have a director. You don't have any way to run it.' As a matter of fact, I tried to get ARVO [Association for Research in Vision and Ophthalmology] to vote to have an eye institute and they wouldn't do it."⁴⁵ Professor Herbert Kaufman, M.D., also remembers that some academic ophthalmologists refused to get behind the effort, fearing that if it failed, NINDB would take the blame and ophthalmology would suffer as a result. They also worried that the government would not hire a competent individual to run the institute.⁴⁶

The organizational and management contributions of RPB and David Weeks surely made a significant difference at this critical time. Indeed, Dr. Becker later stated that Weeks "played a key role in establishing the NEI. We never could have done this. We never could have gotten through the red tape without Dave Weeks' efforts."⁴⁷ Under Weeks' leadership, RPB convened seminars for science journalists that offered calculated opportunities to disseminate information about the pervasiveness of eye diseases and missed research opportunities. At a four-day seminar held in Arlington, Virginia, in November 1965, scientists gave presentations on blindness problems. Jules Stein made the introductory remarks, averring that only a "sliver of the nation's research dollar was being given over to the enormous problems of eye research." That the already large number of blind was increasing was "the result of their excommunication from the benefits of the current science explosion." To hammer the point home, RPB released a press statement with the headline "Blind Abandoned by Medical Science, Eye Research Sponsor Charges."⁴⁸

Other developments bolstered the argument for establishing an eye institute. RPB funded a nationwide survey on the status of eye research at American medical institutions. Thomas Duane, M.D., Ph.D., took a sabbatical from Jefferson Medical College in 1963 to complete the survey research, visiting medical schools and other research institutions throughout the country.⁴⁹ Duane presented his report to the American Association of Ophthalmology and Otolaryngology in 1964, and a year later RPB published it as

*Ophthalmic Research: USA—A Comprehensive National Survey of Eye Research.*⁵⁰ It contained criticism of current vision research activities and concluded that it was imperative for the federal government to plan a separate eye institute.⁵¹ RPB and Weeks also commissioned a Gallup poll on public attitudes to vision. The results indicated that the public only feared cancer more than blindness. RPB gained a lot of mileage out of this poll, later referencing it in testimony before Congress on the need for a new institute.⁵²

Edward McManus, NEI's long-time second-in-command, recently mused, "There is an NEI mythology that Jules Stein contributed millions of dollars to start the NEI. I don't know if that is true or not. Really, the key was hard work by the ophthalmology academics and Dave Weeks, although the help of RPB, Jules Stein, and Mary Lasker in getting NEI before Congress and arranging hearings was also critical."⁵³

Lobbying and Proposed Legislation

In the mid 1960s, a lobbying campaign for a separate institute began in earnest. Dr. Duane introduced Dave Weeks to Representative Frederick B. Rooney, a Democrat representing Duane's district in Pennsylvania. Weeks convinced Rooney to support the drive for an eye institute, and Rooney submitted establishing legislation to the House on January 27, 1966. Other similar House resolutions were introduced during the same session. In the Senate, Lister Hill, chairman of the relevant committee, submitted an eye institute bill. None of the bills were approved by committee, despite considerable congressional support.⁵⁴

Securing the passage of new legislation, even with the formidable array of forces that Stein and Maumenee had marshaled, was still to require heroic effort. The forces of opposition, which included Public Health Service officials, NIH top leaders, and neurologists, were strong. Both NIH Director James Shannon and NINDB Director Richard Masland opposed the institute, although according to historian Ruth Harris, they "admitted that problems did indeed exist in conduct of the National Institutes of Health eye research: inadequate manpower, inability of the institute to recruit a senior ophthalmologist to administer all eye research activities, and insufficient emphasis on non-clinical research." Masland suggested strengthening the national eye research program by upgrading training and program leadership, and establishing satellite eye research centers.⁵⁵

To many it was never clear why NIH leadership failed to validate the eye institute movement, instead resisting to the end. This would later be the same approach that NIH leadership took regarding an arthritis institute in the 1970s. Perhaps it is the nature of the bureaucratic mind to resist change and attempt to assert autocratic control over complex organizational challenges.

Renewed Effort

When George Wald and Haldan Keifer Hartline (NINDB extramural grant recipients) won the Nobel Prize for medicine in December 1966 for their studies of visual pigments, eye research gained increased attention and respect. The award came at an opportune time. Multiple bills were once again introduced in both the House and Senate in 1967, during the first session of the 90th Congress.

On September 12, 1967, Representative Harley Staggers, the Democrat from West Virginia, introduced H.R. 12843 to establish an eye institute. Dave Weeks worked tirelessly in late 1967 and early 1968 to shepherd the legislation through to passage, traveling between his New York base and Washington. Mary Lasker helped by obtaining access to congressional players. Weeks later described their efforts:

Well, Mary was a very quiet influence from behind the scenes. I don't know exactly what Mary did as far as her contributions were concerned, but my impression was that she gave to the key congressmen on the Appropriations Committees about \$500 each year—which wasn't enough to create a problem where people would focus on her but it gave her the entrée. When she called, she got the chance to talk to the Congressmen or the Senators. She didn't have to talk to an aide.⁵⁶

This new legislation was opposed by the Department of Health, Education, and Welfare (DHEW)*, the parent agency of the PHS and NIH. Dr. Philip Lee, a DHEW Assistant Secretary, communicated the department's unwillingness to support a separate eye institute or even efforts to increase the eye research budget.⁵⁷ The Secretary of DHEW, John W. Gardner, held that eye research was already strongly represented within NINDB; therefore, a new institute was not “justifiable.” A new institute, in his view, would only make administrative management of eye research worse. He thought it would lead to “fragmentation of efforts,” a lack of collaboration in eye research, and problems in administrative management.⁵⁸

On October 31 and November 1, 1967, the House Subcommittee on Public Health and Welfare of the Committee on Interstate and Foreign Commerce held hearings on the proposal for a national eye institute. William H. Stewart, M.D., the Surgeon General, voiced resistance to the proposal, stating that NINDB had fostered great progress in eye research, and that creating a separate institute would only isolate eye research from other fields, disrupting existing relationships and collaboration with other fields. Dr. Richard Masland formally registered NINDB's opposition.⁵⁹

* The Department of Health, Education and Welfare, as it was known from 1953 on, was renamed the Department of Health and Human Services in 1979 when a separate Department of Education was created.

Powerful Testimony and Success

Several congressmen, ophthalmologists, and Jules Stein were key witnesses in favor of the proposals. Most of the prominent ophthalmologists leading the eye institute charge testified at the November 1 hearing. They made a cogent case, presenting an organized, tightly knit argument. RPB had apparently finalized much of the testimony to ensure coordination without overlap. Indeed, Dr. Cogan later said that he would have preferred to use more of his own words.⁶⁰

Setting the stage, Dr. Ralph Ryan discussed the immense scope of eye diseases. Previously employed at NINDB, he testified about the lack of funding for eye research, although he took care to praise NINDB for its efforts. Ryan's testimony surely held particular weight given that he was reportedly Representative Staggers' family ophthalmologist for some 25 years.⁶¹

Professor Herbert Kaufman, from the University of Florida, College of Medicine, provided testimony about the huge number of eye-related research grant proposals left unfunded at the NINDB. Kaufman recalled recently that his "role was to talk about how the system, of which I was a product, could really result in basic knowledge and progress against blinding eye diseases, and how difficult this was to facilitate at a combined institute."⁶²

Dr. Edward Maumenee affirmed the necessity of a separate institute—one headed by an ophthalmologist, not a neurologist—because most blinding diseases were not directly problems of neurology. It was "misleading," he said, to claim that "the eye is an extension of the brain and that therefore research on blinding eye disease is closely related to neurology. There are connections, of course, although only the retinal tract itself is an extension of the brain." Furthermore, the eye offered a unique anatomical area to study basic metabolic and physiological processes.⁶³

Dr. David Cogan also pointed to the lack of correlation between ophthalmology and neurology. Ophthalmology, he explained, as the oldest of clinical specialties and unique with no parallels, should not be treated as a surgical specialty. Recent ophthalmic advances had not been in surgery but in diagnosis, recognition, and treatment of disease. Moreover, he had found that one-quarter of the patients in his hospital had eye problems, while only 3 percent had neurological disorders.⁶⁴

Dr. Michael Hogan pointed out that universities were in the process of—or had already created—separate departments of ophthalmology, thus establishing strong precedent for separation. There were no medical schools, he claimed, that integrated ophthalmology and neurology departments. He described how independent departments of ophthalmology had superior research records when compared with combined departments of ophthalmology

and surgery. Only with separation could there be adequate support and effectiveness, he concluded.⁶⁵

Dr. Frank Newell testified that the time was ripe for an eye institute because of the well-developed state of ophthalmic knowledge and tools: “The study of the eye and its diseases has thus reached that auspicious moment when giant advances are possible, both in treatment and the discovery of the causes of blinding eye diseases, provided there is adequate leadership and properly oriented research.”⁶⁶

Dr. Thomas Duane was especially persuasive in referring to the ophthalmic study he had completed for RPB. In visiting numerous institutions and speaking with the medical community, he had found that most supported a new institute. He closed with an indisputable point: only when neurology had separated from the mental health institute had it had grown and developed.⁶⁷

Dr. Bradley R. Straatsma discussed how mounting any sort of “scientific attack” on ocular malfunction was handicapped by the dysfunctional organizational structure that clustered vision disorders and blindness with neurology, neurosurgery, and otolaryngology. This must be changed, he argued, because (1) it was incorrect to believe there was a special, overriding relationship among these disciplines; (2) it forced NINDB leaders to divide their attention among disparate fields of medicine; and (3) it did not provide an optimum framework for a scientific attack on vision disorders and blindness.⁶⁸

Jules Stein delivered the coup de grâce when he castigated naysayers for opposing the proposal for mere administrative reasons, especially at a time when so many suffered from eye problems. It was “a national disgrace” that eye research lagged behind other research areas. Claiming to be only a “layman,” he was there to register a “public demand” for help.⁶⁹ With its can-do attitude, his speech epitomized post-World War II rhetoric and implied that Americans could rid the country of visual dysfunction if only enough science and technology were thrown at the problem.

An unscheduled witness, John F. Nagle, Chief of the Washington, D.C., office of the National Federation of the Blind, caused a tense moment. Dr. Newell later recalled how the audience had waited anxiously as Nagle, guided by a white cane, took the witness chair; for at a previous hearing, Nagle had “removed his artificial eyes and thrown them on the table in front of him to emphasize that eye research could not restore his vision.” The audience “wondered if Mr. Nagle would plead for more funds to educate, rehabilitate, and aid the blind—traditional areas of appeal by blindness groups. Instead, Mr. Nagle provided strong support for a national eye institute.”⁷⁰

Representative Rooney, who had introduced the original bill almost two years earlier, summed up the arguments for a new NEI:

- Blindness was a national and worldwide problem. An estimated 1 million people in the United States were functionally blind; throughout the world, more than 10 million were totally blind.
- In a poll taken by the Gallup organization, the American people indicated that fear of blindness ranked second only to fear of cancer as “the worst thing that can happen.”
- Accidents accounted for only 5 percent of vision loss, while disease caused most people’s blindness.
- More than 80 percent of all cases of blindness resulted from diseases with causes unknown to scientists.
- A small percentage of the blind would be rehabilitated, but rehabilitation and caring for the blind were not long-term solutions.
- The cost of blindness in the United States amounted to more than \$1 billion annually.
- Only about 15 percent of the total budget for the National Institute of Neurological Diseases and Blindness went toward eye research in 1967—\$18 million out of \$116 million.
- It was questionable whether ophthalmologists should be working under neurologists, as they were at the present Institute.
- Eye diseases were unique and not necessarily related to the central nervous system; thus, research required professionals specifically trained in the field of eye research.⁷¹

Despite the vociferous support and seemingly valid rationale for an independent national eye institute, the bill languished. Dr. Ralph Ryan saved the day by helping to pry the bill out of committee. Congressman Staggers, who represented Ryan’s district, told the doctor, “I have heard from the ophthalmologists, the optometrists, and the researchers, but I have not heard from the American people.” At Ryan’s urging, Lions Clubs around the country mounted a write-in campaign; about 100,000 letters and telegrams reached Congress, urging votes for a new NEI. This massive campaign provided Staggers with the ammunition needed to convince other committee members to send the bill on for a final House vote.⁷²

Dr. Kaufman recalls that the letter-writing helped bring out “the feeling of grass roots support for the institute, and that was very valuable.”⁷³ After all, Helen Keller in 1921 had dubbed Lions Club members the “Knights of the Blind.”⁷⁴

The bill to create a new national eye institute made it out of committee, but the situation still looked grim. Finally, as a result of the constant lobbying of RPB and Dave Weeks, the bill passed in both houses on a voice vote. Reportedly, Luke Quinn carried the approved House bill over to the Senate for action—a highly unusual move.⁷⁵

Then, the institute proponents learned that President Lyndon Johnson intended to veto the legislation. Again, Jules Stein and RPB came to the rescue. Stein traveled to Texas with

a personal friend of President Johnson. The President was persuaded to approve the legislation,⁷⁶ and the bill to establish NEI was passed into law on August 16, 1968. The President's press statement read:

Nearly every family in America has at least one member suffering some form of vision problem or eye disease These tragedies need not occur. There is much that remains to be learned The National Institute will build on the great work that has been carried on by the National Institute of Neurological Diseases and Blindness It will concentrate its efforts on this major health problem by supporting and conducting needed research and, equally important, by helping to train the specialists to provide the diagnosis and treatment that can eliminate much of the eye diseases.⁷⁷

Once the legislation was in place, the NIH leadership, to their credit, dropped their staunch opposition and gave their support to NEI. In a recent interview, Dr. Murray Goldstein remarked that NIH leaders traditionally got behind a new institute, even if initially opposed. Once the dye was cast, NIH wanted to help the newcomer become the best possible, an attitude that was good for all involved. In like manner, most eye scientists welcomed the Institute, Dr. Dowling recalls, for now the eye would be "in the forefront in a way that it had not been."⁷⁸

Chapter 2

Organizing for Research

The First Years at NEI

NEI's start was not auspicious. Congress failed to appropriate any start-up funds for Fiscal Year 1969. A similar situation had occurred twice before, first with the creation of the mental health institute and then with neurology. In NEI's case, according to Ruth Harris' history article, Dr. Shannon feared that using NINDS money to fund the new eye institute might cripple neurology research programs because NIH was facing severe funding cuts. To save money, Shannon had Dr. Edward F. MacNichol, Jr., serve both as director of NINDS* and as acting director of the new eye institute. For the time being the institutes shared responsibility for existing intramural research.⁷⁹

After NEI was established, the search for a director got underway and the leading eye researchers and academics were consulted about potential candidates. In the end, Dr. Carl Kupfer was chosen. Bernard Becker, one of the most respected academics in the field, recommended Kupfer for the job. Becker had been the resident in charge when Kupfer was his junior at Wilmer Eye Institute and had subsequently worked with him on committees and socialized with him at meetings.⁸⁰

Dr. Kupfer assumed the position of NEI director in January 1970, taking over from Acting Director MacNichol. Kupfer left his position as chair of the Department of Ophthalmology at the University of Washington Medical School in Seattle, where he had held administrative, teaching, and patient-care responsibilities and directed all departmental scientific endeavors. Before that, he had been assistant professor at Harvard's Howe Laboratory, a research fellow, medical resident and intern, and had graduated from Yale and Johns Hopkins universities. Kupfer had research accomplishments in the control of intraocular pressure and the anatomy of the connections between the eye and the brain, and he was on the editorial board of *Investigative Ophthalmology*. He was familiar with NINDB's extramural program, having been a member of the NIH Vision Research Training Committee and of the NIH Neurology Program–Project B, as well as a recipient of extramural grants.⁸¹

* In August 1968, NINDB was renamed the National Institute of Neurological Diseases; two months later the name was changed to the National Institute of Neurological Diseases and Stroke (NINDS) (see NIH History website; PL90-489 and PL90-636).

The Scope of NEI's Research Portfolio

When Dr. Kupfer agreed to become director, he assumed that the new institute's research program would encompass the entire visual system, from the sensory input of a visual stimulus through the motor outflow moving the eyes to look at the stimulus. He discovered, however, during an orientation meeting that the program mandate of NEI was to be severely truncated. Kupfer recollects the following:

Soon after accepting the directorship of the National Eye Institute in August 1969, and winding down my duties in Seattle, I was asked to come to Bethesda in late October 1969 to see Dr. Robert Berliner, the deputy director for science. Dr. Berliner was a respected renal physiologist who had held several important research and administrative posts at NIH. I had first met with him the year before, when I was being recruited for the directorship, at the annual meeting of the Federated American Societies for Experimental Biology held in Atlantic City, New Jersey. Berliner met with me in between attending scientific sessions and bird watching (his passion) and convinced me of the excellent opportunity the position presented. Now, I was about to meet with him again. In his position within the NIH director's office, Dr. Berliner was in charge of all scientific programs, and he had been given the responsibility of negotiating the research content of the new NEI research program. I soon found out that that was what I had been called there to discuss.

Our meeting in his office started out pleasantly. We discussed his participation in one of the small scientific meetings sponsored by the Josiah Macy Foundation in the mid-sixties dealing with the regulation of the flow of aqueous humor in the eye. I recalled that when I had first read the Proceedings of this meeting, I had thought that his work fit in quite well; Berliner was a world-class expert on the kidney and the secretion of urine, a function that in some respects could be viewed as analogous to that of the ciliary body tissue in the eye, which secretes the aqueous humor. Eventually we turned to the topic that I had been summoned to discuss—the make-up of the research grant portfolio that was to be transferred from the Neurology Institute to NEI. Dr. Berliner mentioned that the NINDB staff had held several discussions about what portion of the research portfolio would be transferred to the new institute. Of course this was a very important question for me, as I wanted to know what our responsibility in covering the vision research area would be. He peered up at me through his glasses, which he was noted to do, and said, “Well, the decision has

been made to transfer to the Eye Institute all research up to and including the ganglion cell in the retina. But the optic nerve and all the visual system of the brain itself will remain with the Neurology Institute.”

At first, I thought he was joking because it was well known that the optic nerve is part of the extension of the ganglion cell from the retina into the brain where the act of “seeing” actually takes place. The extension of the ganglion cells (called axons) into the two optic nerves represents about two million nerve fibers and constitutes about 38 percent of all the nerves entering the brain. These optic nerve axons make connections with brain structures, which in turn connect with large networks of nerves throughout the brain; all of this together provides the high quality of vision we possess. In essence, he was proposing to limit NEI to the eye itself and reserve the major portion of the visual system for Neurology. So I laughed and I said, “That’s pretty funny, you must be joking.”

“Oh, no,” he said, “I’m not joking.”

“Well,” I responded, “how does one conduct research where the ganglion cell is in one institute and its axon and all its connections are in another?”

He replied, “I really don’t know the details, but that’s the decision that Neurology has made and I think that we should proceed with this.”

And I said, “You’re serious?”

And he replied, “Absolutely.”

I thought to myself for a moment and stated, “Well, sir, if you are serious I think you’d better start looking for a new director of the National Eye Institute.” And I got up and walked out.

I discussed this with my new staff at NEI, as small as it was at that time, and with my family, of course, as this was such a remarkable development. My conception of the NEI was that it should support the study of the entire visual system.

As part of the visual system, the eye serves to focus images clearly on the retina where some processing of form and color takes place. However, the major visual processing of these images occurs in the complex system of the brain. This processing needed to be understood if we were to know how an image on the retina is transformed into a perceived visual experience. Our research would continue the efforts to map anatomically all the normal visual pathways, as well as to expand the exploration already begun of the normal function of individual pathways so as to finally understand how “vision” is accomplished by the brain. I believed that attaining this goal was possible. Indeed, there seemed a better chance of coming to understand the fundamental brain mechanisms underlying sensory-motor coordination of vision than any other system in the brain, such as taste, touch, smell, audition, or movement. At that time, the complex visual/oculomotor system, in which the sensory inflow is light and the motor outflow is eye movement, was understood better than all of the other systems that the brain helped control. Researchers could precisely measure both the sensory and motor portion of this coordinated activity in human volunteers. Furthermore, researchers had recently developed new methods of experimentation with alert and awake Rhesus monkeys that would allow them to further explore the relationship of brain activity to vision. Research had already shown that visual perception and eye movement in monkeys and humans was almost completely identical. By studying these monkeys, we could infer how the human visual system functioned. This mode of experimentation allowed researchers to study the organization of the visual/oculomotor system and how it works in humans, both normally and when it fails as a result of disease or trauma. It also permitted a wide variety of experiments to be conducted with a high degree of success, furthering the understanding of visual function. These avenues of research offered exciting possibilities—NEI simply could not afford to let this promise slip away. Our research mandate absolutely had to cover the entire visual system.

Several days later, Dr. Berliner called me back into his office and said, “Well, we’ve talked with Neurology and they asked me to find out what is it that the NEI wants as their responsibility. Would you please tell me?”

I responded, “It’s quite simple. We want responsibility for the normal structure and function of the visual system from the sensory input of light into the eye to the motor outflow as measured

by eye movement and all structure and functions in between. Anything short of this really doesn't make scientific sense."

Implicit in my statement was the understanding that if the optic nerve or any another portion of the vision system were to be studied because it was affected by epilepsy, cerebral palsy, multiple sclerosis, or other diseases best understood by the neurologist, NINDS would play the major role.

He took this information back to NINDS and a few days later, he said, "Well, Neurology will relinquish the visual system research reluctantly."

That is how the scope of the research responsibility of the NEI was established.

I believe that Dr. Robert Marston, who had succeeded Shannon as NIH director and encouraged me to accept the NEI directorship, had had some influence in the decision. He believed that he had to help make NEI the best it could be. I think it was the possibility of my returning to Seattle and leaving the NEI without a director [that] convinced NINDS to change its mind.

Needless to say, it was difficult for members of the Neurology Institute to have a significant amount of their portfolio taken away. Even at the time I could understand why they tried their best to maintain control over as many of the research grants related to the visual system as possible. Some of NINDB's most outstanding grantees—neuro-physiologists, neuro-anatomists, and other specialists—centered their research on the visual system, and under my organizational scenario, their grants were to be transferred to the NEI. In particular, the brilliant research of David Hubel and Torsten Wiesel (whose grants were transferred to NEI) was progressing rapidly in understanding the coding of visual images in the visual cortex and adjacent brain areas. A Nobel Prize for this work was certainly a possibility.* If this came about, Neurology hoped that the scientific community would recognize that NINDB had supported the investigations leading to the Prize. Such recognition would tremendously enhance the reputation of the neurology grant program. In addition, about 15 percent of NINDB's Extramural grant funds were invested in the visual

* Hubel and Wiesel were co-recipients of the 1981 Nobel Prize in Physiology or Medicine.

system. It would be a major blow to lose this amount of the resources from their grant funds.

Of course Neurology had several reasons to keep the visual system research portfolio in NINDB. But it was clear to me that the eye could not stand alone as the only part of the visual system in the NEI portfolio. If NEI had failed to incorporate the entire visual system into its research portfolio, it would have been known as the Eyeball Institute and become the laughingstock of the entire scientific community.⁸²

Organization

The recruitment of capable and talented staff was essential if NEI was to succeed. The position of executive officer was among the most important. Dr. Kupfer recalls the search process for someone with the right temperament and capabilities:

Soon after I accepted the director position, interviews were arranged for me to choose an executive officer for the NEI. One question I asked each candidate was, “What should the role of executive officer be?” When I had been with the Air Force, it had been my experience that the executive officer served as the clearing house for all matters pertaining to the base and the colonel in command. Some of the interviewee’s answers were quite long and involved, but one applicant, Gil Hill, replied, “My job is to keep you out of Fort Leavenworth!” So I hired him.⁸³

Kupfer set about organizing a structure for NEI. In 1970, NEI established its intramural division. Accompanying that was a laboratory of vision research and a clinical branch. Kupfer believed that while the intramural investigators who had transferred from NINDB had performed well with limited resources, he wanted to seize the opportunity to expand the program and assemble a critical mass of investigators focusing on immunology, biochemistry, and neurophysiology. He set up four laboratories within the vision research laboratory: biochemistry, experimental embryology, experimental pathology, and physiology. Over the years the structure of NEI would change modestly, reflecting disciplinary developments. For example, in the late 1970s and early 1980s, two new intramural labs were added: sensorimotor research (1978) and molecular and developmental biology (1981). In 1970, Kupfer also formed the Office of Biometry and Epidemiology in order to develop the research areas of ophthalmic epidemiology studies and clinical trials, a high priority for him. (See Intramural and Clinical Trial Chapters 4 and 6.)

With the transfer of the ophthalmology research portfolio from NINDB to NEI, it was important to ensure that the extramural program continued to function without interruption. Right away, in 1971, Kupfer established the Office of the Associate Director of Extramural and Collaborative Programs to administer extramural programs. He expected that hiring a competent staff to administer the institute's extramural funding program would be difficult. NIH grants administrators needed to have specialized knowledge of complex government procurement procedures, as well as intimate awareness of the cultural mores of NIH and its scientific community. Experience, too, played a substantial role in achieving success. It was not easy to find a suitable person with the right qualifications to assume responsibility for the extramural grants program. Fortunately, Kupfer and newly hired Executive Officer Gil Hill were able to take advantage of a fortuitous set of circumstances and hire highly qualified professional staff to assume the daunting task of running the new extramural grants program. Shortly after NEI formed, the National Institute of Environmental Health Sciences (NIEHS), a relatively small institute, was relocated from Bethesda to North Carolina. Many of its staff, including the group that managed the extramural program, did not want to move from the Washington, D.C., suburbs. The NIEHS extramural program, which was similar in size to that of NEI, was ably led by Sam Herman, the research grants administrator, and managed by Anna Marie Perrell, the chief grants administrator. Kupfer and Hill seized the moment and invited Herman and Perrell to join NEI and manage its new extramural grants program. Both accepted and they brought with them almost their entire group of about 35 staffers. As a result, NEI had a running start in the administration of its new grants programs.⁸⁴

With these moves Kupfer had the institute up and running in a short time, although, of course, there was still a great deal of work to be done. On July 27, 1972, Kupfer was presented with a Special Citation from the Secretary of HEW, which read, "In recognition of his outstanding performance in the development of the National Eye Institute." Upon receiving this award, Kupfer said that the previous two years had been the "most exciting time of my life and that of my family." More than 35 years later, he summed up his efforts modestly saying, "*Something* right must have been done in the first two years of establishing the National Eye Institute."⁸⁵

Kupfer made additional difficult decisions in molding NEI. William R. Raub, Ph.D., served as associate director of the institute for a few years before assuming other NIH top leadership positions. Bill Raub brought to NEI his expertise in computers, a relatively new technology in medico-science research. He was prominent in the development of the PROPHET, a specialized computer system for handling information on pharmacology research and chemical/biological interactions. In 1973, Kupfer hired Edward McManus as executive officer to replace Hill, who left for another opportunity. The NIH leadership suggested their own preferred candidate, but McManus had a great deal of general administrative

experience, was an expert in budgeting and planning, and had special training in organizational and management work—exactly the sort of skills that Kupfer believed were needed to make NEI successful.⁸⁶ Before coming to NEI, McManus had worked at the intramural program of the National Institute of Mental Health and had spent a year with the Division of Research Facilities and Resources, which oversaw one of NIH’s largest extramural programs, so he knew “the ins and outs of the two major program areas of NIH.”⁸⁷ He had also worked with the National Library of Medicine. In 1972, he had spent a sabbatical year getting a master’s degree studying methods for dealing with the major problems that bureaucracies faced and how to plan strategic direction, assign priorities, and rationalize budget making. This training helped him identify the major management challenges confronting NIH and ways of coping with them.

McManus recalls:

I had had satisfying experiences working as an administrative officer in the intramural program of the NIMH, where I worked in close proximity to many famous and soon to be famous researchers. That made me a real fan of the in-house research program at NIH, which of course was Carl’s major interest also. The two of us teamed up as real advocates of a strong NEI intramural program.

When I first arrived at the NEI, it seemed like an organization under siege. NEI’s budgets had been relatively flat, despite the high expectations for the new institute from its own community. The resources—especially more space and people—needed to launch new and expanded programs were not forthcoming. Carl was a fiery, innovative leader with a distinct leadership style and philosophy that was bound to flourish if he could only muster the resources required. I saw obtaining these resources as my job, and within two months of my arrival at NEI, I was planning a management conference that would allow the superb staff Carl had put in place to develop, under his leadership, a management framework that would enable the institute to develop rapidly.

I knew from my academic background and my experience at NIH (especially at the National Library of Medicine where I had been the Finance and Planning Officer) that strong management planning combined with an extensive political offensive would be required if we wanted to survive, let alone expand. A political thrust would have to involve our own research community, our outside constituency, and the NIH leadership. Asserting leadership in management planning and developing political constituencies

was not the normal role for an executive officer at the NIH. The EOs [executive officers] were usually concerned with operations and providing administrative support, although Gil Hill had been somewhat involved in planning and political matters. Carl, however, wanted more, and he encouraged me to bite off as much as I could chew in these arenas.

On the operations level, such as budget, procurement, travel, and personnel, I jumped right in, especially supporting Carl in building up the intramural program—including recruiting the best scientists. With the extramural, Carl’s emphasis on the RO1 grants, coupled with a small budget, resulted in the program running smoothly except for scarce funding and the need for developing a framework for priority setting, which we dealt with through program planning.⁸⁸

Advisory Council

Like the other entities at NIH, NEI was subject to general legislative provisions mandating that each institute organize and sustain an advisory council.⁸⁹ Appointed by the Secretary of Health, the National Advisory Eye Council was to advise, consult with, and make recommendations to the secretary and the director of the National Eye Institute on matters related to the activities carried out by and through the NEI, and the policies respecting these activities.⁹⁰

The NEI council’s primary function, as with the other institute councils, was to review and approve research grant applications already reviewed and approved by a study section of scientific experts who examined technical merit. Over the years, the council’s role would expand from reviewing grants to being involved in program planning. (See Chapter 3 on Strategic Program Planning.)

NEI’s first advisory council was created before Dr. Kupfer’s arrival. The National Advisory Eye Council (NAEC), as it was called, was composed of 12 leaders in ophthalmology, optometry, and basic sciences, and held its first meeting April 3–4, 1969, to review and recommend grants.⁹¹ In general, the NAEC held meetings every four months.

Once Kupfer arrived, he and his top staff had a special interest in the council, believing it had crucial functions. Moreover, Kupfer wanted council members to feel they had a stake in NEI’s success. Several early council members had been instrumental in establishing the new eye institute, and to be sure, they had every reason to want NEI to succeed. “This was their baby, and they wanted to make it work,” explains McManus. Looking at it retrospectively, Kupfer believes the council had strong leaders who knew how to motivate,

manage, and bring out the best in the other members. Still, Kupfer acknowledges that during his tenure as director, he ached to assert tight direction and control, but he held back so as to allow the council members some measure of flexibility and autonomy.⁹²

Over the years, NAEC assumed a more powerful role in helping to guide the institute, compared to the advisory councils of other NIH institutes. The NAEC members provided guidance on policy issues and made important contributions pertaining to the day-to-day management of the institute's programs. The following is a selective listing of policy issues that NAEC was heavily involved with:

- Research funding options
- Adequacy and mix of current funding options
- Increasing costs of research grants
- Increased indirect costs as a proportion of the total cost of grant
- Level of support for research training/career development awards
- Encouraging greater participation of minorities in vision research
- Animal welfare issues
- Role of intramural research program
- Scientific priorities
- Scientific misconduct and conflict of interest.

The council also enlarged its role with respect to strategic program planning and made recommendations about program priorities. Over the years, the council performed admirably in implementing the expanded mandate of developing the strategic vision and priorities for the institute. Some NIHers—though certainly not everyone—admired NEI's management and planning efforts. In looking back, some council members praised the NAEC. Stephen J. Ryan, M.D., currently with the Doheny Eye Institute of the University of Southern California, served on an NEI study section and subcommittee, as well as the NAEC. He recollected that during his tenure on the council, "It was clear that [Dr. Kupfer was] a strong leader, but I wouldn't use the word bulldoze You always want the strongest possible CEO for any organization. In every organization, it's all about leadership. At the end of the day it comes down to one person, and that is the CEO of the organization." He thought that Kupfer knew how to both tap members' particular expertise and balance their strong personalities. "As I remember, we didn't have any shrinking violets on the council . . . and there could be disagreement of opinion. At the end of the day, everyone on the council understood that Dr. Kupfer was the director and it was his decision. I think everybody understood and respected that."⁹³

Some council members retrospectively assessed the council's importance during their tenures a bit differently. One thought that the members "really didn't have much to say

about the management of the institute.” Rather, “The meetings of the council always seemed perfunctory and many of the actions were really already basically determined by the action of the very competent staff members of the National Eye Institute and the committees of consultants that really made 98 to 99 percent of the decisions. There were, though, several minor policy items that became important as the Institute advanced, and in those matters, the council played a very important role.”⁹⁴ Another recently said, “We certainly were asked our opinions of many things by Carl. I never felt, though, that we had very much clout with regard to changing NEI policies. While I was on the council, most of the focus was on the funding of grants and program planning. We also discussed the fairness of study sections and what we should do about high program relevance, and so on and so forth. So from that point of view it was very valuable.”⁹⁵

In contrast, Kupfer and McManus viewed the council as essential to NEI’s success. They eagerly prepared for meetings with council members who represented the best of the vision research community. They looked forward to hearing input and recommendations from the experts who sat on the council.

Why then this apparent disconnect, this contrast in perspectives on the value of the council? Perhaps because some of the NAEC members also served as university committee members or were on the boards of nonprofit organizations or private companies, and they expected the NAEC to function in the same way. Such groups usually had much greater authority than the NIH institute councils, whose members served only in an advisory capacity in a limited policy area. Some of the council members were used to serving on bodies that had the authority to hire and fire an organization’s top staff and approve or disapprove an organization’s actions. Of course this could not be the case in a highly bureaucratic government organization, where the lines of authority trace through the executive branch and Congress. NEI and its council were circumscribed by law. Despite this discrepancy in the perceived importance of the role of the National Advisory Eye Council, the successive advisory councils operated very effectively for NEI.

Implementing a Philosophy

What still needed to be done was to implement the director’s philosophy on the mechanics of NEI’s Extramural Branch (EM), which operated differently from similar programs at the other institutes. Despite the branch’s new look in terms of priorities and procedures, the EM staff took to the different approaches with enthusiasm. It helped that their offices were located on the same floor as the rest of NEI space. This facilitated the exchange of information and bonding among staff from the various NEI components, including intramural, program planning, information, personnel, budget, and administration. Kupfer had an experienced and capable team to help implement his new philosophy of program support,

and this allowed the director and his top staff to direct their energies to other high priorities such as increasing the budget. This strategy paid great dividends in the difficult years to come.

The Director's Views on Leadership

It is fitting to conclude this chapter with Dr. Kupfer's views on leadership that he drew on in building the institute. Over the years and with experience, he refined this philosophy:

It became clear to me when I was first hired and had the standoff with Dr. Berliner about NEI's research portfolio that there were going to be other areas of differing attitudes and opinions among administrators in my capacity as director. This indeed is a situation that all directors must face and come to terms with. I realized it would behoove me to develop specific strategies for dealing with problems as they occurred, so that resolution of a problem could be reached quickly and before a situation got out of hand.

Over time I learned to implement one of three options as the situation warranted. In some cases, the positions put forward by other organizations really did not seriously impact NEI, and therefore accommodation was a reasonable strategy. In other cases, the differences of opinion were such that negotiation and accommodation was needed on both sides, and I encouraged this to be done in a fair and gentlemanly manner. And in some situations, I decided that my position was non-negotiable (as was the case with the scientific scope of the NEI research) because any alternative completely ran in the face of what I recognized as being scientifically valid and could not be sustained in a rational manner.

This division into three groupings was of value for me throughout my tenure as NEI director. I believe this overall strategy helped me to perform my responsibility to protect the resources of NEI and allowed me to fulfill my duty to the American taxpayer by seeing that NEI appropriations were used in a productive and scientifically valid manner. This ultimately enabled the research supported by the NEI to improve diagnosis and treatment of diseases of the visual system and thus alleviate blindness and visual disability.

Chapter 3

Strategic Program Planning and the Five-Year Plans

Introduction

Once the organizational structure was in place, Carl Kupfer and Ed McManus began to look for managerial and planning methods that were more innovative than those traditionally practiced at NIH. Mindful that NEI was a public institution, Kupfer wanted to (1) develop a national program for vision research, and (2) dedicate it to finding the causes underlying eye diseases and vision disorders and to developing therapeutic treatments. Moreover, NEI staff should know where they were going and how to get there—the institute needed a sort of road map, one that showed alternative routes but clearly marked out the best one. In a few short years with Ed McManus’ guidance and the help of others, NEI developed a new planning approach. Termed here “strategic program planning,” this approach drew on new management theories. By no means born fully mature, planning developed and grew more sophisticated over the years. As it evolved, strategic program planning at NEI came to encompass conscientious planning, prioritization, and the clear statement of goals. The concepts involved were most fully articulated in the five-year plans produced by the institute.

Toward Strategic Planning

NEI’s turn to strategic program planning came at a time when there was increasing impetus in the federal government toward managerial planning as a way to rationalize decision making regarding the national budget and make government bureaucracies more efficient. In 1965, only a few years before NEI was established, President Lyndon Johnson mandated that the U.S. Bureau of the Budget implement on a government-wide basis the Planning-Programming-Budgeting System (PPBS), similar to the system already in use at the Department of Defense. As conceptualized by proponents, PPBS offered “an approach to decision making designed to help make as explicit as possible the costs and consequences of major choices and to encourage the use of this information systematically in the making of public policy.”⁹⁶

Secretary of Defense Robert McNamara had first introduced PPBS to the government in 1962 when he implemented it throughout Defense with the help of a group of theoreticians and scientists—the “whiz kids”—that he brought to the department. Economists Charles Hitch and Alain Einthoven transferred from the RAND Corporation, where they had been refining systems analysis and operations research, both of which drew on multiple disciplines, including economics, statistics, mathematics, industrial engineering, and logistics. Their work formed the basis for PPBS. McNamara, who had studied and taught at Harvard Business School before joining the Ford Motor Company and then the Defense Department, had a long-standing interest in applying technocratic methods to bureaucracies. As one congressional research report put it, “PPBS attempted to integrate planning and budgeting functions through modern systems analysis and cost-benefit analysis to review alternatives, costs, and consequences.”⁹⁷ Crudely put, the goal was to be able to know and compare the cost-benefit ratio of programs in order to choose the best option.

William Gorham, the assistant secretary of the Department of Health Education and Welfare [DHEW], described the sentiments behind analytical efforts to plan programs as they applied to that department:

This year, at the direction of President Johnson, all agencies of the Federal Government are embarking on a new, difficult, and challenging venture. They are making a systematic effort to identify the objectives of their programs and to analyze the effectiveness of alternative programs aimed at reaching these objectives. They are questioning present approaches, seeking new ones, and using the tools of the analyst to compare the costs and benefits of the new and the old.

The health area is one in which the need for good analysis is particularly urgent. The talents of the economist must be used along with the physician—not only to estimate the cost of mounting new health programs—but to estimate the cost to the Nation of not doing so.⁹⁸

While certain PPBS requirements were revoked in 1971—just one year after NEI was set up—the managerial, planning, and goal-setting concepts it embodied were lasting. Subsequently, presidential administrations implemented other managerial initiatives: the Nixon administration ushered in “Management by Objectives,” the Carter administration applied “Zero Base Budgeting,” and President George H. W. Bush instituted “Total Quality Control.” In 1993, the Government Performance and Results Act (PL 103-62) codified into law managerial and planning activities.⁹⁹ The overall trend was toward greater planning—both short- and long-term methodical analysis, greater management from the top, and

budgetary prioritization. This shift toward a technocratic managerial mode in government affected developments at NEI and corresponded neatly with Kupfer's desire to aggressively manage NEI programs and McManus' interest in promoting strategic program planning.

NIH and Program Planning

While Kupfer and McManus found the notion of rigorous and sophisticated planning appealing, programming efforts at NIH overall were minimal, even by the early 1970s when NEI's strategic program planning method began to take shape. The NIH model was laissez-faire. Neither the NIH leadership nor the biomedical research community had much interest in strategic program planning, particularly as applied to extramural resource allocation, despite mounting pressure from the upper echelons of government to rationalize programs and funding. Indeed, for some NIH scientists, the concept of strategic planning seemed alien. They had little regard for it and thought it ill-suited for science. At that time, most NIH scientists and scientific directors and the research community at large tended to believe the less management the better in order to protect the creativity and independence of individual scientists so essential to making discoveries. Ed McManus recalls that in general, the scientific community was of the opinion that "the individual genius of the scientists" should guide the direction of the institutes and the research they funded.¹⁰⁰

In a recent oral interview, Thomas J. Kennedy, M.D., NIH Associate Director for Program Planning from 1968 through 1974, claimed that during his tenure, his office "never did program planning at the NIH"—at least as fully conceptualized by PPBS and other initiatives. In his perception:

The Office of Program Planning at NIH . . . didn't worry about policy issues—that's one thing, and it wouldn't touch scientific planning with a 50-foot pole. And I don't think the front office would either. I mean, they just thought that the best planning was to see what the scientists were interested in and try to figure what major shifts were happening with the research grant applications that were coming in because that's where the brains were.¹⁰¹

At that time, Kennedy and others in the medical scientific community firmly maintained that it was not possible to apply detailed planning methods to biomedical research—they believed that there was just too much uncertainty about research outcomes.

NIH as a whole did not follow a formal planning process in its management of research programs. Rather than developing a clear statement of program activities, objectives, and goals—the first steps in strategic planning—NIH took a wide view of its research activities. NIH defined its programs broadly instead of creating narrow programs specifically

aimed at curing or treating diseases. It was not common practice to solicit or give preference to grant applications to fulfill a stated goal or objective developed through a formal planning process. Good science was the standard against which grants were to be judged—not by how well they fit into program objectives, a standard which by definition seemed formulaic and artificial. The NIH leadership believed that its primary role was to provide support for the best science out there. Moreover, there was bias in favor of basic biomedical research over clinically oriented research. In general, many at NIH believed that management tools such as strategic program planning could not be efficacious in organizing NIH research programs.

NIH implemented a modicum of planning in assigning research to the different institutes. The logic was simple. The individual institutes were assigned specific program areas reflecting their research interests and specialties. Grants projects were grouped together at the institute level, roughly clustered by topic. For example, research projects clearly related to neurological issues were assigned to NINDS, those relating to oncology were pegged to the National Cancer Institute, and so forth. NIH administrators believed that amalgamating grants projects along such lines should satisfy the budget planning and data-gathering requirements increasingly imposed from above. However, they compromised where they could. In deference to a new requirement for developing manageable program entities, for instance, institute program areas were narrowed to enfold smaller clusters of grants directed at a specific research goal, such as a treatment for cancer or a specific eye disease cluster such as retinal diseases.

In terms of managerial oversight, NIH in general assumed a loose posture. While NIH took an active role in the research process by soliciting individual grant applications from the research community and providing support for the best ones, its role in large part ended there. The individual institutes rarely attempted to directly manage grants, and in most cases gave researchers almost complete independence in carrying out their projects.

The specification that organizations identify more than one approach to achieving an objective was crucial to the new planning methodologies coming into vogue in the early 1970s. For example, at one point the Office of Management and Budget (OMB) required that organizations use evaluation methods such as cost-benefit analysis to determine the optimum method for achieving an objective or developing a solution to a problem. NIH administrators, however, believed that the long-standing peer review system of evaluating research grants proposals should suffice to meet such requirements, and that it functioned better, anyway, than the new managerial initiatives so unsuited to science.

NIH used the peer-review system to determine the scientific or technical merit of grant applications, the only criteria that many scientists thought important. NIH had a network of scientific review committees called “study sections,” composed of experts predominately from the external research community. The Division of Research Grants (DRG)

at NIH appointed and managed the study sections and reported directly to the director of NIH. Thus, the study sections retained an appearance of objectivity, as well as an outward show of independence from the different institutes.

A study section—usually organized around a scientific discipline—reviewed all grant applications assigned to it, judged each for scientific quality, and assigned every application a numerical rating. After this so-called “first level of review,” the scores were forwarded to the appropriate institute—Cancer, Diabetes, Neurology, and the others. As the next step in the peer review process, staff members presented the rated applications to an institute’s advisory council, established by statute. Each council reviewed the study section’s ratings for the grant applications assigned to their respective institute. Most if not all of the councils were required by law to give final approval before any project could be funded.

The Development of Strategic Program Planning at NEI

Ed McManus was pivotal in helping NEI develop its strategic program planning method. McManus brought to NEI his experience in management and familiarity with the new theories behind PPBS and like initiatives. He had worked for the Navy in contract management before joining the Mental Health Institute, where he had been in charge of the intramural program budget. From 1972 to 1973 he was responsible for planning and finance at the National Library of Medicine (NLM). Through a federal government program, McManus received advanced training in public policy and administration at the University of Wisconsin during 1969 and 1970. In his graduate work, McManus studied the legislative and budgeting processes as well as techniques such as “managing by objectives” and “management by small groups,” approaches that proved particularly effective for his work at NEI.

McManus gained an appreciation of the analytical elements of PPBS during his graduate work. His master’s thesis examined methods of allocating resources for biomedical research. McManus had chosen this topic because he and fellow managers had found the allocation of resources at NIH to be a major problem. They observed that NIH leaders—all scientists—who made the allocation decisions thought that NIH programs did not lend themselves to the management approaches that were becoming conventional elsewhere. These scientists disregarded managerial techniques, holding that the uncertainty intrinsic to the medical research process, especially in basic research where the goal was to discover something new and perhaps never before imagined, made planning impossible. To be sure, this complaint had validity, but uncertainty pervaded the research process in all kinds of disciplines, including extremely complex technological research taking place in other agencies also subject to new managerial demands.¹⁰²

McManus came to believe that NIH could adapt some elements of PPBS and similar initiatives for its own purposes, particularly to help formulate goals and objectives. While

PPBS as a formal executive initiative did not last, its basic concepts of strategic analysis and programming continued to inspire McManus, even as additional planning and budgetary requirements were imposed.¹⁰³ Despite NIH's disregard for their utility, McManus believed that strategic program planning tools, such as cost-benefit analysis and priority setting, could be used to systematically compare alternative approaches to solving disease problems. This dovetailed with Kupfer's strong belief that planning and priority-setting in general should underpin the management of NEI programs.

In developing a plan for NEI and determining the foci of the institute's programs, Kupfer and McManus wanted *priorities* to influence funding decisions. At first they were not sure how that should be done but knew they did not want to merely increase or decrease funds evenly across the board—the NIH gold standard for adjusting to budget changes. Kupfer wanted something different for NEI and instinctively gravitated toward planning mechanisms, even though he was not yet familiar with the specifics of the new management and planning theories. “We wanted to have some way to get a hold of what we were supporting,” Kupfer explains. “I didn't know the term ‘strategic planning,’ and I didn't know the term ‘program planning,’” but “What I did know was that in all research activity you've got to decide where the biggest payoff was and pursue that.” While quality was of course important, Kupfer and MacManus wanted to set program priorities and then judge grants according to relevance—not just whether they typified “good” science. They wanted the clinical aspects of a proposal to have value—not just the technical quality or basic science aspects.¹⁰⁴

Dr. Dowling offered his perspective on the strategic planning program:

I think it is useful every four or five years to see where a field is at, where it might go, and where resources might be profitably put. And that was always the idea behind program planning What tends to happen in science, in my view, is that people swarm. There's a topic that is hot and everybody focuses on that, and they are beating it to death. But on the other hand, there may be something that really is ripe for the taking, and yet no one is working on it. And this is where program planning is very useful in my view, to point out opportunities that people have not appreciated. I think it is also important to designate areas of high program relevance. That is, where you need to have a few grants researching a particular problem The [NEI] program plans were done thoughtfully and were of great use in thinking about where the next areas were, in which we can really make advances.¹⁰⁵

The Management Retreat and the Statement of Principles

As NEI got off the ground, the initial approach to planning (1970–1971) was limited and similar to the other institute’s planning methods. It was not very long, however, before Kupfer and others decided to shift to a higher gear and more actively promote what later came to be known as strategic program planning.

McManus and Kupfer shared the goal of developing a framework that NEI could use for setting priorities and planning programs. Thus, Ed McManus organized a management retreat for key NEI staff, which was held in September 1973. There, the attendees hashed out a viable framework, developing a set of program management principals and a taxonomy for delineating research programs. In doing these two things, they had developed a framework that NEI and its advisory council could refer to in establishing goals, objectives, and research priorities. As a result, NEI had operational guidance for carrying out the institute’s programs—a tool that would serve NEI well over the next decades. This development marked a watershed in the institute’s history.

The retreat group found it difficult to categorize the different ophthalmic research programs that NEI should fund. Most grants did not fit into any single program area and many focused on basic science issues. Finally, the group agreed upon five major program areas that would constitute the institute portfolio: (1) cataract, (2) glaucoma, (3) corneal diseases, (4) retinal and choroidal diseases, and (5) sensory-motor disorders and rehabilitation. With minor modifications, this taxonomy has guided the institute for more than 30 years. Establishing rational program areas was essential to any program planning effort where goals, objectives, and priorities had to be set.

The set of operational principles developed at the retreat embodied in-depth program planning and represented sound managerial techniques for conducting a national program in vision and eye research. The minutes of the meeting list the principles as follows:

- a) in general, favor research closer to human disease, that is, favor vertebrate over invertebrate, mammal over vertebrate, monkey over mammal, and clinical over monkey;
- b) prevention rather than rehabilitation;
- c) in general, stress research on the most common causes of blindness;
- d) support NEI programs in terms of etiology, diagnosis, and treatment in order to determine if there is a sufficient base on which to build a targeted program for improved clinical diagnosis and therapy;
- e) stress the relevancy of research to the NEI and NIH mission; and

- f) place prime emphasis on the research grant mechanism in support of research, using other mechanisms such as contract sparingly, only to meet specific program needs determined by the NEI.¹⁰⁶

While this tactical policy guidance might appear modest today, at the time its implementation was quite controversial. Not only was the act of articulating such a framework for program planning revolutionary, the content of the principles was innovative, especially that embodied in (a), (c), (d), and (e) above. Item (b), which stressed prevention as an overall guiding concept for the program, was for the most part accepted by the vision research community, primarily because many researchers were already working in the general prevention area.

More controversial were the items that emphasized clinical research on diseases and disorders as a major focus of NEI. The emphasis on human clinical research in item (a) seemed to buck the trend of favoring basic science research. This caused concern among some basic scientists who were working on mechanisms of the visual system and not directly on cures or treatments for diseases. Some scientists interpreted the guiding principles as a threat to their funding opportunities, speculating that NEI would give preference to disease-related research. They were unsure of how basic science grants would fit in to the program. Other researchers feared that NEI would fund an application merely because it mentioned a disease repeatedly and not because of the proposed project's inherent scientific creativity and merit. To assuage apprehension, NEI subsequently released program objectives geared toward basic biology and assigned priority designation to such research when appropriate.

Principle (c), which stressed research on the most common causes of disease, articulated the concept of program balance; that is, that the number of grants and the amount of dollar support ought to be commensurate with the burden of illness caused by the disease. For example, if retinal diseases accounted for 30 percent of the problem, they ought to receive 30 percent of the funding.

Principles (d) and (e) caused consternation among some basic scientists. They thought that looking at etiology, diagnosis, and treatment in building targeted programs for clinical uses would threaten their funding opportunities, and that emphasizing NEI's public mission of finding treatments for diseases would result in favoritism toward clinically oriented, disease-focused research. Finally, (f)—preferring the research grant mechanism over contracts—was a signal to the research community that NEI management wanted to influence the direction of research by implementing principles (a) through (e). NEI viewed the contract mechanism as a tool for shaping the direction that research should take. Contracts at NIH were generally used to achieve a targeted objective of a particular institute. In research contracting at NIH, the objective, the approach, and the timetable all had to be specified and knowable in order to have cost competitions for bidders. This was difficult to do with

scientific research. National Cancer Institute staff thought differently and attempted to use contracting aggressively. In contrast to NCI, NEI used the contract mechanism sparingly and only in rare instances when the institute had in-house expertise in the desired field. (See the contracts section in Chapter 5.) NEI staff encouraged researchers to continue to devise and submit research proposals that they believed were viable and important. In the final analysis, NEI wanted the research community to develop their own proposals, but within certain parameters.

In developing its strategic program planning, NEI relied on four elements intrinsic to PPBS and other goal-oriented managerial methods. First, objectives should be identified and examined in each major area of activity. Second, the outputs of a program should be analyzed in relation to its objectives. Third, total program costs should be measured over a period of years. And fourth, long-term objectives should be formulated through multiyear planning efforts. The staff at NEI found it nearly impossible to implement a fifth element: that alternatives should be analyzed to find the most effective way of attaining program objectives at the least cost. This presupposed the capability to know the outcome and evaluate its cost, a difficult task in biomedical research. For example, PPBS aimed to quantify alternative means of achieving an objective in order to deduce the most effective option. In a research project examining a treatment for diabetic retinopathy using the main tool of PPBS cost/benefit analysis, one would have to be able to specify the exact cause of the disease and how it could be treated. How can one cost-out a treatment approach before the research developing it is completed? The benefit side was equally confusing. How does one quantify suffering prevented?¹⁰⁷ *

The National Advisory Eye Council and Program Planning

Not only the staff of NEI, but also the institute's consultative body, the National Advisory Eye Council, assumed a proactive role in encouraging NEI to develop and implement strategic program planning. The council was "chomping at the bit to do something different," recalls McManus. With the help of Kupfer and other staff, especially Julian Morris, the council provided guidance for implementing sound managerial techniques and a national program for conducting vision and eye research.¹⁰⁸

NEI's first such advisory council, which served from 1969 through 1974, was composed of 12 members appointed by the Secretary of Health and Human Services. They came from institutions outside the federal government: eight represented various scientific

* Because of McManus' interest in such questions, NEI, under the direction of Carl Kupfer and Leon Ellwein, coordinated research in the 1980s and 1990s to calculate the quality-of-life potential benefits from breakthroughs in eye treatments; this work is still in the developmental stage. Over the past 30 years, researchers have attempted to develop methods for quantifying benefits; few if any are being used in NIH resource allocation decisions.

disciplines, and four were knowledgeable laypersons representing the general public.¹⁰⁹ Succeeding councils had a similar composition, and members usually served for four years.

The first council functioned much like the other institute councils. Council meetings focused on recommending or disapproving individual grants proposals. In general, the council met three times a year, usually for an entire day. For a few hours the members discussed general items, then for the rest of the day they reviewed the applications for research funding (usually numbering in the hundreds).

Still, from the beginning the first council members exhibited an interest in being part of institute planning. From 1970–1972 the council embarked on a mission to assay the state of vision research, *The National Vision Program Planning Report*. Members hoped the survey would help them determine the research areas that were the most important, those which deserved further exploration, and those that held the most opportunities for researchers. They wanted to be able to form recommendations on the direction that NEI should take in its support of research. The council created task forces led by a few key leaders in related scientific disciplines to survey research fields and areas of interest related to ophthalmology, including retinal and corneal disease research. The council prepared reports based on the information gathered by the task forces. These were primarily descriptive documents containing “wish lists” of projects and areas to be funded. The council did not go so far as to set research priorities, nor did it establish goals and objectives. This was not yet strategic program planning—but it was a start.¹¹⁰

Gradually the NAEC began to assume a more active role in directing the institute’s programs and decided to help implement sophisticated planning measures. Some members of the group believed they should be responsible for providing advice to NEI’s top management regarding major policy issues, such as research priorities, in addition to performing its regular task of approving individual grants for funding. Thus, the members sought a role for the council that was more akin to the private sector committees and boards they sat on. The NAEC eagerly took on this more activist role probably because only a few short years before, many of the members had been actively engaged in creating NEI. The scientists sitting on the council—Straatsma, Newell, Maumenee, and others who had worked so hard to create the institute—were eager and willing to assume leadership in determining NEI’s programs and priorities.¹¹¹

As with the other institutes, the advisory council for NEI was statutory. The NAEC was authorized by Section 452 of the Public Health Service Act (42 USC 289J) “to advise, consult with, and make recommendations to the Secretary [of Health] on matters relating to the National Eye Institute.” However, the NAEC interpreted the establishment legislation more broadly than the other NIH councils. The members believed that an activist role was well within the council’s legislated mandate and charter, and the NEI staff concurred.

Section 452 of the Public Health Service Act (42 USC 289J) explicated the council's responsibilities: "The National Advisory Council advises on matters associated with the support of research with respect to blinding eye diseases and visual disorders associated with general health and well-being. Further recommendations are made to provide training and instruction and establish and maintain traineeships and fellowships through grants to public or other nonprofit institutions."¹¹² The NAEC Charter included the phrase, "Makes recommendations to the Secretary and the Director, NIH on matters relating to diagnosis, prevention, and treatment of visual disorders and to the mechanism of sight and visual function."¹¹³ This was interpreted to provide a broader role for the council.

Members' active participation in shaping NEI's programs set the NAEC apart from the other NIH advisory councils, which—except for the cancer institute's council—were content to primarily engage in reviewing grants, fellowship, and training applications. Those councils generally followed a narrow interpretation of the duties listed in the enabling legislation. As a matter of tradition they seldom delved into policy matters. Usually the top scientific staff at an institute preferred to retain its prerogatives in decision making.

Vernon B. Mountcastle, M.D., a leading neuroscientist and council member from Johns Hopkins University, early on voiced his trepidation about NEI's planning effort and new management framework. At the November 1973 council meeting, when the members first approved the new planning framework stemming from the management retreat, he commented that "there was no need to second-guess the study sections." In other words, Mountcastle thought that the study section process of reviewing for technical merit and assigning numerical ratings was good enough for making funding decisions. Other members criticized program planning as an attempt to "direct science," and this concern emerged repeatedly over the next few years, reflecting scientists' traditional distrust of anything resembling bureaucratic management. Several years later at a June 1978 council meeting, there were still misgivings. NAEC member Lorrin A. Riggs, Ph.D., a renowned basic scientist, raised this issue again, pointing out that some investigators were "concerned that the [five-year] planning reports might signal a move toward greater direction of research by NEI."¹¹⁴ Despite these reservations, the council members always moved forward after a period of soul searching over the implications of "directing" science and renewed their vows to pursue a policy of "gently" managing the developing NEI program.¹¹⁵

In a recent interview, Dr. Bradley Straatsma recalled the council's struggle with fundamental questions about program planning. Most did not question the need for program planning but, he said, "it was a new activity and there was substantial doubt about how we should go about it. Would this become something that directed and forced people to do certain kinds of studies and thus interfered with the freedom of intellectual activity?" Straatsma came to believe that the planning process helped people to understand what research was be-

ing done, brought experts together to brainstorm about what ought to be done, and provided a way to estimate fund requirements. “There is no question in my mind that the planning process was valid in terms of its preservation of freedom for the investigators, its ability to focus the attention of the community as a whole on the areas that needed to be studied, and most of all its practical and political importance in bringing about resources to accomplish the task.”¹¹⁶

Before formal strategic program planning got off the ground at NEI, the NAEC struggled with the task of making difficult resource allocation decisions pertaining to grants funding. Many worthy project applications were submitted, but only a limited amount of funding was available. In its first few years of existence, NEI had only enough monies to fund 50 to 60 percent of grants approved and ranked by the study sections. Study sections were responsible for the initial scientific review of grants and were made up of committees of advisors who ascertained the scientific merit of research grant applications. They assigned a numerical score from 100 to 500 (100 being best), but all management decisions of whether to fund or not fund a grant were left up to the institute and council.

NIH and NEI had thus far supported meritorious research grant proposals based on the scientific priority rating assigned to it by the study sections. The notion of consciously tampering with this system to achieve program goals or narrowly focused disease-eradication objectives—an even more disturbing prospect—created concern among many in the basic vision research community.

Still, the NAEC did not merely rubberstamp the decisions of the study section, especially as the council became more proactive. Thus, the NAEC assumed what might be considered a more operational role in reviewing individual grants. Members feared that in the first level of review, clinically oriented grants were not competitive because the study sections tended to have a clear bias toward supporting basic science grants. In judging applications, members went beyond the sole criteria of scientific merit used by study sections and attempted to deploy additional criteria. Members now discussed raising a specific project above others for funding consideration on the basis that it seemed more clinically relevant. Before NEI had program planning and a mechanism for balancing program relevance, such discussion usually turned into a general debate about overall research program priorities, how to set them, and the best way of achieving greater program balance (for example, funding cataract research versus retinal research or basic research versus clinical research). The grants debates usually ended in failure and confusion because there was no overall priority framework for vision research in place to guide decision making. Thus, the council embraced the management initiatives to establish priorities through systematic program planning.

Some council members emphasized disease-oriented priorities, and this focus reflected professional goals and personal motivations as well as an altruistic desire to help those

afflicted with vision disorders. Ed McManus theorizes that “a lot of the researchers were in departments and divisions of ophthalmology, and they wanted money to go to their places,” especially because clinical research had traditionally been slighted at NIH. Moreover, even “if you had been a top scientist but were at a department of ophthalmology, that was a strike against you.” Now, having a say in planning priorities offered opportunity—a way to jockey for better positioning in the research community and at the same time help people.¹¹⁷ This twining of motivations is, of course, no better or worse than what occurs in most of the “helping” professions.

Strategic program planning addressed one of the major concerns of the council—program imbalance. For example, there was little basic research being supported by NEI in 1974 in diabetic retinopathy (a major blinding eye disease) within the retinal diseases research program. Yet, visual transduction, another basic retinal research area, had support for more than 100 research grants—about one-fifth of the total institute grant support. Planning could help rectify such imbalances in the research portfolio by basing priorities upon needs and opportunities. To determine imbalances, information about the scope of various diseases was gathered and a complete analysis of research already underway was developed. A program planning subcommittee of the NAEC was set up under council member Dr. Bradley Straatsma and included Dr. Vernon Mountcastle, Dr. Everett Kinsey, and Dr. Mansour Armaly.¹¹⁸ Julian Morris provided necessary staff support and played a major role in this and all aspects of program planning.

In government organizations, planning is seen as one of the major components and responsibilities of the line manager of the organization, that is, the director. For multiple reasons, the NAEC—a part-time group of advisors that met only intermittently—assumed significant planning responsibilities, with NEI’s blessings. First and foremost was the desire to obtain a wide array of scientific input from all fields of vision research; the council membership, with its broad base, provided the opportunity to do so. Second, NEI management understood early on that the culture of biomedical research would be more amenable to a “bottoms-up” approach to priority setting (as opposed to NEI staff or the federal government making these determinations and imposing them from the top-down). Third, it was important that the vision research community be part of the planning process. Finally, budgetary recommendations carried much more weight when made by a group nominally outside of government control. In fact, all government employees were under strict anti-lobbying laws, and regulations required that employees support the President’s budget proposal for their agency, even if questioned or prodded by congressional committees who might want a different answer. The NAEC, however, would not be muzzled by the OMB or its political operatives at the Department of Health Education and Welfare. Thus, the NAEC became an advocate for the institute’s budget needs, especially when the executive budget seemed too low.

The Five-Year Plans

There now have been several five-year plans prepared by NEI and NAEC. Those completed under Kupfer's tenure were drafted by NAEC subcommittees chaired by eminent ophthalmologic educators.*

NEI's five-year plans incorporated strategic program planning principles and elements derived from the PPBS framework. Over the years, they grew more sophisticated in strategic and planning capabilities. They encompassed statements on goals and objectives, cost estimates of the overall eye disease problem, detailed analyses of ongoing projects, priorities for future research, projected costs of priority research, and information on program areas. At base, perhaps, they simply functioned as an excellent "communication vehicle"—a forum for provoking discussions that otherwise might not have occurred.¹¹⁹

The First NEI Program Plan, 1973-1977

The first plan, covering the years 1973 through 1977, was basic in its outline; it described the program in detail and articulated research goals, objectives, and priorities. Julian Morris led the effort to develop this plan. Primarily descriptive in nature, the plan outlined the institute's program and provided a comprehensive listing of all possible projects that could be supported.

This first plan failed to provide an in-depth analysis of vision research outside of NEI or address in detail the significance of blindness and visual disability. Later, it was shown how vision disorders and eye disease were major problems that research programs did not address to any great degree; only a massive government-supported research program would suffice. The plan also concluded that NEI should develop stated policies to guide new research initiatives such as clinical trials, and that NEI's top management should have support and input from the best researchers in the extramural community, as well as its public constituency. The plan discussed expanding intramural research and international research, controversial moves that some vision research scientists believed would create more competition for resources.¹²⁰

* Bradley Straatsma, M.D.—1973-1977 Plan (Jules Stein Eye Institute, University of California-Los Angeles School of Medicine); A. Edward Maumenee, M.D.—1978-1982 Plan, (Wilmer Eye Institute, The Johns Hopkins University Hospital), Thomas D. Duane, M.D., Ph.D.—1983-1987 Plan (Wills Eye Hospital, Jefferson Medical College, Philadelphia); Stephen Ryan, M.D.—1988-1992 Plan (Doheny Eye Institute, University of Southern California, Los Angeles); John Chandler, M.D.—1993-1997 Plan (University of Wisconsin School of Medicine, Madison); Eve J. Higgenbotham, M.D. (University of Maryland School of Medicine, Baltimore); and David C. Beebe, Ph.D. (Washington University School of Medicine, St. Louis) —Co-chairs, 1998-2002 Plan.

Interim Report of the National Advisory Eye Council, 1976

The council thought that the first plan had a major shortcoming: no arrangements had been made to gather more information on current research. To assess needs and opportunities and establish program priorities, the council wanted an in-depth analysis of what was already being supported in vision research and what research needed to be conducted. Furthermore, the council wanted NEI to provide for “periodic distribution of vision research program planning material to the research community.” NEI responded to this recommendation with its 1976 publication, *Support for Vision Research: Interim Report of the National Advisory Eye Council*.¹²¹ The volume included a listing of individual projects supported by NEI and a summary of research supported by other government agencies and private philanthropic and voluntary health organizations. WESTAT, Inc., a well-regarded statistical survey group, prepared a comprehensive analysis under contract support from NEI. In its depth, scope, and rigor, this effort differed from other anecdotal attempts by the vision community to collect and analyze data regarding ongoing eye and vision research. The study concluded that NEI was funding 85 percent of all supported vision research in the United States, although as the report made clear, not all research had been accounted for, especially that done by pharmaceutical companies, which for privacy purposes would not divulge the detail and extent of their research. The study maintained that the amount of pharmaceutical company funding was not large. With this published analysis, it became difficult for anyone to persuasively argue that vision research was adequately supported by the private and nonprofit sectors. If eye research was to gain additional funding and advance, it appeared that it would have to be through NEI-supported research. This data allowed NEI staff to argue that they used a rigorous process to determine research priorities, many of which were not being supported by other institutions, nor were they likely to be. Subsequent to the 1976 volume publication, NEI annually undertook the arduous task of gathering, analyzing, and interpreting data concerning ongoing research, a crucial part of the planning process. In 1977, NEI created the Program Analysis Section, staffed with individuals who possessed computer skills as well as a scientific background in biology.

The *Support for Vision Research* volume also contained figures on the number of Americans affected by eye disease and visual impairment. In devising its plans, NEI targeted both Congress and the public, with the aim of gaining support for increased appropriations. NEI competed with the other national institutes for scarce research dollars, so in order to influence policymakers, the case had to be made that eye disease and visual disability were serious problems. Thus, NEI commissioned a separate study by WESTAT, Inc. (also included in the volume) that estimated the economic impact of eye disease and vision impairment. Dorothy P. Rice, a medical economist, had pioneered studies on the economic burden of illness at the Social Security Administration and later as director of the National Center for

Health Statistics.¹²² NEI's study was among the first economic studies to analyze the financial impact of a discrete eye disease area from a cost perspective. The costs of eye disease and its antecedents, in dollar terms, were staggering at that time, amounting to over \$5 billion according to the WESTAT study. NEI staff used this data extensively when seeking additional appropriations from Capitol Hill.

The Second Five-Year Plan, 1978-1982

The second five-year plan authored by the NAEC was called *Vision Research: A National Plan, 1978-82*. It filled three separate volumes containing the council's latest findings and recommendations with respect to each NEI program. A significant number of scientists, almost 200, participated in developing the plan, including scientists from other fields who had interesting ideas related to vision research, which broadened the pool of knowledge. These scientists were organized into working panels that met multiple times to analyze progress in various research areas. Following a rigorous format designed by Julian Morris and NEI staff, the panel reports contained recommendations and suggestions for future priorities. These panel reports were then combined into a single report for each program, such as retinal disease, corneal disease, glaucoma, age-related cataract, and others; these were published as part of the second five-year plan.

Training

The volumes also included a special section for vision research training and career development. Manpower development was deemed especially important by the NAEC planners in light of new legislation that adversely affected NIH training programs. OMB recommended discontinuing graduate training and fellowship grants. NEI and academic ophthalmology departments had found such grants vital in the support of advanced clinical and research training. Some budget overseers concerned with the use of federal funding rationalized that NIH should be giving training grants to researchers headed for a career in academia and not to those going into private practice, as the latter could easily recoup educational expenses. Congress enacted new training legislation and NIH issued new guidelines. NEI staff had already anticipated many of the changes, and the institute's programs were easily modified to adapt to new rules. NEI reoriented support to cover training for only those clinicians committed to research careers. Regrettably, the cessation of graduate training grants resulted in a sudden reduction in financial support for ophthalmology departments. Additionally, the National Academy of Sciences (NAS) had been selected under this new legislation to analyze existing training programs in biomedical and behavioral science and recommend any changes that were needed. NEI's second five-year plan report addressed these training issues and recommended increased levels of vision research manpower; these

recommendations were backed by a detailed justification that was made available to the NAS as it conducted its study on biomedical training. Thus, this second NEI Vision Research Plan allowed the institute to solidly position itself to deal with threats to its training programs.¹²³

Policy Issues

Several additional recommendations on program and policy issues discussed in the second plan were used by NEI management to guide its programs. These included ensuring that clinical research and clinical trials were made a priority and received adequate support. On the other hand, support for large research centers and program project grants (also known as umbrella grants) was widespread at the other NIH institutes. Dr. Kupfer, however, believed that the competitively-based individual project grant was the best way to advance vision science, and like-minded council members thought that NEI should fund only this type of research grant. Thus, the second plan recommended this as policy. As a result, NEI chose not to fund large, expensive multi-program projects and comprehensive center grants, the only institute at NIH to pursue such a course. NEI continued to fund small core grants for groups of researchers who already held individual project grants and who needed to share research facilities, such as those for tissue culture capability, machine shops, or special animal holding areas.

Technology Transfer

The management staff at NEI, and at NIH generally, were interested in technology transfer, or what might be described as the interface between research and health care delivery. In the eye care field, research advances resulted in new devices and surgical approaches, such as intraocular lens implants in cataract surgery and medical treatment of diabetic retinopathy, which could potentially add billions to the health care bill of Americans. The plan suggested that managers should carefully consider such issues as how best to “assure the effective and appropriate application of new knowledge gained through research to practical uses in health care,” a longstanding problem in all areas of medicine, including eye care. They should also ask questions, such as: Were new technologies safe, efficacious, and cost-effective? Who would determine this and what would be the role of NEI in developing the data to make these judgments? The second plan further maintained that “critics have pointed to, for example, the high cost of such so-called ‘half-way technologies’ as renal dialysis and some of the complex and costly therapies for cancer. Although many of the cost-impact criticisms of research are arguable, such concerns must be taken seriously.”¹²⁴ Some new technological advances, such as lens implants and cataract surgery as an alternative to using eyeglasses, were not fully evaluated in clinical trials before being implemented; nevertheless, they became associated with higher costs of eye care. Policymakers often looked to NIH to

answer whether these advances were worth pursuing—although, of course, there were many different, subjective ways of valuing “worth.”

The second plan recommended that NEI move only cautiously into the field of technology transfer. This reflected the concerns of some council members who tended to become apprehensive any time the institute moved outside its core function of supporting research. As such, the council advised that NEI focus on validating new as well as established surgical and medical interventions, such as treating optic neuritis with oral prednisone (which ironically was thought for over 50 years to be beneficial until a clinical trial demonstrated otherwise). The council also encouraged the dissemination of research results.¹²⁵ The emphasis on validating new interventions or developing data on the safety and efficacy of new devices and treatments in eye care gave a great boost to NEI’s clinical trials program. Likewise, stressing the importance of disseminating research results gave major impetus to the establishment of the National Eye Health Education Program, which supported major eye health initiatives in glaucoma and diabetic retinopathy.

NEI’s scientific constituency, whose first inclination was to support a narrow program of basic eye and vision research, increasingly bought into the concept of a much broader national research program that included clinical trials, the evaluation of new technologies, and information dissemination.

Neurobiology

The second five-year plan also addressed neurobiology (a term encompassing most neuroscience research), a major NIH science program that cut across institute interests. NAEC members wanted vision research, backed by NEI, to be a major part of this program. Neuroscience was fast becoming a research frontier of biomedical science and had attracted a number of frontline scientists who researched the visual system.¹²⁶ NEI became a major player in neurobiology, which served to enhance its reputation and helped it better compete for resources with other NIH institutes.

The Third Plan for Vision Research: A National Plan, 1983–1987: Priorities

The third five-year program plan, covering 1983 to 1987, updated subjects addressed in the previous plans including priority setting, a topic that caused great concern throughout the history of the five-year plans. The third plan redefined the conceptualization of priority setting.

The research community traditionally defined priorities in the sense of technical scientific priorities, as established through the peer review process, with expert scientists in study sections determining the scientific merit of an application. In general, study section members deemed the scientific priority of individual projects to be higher than that of center grants or

research program project grants. Thus, the research community believed that priorities were already being more than adequately addressed. In contrast, all of NEI's five-year plans made the statement that "a priority is a research need judged to be of particular importance in terms of fulfilling a program goal."¹²⁷ This refers to *programmatic* priority rather than *project* priority; the concept is essential to any overall systematic approach to management of programs. A project was usually an individual grant, whereas a program might be a collection of 50 to 200 grants. A program was related to a major goal of the institute such as treating retinal diseases and would include specific objectives for achieving this goal. A project, on the other hand, was represented by a discrete research proposal submitted by an investigator to pursue a line of research, such as understanding the concept of gene sharing as a fundamental principle of evolution and protein multi-functionality, or an application might propose to look at the neuronal correlates of visual spatial attention and the close relationship between visual spatial attention and saccadic eye movements.

The third plan refined priority setting as a concept and set forth two types of research priorities: the first, *Program Base Priorities*, encompassed "research areas that should continue to be supported essentially at current levels of activity for the next five years." The second, *Program Development Priorities*, encompassed "research areas that warrant new or added support for the next five years."¹²⁸ Representing a compromise, these two listings acknowledged existing grants in priority areas; the program base areas, however, were not designated for expansion. NEI management would have rather had one set of expansion priorities. Priority areas that would gain new funding were to be termed *developmental priorities*.¹²⁹ Most researchers wanted the program area under which their research fell to receive the designation "developmental priority" because they thought that would improve their chances of receiving grant funding.

The third plan's policy section contained a long discussion in defense of the in-house intramural research program, providing some cover against criticism. Many critics in the outside community who had to compete for research funding believed that intramural researchers (NEI staff employees) had an unfair advantage because the intramural program received an annual appropriation directly from Congress. The NAEC planning subcommittee endorsed the intramural program and recommended, among other things, that it "take advantage of the unique resources and environment of the NIH campus in carrying out the priorities of this plan and to serve as a national resource for the training and career development of basic and clinical vision researchers."¹³⁰ The institute hoped that the council's discussion of intramural policy would help convince extramural grantees that intramural scientists did not receive preferential treatment.

The third plan strongly pushed implementation steps to ensure that council-approved priorities were actually carried out. It especially encouraged "designating some approved

grant applications as having *High Program Relevance*, thereby placing them in a more favorable position for funding than would otherwise be the case.”¹³¹ This meant that in practice, if a grant received this designation, 50 points were taken off of its score. If the score for the grant was initially 300, the new score would be 250. In most budget years, 250 was the cut-off point for funding, so high program relevance usually meant a decision to fund the grant.

Low Vision and Rehabilitation

With the third plan, a new program area, Low Vision and Rehabilitation, was added to the five existing NEI programs. The planning subcommittee stated in the third plan that there was a need “to develop, organize, and coordinate research on visual impairment and its rehabilitation.” Much of the research in this field was aimed at maximizing residual vision, that is, the vision that remained to an individual after he or she had been determined to be legally blind from disease or injury; it included major developmental efforts in optical and electronic fields. Research in this field was usually different from basic vision research, but these studies could potentially have enormous impact on the patient population. Thus, through the council’s planning process, the case was finally made that NEI should embrace low vision as a program area.¹³²

NIH Biennial Reports

The development of the first three NEI five-year plans required extensive effort by the council, NEI staff, and the outside scientific panels. These were times—the late 70s and early 80s—of extremely limited staffing at NIH, and only a few positions could be added to NEI for planning and analysis purposes. In 1984 Michael P. Davis accepted an offer to join the Office of Program Planning and Evaluation because he was excited about NEI’s aggressive stance toward program planning. He remembers being impressed by the process once he understood it better, particularly as NEI program planners sought consult in ways that leaders at other institutes did not: “You asked people—trusted advisors, experts in the field—what the next steps should be, and you didn’t confine it to a very small group or just one or two people who were very vocal.”¹³³

Even though NEI had a planning apparatus in place and program area organization was being solidified, progress was not as rapid as desired. In 1984 an NAEC program planning subcommittee was established. It helped to oversee planning activities and started a midcourse evaluation of the next plan. This evaluation included the tracking of extensive data gathered by NEI staff on grant submissions and researchers’ responsiveness to the priorities set forth in the 1983–1987 plan. That is, they tracked to what extent researchers were responding to stated priorities by submitting applications and how many were ultimately given funding. This analysis was the basis for recommendations for the period 1988 to 1992.¹³⁴

Around the same time, Congress mandated that NIH prepare biennial reports on all activities of each institute. Instead of publishing a five-year plan for Fiscal Year 1988–1992, NEI used the materials usually generated for its plans to serve as background for the report it was required to submit. The information derived from the tracking and evaluation activities of the council subcommittees and its outside scientific consultants was used for the *Biennial Report of the National Institutes of Health*, published in 1989. The planning process differed from earlier efforts in that the NAEC scientist panels considered what were called *areas of special emphasis*. These were one or more research topics in each program that the director, council, and staff identified as having particular urgency. Rather than consider the entire range of research in each program, as had previous groups, these panels focused on some of the chief barriers to progress in each program. A common theme was the need to focus on seemingly intractable problems, such as the prevention of vision loss in macular degeneration and glaucoma, as well as the latest knowledge and techniques from such cutting-edge fields as immunology, molecular biology, and cell biology.¹³⁵

One of the features of the required biennial reports was that they could not be edited or censored by the administration. Therefore, NEI drafted a “professional judgment budget” recommendation for inclusion in the NIH report. Previously, professional judgment budgets had been included in the published NEI plans and they had differed significantly from the President’s budget proposal for NEI, a bold move because employees were supposed to fully support the President’s budget. For example, the proposed increase in NEI’s first plan (1975–1979) was \$75 million—considerably more than the few million-dollar increase proposed by the President over the 1974 appropriation. NEI management took advantage of NIH’s increasing focus on strategic planning—through the biennial plans—to have its research priorities included with NIH priorities and to make sure its budget requirements were published in the biennial reports as an official governmental recommendation.

The biennial planning process, a result of legislation, demonstrated that Congress as well as the executive branch was interested in planning. NEI used the NIH biennial planning process to supplement its own planning, particularly during the period 1988 to 1993, when staff were overwhelmed by data analysis and reporting requirements. Unfortunately, Julian Morris, chief of the Planning Office, was ill, further stretching NEI’s planning capabilities during the 1980s. According to Mike Davis, these years constituted a “hole” in the NEI planning process.¹³⁶

The Fourth Plan, FY 1994-1998: Vision Research National Plan

NEI and NAEC regained planning momentum in the early 1990s. The fourth five-year plan was the first comprehensive update of the total NEI program since the 1983–87 Plan.¹³⁷ It served as one of the major communication vehicles for disseminating the results of

a National Survey conducted by NEI and Lions Club International. The survey found “that among five potential disabilities—loss of eyesight, memory, hearing, speech, or an arm or leg—42 percent of the respondents considered the loss of eyesight as the worst disability.”¹³⁸ This forcefully underscored one of the main themes of this planning document, that eye research on the prevention and treatment of blinding diseases should be a major national health research priority.

The council and institute demonstrated growing interest in policy areas such as the economic and social cost of blindness and visual disability. This went beyond discussion of such issues in the published report. At two widely publicized meetings open to the public, NEI staff and council members met with representatives from a number of scientific and philanthropic organizations that supported vision research. Although NEI traditionally developed policy with input from the scientific community, these meetings were the first where “a diverse group of organizations was assembled solely for the discussion of policy matters, particularly the question of how best to maintain the viability of the national vision research effort in times of fiscal stringency.”¹³⁹

The fourth plan singled out clinical and epidemiologic research for special emphasis. In recognition of the importance of this research, “NEI established a Cooperative Clinical Research Branch within the Extramural and Collaborative Programs with the aim of improving the design, implementation, management, and analysis of clinical trials and epidemiologic research.”¹⁴⁰ The council had approved this initiative, and actively encouraged NEI to conduct additional clinical trials.

The fourth plan also made changes to how the council handled the ever-vexing problem of defining research program priorities. Earlier plans had recommended that priority areas were those deemed to be of greatest need and opportunity. In this plan, the council “felt that the areas of greatest need and opportunity should be described in terms of the research questions that must be asked in order to provide new information or knowledge in that area. These questions, therefore, constitute the recommendations or research priorities of the planning panels.”¹⁴¹ In practice, using these questions as stand-ins for research priorities did not signify much of a change from the original statement on research priorities, for priorities had regularly been stated as questions. Now, however, they were to *always* be stated as questions. A method had finally been developed that council planning bodies found satisfactory for dealing with research priorities, a subject that was very important to NEI policymakers. The phrase *significant research questions* was better suited to the language of science than the management term *priorities*, and therefore more readily acceptable to bench scientists.

Coinciding with the development of NEI’s fourth plan, NIH, under its new director Dr. Bernadine Healy, decided in 1990 to develop a strategic plan for NIH as a whole. With

the fourth plan in its final stages of development, NEI staff could readily identify goals, objectives, research priorities, and other initiatives that easily fit within each major category of the NIH plan. Overall, NEI selected 30 major initiatives from planning panel deliberations, which were included in the development and finalization of the NIH plan.¹⁴² NEI was able to input priorities pertaining to a broad set of subjects, ranging from immunology to clinical trials to neurobiology. The planning processes NEI already had in place once again allowed the institute to be well positioned for claiming a place in NIH and DHEW initiatives.

The Five-Year Plan, FY 1999–2003

The fifth plan was developed in an environment much more partial to program planning. NIH had begun to accept the notion of strategic planning with the three biennial reports required by Congress in the late 1980s. It had also embarked upon a formal strategic planning process in 1992 with Dr. Healy's NIH planning effort. Moreover, there was increasing interest in priority setting and strategic planning processes throughout the federal sector. The Government Performance and Results Act (GPRA), signed into law in 1993, enacted provisions making federal agencies accountable for achieving program results through the establishment of program goals and objectives against which progress could be measured.¹⁴³

The fifth plan benefited from the input of more than 100 technical experts, down from a high of 350 consultants who had worked on the fourth NEI plan. For the first time, the internet was used in the planning process. Through the NEI homepage, comments from scientists throughout the vision research community were solicited “on the most significant accomplishments or advances since the last plan,” as well as “the most important vision research questions that should be addressed during the next five years.”¹⁴⁴

Low Vision Research

The fifth plan discussed a key research accomplishment previously identified as a priority. It involved the development and evaluation of new technologies to assist people who were blind or severely visually impaired and had difficulty moving about. One such technology involved fitting people with hand-held devices that received electronic signals from transmitters installed in signs, a tool which could be used to guide people with vision problems.¹⁴⁵ The planning process, in recommending the establishment of this program area as a priority, demonstrated its value.

Health Services Research

In this fifth plan, health services research also received a boost. A special Health Services Research Working Group was established to flesh out research recommendations

in this area. NAEC and NEI leaders believed that it was “critical to understand the delivery and use of vision services to best prevent, diagnose, and treat eye conditions and reduce the risk of visual impairment.” To meet that “challenge, NEI and the NAEC decided to highlight health services research as a scientific area of interest in vision research for the next five years.”¹⁴⁶ An example of the research supported in this area is as follows: NEI-supported research had found that many people with diabetes did not receive the dilated eye exams essential to diagnosing diabetic retinopathy. NEI encouraged and funded studies to discover why the medical system was failing these patients at high risk for eye problems. Additional studies were aimed at eye care providers and diabetics in order to increase dilated eye exams. With support and input from the council, NEI had again used the program planning process to incorporate a broader definition of vision research than had been anticipated by the institute’s founders; now health services research was considered a significant component of NEI’s mandate.

Implementation of the NEI Plans

Carl Kupfer and Ed McManus knew that planning on its own had value, but unless it was tied in to everyday program management, it would have a very limited impact. In a recent interview, Dr. Thomas Kennedy, Chief of Program Planning at NIH in the late 1960s, pointed out that many still questioned the value of planning at a staff meeting held by the DHEW secretary in the 1980s. Several agency heads and staff expressed skepticism when asked about the value of management planning programs.¹⁴⁷ Given this lack of enthusiasm among government administrators, NEI—already dedicated to this notion for almost two decades—was certainly at the front in the health field with regard to strategic planning.

NCI’s highly touted national plan, developed in the early 1970s, was viewed by some at NIH as falling short of being a real factor in the management of programs at NCI. NEI management was determined that this would not be the case with the vision research plans, and along with the council, took several steps toward this end. NEI widely disseminated the national plans to the research community and the general public. The NAEC was encouraged to use the plan to give a high program relevance recommendation to individual grants based upon program priorities; this placed the grants in a more favorable position for funding. NEI posted notices in leading scientific journals and made announcements encouraging investigators to submit grants in specific areas of research as outlined in the plan. The council also periodically reviewed data analysis to evaluate progress in attracting researchers to priority areas.

The plans recommended training and career development of new scientific manpower; special groups formed to review training in the vision sciences emphasized research training for clinicians and other investigators, who would in turn implement institute

priorities. The plans advised that core center grants be financed to foster an environment conducive to multidisciplinary research, recommended special research resources such as laboratory animal breeding colonies and human donor tissue, and called for consortium grants that pooled scarce resources as a means to pursue projects related to the priorities of the plan. The institute was urged to use its intramural program to take advantage of the unique environment at the NIH campus in Bethesda, Maryland, to serve as a national resource for the training and career development of basic and clinical vision researchers.

The council further encouraged “the transfer of scientific knowledge and the dissemination of information to practitioners and the general public to help in achieving the NEI’s long-range goal to improve the visual health of the American people through research.” Finally, NAEC planners called for NEI to participate “in international activities and agreements that would provide a knowledge base for world-wide efforts to prevent blindness.”¹⁴⁸ These latter two recommendations bolstered support for the expansion of NEI International Programs and the establishment of the National Eye Health Education Program.

Impact of the Five-Year Plans

The five-year plans had a major impact in helping to increase the budget of the institute dramatically between Fiscal Year 1970 and Fiscal Year 2003. The series of five-year plans served as a rallying point for vision researchers and helped enlist new supporters. NEI’s first budget was almost \$23 million. The first few years of its existence saw only modest budget increases through Fiscal Year 1973, primarily because the NIH budget as a whole was being squeezed by the “guns versus butter” debate accompanying the Vietnam War. Nevertheless, NEI’s budget increased to more than \$510 million in Fiscal Year 2001; no doubt the publication of the plans and related efforts contributed to this success.

The plans usually provided a crisp programmatic structure encompassing cataract, cornea, retinal disease research, and other areas of vision research. They contained discussions about expanding research in specific disease-related programs, such as diabetic retinopathy and retinitis pigmentosa; the rationales were based on solid scientific and managerial notions.

There were several groups that these five-year plans were intended to reach. The first encompassed the scientific community in general and the vision research community in particular. NEI focused on disseminating information to the broader scientific community so as to attract new scientists into the expanding eye and vision research field. Scientists in disciplines such as neurobiology, immunology, molecular biology, and epidemiology came to believe that they could play an important role in NEI’s program.

With its plans, NEI targeted decision makers within the executive branch of government who controlled the purse strings. Budget recommendations in the plans were used to

influence various audiences. To bolster support for the highest possible budget level, NEI staff carefully crafted persuasive justifications and submitted them to the NIH director, the individual in charge of the first-level of decision making about the NEI budget. This was one of many steps in the budget process that wound its way through DHEW and eventually to OMB, in the Office of the President. The five-year plans were also directed toward the general public and the special patient publics interested in specific eye diseases, such as age-related macular degeneration and retinopathy of prematurity (formerly known as retrolental fibroplasias or RLF). Health advocacy groups often used these materials to argue for additional funding. This point cannot be overemphasized: public advocates had at their disposal a rationally based consensus document that supported annual requests for eye and vision research appropriations. When a supplicant for NEI was asked, “What are your priorities?” the plan set them out in detail. When the question was asked, “Well, how big is this problem of eye disease anyhow?” the plan spelled out the extent of the problem.

Congress was perhaps the most important audience for NEI’s strategic plans. Nothing was left to chance. At the end of each of the planning cycles, relevant congressional committees were sent copies. Members of the research community and advisory council briefed committee leaders and congressional staffers on the plan.

NEI used the plans extensively in managing its programs, sponsoring workshops that addressed priority areas such as retinal pigment epithelium research and the cross-cutting area of immunology. These workshops were intended to attract new investigators, interest existing investigators in new approaches, and to generally signal the institute’s intent in fostering priority-designated areas such as ophthalmic genetics, molecular biology, clinical and experimental immunology, clinical trials, and epidemiology.

The five-year plans were also widely disseminated to the research community. Many vision scientists used these plans as a ready reference source to refer to in deciding exactly how to present their individual research grant proposals for funding to NEI. Dr. John Dowling referred to the plans as “useful to himself and other scientists in his lab” when “preparing research applications to the NEI.” Special presentations on designated research priority areas were made at annual meetings of the Association for Research in Vision and Ophthalmology where many vision researchers gathered. Dowling remembered that when a new plan was released, readers would make comments such as, “One of the things the committee pointed out was very interesting to me and I am going to put in a grant to do that.” Dowling affirmed that was “part of the management strategy”—to point out areas where research should be done.¹⁴⁹ NEI staff members were also encouraged to advance projects for special consideration that were in line with the plan’s priorities. The series of five-year vision plans often had dramatic outcomes. For example, research on pigment epithelium was initially designated for priority consideration. While there was almost no research in this area in the early 1970s (see 1973 Plan), it increased over the next few years. Immunological

research received a boost during the 1970s and 1980s from this planning effort, including the establishment of a clinical immunology lab at the NEI intramural program. Molecular biology also expanded greatly during the same period. In part, this growth occurred across the board in science, but also because NEI proactively sought to expand the number of scientists in this emerging discipline who became vision researchers. This included establishing a laboratory of Molecular and Developmental Biology within the NEI intramural program. Clinical trials, epidemiology, and biostatistics also received great emphasis during the first three planning periods. Clinical trials especially flourished as a result of being assigned priority status. In NEI's first budget for Fiscal Year 1969, no clinical trials were supported; in Fiscal Year 2000, there were 60 separate trials being supported or that had been completed.

Program planning has become increasingly accepted. Importantly, it helped foster vision research that cut across several disciplines or areas of study such as immunology, genomics, and inflammation. Program planning allowed NEI staff to interact with the extramural community in identifying topics that extended horizontally across individual programs, such as proliferation of blood vessels of the iris and retina in diabetes, gene sharing in the lens and cornea, and above all, in the numerous clinical trials.

* * *

In a 2005 interview, then NEI Deputy Director Jack McLaughlin discussed his earlier uncertainty about program planning. He joined NEI in 1980 as the extramural program director, in the fundamental retinal science area. With a Ph.D. in neuroscience from the University of Rochester, McLaughlin had concentrated on research in the NINDS laboratory of Dr. W. King Engel before working briefly in the NIH grants associate extramural program. McLaughlin felt "like anyone just leaving the [research] bench" that program planning was a "pretty alien, foreign, concept."

To say the least, then, I think most people in my position are very skeptical at first about the idea that you can plan; we thought going into it that the institute was trying to come up with a blueprint of how research ought to get done. But I think the more we came to realize what it is and the way program planning has evolved over time, it really is a broad statement of needs, of goals, and opportunities and how those relate to each other. The other thing over time that was important was that we didn't just put the plan on the shelf; we actually looked at it as a framework for thinking about the science in our portfolios, of managing the programs, and as a source of concepts for various program activities that were implemented because of the plan and its discussion. Speaking for myself and other program directors, we thought it was a necessary evil, but not one that we rejected immediately upon moving into it.

But we knew it was a lot of work, involving lots of scientists both extramurally and intramurally. A lot of effort was put into it, but in the end it was a worthwhile project, something that we can be proud of.¹⁵⁰

Mike Davis, in NEI's Program Planning Office, has considered the effects of strategic program planning on NEI since his arrival in 1984.

I've looked at all different ways to see what the real impact and what the imagined impact was and so forth, but I honestly think that the best impact was on the vision research community . . . the best part of all was assembling the people who are experts in the field and tasking them with the responsibility of looking into their crystal balls or using their expertise to tell you where the next breakthroughs were going to come. Where should we invest the money? What should we do? And every person involved in that took it extremely seriously. The fact that they actually sat down and thought about it for a day or two days, thought about what the priorities should be—of course there will be some people who would say, yeah, my area. But when you get the scientists together, and they start on this roll of which way should science go . . . the good ideas come out. That was the best thing that came out of strategic planning. I think it put the Eye Institute ahead; people were able to understand the process. It wasn't the imagined increases in budget, it wasn't any of those other things, but it was more of an intangible thing that you made the people that counted think about it. And if we assembled 20 people per program, and we had a hundred folks who came and thought that seriously about it and analyzed what progress had been made, thought about where it ought to go—if we had a hundred great new ideas that came in just from those people as a result as strategic planning, it was worth it. And that was the advantage.¹⁵¹

Chapter 4

The Intramural Research Program

Intramural Ophthalmology at NINDB

The ophthalmology program at NINDB, from which NEI's intramural program eventually took root, got off to a slow start. Although NINDB had administrative funds for the first year after becoming separate from NIMH, Congress had not appropriated research or training funds. NIMH, previously responsible for neurology, covered intramural funding until congressional monies became available. For the time being, Seymour Kety, M.D., assumed dual responsibility as the scientific director for both NIMH and NINDB intramural programs. Through his advocacy, NINDB acquired the budget, space, and resources—no mean feat—that made it attractive to researchers. Particularly adept at spotting talent, Dr. Kety recruited several promising young investigators in the 1950s: Roscoe Brady, Sanford Palay, William F. Windle, Kenneth Cole, Karl Frank, Julius Axelrod, and others, all who proceeded to make a name for themselves in neuroscience. The intramural leaders were of course neurologists. G. Milton Shy, an outstanding clinician and laboratory researcher in neuromuscular disease, served as clinical director and was succeeded by Maitland Baldwin, a neurosurgeon.

While the neurology aspects of the NINDB Intramural Research (IM) program expanded with laboratory-based research programs in biochemistry, biophysics, spinal cord neurophysiology, and electron microscopy, there was no commensurate effort to establish an intramural program in ophthalmology during the first half of the 1950s. NINDB made a feeble attempt in 1953 to establish an intramural ophthalmology branch. Two ophthalmologists were hired, William M. Hart and Ralph Ryan, who both left within a short period of time. One physicist, one chemist, one technician, and two stenographers were also hired.¹⁵²

Not until 1955 was NINDB able to recruit Professor Ludwig von Sallman, a distinguished research ophthalmologist from Columbia University College of Physicians and Surgeons, to be chief of the Ophthalmology Branch. As chief, he built up the ophthalmology program such that at one point there were as many as nine full-time research ophthalmologists. A renowned clinical researcher, von Sallman established a laboratory for experimental studies divided into several sections: chemistry, pharmacology, cell biology, physiology, and

cytology/histopathology. The branch also had a very active clinical service that conducted ophthalmic consultations at the new NIH clinical center.¹⁵³

NINDB's in-house eye research had some important successes. Out of the intramural program came the discovery that prolonged doses of the drug chloroquine, an anti-malarial drug used to treat rheumatoid arthritis, could cause blindness; treatments for herpes infection of the cornea; the finding that toxoplasmosis was a frequent cause of uveitis, a serious eye disease; and advances in the surgical treatment of retinal detachment and cataract.¹⁵⁴

The ophthalmology branch pioneered the development of electroretinographic testing for assessing patients with hereditary retinal diseases, and helped to train specialists in this field such as Eliot Berson, M.D., a clinical associate from 1966 to 1968. Berson gained the opportunity to work with a talented assembly of retinal specialists at a time when only a few clinical investigators were focusing on retinal degeneration. He became a professor at Harvard Medical School and expert in retinal disease and electroretinography. "In retrospect," he recently stated, "NIH was leading the way during that period and my experience there was a very critical part of my training." Dr. Berson found von Sallman a wonderful but demanding mentor. Berson remembers, "He insisted that as part of my education I should go to the NIH library a half day each week and, with the aid of an interpreter of old German, review the atlases that contained drawings of retinal diseases made in the early part of the twentieth century before they had fundus photography."¹⁵⁵

Herbert E. Kaufman, M.D., a clinical associate at NINDB some years before Berson, remembered thinking that some of the research lacked quality when he was with the branch in the late 1950s. At that time, Kaufman was doing basic science research on toxoplasmosis as well as performing patient services. Dr. Kaufman recalled that when he complained to von Sallman, the branch chief wisely said, "If the opportunity is there, the quality will follow." Over his long tenure as a university professor, Kaufman came to realize that Dr. von Sallman's insight had proved correct.¹⁵⁶

Von Sallman was particularly interested in clinical research and tended to emphasize that role for the intramural branch. The Ophthalmology Branch provided ophthalmic consulting services to patients participating in research protocols from other institutes and for the NIH Clinical Center, which first opened to patients in 1953. While time-consuming, this was an important function for the NINDB ophthalmologists. Indeed, they performed so well that their clinical responsibilities tended to increase each year. In 1957, NINDB provided a total of 1,618 consultations to the NIH Clinical Center; 1,055 (65%) of these were ophthalmic consultations provided by the Ophthalmology Branch. The ophthalmology intramuralists produced some important clinical research, publishing several excellent articles in peer-reviewed journals describing the signs and symptoms that had been correlated with the patient

pathologies.¹⁵⁷ Yet, always on call for patient examinations, they did not have much time to attend research meetings and the like.

The Ophthalmology Branch's emphasis on clinical consultation, research, and training partially resulted from insufficient space for laboratory research and partially from inadequate funding for recruiting trained vision researchers and supporting large dedicated research projects. Also, there was a ready supply of clinical ophthalmologists who were serving their military commitment as a result of the ongoing doctor's draft.

In the Fall of 1964, Paul O'Brien, M.D., joined the Ophthalmology Branch then located on the NIH Bethesda Campus in Building 10, a renovated structure that contained old laboratories inherited from another group. Dr. O'Brien remembers that the labs were not the best design for ophthalmic research, but "You just used what was there and lived with it." To have some research space, O'Brien converted a 6-by-10-foot module space for use as a cold room, even papering it with black plastic. That was the only increase in space allocation O'Brien remembered during his time with NINDB.¹⁵⁸

Ophthalmology Branch staff, for the most part, were able to acquire the everyday equipment they needed and sometimes major pieces of equipment such as an ultracentrifuge. Nevertheless, they had no input into—or even knowledge of—the branch budget, reflecting a managerial practice that probably was not unusual for that time. The ophthalmic researchers had a good relationship with the institute's scientific director and the staff of the NINDB intramural program, but they rarely worked with other institute scientists. According to O'Brien, ophthalmology's basic researchers "pretty much stayed within their branch and stayed on the outside of the larger NINDB community."¹⁵⁹

Many years later, just before coming to NIH in 1970, Dr. Kupfer asked Dr. von Sallman about ophthalmology's resources at NINDB, especially laboratory space. The two had first met in 1950 at Columbia University where Kupfer was completing a summer research fellowship. Their laboratories were on the same floor, and von Sallman had often asked Kupfer how his research was progressing. Looking back, the professor responded to Kupfer's question humorously, stating that when he arrived at NINDB "he was given about 3,600 square feet of space consisting primarily of clinical facilities including a 26-bed inpatient ward. In 1969 he still had about 3,600 square feet of space!" According to Kupfer, von Sallman felt that the laboratory research component had failed to receive the support it needed to reach critical mass and flourish.¹⁶⁰

Although clinical research was important and carried out in an outstanding manner under Dr. von Sallman's tutelage, there was a need for additional basic fundamental laboratory research oriented toward exploring the mechanisms of vision function and disease in eye

tissues. That would help balance the research efforts and bridge the gap between the laboratory and the clinic, the “bench and the bedside.”

Dr. Kupfer explains:

I tried to understand why the NINDB intramural research leadership did not support ophthalmic research to a greater extent within the intramural laboratories. After all, these were excellent researchers in their own right who wanted to support excellent research in another portion of the brain, namely the eye. As I met more brain researchers and neurologists, I realized that they did not even consider the retina and associated structures such as the cornea and the lens as part of the central nervous system subserving vision. They viewed the eye as part of the peripheral nervous system. I became so exasperated with this perspective that I began my remarks at presentations with the provocative statement that the brain is an outpouching of the eye! This certainly attracted the attention of the audience. From my discussion with NEI researcher Joram Piatigorsky, I found this claim might even be scientifically valid! Piatigorsky stated: ‘It is fascinating that eyes, defined as light receptors eliciting a behavioral response, exist in some unicellular organisms and jellyfish. There has even been speculation by Walter Gehring of the University of Basel, Switzerland, that photoreception in higher metazoans, including vertebrates, may have originated in a process which by photosynthetic cyanobacteria were incorporated into red algae as chloroplasts; red algae in turn were taken up by dinoflagellates as secondary chloroplasts, and finally symbiotic dinoflagellates contributed genes to jellyfish, leading to the evolution of sophisticated eyes. Such an early derivation of photoreception, as well as the current presence of eyes in species lacking a defined central nervous system, raises the possibility that eyes predate the evolution of brains. In other words, the commonly held idea that the eye is an outpouching of the brain may be evolutionarily reversed— i.e., the brain may be considered an outpouching of the eye!’

From a practical point of view, it seems reasonable to evolve a receptor (eye or other sensory organ) before elaborating a complex apparatus (brain) for processing the resulting signals. Finally, there are certain phenomena found in the retina that some neurobiologists and neurochemists think do not apply to the rest of the brain. Perhaps part of the reason for this misunderstanding may be attributed to the fact that the retina is not under the skull or in the spinal cord; thus it is easy to think it is part of the peripheral

nervous system. In addition, there are some unusual mechanisms in the retina. For example, in the outer retina, there are neurons that respond to light only with sustained graded potentials, without generating action potentials. Some researchers feel that this is not relevant to what is happening in the brain proper. However, many of the mechanisms found first in the retina are later found elsewhere in the brain. Two examples are in order. First, in 1985, it was discovered that dopamine modulates glutamate receptors in retinal horizontal cells. Five years later, this was ‘discovered’ to occur in the brain—with virtually no mention of the retinal receptors research. A second example is a recent paper describing the neuromodulation of gap junctions in the brain. Although the paper mentioned that this had been shown in retinal horizontal cells, the paper implied that the retina was not really part of the brain.

In summary, NINDB laid claim to the central nervous system as being part of its research area. But, since the retina was not under the skull or in the spinal cord, it was relegated to being part of the peripheral nervous system. Hence, retinal research was peripheral to the NINDB’s mandate. This may have been the basis for lack of laboratory research support.¹⁶¹

To be sure, the NINDB leadership appreciated—to a degree—the major health impacts of select eye diseases. The success of the NINDB-sponsored study establishing the cause of retrolental fibroplasia spurred NINDB to steadily increase intramural funding for eye disease. Still, from 1957 to 1960, the support of vision research funding as a portion of the total NINDB appropriation varied between 17 and 18 percent, while from 1961 to 1966 it varied between 13 to 16 percent.¹⁶² This decrease occurred despite the Ophthalmology Branch’s contributions to eye treatments. The lack of commitment to vision research was further evidenced in NINDB’s 1964 list of plans for the next 10 years, which listed as high priorities degenerative diseases and nervous disorders that involved the brain and affected children, but gave lower priority to comparable degenerative diseases involving the visual system.¹⁶³

In establishing its Epidemiology Branch, NINDB had the opportunity to promote important visual research. For the most part, however, the branch focused on kuru disease research, led by Carleton Gajdusek and Clarence Gibbs, and on Nancy Wexler’s work on Huntington disease; this research ultimately had resounding success. Less successful was the Perinatal Project; it had a grand design, but “its contributions to neuroscience have not been so clear,” according to the chronicler of the institute’s history.¹⁶⁴ The lack of ophthalmologic leadership in the institute’s Epidemiology Branch resulted in at least two missed

research opportunities. In 1957 a small field program in glaucoma “proved to be a failure in our hands,” according to the branch chief.¹⁶⁵ The Epidemiology Branch was reorganized in 1967 with five new sections, one of which dealt with blindness statistics. Unfortunately, NINDB was unable to recruit an epidemiologist with ophthalmic training.

Establishing the Intramural Program at NEI

Once NEI was established, there was of course new opportunity to create a well-staffed and funded intramural program devoted to visual research. Although NEI inherited some employees and programs from NINDB, the NEI director had the flexibility to choose many of the individuals who would staff the new institute. Nine out of 11 laboratory researchers who had been in the Ophthalmology Branch of NINDB requested to be reassigned to NEI. They, along with the clinical ophthalmologists who transferred, served as the foundation for the new NEI intramural program.

Certainly, the NINDB intramural vision researchers had been aware of the movement for a new institute, and according to Dr. O’Brien, most of them anticipated that a separate institute would offer better opportunity. Of course, they were also apprehensive because “nobody knew what was going to happen, particularly with section structures and things of that sort. People were concerned they might lose some of their autonomy.” Before long they felt “a certain amount of relief” because Dr. Kupfer exhibited “a great deal of interest in what was going on intramurally,” and was “interested in specific projects and what people were doing and wanted to know about it.” In a recent interview, O’Brien laughingly recalled that until the researchers got to know Kupfer better, some trepidation remained: “We didn’t know whether Dr. Kupfer was accumulating all this information in order to axe people But, at least this was an administration that was interested in what was going on in the laboratory.”¹⁶⁶

Dr. Kupfer recalls that he “was very much aware of the need to build a strong intramural research program in both the laboratory and clinic as soon as was feasible. At NIH, the coin of the realm was the size and quality of the intramural program.” Although *not* a believer in staff meetings, he initially held weekly get-togethers with the intramural groups. While O’Brien acknowledged this helped intramuralists better understand the administration of the institute, the scientists sometimes got “antsy,” feeling they would “rather be in the lab, finishing an experiment.” Yet, it was very important, Kupfer remembers, for him to “show the intramural scientists that they were number one” and meetings were one of the few ways he could do that. Still, O’Brien remembers his frustration early on “that every little decision, every little this, every little that,” had to go through Kupfer’s office for approval. But he understood—Dr. Kupfer felt that was the only way he could learn the job, having never worked for the federal government before.¹⁶⁷

In 1971 and 1972 most of the NEI intramural scientists doing lab research moved from Building 10 to 6, where they had more space and better laboratories than before, although space would always be tight and never ideal. Scientists doing certain clinical research activities (immunology and genetics) stayed in Building 10. NEI also acquired a small area for an animal operating room and animal holding facilities in Building 9.¹⁶⁸ Dr. Kupfer recounts how space had been a priority for him when starting at NEI:

In my discussions with Dr. John Sherman [NIH Deputy Director] during my recruitment, I had conveyed my desire that NEI's intramural program be at the forefront of vision research. This meant adequate space, personnel, and budget. Dr. Sherman was very understanding, and subsequently he tried to comply. Funds were limited, though, as the ongoing Vietnam War drained much of the government's budget.

Fortunately, space materialized quickly. The entire second floor of Building 6 and a library/conference room on the fourth floor were renovated for our laboratory intramural staff. This was approximately 8,400 square feet. We were given limited space in the Clinical Center for outpatient clinical activity, and an inpatient ward of 26 beds.

I had requested that an additional small space in the basement of Building 6 be allotted for an electron microscope that I knew was necessary if recruitment of a top-flight anatomist was to be possible. For reasons that were not clear, Bob Berliner urged that we house the electron microscope in one of the labs on the second floor. Yet, I knew that the previous tenants had located their electron microscope in the basement out of concern that vibrations and slight movements would damage the quality of images if the equipment was housed on the second floor. Berliner felt I was being unreasonable, with almost 8,500 square feet available! Why was I being so difficult? Suddenly, in the midst of the stalemate that followed, Bob acquiesced. I suspected that he consulted with electron microscopists who universally would have expressed the need to minimize vibration. That was possible in the basement, but probably not on the second floor.¹⁶⁹

There remained the need to build a strong intramural managerial infrastructure. What would be the guiding philosophy of the IM research program, housed on the Bethesda campus of NIH, and funded with 10 percent of the NEI research budget? It certainly should not compete with the extramural research program, which supported vision research in medical schools, research institutes, and schools of optometry, and consumed the bulk of the NEI re-

search budget—approximately 90 percent. The intramural program should not just duplicate the extramural program, but take advantage of opportunities unique to intramural scientists.

NEI Intramural Attributes

The NEI leadership team carefully crafted the philosophy of the intramural program, fine-tuning it over the years. Analyzing the program retrospectively, at least seven important attributes characterize it:

(1) NEI leadership felt the IM program should be involved in research areas that were understudied but important enough for development or expansion. For example, NEI filled a gap in the vision research portfolio by enticing Robert H. Wurtz, Ph.D., and his entire Laboratory of Sensorimotor Research to join NEI, just as they were about to leave the National Institute of Mental Health for academia.* Wurtz arrived with a very strong group of researchers. They focused on the central nervous system mechanisms of eye movements in awake-behaving monkeys, a model he developed. This laboratory opened up the entire field of laboratory research on problems related to cognition using this experimental model. In 2008 Wurtz is still with NEI and a leader in his field. Over the years, his research has focused on how the brain processes sensory information for perception and the initiation of movement.

Capability to close a second research gap came when Joram Piatigorsky, Ph.D., left the National Institute of Child Health and Human Development and joined NEI in 1981 to establish one of the earliest laboratories of molecular and developmental biology of vision. This laboratory opened up the practice of using molecular biology and genetics laboratory techniques, including gene expression and genetic engineering, to understand mechanisms of the lens. Dr. Piatigorsky continues as chief of this lab.

(2) A second attribute was the understanding that if the extramural scientific community was to acknowledge the rich research findings emerging from NEI laboratories and begin to apply for and receive research grants in related areas of research (molecular and cell biology, for instance), it was incumbent upon the intramural program to maintain the highest standards of research. The intramuralists needed to be among the very best in the world in their fields of research and/or open up new research areas.

Thus, as molecular biology of the lens became more popular in the extramural community, Piatigorsky extended his research to the cornea with exciting results. The programs of Wurtz and Piatigorsky were good examples of maintaining a leadership position in their

* Robert H. Wurtz gained a Ph.D. in Physiological Psychology. He worked with NINDB's Laboratory of Neurophysiology and later with NIMH's Laboratory of Neurobiology before establishing, in 1978, NEI's Sensorimotor Research Laboratory.

respective research fields, as extramural scientists began to further explore molecular biology and the alert awake-monkey model.

(3) A third attribute was the emphasis put on developing translational projects where laboratory results could be used by clinical researchers to test hypotheses potentially improving diagnosis and treatment. Close juxtaposition of laboratory and clinical research was essential for this type of research to prosper. An excellent example of laboratory and clinic collaboration was the galactosemic monkey model of diabetes, where the hallmarks of most of the pathologic changes of diabetic retinopathy were induced in the monkey eye. The clinical researchers were then able to study and understand the histopathology of changes in the retina (such as the role of aldose reductase and the selective drop out of the intramural pericyte). They also began to understand the process of devising therapies (such as aldose reductase inhibitors) to prevent the development of diabetic retinopathy. Currently, pharmaceutical companies are trying to develop such a treatment.

(4) The institute encouraged the interdependent advancement of clinical trials, biometry, and epidemiology as they related to the eye, fields that were almost nonexistent before NEI. It was essential to develop and maintain the infrastructure of biostatistics, a field integral to laboratory and clinical research. Biostatistics is especially critical and plays an intimate role in randomized clinical trials and epidemiological studies. Cancer and heart epidemiology studies and clinical trials had been developed and in some cases perfected in their methodology at NIH during the 1950s and 60s. NEI took advantage of this reservoir of knowledge by recruiting and working with seasoned, senior biostatisticians.

(5) NEI encouraged scientists to engage in long-term, high-risk, high-payoff projects. In-house researchers could take advantage of IM funding that was available for periods of 10 years or longer—at least twice the traditional five-year limit of the extramural grants (although they were renewable). Because scientists in the intramural division did not go through a peer review process, as required of extramural scientists every five years or less, they had the opportunity to plan and conduct high-risk, high-payoff, long-term research that had been reviewed carefully by the laboratory chief, NEI's scientific director, and, if necessary, by outside consultants. Such high-risk research usually did not fare well in extramural grant study sections because too many unanswered questions remained, grant renewal was based upon measurable progress, and future experiments were difficult to plan. The intramural laboratory was the ideal locus for this type of research. As one of NEI's scientific directors put it, "You can mobilize your [intramural] program to really zero in on the problem."¹⁷⁰

One excellent example of high-risk, high pay-off research is the long-term observational study of patients with gyrate atrophy of the retina and choroid, a degenerative disease eventually ending in severe visual disability and blindness. This study looked at whether an arginine-restricted diet given to patients with gyrate atrophy could slow down or prevent

the progression of the disease. The study concluded that adhering to an arginine-restricted diet would lower the plasma ornithine level below an average of 5.29 to 6.61 mg/dL, which slowed the loss of visual function as measured by sequential electroretinography and visual field examinations.¹⁷¹ To avoid drop out, patients were constantly contacted by telephone and/or letters. Data was collected during sequential visits to the hospital over long periods of time. For an extramural investigator, carrying out such a project would have been very difficult, considering the large budget required and the study sections' reluctance to expend limited financial resources on a long-term, high-risk proposal.

The intramural program also offered an opportunity to conduct phase I and II clinical trials where the difference between the treated and control cases required a modest sample size. The initial costs required to erect the managerial infrastructure were so high that extramural scientists would have needed considerable resources to gear up and carry out such clinical trials properly. The intramural program successfully conducted such studies on ocular AIDS.¹⁷² There were other successes as well. One non-AIDS study looked at the treatment of corneal crystals in patients with cystinosis where one eye was randomly chosen to receive treatment while the fellow eye received placebo drops.¹⁷³ Using only a small number of participating patients, it was possible to show through statistical analysis that the treatment was beneficial.

(6) A sixth attribute related to the proximity of NEI's Bethesda location to Capitol Hill, only 10 miles away in Washington, D.C. Congress learned about the NEI intramural programs from annual appropriation hearings, and occasionally a member would visit NIH to discuss ongoing eye disease projects of particular interest to them and to learn more about the latest research at NEI. In essence, the intramural program was the face of vision research throughout the country.

(7) Finally, the seventh attribute encompasses the excellent medical care vision patients received as part of a research protocol. It is not always appreciated that patients travel and stay at the Clinical Center's hospital or nearby outpatient facilities at NIH expense and receive all diagnostic and therapeutic care at no charge. Patients who receive routine tests from their local physician are reimbursed by the Clinical Center. These policies facilitated the recruitment and retention of patients for trials.

Fashioning the Office of Biostatistics and Epidemiology

Given the importance of statistics for clinical research, one of Dr. Kupfer's highest priorities was to establish a first-rate biometry unit that would pioneer new efforts in ophthalmic epidemiology, an underdeveloped research field. Even by 1970 only a few of the larger institutes had a biometry unit. Kupfer, however, believed that if NEI was going to sponsor

first-class research, especially clinical trials, the staff would need input from biostatisticians and epidemiologists.

Dr. Kupfer was fortunate to successfully recruit Harold Kahn, a senior biostatistician and epidemiologist from the Heart Institute. Kupfer assigned him the job of setting up NEI's new Office of Biometry and Epidemiology (OBE).^{*} Kahn's task was difficult, hampered by the lack of researchers trained in or doing epidemiological work on visual diseases. Moreover, fashioning a brand new unit required reorganizing all the ophthalmic research activities and personnel inherited from the NINDB. In this era of tight budgets, this meant dismantling programs and activities that did not suit the goals and philosophy of NEI's top staff, and constructing new ones that did.

One casualty was the Model Reporting Area (MRA) study. NINDB had first set up MRA to have at least some ophthalmic presence in the field of epidemiology. The program had been organized in 1962 with the help of the American Foundation for the Prevention of Blindness and the U.S. Public Health Service's Chronic Disorders Division. NINDB had coordinated MRA operations through its small Section on Blindness Statistics in the Biometrics Branch. Participating eye care professionals in each of 16 states^{**} captured data from patients on visual impairment and blindness and its causes, reporting to a state coordinator who in turn passed the information on to the staff at NINDB for compilation and analysis.¹⁷⁴

MRA had problems even before the shift to NEI. Minutes taken from the June 22-23, 1967, meeting of the National Advisory Neurological Diseases and Blindness Council, comment that "defects in the Model Reporting Study are to be considered at the next meeting." Subsequent NINDB meeting minutes do not report any further discussion of MRA, probably because of its pending transfer to NEI.¹⁷⁵

As NEI staff examined the research portfolio inherited from NINDB, they uncovered flaws in the conceptualization of the MRA study. For one thing, the method of data collection generally resulted in underreporting of the total numbers of visually impaired individuals. Eye care professionals were often reluctant to provide the detailed information requested by MRA, and many patients were unwilling to have it known they were blind. The NEI staff concluded that the data generated was ambiguous and a poor indication of the true prevalence and causality of blindness. The minutes from the second meeting of the National Advisory Eye Council, held June 26-27, 1969, state that the "register of a state does not contain all of its blind population and the magnitude and composition of the unregistered portion are unknown."¹⁷⁶ Given these factors, NEI staff believed that there was not much to be gained from the study; it would not lead to a clearer understanding of blindness and its causes. For these as well as other reasons, NEI terminated the program.

^{*} OBE became the Division of Epidemiology and Clinical Research in 2000.

^{**} Vermont, New Hampshire, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Virginia, North Carolina, Georgia, Louisiana, Kansas, South Dakota, New Mexico, Utah, and Oregon.

MRA personnel had performed the work satisfactorily and competently; however, they were not trained as research biostatisticians or epidemiologists. Kupfer wanted individuals trained in these areas in order to create a first-rate biometry unit, but given that NEI had not been granted any additional staff positions, some or all of the MRA personnel would have to go. For every person placed elsewhere or retired, Kahn was allowed to recruit an epidemiologist, biostatistician, or whatever type of scientist he felt the unit needed to be successful.

Dr. Kahn showed tremendous compassion in transitioning the MRA personnel, finding each of the 15 staff members another position at NIH or lending tremendous support to those ready to retire. In a little over a year, Kahn did what most bureaucrats would consider impossible within the slow-to-change federal bureaucracy: he phased out one entity and created an entirely new one, the OBE. Kahn took on a difficult task, accomplished it with a minimum of hard feelings all around, and at the same time hired the type of experts needed to do first-rate epidemiological and clinical trials projects.

Dr. Kahn assembled an outstanding group of individuals to staff the OBE's three new sections/branches: Biometry, Epidemiology, and Clinical Trials. He started with his former colleague Fred Ederer, who had gained extensive experience in biostatistics and clinical trials in his 15 years with the National Cancer Institute and the National Heart Lung and Blood Institute. Ederer had a B.S. degree in mathematics and science from the City College of New York, an M.A. degree in statistics from American University, and had completed graduate work in biostatistics at Columbia and Stanford Universities. Ederer took charge of the Clinical Trial Branch and played the roles of mentor, teacher, leader, and manager. Roy C. Milton, Ph.D., was with NEI from the very beginning, and at various times served as Biometry Branch chief and as deputy director of the Division of Biometry and Epidemiology. He was a project officer for NEI's Framingham Eye Study and was involved in various studies on the role of risk factors associated with adult cataract and xerophthalmia found in children with vitamin A deficiency. Dr. Milton retired from NIH in 1996. Marvin J. Podgor, with a Ph.D. in statistics, joined NEI in 1973 and became chief of OBE's statistical methods and analysis section. Podgor helped develop a method of combining procedures and data from multiple scientific models that could be used in a variety of biomedical applications. He was with NEI until his premature death in 1998. Dan Seigel, D.Sc., another important intramuralist, replaced Harold Kahn when he retired.¹⁷⁷

OBE's success in recruiting outstanding staff was certainly facilitated by the fact that NIH was one of the most productive centers for epidemiology, clinical trials, and biostatistics anywhere in the world in the two decades preceding NEI's founding. Many of the leaders in case-control study and clinical trials methodology received their initial training at NIH. Over the long term, NEI's recruiting was further enhanced by having an active training program for Fellows and students.

In fact, two outstanding researchers, who had first joined the OBE staff as Fellows, later became permanent members: Frederick (Rick) Ferris, III, M.D., joined the Clinical Trials Section, and Robert Spurdeto, M.D., joined the Epidemiology Section, later becoming its chief. Ferris came to NEI in 1973 after completing a medical internship at Johns Hopkins with only minimal training in ophthalmology, but he had significant experience in statistical analysis, which proved a great asset for NEI. Ferris played an important role in NEI's diabetic studies and macular degeneration clinical trials. Ferris currently heads the Division of Epidemiology and Clinical Trials (the later incarnation of OBE) and serves as NEI's Clinical Director.¹⁷⁸

Having the OBE made it easier to achieve the chosen missions of the NEI intramural program: boosting epidemiology research on diseases of the visual system and establishing in-house capability in clinical trials.

Intramural Leaders

Among Kupfer's first acts as the new NEI director was to recruit Jin H. Kinoshita, M.D., from the Howe Laboratory at Harvard Medical School, to serve as Science Director (SD). This was a quite a coup, since Kinoshita was a full professor with a successful teaching and research career, and it was uncommon to switch from academia to the NIH intramural programs. One of the most respected ophthalmic biochemists of the time, Kinoshita had wide-ranging interests beyond his research on the lens. He was a perfect choice to serve as NEI's new chief of the Laboratory of Vision Research, and later as the institute's scientific director. Kinoshita brought several colleagues with him, including Toichiro Kuwabara, an outstanding experimental pathologist known worldwide, and several junior researchers. Not coincidentally, Kupfer had spent eight years with David Cogan's Harvard lab, refining his research skills under the mentorship of Cogan, Kinoshita, and Kuwabara. Now, the tables were turned, and Kupfer was in charge. The addition of these two senior researchers immediately boosted the intramural program's image as having great potential for doing high-quality research.

In a few years, Kinoshita's colleague and Kupfer's mentor, David Cogan, also joined NEI. When Cogan, the chair of Ophthalmology at Harvard Medical School and director of the Howe Laboratory, reached mandatory retirement at age 65 in 1973, Dr. Kupfer proposed that Cogan spend a sabbatical year at NEI to explore whether he might want to join NEI as a senior scientist. One year was too long, Cogan said, so Kupfer "slowly and incrementally reduced the time commitment and eventually Dr. Cogan reluctantly agreed to come for three months." He remained with NEI until his death 20 years later, in 1993. During that time, he was extraordinarily productive in research and worked closely with junior researchers, encouraging their research activity and helping them find positions in scientific establish-

ments worldwide. Cogan gave additional credibility to the program; he was widely known and respected throughout other research fields as a superb pathologist, clinician, and teacher. He fostered an environment of collegiality and mutual assistance, qualities that Cogan held in high regard. “Dave Cogan was the father of us all,” Kinoshita said. “He’s the one who really brought basic scientists into ophthalmology, which was unusual in his day.”¹⁷⁹

Dr. Kinoshita shared the same fine qualities. When recently asked if he had a philosophy for the IM program, Kinoshita chuckled and said, “Well, if I had a philosophy, I wouldn’t know it. But you know I was interested in people who had great imagination and research abilities, and that’s essentially what I followed.”¹⁸⁰ This paralleled Albert Einstein’s philosophy that “Imagination is more important than knowledge.” Kinoshita embodied many of the aspects in demand but not much in evidence among NIH scientific directors. As a senior investigator with an already impressive bibliography, he felt it unnecessary to direct his own laboratory.* Kinoshita assumed the role of mentor to the young researchers working in the many areas in which he was both interested and knowledgeable. He helped guide researchers towards an appropriate direction, based upon his many years of experience.¹⁸¹ Kinoshita ensured the IM program had adequate resources for both laboratory and clinical research, affirming that both types were necessary if translational research was to thrive. Understanding the value of easy access to the NEI leadership, Kinoshita located his office adjacent to both Carl Kupfer and Ed McManus in the administrative building, only a few minutes walk from the laboratories. The intramural scientists who came to his office to discuss their findings found him eminently approachable. McManus remembers that Kinoshita “brought science to the sixth floor” and kept the top management abreast of the research progress. McManus recently told Kinoshita, “When Joram [Piatigorsky] came all excited to see you, you would come running over to me and we would grab Carl, and it was those little things, I think, that were very important for bringing Carl closer to what was going on!”¹⁸² In addition, Kinoshita facilitated the process of recruiting new scientists to the intramural program and obtaining funding approval—it required tremendous negotiation skills to convince the appropriate oversight board of the scientific importance of starting new laboratories.

Assessing the Intramural Program

A Birds-Eye View

In May 1991, NIH Director Dr. Bernadine Healy asked Dr. Kupfer to serve as acting Deputy Director of Intramural Research (DDIR) at NIH. Kupfer served in this position from 1991 to mid-1992, while continuing as NEI director. As the senior official in charge of all NIH intramural activity, he had a birds-eye view into the mechanics of the intramural

* Dr. Kinoshita was so unassuming and dedicated to knowledge that he went back to Boston to take a three-month course in molecular genetics, even though he was a senior NEI official (Kinoshita interview, p. 11).

programs of each institute. The DDIR met bi-weekly with all the scientific directors to take action on promotions, advise the NIH director on allocating resources and space for laboratories and clinics, and process applications from the institutes for post-doctoral fellowships and junior and senior positions, among other things. A scientific director (SD) controlled the budget and size of an institute's intramural laboratories and clinical branches. At the same time, scientific directors almost without exception directed their own laboratory, staffed by senior and junior laboratory and clinical researchers. This practice raised questions about conflict of interest. The SDs had to make decisions about the allocation of resources to laboratories that were in competition with their own.

There were other concerns related to NIH researchers' biases: the preference shown to fundamental or basic laboratory research versus clinical research, the favoritism toward investigating the functions of biological mechanisms, and the partiality given to hypothesis-driven investigations rather than epidemiological, clinical trials. In general, clinical research received less support in terms of space, personnel, and budget. Since the clinical director (CD) of an institute was under the direction of an SD, clinical research was subsumed under laboratory research. That organizational structure tended to reinforce the notion that basic research was preferred over clinical. While an SD might be an excellent bench researcher, they usually had a Ph.D. rather than an M.D., and a limited understanding of clinical research. Even when they had clinical training, the SD often felt compelled to "second guess" the CD and would fail to provide the resources or moral support needed to mount a successful program.

As acting DDIR, Dr. Kupfer also noted a reluctance to promote staff on the basis of clinical research accomplishments in the absence of laboratory research credentials. There were rare occasions when he approved the promotion of a productive investigator doing outstanding clinical research despite the SDs' vote to deny it.

In 1991, while Dr. Kupfer was functioning as the acting DDIR, Dr. Healy asked him to form a Clinical Research Advisory Committee (CRAC) to look at NIH clinical trial protocols. The CRAC committee consisted of experts in biostatistics, epidemiology, the clinical directors of three institutes, ethicists, and a layperson. Donald Lindberg, M.D., director of the National Library of Medicine and a pioneer in applying computer technology to health care issues, chaired this committee from 1991 to 1992. The committee reviewed a random sample of 55 out of 1,100 active protocols, covering a wide variety of research projects initiated by NIH institutes. The most pressing problems involved the lack of statistical considerations in many protocols and the absence of biostatisticians on some of the Institutional Review Boards (IRBs). Considering the high number of biostatisticians at NIH, it seemed possible to have an experienced biostatistician on every IRB. One of the panel's three recommendations stated: "From the point of view of good science, the fact that many

protocols give little evidence of statistical considerations is a serious shortcoming. There are sufficient numbers of biostatisticians at NIH so that an institution with the stature of NIH should be able to assure itself that data collected in the protocol have statistical validity consonant with the nature of the science being performed.”¹⁸³ While the value of biostatisticians was overlooked by physicians conducting clinical trials when NEI was founded, as late as 1991 it seemed that some NIH clinical researchers still ignored the value of having biostatisticians participate in designing clinical research protocols. Indeed, some 35 years earlier, the NIH director had attempted to dissuade such views by asking Harold Dorn, Jerome Cornfield, and other statisticians to provide services to institutes lacking statisticians and to help them set up statistics programs (see Chapter 6: Randomized Clinical Trials). Fortunately, statistics have become more valid in clinical research, not only at NEI but in all clinical research protocols supported by NIH.

The Blue Ribbon Panel

As a result of congressional inquiry about intramural programs, NIH prepared *The Report of the External Advisory Committee (EAC) on the Intramural Research Program of NIH* (April 11, 1994) during Dr. Harold Varmus’ tenure as NIH director (1993–2000). Consequently, individual reviews of each institute’s intramural program were carried out by outside committees. In late spring 1997, a Blue Ribbon Panel was established to examine the NEI intramural program.¹⁸⁴

Dr. Kupfer welcomed this activity because the intramural program was so important to the success of NEI. It also seemed an ideal opportunity to strengthen the program’s management and leadership, particularly in the clinical research arena. The panel finished its review of NEI in 1998, providing a detailed and inclusive report.

One discussion stands out. The committee articulated some important insights into NEI’s unique ability to conduct high-quality ophthalmic clinical research—a valuable asset for NIH. Considering the health care environment in the United States, the committee did not think it likely that ophthalmic research had many equivalent facilities. Thus, it should be a high priority that this resource be protected and enhanced. As new clinical projects came under consideration that could have beneficial effects for patients with incurable or non-preventable eye disorders, the NEI Clinical Branch should be able to turn on a dime to take advantage of these opportunities. Indeed, the Clinical Branch and its unique facilities have proven to be an ideal setting for translational research (cytomegalovirus retinitis, the retinal degeneration of gyrate atrophy, and severe uveitis), encompassing small phase I and II clinical trials to determine the safety and efficacy of potential therapies for diseases causing blindness (including uveitis and nephropathic cystinosis) and epidemiologic studies such as case-control and cohort studies (Framingham Eye Study).

The Blue Ribbon Panel also expressed grave concerns about the size, location, and configuration of NIH space for clinical research involving patients with severely reduced vision, and it suggested that more resources might be devoted to this problem. For example, when the Ambulatory Care Research Facility (ACRF) opened in 1981 to provide outpatient facilities to the institutes, the NEI clinical intramural program was excluded.¹⁸⁵ Instead, NEI was offered a former unit designed for premature infant research, consisting of three small floors connected by an elevator. The space was not only inadequate to house outpatient examining rooms and diagnostic and therapeutic equipment, but the location and arrangement required patients, even those with markedly reduced vision, to stumble their way from one floor to another. This clinical space also contradicted the NIH dictum that the laboratory and the clinic should be next to each other for successful translational and collaborative research. NEI's clinical space, where patients were being studied for genetic, immunologic, and infectious diseases, was physically separated from the laboratory (in which the basic science of these diseases was being studied). The facilities were inadequate in terms of contiguous space allocation, close location of patient care area and research laboratories, and availability of technical and equipment infrastructure for the conduct of clinical research. Efforts to explain to NIH's deputy director for Intramural Science as to why this space was inappropriate for a clinical unit were to no avail. Finally, NEI took the unprecedented step of approaching the NIH Director, Donald Fredrickson, M.D., whose staff obtained for NEI more adequate clinical research space in the ACRF. Without such a proactive leadership, the quality of clinical research at NEI would surely have declined.*

The panel also addressed the question of tenure. NEI's IM laboratories had a hierarchical internal structure and each was headed by a laboratory chief who controlled the research and resources. The degree of training and mentoring was uneven, and some laboratories lacked interaction within or among research groups. The question was raised about whether to implement a tenure system (potentially limiting the flexibility needed to maintain innovative laboratories at the cutting edge) or a non-tenure system (that would provide a five-year contract for junior scientists and a 10-year contract for senior scientists). A non-tenure system would allow NEI to discharge staff who did not carry out first-rate research, while allowing them to recruit new scientists. These suggestions are still under discussion.

The panel also recommended that NEI create a new position for a director of the IM program who would develop and implement a long-range strategic plan. In developing a plan, the director would reevaluate the scientific direction and resource allocation of the present program, consider and develop new research areas with appropriate recruitments, institute

* The Committee noted that with the construction of a new hospital, NEI was once again given inadequate clinical facilities.

training and mentoring programs, and strengthen the criteria for and the management of a tenure-track system. Highly respected vision scientists would attract outstanding junior scientists and postdoctoral fellows. With these changes, the panel predicted that the NEI intramural program could be the leading vision research group in the United States.

Chapter 5

The Extramural Program

Introduction

By the time that NEI was authorized, all of the existing NIH institutes had already established extramural research programs in support of laboratory and clinical research using various grant mechanisms. The framers of the NEI legislation planned to do the same. They envisioned a broad program encompassing a variety of well-funded grant mechanisms and focusing especially on individual investigator-initiated research grants.

Over the years, NEI's extramural grant program funded eye research at medical schools, universities, and research institutions across the country. Indeed, it rapidly became the predominant source for funding university programs in vision research. It represented the majority of NEI's overall work as well. From 1970 to 2000, approximately 90 percent of NEI's research funding was allotted to the extramural program, with 10 percent directed to the in-house intramural research program.

Establishing the NEI Extramural Program

Despite the paucity of initial funds from Congress, the new NEI staff knew that somehow they had to keep the extramural program grants program in operation during the transition from NINDB to NEI. It was essential that the ongoing extramural research being conducted by grantees continue uninterrupted in order to maintain high-quality research. Therefore, the first grants given funding priority were those Type 2 grants (defined as competing continuation grants) that had received high-priority scores in the initial selection process and were up for renewal. This would ensure a continuation of a high-quality research base. It was also important to fund new grantees in order to expand the amount of high-quality research on the visual system overall. In consultation with the National Advisory Eye Council, NEI's managers made the difficult decision to reduce funding of all ongoing Type 5 research grants (defined as non-competing continuation grants) by 15 percent across the board. These were grants with committed funding set aside for approximately two to four years. A funding reduction would slow down progress but not stop it completely. Thus, NEI

maintained the ongoing research base while freeing up some money to make Type 1 (new) grants and Type 2 (renewal) grants available.¹⁸⁶

This funding decrease for Type 5 ongoing grants came as quite a shock to the research community. They had high expectations, and rightly so, that the creation of an independent NEI would result in improved financial support for their research, not reductions. How discouraging it was that as its first major policy action, NEI had to resort to a severe cutback in order to have some money to fund other types of grants.¹⁸⁷

Once they had a small pot of money to work with, the NEI staff and council members determined to implement a policy of funding all approved extramural research grants of high priority. This was accomplished slowly; NEI staff carefully monitored all of the institute's expenditures and nudged NEI's budget appropriations upward. The immediate goals were to achieve full funding for all high priority research grants and expand the size of the research base by approving new ones; this meant temporarily limiting overhead costs.

By 1975 NEI was on a sound fiscal basis. The grant portfolio and the amount of appropriations from Congress had increased in size each year. All high-priority grants for which funds were available were approved and funded fully or at least close to their requested amount. Moreover, NEI's research program was manifesting success. The first Vision Research Program Plan had been released (see Chapter 3 on Program Planning) and strategic program planning had been initiated. The impressive results of a clinical trial testing the efficacy of photocoagulation for treating diabetic retinopathy had been published, showing that treatment was very effective in reducing blindness (see Chapter 6 on Clinical Trials). The overall budget of NEI more than doubled from \$24,342,500 in 1970 to \$50,212,000 for Fiscal Year 1976. At this point in time, NEI was perceived as the largest and the most productive of all organizations involved in vision research, ultimately accounting for approximately 85 percent of all the high-quality vision research in the United States.

The majority of the extramural research portfolio inherited from the NINDB was composed of *investigator-initiated grants*, but also included several *program project grants* and *center grants*. Each investigator-initiated grant was relatively small (tens of thousands of dollars) and provided support for a single senior investigator and one or two support personnel, as well as supplies and equipment necessary to complete a research project. In contrast, program project and center grants were 10 to 20 times more expensive because they supported several investigators, trainees, visiting scientists, and sometimes expensive equipment costing in excess of hundreds of thousands of dollars.

ROI Grants

Research grants are currently part of the “R” series of extramural grants. The Individual Research Project Grant, known as an RO1 Grant, is used to support a discrete, specified, circumscribed project to be performed by the named investigator(s) in an area representing his or her specific interest and competencies. Also known as the traditional or regular NIH research grant, the RO1 has been the principal mechanism of NEI support for investigator-initiated basic and clinical research conducted by both new and more experienced scientists. It is also the type on which NEI has focused the majority of its resources. The RO1 designation indicates it is a new investigator-initiated grant application; an RO2 designation refers to renewal of a grant (originally an RO1); and the RO5 designation indicates that the grant is within the period of ongoing funding, usually two to four years.

Currently, RO1s can be initiated by an investigator or granted in response to a program announcement or request for application distributed by one of the NIH institutes.* For an investigator-initiated research grant, the applicant specifies his or her own focus or stated objective, designs the series of experiments, reports the outcome, and interprets the importance of the research to an institute’s stated program interest. Technically, RO1 Grants are awarded not to individuals but to the institution sponsoring the investigator and providing the infrastructure—laboratory space and equipment, academic support, and administration. One researcher is listed as the “principal investigator” and maintains full responsibility for carrying out the research according to the stated plan; other researchers may be named on the application.¹⁸⁸

For NEI, Dr. Kupfer wanted the investigator-initiated RO1 research grants to be the mainstay of the extramural program, believing that they would be the most efficient and productive in using scarce resources. Moreover, he also believed that these types of grants would maximize the creativity of the scientific community that NEI supported, a consideration that was deeply important to him.

Ed McManus recalls that he agreed with Dr. Kupfer:

On the extramural side, I was absolutely convinced that Carl’s philosophy of relying upon the RO1 as our main instrument of support was right on target and was a potential winning philosophy. This was real leadership and bucked the trend at NIH, which was emphasizing research center and multi-project grants. I had been exposed to large grant programs at NIH in my earlier years and these did not seem to have the same potential as relying on the genius of the individual investigator through an RO1. I knew

* An announcement by an NIH Institute or Center requesting applications in the stated scientific areas. Program Announcements (PA) are published in the NIH Guide for Grants and Contracts. Go to Program Announcements at (http://grants.nih.gov/grants/guide/search_help.htm).

from my experience in the intramural program that the individual scientist is where the emphasis should be. That was Carl's philosophy for the extramural program, and my job was to happily implement it.¹⁸⁹

From the start, investigator-initiated RO1 research grants were NEI's principal mechanism of research support. The NEI leadership favored this particular mechanism because it appeared to yield the highest quality data in the most cost-effective way. The emphasis was placed solely on the principal investigator's research credentials and ability to produce first-rate fundamental and clinical research on mechanisms of eye health and disease.

The funding for RO1 grants usually covered a relatively short period of a few years, meaning they turned over and came up for renewal every three to five years, but occasionally more often. This meant that NEI RO1 grantees had to re-compete in the NIH grants process. NEI tried to fund RO1 grants for as long a period as possible to create a stable funding environment. Other institutes took a shorter view. NEI averaged almost four years of support for an RO1 grant, whereas the average of other institutes was approximately 3.1 years.

An RO1 grantee could later apply for a continuation grant, called an RO2, to renew and continue the support beyond the time period covered by the original RO1 grant. The continuation application would be considered if progress had been made and the proposed experiments to be carried out continued to drive the hypothesis on which the original grant had been based.

Over the years, the institute's extramural staff was able to manage these RO1s effectively because of their relatively small size and scope. Several administrations and congresses imposed budget cuts on NIH, which usually meant, according to NIH tradition, that all RO1 grants were reduced equally across the board. Ironically, such reductions generally freed up additional funds, resulting in higher funding rates for approved new and competing grant applications. Of course, this is what the advocates (usually the Office of Management and Budget) of this approach wanted to show—that even with a smaller budget for NIH and the different institutes, NIH could still sustain high funding (or success) rates for new grants.

The strategy of equal cuts across the board might have been appropriate for the other institutes, which had considerably higher average costs for their RO1s, but NEI was already implementing an active cost-cutting approach to its grants program and any further budget reductions would cause severe problems. Through active management, NEI reduced its grants to such a low level that often there was no room for more cuts.

This sort of thing happened off and on from the beginning of the institute until 2000. Congress would reduce its RO1 budgets, but NEI would not have flexibility to enforce the

across-the-board cuts favored by the NIH administration because it had the leanest RO1s of any institute in terms of dollar amount. So, NEI and its advisory council would resist these across-the-board reduction efforts and take an alternative approach. Instead of applying equal cuts, the institute's extramural staff would determine the size reductions for each RO1. That amount was based on the importance of the research question being asked, the progress being made, the track record of the investigator, the numerical funding priority, and other financial considerations.

The strategy to emphasize cost-efficient RO1 grants was aided by the program relevance mechanism that the NAEC implemented. The council targeted about 10 percent of grants approved by the study sections to receive the designation "high program priority." These grants were accorded special consideration for funding. Of these, about 20 to 30 percent were given better (lower) scores, thus making them eligible for funding. This mechanism increased the effectiveness of the NEI grant program by ensuring that the grants with the highest potential for clinical payoff received funding.

Through intensive managerial oversight, NEI grants, primarily RO1s, only increased in cost by 76 percent from 1980 to 1989; whereas, overall, the cost of NIH grants increased 98.3 percent on average. Since NEI supported primarily investigator-initiated RO1 grant applications, NEI's success rate was among the highest of all the institutes, usually in the 40 to 45 percent range. The success rate was calculated by dividing the number of grants funded by total approved grants considered in that particular round. For example, NEI might have a budget of \$10 million and allow program project grants averaging \$1 million each to compete; if 200 applications were received, 10 grants could be funded, resulting in an approval rate of 5 percent ($10/200 = 5\%$). On the other hand, if only RO1s averaging \$100,000 each were allowed to compete, this same \$10 million would result in an approval rate of 50 percent ($100/200 = 50\%$). This success rate continued through the late 1990s.

While such efficiency was a positive feature for attracting and retaining scientists to vision research, it also could be a liability in seeking budget increases. A scientist might look at the high NEI success rate and think, "I have a good chance of receiving funding here," and then submit a grant application. On the other hand, a budget analyst or congressional staff member might use the high success rate as a justification for concluding that the institute did not need more funding because it was already funding 50 percent of approved applications, whereas NIH as a whole was only funding 37 percent.

By Fiscal Year 1990, RO1 type grants were by far the most predominant grant at NEI, accounting for 82 percent of the NEI extramural budget. In comparison, they accounted for only 57 percent of the total NIH extramural budget.¹⁹⁰ In all, NEI was considered an "RO1-friendly" institute, one aimed at tapping the creativity of individual investigators. It was a

champion of conducting basic and clinical research on the visual system in a manner unfettered by pork-barrel politics.

Program Project Grants

In contrast to the RO1 research grant, which relies on a single investigator submitting a research proposal and acting as the principal investigator, the *program project grant* supported a consortium of investigators: several senior, junior, and untested researchers who were undertaking a broad series of experiments loosely related to a central theme. The major research focus usually reflected the interests of one or two senior investigators with the junior members playing a support role. In theory, the program project grant was supposed to provide a training ground for young investigators; in practice, the young investigator often functioned merely as a technician for senior researchers without close supervision or an involved mentor.

Dr. Kupfer recalls his rationale for preferring individual research grants over program project and center grants:

The story begins in 1967. I was a member of the Neurology Program Project B study section for 1967 through 1969, which reviewed program project and center grants for the NINDB. This study section had the responsibility of reviewing the grant and determining the relevance of the research to be supported. We also considered the principal investigator's competence in organizing and carrying out the complex administrative details involved and ability to coordinate the research plans of multiple personnel, some who participated for only a few months while others participated for the full grant period.

What struck me as inconsistent was that a grant proposal usually listed a senior ophthalmologist as the leader and perhaps one or two other senior researchers. However, it often appeared that the bulk of the funds (and very often these grants would run to one or two million dollars each) were to be used to support junior staff just getting started in research. It disturbed me and other study section members that the junior staffs' research proposals were often poorly defined, which suggested that the grant was not reviewed critically by the senior staff before submission. Frequently the involvement of the senior staff on the grant was never clearly delineated. As a result of these shortcomings, it seemed the productivity of this type of grant mechanism was always less than expected, given the large expenditure of resources that went into them. These concerns, however, were never discussed in our

meetings and played little or no role in whether the study section approved the grant with a high enough priority for funding. We were told to look at the relevance of the grant in furthering vision research and [as an] opportunity to bring new investigators into the field.

I soon gained hands-on experience with the program project grant. I became chairman of Ophthalmology at the University of Washington School of Medicine in Seattle in 1966. The department had two senior investigators and four junior researchers. Our junior staff was trying hard to identify research areas for which a proposal could then be submitted to NINDB for individual research grant support. One of the investigators was an electron microscopist who showed great promise as a researcher. This individual obviously needed to have access to an electron microscope, which in those days cost about \$250,000. How could a junior investigator justify such a large expenditure on an individual research grant?

I spoke with Dr. Matilda Soloway who was a kind and conscientious grants manager at NINDB. She advised that we apply for a program project grant detailing how many members of the department or other departments would need to use an electron microscope for research, justifying the purchase of such an expensive piece of equipment.

This seemed like excellent advice, and I went about conducting staff meetings and encouraging the senior investigators to decide how they could best make use of electron microscopy within their own research projects. There was no doubt that an electron microscope was required to bring this junior researcher with excellent potential into the department. Such access to an accomplished electron microscopist in one's own department would offer new approaches by the senior staff to solve some vexing problems and open new research opportunities to relate structure and function. Anatomical study of ocular structures was somewhat ancillary to our department's main research efforts in biochemistry and physiology; nevertheless, the professors were committed to the department and designed studies requiring an electron microscope that would complement their main research projects. They also helped the younger staff focus on particular topics that were of importance and could be solved using this technique.

NINDB then arranged a site visit to determine through direct discussions with the principal investigator and the other participants the scientific value of this grant proposal and whether the

personnel, collateral equipment, space, and resources were available to carry it through if funded. The afternoon before the day of the site visit—when the site visitors had already reached Seattle and were settling into their hotel facilities—our two senior investigators asked to see me. They both came in to my office, obviously quite uncomfortable. When I asked what was on their minds, they told me that they would like to withdraw their names from the proposed program project grant! I was absolutely aghast and said, ‘Don’t you realize that there’s a site visit tomorrow morning at 9:00? You want to withdraw your name before that?’

‘Yes, that’s the honest thing to do,’ they replied.

‘Can’t you wait until after the site visit and then if you decide that you don’t want to participate, you can withdraw?’ I urged. This discussion went on for about an hour. Their major concern was the amount of time needed in supervising the research of the junior staff when they already were spending considerable time with their own post-doctoral staff and technicians on their own research projects. Each had an NIH research grant given directly to them as the principal investigator. They thought that junior investigators should compete for their own grant support in open competition with other junior investigators nationwide. They thought that researchers should rise or fall depending on their own abilities rather than hanging onto the coattails of senior investigators leading a group grant. I finally convinced them that without their support, there was no chance of obtaining an electron microscope for the department or recruiting this promising researcher. If they still felt the need to withdraw, they could do that following the outcome of the site visit, but I desperately needed them to be present. If they did not want to be as forceful and positive as they could, that was their decision, but it would be most embarrassing for the two senior investigators to withdraw on the eve of the site visit.

Fortunately, they agreed. The site visit went very smoothly, and the visitors were quite impressed with the facilities of the young department. Subsequently, we were granted the program project grant. The senior investigators were lukewarm about having anything to do with it, but were collegial and also helped the younger investigators formulate research grant proposals on their own.

This lesson, however, was thoroughly embedded in my mind as indicative of the basic weakness of a program project or center grant. The point is that senior investigators do not need the program project mechanism because they can compete successfully for their own NIH individual research support. In addition, they prefer to choose their collaborators and not be limited to a group of junior investigators who might have different scientific interests.

Junior investigators had other requirements for receiving an individual research grant. They needed to spend two or three years as a Fellow working on one aspect of a scientific project they formulated themselves and completed under the supervision of the principal investigator of the NIH research grant. They could obtain small amounts of funds from non-federal sources. They could also develop a small research project for which they could then request a financially modest research grant. These approaches enabled the young investigator to generate preliminary data that could demonstrate their research potential and be used to write a more ambitious grant proposal. The value of preliminary data from well-controlled experiments, which generates new hypotheses, helps the study section members recognize the high potential for success. I think that these are the steps that many of us in the vision research community took to begin our research career; young investigators should have to make the rigorous effort to outline, present, and defend their proposed research. Hence, based on these experiences and considerations, NEI did not include program project grants or large center grants when it formulated its program of extramural research grant support. The bulk of NEI research monies supported individual investigator-initiated research grants.¹⁹¹

The policy of not funding large program project grants was part of Dr. Kupfer's founding philosophy. These grants were too expensive, overly difficult to manage, and even harder to "turn off" (i.e., cancel or discontinue funding if the quality of the research began to deteriorate). The various eye advisory councils over the years accepted this philosophy. The NEI council emphasized this preference in NEI's *Strategic Plan In Vision Research: A National Plan 1978-1982*, stating: "Investigator-initiated research [RO1 grants] should continue to be the mainstay of the National Eye Institute's program Thus, the first priority of the NEI must be to nurture investigator-initiated research primarily by means of research project grants."¹⁹² Dr. Jack McLaughlin, formerly Deputy Director of NEI, recalled his favorable impression of the grants program when he joined the institute in 1980: "Well, coming out of the laboratory myself, I think it was music to my ears that the RO1 or single

investigator type of award was still going on and the highest priority in terms of a funding mechanism for the institute.”¹⁹³

The Cooperative Research Project Grant

Another mechanism, known as the *cooperative research project grant*, further allowed multidisciplinary collaboration among investigators in physically separated institutions throughout the United States. If several investigators located in different institutions across the United States wanted to collaborate, each could submit an individual research grant covering that portion of the research project for which he or she would be responsible. This grouping of individual grants would be reviewed together, if necessary, by a special study section. The group of grants would be funded together if deemed of high priority. The point was to provide flexibility for scientists in physically disparate locations to collaborate and at the same time continue to preserve NEI’s major funding mechanism for research support—the RO1.

Core Grants

During the 1970s, a recurring discussion occurred at council meetings concerning the support of large program project and center grants. Over the years, some NAEC members were more partial to these types of grants than was Dr. Kupfer, who remained fundamentally opposed. The difference in viewpoints became evident during NAEC program planning sessions. Some members of the council argued that program project grants should be considered in small numbers. Dr. Kupfer was not in favor of this. After a decade of disagreement, the council and NEI staff compromised. NEI implemented an additional type of funding mechanism called a *core center grant*, which was based on a concept already in place at a few other institutes, most notably the National Cancer Institute.

The core center grant was used primarily by those who already had their own research grant support. The purpose of the core grant was to concentrate support for and maximize usage of core facilities, equipment, and technical support that different projects commonly required. It saved putting the costs of each small research facility into its own research grant. Previously, each of the several grantees comprising the core grant group would have had to ask for service support for her/his own RO1 project grant. Core grant funding was made available to an individual investigator who submitted an application requiring several types of research facilities or pieces of equipment that were essential to the support of several ongoing research operations. Facilities for research might include a biochemistry or genetic cloning lab, a photography or machine shop, a tissue culture processing area, or a small animal holding area. Large expensive equipment that would be used jointly, such as an electron microscope and accompanying technical support to manage it, could also be funded

under this mechanism. The core grant provided such facilities to several investigators, each holding an RO1 or RO2 grant, and supplied laboratories in physically contiguous space, such as several departments in a medical school, university, or dedicated research building. Other grantees, as well as junior researchers engaged in their first research projects, might also be given access to the facilities. Thus, core grants could serve as the glue that brought many investigators and their projects together, facilitating a high degree of scientific cross-fertilization. RO1 grants did not cover such facilities or large instrumentation because they would cost more than the usual amount of RO1 funding.

Many other institutes at NIH included some research funding under the core grant, but NEI imposed a strict funding ceiling on each core grant, as well as program totals. The financial ceiling was raised every few years in the face of inflation and the high cost of research in such a technology-oriented field as vision research. NEI managed these grants very tightly.

Every other NIH institute had large program project and center grant activities, with each of these umbrella grants sometimes amounting to millions of dollars over multiple years. This gradually eroded the funding flexibility of many of the participating organizations, and it was very difficult to “turn off” one of these centers once they were funded. This was the case even with NEI’s program, modest as it was in relative terms. Once competitors understood the core grants and saw the large amount of funding they involved, many in research-oriented universities clamored to win a core center award. No other NIH institute ever replicated NEI’s “bare bones” core grant program. NEI’s ability to stave off demands for larger and more expensive program project and center grants allowed the institute to maintain maximum flexibility to support individual research grants (RO1s), from which most scientists believed the best innovative ideas emanated.

The compromise worked out between the NAEC and NEI’s director to allow core grants served the institute well over the next two decades. It was a more cost-effective alternative than funding several large expensive program project or center grants that could only fund a few investigators in a single department or medical facility; in this way, many more researchers could be accommodated. NEI’s core grant program drew much interest from the community, but it was limited to only modest growth. The NEI program of core grants grew from a few in 1974 and 1975 to more than 25 in 1981.¹⁹⁴ These core grants went mostly to ophthalmology or basic science departments and a few to optometry groups.

The core center grant accommodated the growing complexity of modern research, which was increasingly multidisciplinary and tended to involve many people working within one or multiple university departments. It also fostered inter- and intra-disciplinary work among grantees working on related projects. In retrospect, Dr. Kupfer concluded that the core grant “served the purpose very well because a senior investigator was in charge of each

of the units, and this individual took the responsibility to ensure that whatever research was done was of the highest caliber. I think in retrospect that this was a very good decision especially for a small NIH institute needing to grow and use its limited resources wisely.”¹⁹⁵

Construction Grants

In the 1960s, NIH received legislative authority for a construction grants program to build research facilities. Administered through the Division of Research Resources and Facilities, the program funded large grants sometimes totaling in the millions for a single grant. By the late 1970s, only the Cancer Institute and the Heart, Lung and Blood Institute still had a construction grants program. At that point, most of the other institutes, including NEI, did not have specific legislative authority to mount such programs even if they would have had the monies to fund them.

In the early 1980s Dave Weeks, executive director of the group Research to Prevent Blindness (RPB), suggested to the Association of University Professors of Ophthalmology (AUPO) that NEI establish a program of construction grants. AUPO enthusiastically endorsed the concept.¹⁹⁶ Advocates argued that ophthalmology departments needed and expected a certain level of support from NEI. RPB had been the single most active and productive group to have lobbied for an eye institute, and it had subsequently sought funding increases for the new institute on an annual basis. RPB had met with success largely as a result of the efforts of Dr. Ed Maumenee, ophthalmologist to several senators and congressmen, some well placed on appropriation committees. He was also a member of the RPB’s scientific board and a trusted confidant of Jules Stein and David Weeks. Dr. Kupfer remembers how the construction grants program originated:

In the early 1980s, Dr. Maumenee approached me about the possibility of a construction grants program for NEI. I told Maumenee that such a program was not a good idea at that time; NEI was having a difficult-enough time securing adequate funds for individual research grants, the priority mechanism of funding for the new institute—nevermind attempting to fund a construction grants program that would require huge sums of money. Of additional concern was the possibility that if a new program was authorized by Congress, there might not be an additional appropriation provided. If that happened, the new program would have to be funded from available resources, i.e., the existing NEI appropriation, making it even more difficult to adequately fund individual research grants and other ongoing NEI priority programs. Maumenee passed this message back to RPB, but the ball was already rolling.

‘Tanny’ [Nathaniel] Polster, the new RPB lobbyist in Washington, had already drafted construction legislative language. In a brilliant stroke of legislative legerdemain, Polster was able to have the authorization language and funding for a construction program included in a House appropriations bill. Ultimately, the proposal was approved as an item in the Joint House/Senate Conference Agreement encompassing the entire DHEW appropriation bill. Thus, the program was authorized without the Senate Appropriations Committee for the Department of Health, Education and Welfare—ever acting on the construction funding proposal as a discrete decision. Now, NEI had \$3.3 million in construction funding that it really hadn’t sought and about which the NEI director had thought he had discouraged.

It did not take long before a high-level NIH administrator called me into his office and wanted to know why I had engineered a clear effort of ‘budget busting.’ Did I not realize I might have unleashed huge expectations by this potential ‘pork barrel’ type funding? The administrator refused my protestations. Interestingly, my reputation as a political power player became the talk in some quarters and probably did more good for the reputation of the NEI than potential harm in the long run.¹⁹⁷

Meanwhile, the legislation generated huge expectations. Construction grants could be very attractive to academic departments and their elected congressional representatives because of the large size of the grant and types of equipment and facilities funded. Competition for these grants might result in congressional earmarks based on political influence rather than scientific merit. To counteract this, NEI and the NAEC outlined a competitive process that prospective grantees had to follow to receive funding, and to a great extent this program moved ahead without greatly disrupting the overall research grant program. NEI expanded its guidelines for the construction program to allow funding for instrumentation and renovations, as well as new construction. Awards were given on the stipulation that they be matched by funds generated from non-NIH sources. Funding for this program never exceeded \$3.3 million annually and was only included in the NEI budgets for a few years. Had it not been for the leadership efforts of several NAEC members, the construction grants might have polarized the vision research community because NEI could only fund a few. Dr. Kupfer recalls that one particular instance severely tested the mettle of the council:

The University of Oregon received line-item funding of \$1 million for construction of a vision research facility in the Congressional Appropriation Bill for Fiscal Year 1982. Hardly ever in the his-

tory of the NIH had specific projects been identified for funding through the appropriation process, but the originator of this line-item designation was from Oregon and happened to be the head of the Senate Appropriations Committee. NIH grants, including this construction grant proposal, were subject to a program of dual review. Unfortunately, the initial technical review group set up by the NIH Division of Research Grants to review these construction grants disapproved the Oregon request. NEI staff, after researching the law, found that a grant could be funded if it had been approved by its council, notwithstanding the fact that it had already been disapproved by the initial technical review committee. NEI's Executive Officer, Ed McManus, suggested forming a special council subcommittee to recommend a course of action to take on this grant. The group was a blue ribbon cast of leaders from the vision research community. NEI staff and this subcommittee determined that the Oregon ophthalmology department had several research grants that would be approved at that particular council meeting, thus making the university eligible under the council guidelines for a grant award. This allowed the council to approve the grant and not appear as if it were bowing to political pressure. The council ultimately recommended approving the grant and NEI funded it. Construction funding was not forthcoming to any significant extent in future years, but the council had demonstrated its strong leadership role on this controversial grant, a role that continued in major policy matters in the years ahead.¹⁹⁸

This anecdote underscores the unremitting pressure to fund projects based on political considerations and not just scientific merit. The council played an important diplomatic role in fending off these influences.

Contracts

NEI and the other NIH institutes had the legislative authority to award contracts to support logistical sciences, to administer the programs of an institute, and to conduct certain types of research projects. Contracting for research projects was used extensively by the National Cancer Institute in the 1960s and 1970s. Contract regulations required that the funded projects be set forth in detail, and therefore NEI usually used the research contract mechanism to verify a product or specific research objective. In the early 1970s at NIH, this mechanism was viewed as adjunct to the major funding mechanisms.

A contract is subject to a much more rigorous procurement process than an NIH grant mechanism. Contracts are generally used to fund an explicit objective or when an organization knows exactly what it wants to buy and can specify the details of the end product.

Research contracts at NIH and NEI were used mainly as a research support means that enhanced rather than substituted for research grants.

Contracts underwent a competitive process similar to that of grants, and their availability was generally announced in the *Commerce Business Daily* and the *NIH Guide to Grants and Contracts*. Proposed contracts underwent a system of dual peer review: they were first assigned to an in-house ad hoc review committee, which rated them on technical merit. An in-house scientific group then held a secondary review and examined whether the proposals satisfied the program relevance and policy requirements of the institute. This group then made recommendations to the NEI director, who made the final funding decisions and requested final contracting action by the NIH contracting officer. This whole procedure was intended to be more business-like than the grant-in-aid process.

Contracts were a topic of intense deliberations at a management retreat held by NEI in September 1973. The meeting's discussions centered on the problems of administering contracts to procure research for which it was difficult to predict the outcome. This uncertainty led to problems of costing a contract, determining the time of performance, and assessing levels of performance under a contract, among other concerns. How did one really know what was cost-effective if one did not know ahead of time the exact product or outcome one was looking for? And from the contractor's perspective, it was extremely difficult to accurately predict time, costs, and outcome for the intellectual and technical work involved in research, especially when so many variables were beyond control. NEI maintained a policy that research contracts should be used only when in-house staff had the time and the requisite technical and scientific qualifications and competency necessary for providing close oversight of the project. Staff of the Office of Biometry and Epidemiology could serve this function. Moreover, the projects should focus on applied targeted research, a kind that more readily lent itself to monitoring. Epidemiology research and clinical trials were the best examples of this sort of research. This policy, adopted by the NAEC in its first program plan, served NEI well for many years.

NEI began to support research contracts in June 1971 and used them quite frequently during the next 30 years to fund such programs as clinical trials, animal resources, and professional devices. Both nonprofit institutions and businesses were eligible to compete, but all contracts were subject to peer review. There was a lively competition for most of these contracts.¹⁹⁹

After the mid-1970s, NAEC had to approve the proposed contract offerings and receive information on the final contracts that NEI awarded in order to help monitor the contracts program. The contract mechanism was viewed by staff and the council as a minor but important tool in carrying out the research agenda of the institute it never exceeded more than 3 percent of the institute's budget. Dr. Kupfer and many in the research community believed

that research should most often be supported by the grant-in-aid programs rather than by the more constricting contract mechanism.

The contract mechanism was used to fund NEI's first clinical trial, the Diabetic Retinopathy Study (DRS), a second clinical trial (ETDRS), and the Framingham Eye Study, an epidemiologic study (the latter two initiated in the late 1970s). NEI gave contracts support to WESTAT, Inc., to develop problem data on eye diseases in the mid 1970s. Contracts were also awarded for the Diabetic Retinopathy Vitrectomy Study clinical trial, which looked at a new surgical treatment for diabetic retinopathy in the mid 1970s, and for conducting applied statistical studies and clinical trials internationally through the World Health Organization (WHO). This latter contract work, although only costing a few hundred-thousand dollars, was the centerpiece of NEI's international activities from the late 1970s until 2000 (see Chapter 8 on International Initiatives).

Research contract support at NEI began to diminish in the late 1970s as the research grant mechanism became available to support clinical trials. Because the extramural community grantees were increasingly the ones to initiate clinical trials, the grant-in-aid assistance mechanism came to be seen as an appropriate way to support trials. Congress also supported large increases for NIH's grant program, but much less so for the contracts program.

Funding Mechanisms for Clinical Trials

From the start, the expansion of clinical research was one of NEI's priorities—after all, developing treatments was the major reason that NEI was created. NEI, however, inherited from NINDB funding responsibility for several specialized clinical research centers with significant problems. They were expensive, consumed large amounts of resources, did not maintain a high caliber of research comparable to the RO1 grants, and were difficult to terminate because of the major commitment already made to numerous staff members and projects. Decisive action had to be taken. The grantees holding program project or center grants originally awarded by NINDB were notified of an orderly phase-out of the grant and were given the opportunity to submit an RO1 grant application that proposed a core grant.

A second approach to stimulating clinical research involved expanding the support of clinical trials under the RO1 research grant mechanism. This was accomplished by making clinical research topics a priority of the institute within the separate programs in the program planning process. This action resulted in many clinical research grant applications being singled out by the advisory council and given a designation of high priority (or high program relevance). This designation usually led to the grant being funded. NEI also established a special *cooperative clinical research grants program*, funded from the pot of monies used to fund its other research grants.

In the first few years most NEI clinical trials were supported primarily through the contract mechanism. Using a blend of contract and grant devices, NEI was able to exercise more direction over contract programs than grant-in-aid programs. The contract aspects mandated that the NEI project officer monitor the progress of a clinical trial, oversee day-to-day decisions, and ensure adherence to the written protocol.

The cooperative clinical research grants program was funded as a separate program out of the research grant line. Inaugurated in the early 1970s, it soon became the major instrument for supporting NEI clinical trials. As of 1992, more than 22 clinical trials had been supported by this mechanism. By the year 2000, 60 randomized clinical trials had been completed, were in progress, or being planned.

R21 Planning Grant

In the 1970s and 1980s the vision clinical research community was just beginning to become familiar with the scientific methodology required to carry out rigorous randomized clinical trials, as likely was the case with medical researchers overall. The institute began a funding program referred to as the R21 planning grant to be used for developing a manual of operations or protocol for a specific randomized clinical trial. If the protocol was judged promising, an application could be made for a full-scale cooperative agreement research project grant. Some protocols resulted in full-scale clinical trial grants that were funded for the duration by the institute. For example, an R21 planning grant was used for a project on the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (ROP). The research objective was to test the efficacy, safety, and costs of providing supplemental oxygen in moderately severe retinopathy of prematurity (prethreshold ROP). The technical question was whether a small percentage difference in oxygen saturation could be achieved and maintained for the study so that the data would be reliable. The investigators received an R21 and a small group of children were entered into a test run using the proposed protocol. It was shown that the difference in oxygen saturation could be maintained. The full trial then proceeded.

Physician-Scientist Award

The training grant model in place before NEI was created used a one- or two-year period of research training, either in the laboratory or in clinical research, with three years devoted to developing competency in the diagnosis and treatment of ophthalmic disease. Few physicians received this training, which would allow them to make the choice to pursue a research career or clinical practice. If an institute was truly committed to training clinicians to become competent researchers as well as astute practitioners, a training program would only accept candidates who had already spent three years in a clinical residency.

The program should last for five additional years, beginning with two years of lecture, didactic course work, and study in a laboratory research field, including genetics, immunology, molecular biology, or a clinical research field such as epidemiology or randomized clinical trials. This would provide the scientific base. The trainee would then enter a final three-year research training program and simultaneously begin to develop a research protocol containing details of several small experiments with the guidance of an appropriate preceptor.

Under the new NEI Physician Scientist Awards, it soon became clear that achieving the goals of teaching both the theory as well as the practice of research would require more than merely providing funds to individual trainees. Under the *physician scientist grants*, NEI gave broad-based institutional support to departments in order to support the necessary infrastructure of capable teachers, effective curricula, and constructing and equipping adequate research facilities. NEI also used its resources to expand the number of research-oriented trainees by paying a competitive stipend during the five-year research traineeship. The architects of this NEI *training grant program model* expected that a large proportion of the grantees receiving clinical and laboratory training would become academic ophthalmologists rather than entering private practice. The idea was to generate a larger pool of specialists who, in turn, would expand existing departments and create new ones. This would eventually increase research activity, it was hoped.

Research Training

The NEI employed a variety of ways to support training from its inception in fiscal year 1970. It relied heavily on the formal training program, first begun at NIH in 1954, to fund graduate training grants (T01s). These grants supported the institutions where training was carried out and paid for the costs of training individuals. They were awarded primarily to ophthalmology and medical departments; over 72 institutions received support in 1974. NEI also awarded individual fellowship awards from 1970 to 1974 that were called F02s, F22s and F32s. They ranged in number from 17 in 1970 to 36 in 1973 to 80 in 1974.

The National Research Act (Public Law 93-948), passed in 1974, set-up new grant requirements²⁰⁰ and caused major changes to the training and fellowship program.²⁰¹ These changes stemmed from a concern that the T01 training program inappropriately supported the general development of departments of ophthalmology and that the ophthalmologists who received grants tended to go into private practice rather than research. It was thought that practitioners could easily recoup the cost of medical school or specialized training and did not need grants funding. As a result T01s were phased out by the late 1970s.

Training grants or T01s were budgeted at almost \$3 million dollars in FY 1971, approximately 10% of the young institute's budget. In comparison, fellowships were budgeted at \$1.7 million, still a significant amount. By 1977 the T01 training grant budget was only

\$1.2 million dollars as a result of the phase out, and by 1979, the program had ended. NEI's official training program declined from almost 17% of its total budget in 1971 to just over 7% in FY 1977.²⁰² The ophthalmology-oriented organizations that had received TO1 funds experienced a significant decline in income.²⁰³

After 1974 the NEI supported two new types of training and fellowship programs, the Individual National Research Service Awards (F32s); and the Institutional Grants for National Research Service Awards (T32s).²⁰⁴ The NRSA individual fellowships (F32s) were primarily given to laboratory scientists and supported post-doctoral research support for up to three years in research areas of the visual system. The NRSA Institutional training grants (T32s) were provided to institutions to support doctoral and post-doctoral vision research training. Clinical pre and post-residency training was also encouraged under this program.²⁰⁵ Still, the new programs were not tailored to clinical research; only 10% of the total number of trainees each year were MDs. NEI planners who looked in depth at NEI training in 1983 saw an "overall decline in the number of the physicians entering research training programs."²⁰⁶

The NEI formal training program where funds were directly appropriated for training was only one way in which the NEI could support research training and fellows. In addition NEI funded:

1) New Investigator Research Awards (R23):

Another venue for advanced research training that the institute emphasized from the early 70s was the New Investigator Research Awards. This was formerly called the Academic Investigator Award (K04).

2) Research Career Development Awards (K04):

These grants supported salaries for up to five years to NEI grantees who held an active grant.

3) Pre-doctoral and post-doctoral training in emerging and relevant scientific areas such as cell biology, genetics, immunology and virology and in the clinical sciences of epidemiology and clinical trials:

In an effort to enlarge the science base of vision research, NEI began in 1994 to offer a two-week course titled *Fundamental Issues in Vision Research* taught by prominent vision research leaders, all who held NEI research grants. Twenty pre and post-doctoral students not involved in vision research were carefully selected and invited to Woods Hole, Massachusetts. It was expected that the some attendees would be stimulated to conduct research in the field of vision. The course was offered every two years and continues to the present. Although careful records were not kept, word of mouth suggests close to 50% of the students did try for and receive a small grant for vision research from NEI.

The above three categories were funded out of the research grant budget line and were not considered part of the formal training program. That is they were not funded out of the NEI appropriated funds for training and fellowships as authorized by specific NEI/NIH legislation for training. They were still considered training but funded out of programs whose legislative authorization was intended for research support activities.

The amounts expended for the first four of these programs from 1977-81 are shown in the chart below.²⁰⁷ No budget figures were available for the Woods Hole Course.

National Eye Institute Research Training and Career Development Awards, FY 1977-1981

Fiscal Year	Individual National Research Service Award (F22, F32)		Institutional National Research Service Award (T32)		Academic Investigator Award (K07)*		Research Career Development Award (K04)	
	Number	Cost	Number	Cost	Number	Cost	Number	Cost
1977	105	\$1,204,757	43	\$2,440,167	18	\$462,902	43	\$1,369,351
1978	96	\$1,168,520	44	\$2,834,498	20	\$571,304	55	\$1,885,099
1979	107	\$1,364,103	49	\$3,226,098	22	\$628,759	56	\$2,063,378
1980	128	\$1,766,871	42	\$2,737,846	18	\$577,654	52	\$1,854,929
1981	76	\$1,418,087	35	\$2,510,947	9	\$305,921	50	\$1,834,198

*The K07 award is no longer being made. This mechanism was converted to R23, the New Investigator Research Award.

(Original table: Vision Research—A National Plan: 1983-1987; Volume One, The 1983 Report of the National Advisory Eye Council, p. 60)

NEI sponsored research training indirectly. For example, the participants in NEI clinical trials received extensive training and monitoring in the application of the scientific method to clinical research. NEI also supported several training positions within its Intramural Program, and these individuals slowly added to the pool of the highly trained clinicians who carried out carry out the national effort in vision research. Finally, and most importantly positions could be funded within an NEI funded research grant; incumbent could receive extensive research training as he or she participated in the research project. Much training occurred in this manner. Again, most consider NEI/NIH training activity to be that which is supported financially out of the NEI budgeted line item for training. However, as pointed out earlier training and fellowships could also be supported by NEI/NIH in other ways as long as they were part of research projects. Research fellows could be added to research grant budgets and receive financial support for the training that they received as long as they were working on these research projects.



Mr. Edward McManus, Executive Officer, 1973.



(Above) The first NEI National Advisory Eye Council meeting, April 3–4, 1969.



(Left) Dr. Jin Kinoshita.

(Below) Dr. Cogan and Dr. Kuwabara attending the dedication of the Cogan Library at NEI, 1985.





(Above) Mr. Julian Morris.

(Below) Actress Angela Lansbury celebrates the 25th Anniversary of NEI with Dr. Kupfer and Lew R. Wasserman, Chairman of Research to Prevent Blindness, at the opening of the NEI traveling exhibit VISION, April 11, 1994.





(Left) Anthony Adams, University of California Berkeley (UCB) Optometry School Dean welcomes UCB Chancellor Chang-Lin Tien and Dr. Kupfer to the School of Optometry's "Vision Education Day."



(Above) The Priorities and Projects Committee of the newly established International Agency for the Prevention of Blindness, November 1975.



(Above) Dr. Siva Reddy explaining the concept of the Cataract-Free Zone to Dr. Kupfer and Sir John Wilson.

(Right) Dr. G. Venkataswamy and Dr. Kupfer discuss the proposed randomized clinical trial comparing two differing operations for age-related cataract.



(Right) Barbara Underwood, Ph.D.



(Below) Dr. Akira Nakajima, the organizer of the Japanese Exchange Program, discussing the program with Dr. Kupfer.





(Left) Professor Dorairajan Balasubramanian receiving research grant funding supported by NEI.

(Right) China-U.S. Agreement was signed in May 1988 by Dr. Kupfer and Winifred Wenshu Mao, MD, the Director of the Zhongshan Ophthalmic Center, the Sun Yat-sen University Medical Sciences and Deputy, National People's Congress, People's Republic of China.



Chapter 6

Randomized Clinical Trials

Introduction

The story of the development of clinical trials in the twentieth century, in some ways, tracks with the development of other applied fields such as agriculture and engineering. At the core was a battle fought over the value of practical experience versus modern science. Medical practitioners who believed in the paramount value of using personal experience and empirical observation to guide diagnosis, prognosis, and treatment found themselves juxtaposed against those seeking to replace that research model with one that relied on the application of the scientific method. As compared with other fields, the medical community was largely successful in keeping the scientific method out of the forefront of applied research and treatment. NEI's championing of clinical trials was timely, coinciding with the acceptance of the scientific method in biomedicine. Less than a decade after NEI's establishment in 1970, there was near unanimous agreement that medical research and treatment should be based on scientifically designed trials that were verifiable and replicable. The scientific method of conducting clinical research, in brief, came to pivot upon the combined implementation of controls, randomization, and double-blind assessment. The randomized controlled clinical trial (RCT) is now widely accepted as the main method for reliably evaluating the effect of new treatments on patients.

To comprehend the challenges that medical researchers faced as this transformation occurred during the twentieth century, it is important to understand what history they were trying to overcome. Since the time when medical treatments were first recorded, there was little evidence, other than anecdotal, that spoke to the actual effectiveness of particular treatments. Often, a treatment worked only some of the time—and then only because the doctor and the patient wanted it to work, and believed it would, rather than because it had any inherent biological efficacy. Patients could derive benefits from these treatments without any biological rationale, and this came to be known as the placebo effect. Indeed, in their 1997 book, *The Powerful Placebo*, Arthur Shapiro, M.D., and Elaine Shapiro, Ph.D., state:

In fact, the history of medical treatment, until recently, has been essentially the history of the placebo effect. Despite the use of inef-

fective methods, physicians have been respected and honored because they have been the therapeutic agents for the placebo effect. The placebo effect flourished as the norm of medical treatment at least until the beginning of modern scientific medicine.²⁰⁸

For many years, researchers in the medical community were suspicious of the placebo effect—sometimes referring to the “hysterical nature” of healing methods—and both the doctor and patient’s susceptibility to bias or suggestion. The placebo effect, understood in the modern sense, was not specifically identified or even widely considered until the 1950s.

To establish the efficacy of treatments, clinicians had to devise a methodology that would negate the confusing and corrupting placebo effect. The modern randomized and controlled clinical medical trial developed as a rational approach to incorporate the scientific method into clinical research and to control the placebo effect. At the core of such a trial it was imperative that some patients receive the actual treatment being tested and others a benign placebo, and that neither the doctors nor the patients know which patients received what treatment. To many physicians, this rule seemed counter to the prevailing notion that empirical observation should determine treatment and that the practitioner could draw broader conclusions about the efficacy of a specific treatment by assessing whether a patient looked or felt better with the treatment. It was the clinical impression of many physicians that individual patients tended to respond differently to a treatment. Physicians’ skepticism had to be defeated before randomized controlled clinical trials could gain wide acceptance. Many practitioners also found it difficult to accept controlled trials because they seemed to go against the notion of treating only one individual at a time and tailoring treatments to a patient’s idiosyncratic needs—in other words, it seemed contrary to the art of practicing medicine. In a randomized controlled trial, the objective, by definition, was broader: finding ways to effectively treat entire classes of patients, even if this meant that patients given the placebo would receive no initial treatment. Negating the placebo effect through randomization (and thereby allowing for the development of truly reliable and efficacious treatments) was therefore the predicate for ensuring that randomized controlled clinical trials would do what they claimed to do: prove through testing whether a treatment was safe and effective or not. The randomized testing of patient groupings relied on the correct application of statistical science and competent analysis. In addition to these structural challenges, there were also political and theoretical obstacles to overcome before NEI would successfully develop and implement properly designed clinical trials.

The Long Road to Clinical Trials

The *sine qua non* of scientific or “evidence based” medical practice is the well-designed and well-conducted randomized controlled clinical trial. It was not until the mid-twentieth century, however, that this tenet became firmly ensconced. Of course

throughout written history, even as far back as biblical times, there has been testing of medical treatments that drew on some variant of comparison. In his article on the evolution of clinical testing, Abraham M. Lilienfeld describes an early comparative nutritional study recorded in the Old Testament's Book of Daniel. In this story, Daniel compares 10 youths who consume a diet of simple foods to 10 youths who share the King's rich meals and wine. After 10 days, the first group "appeared fairer" and "fatter of flesh" compared to the second.²⁰⁹

It took a long time, however, for the individual elements necessary for a successful clinical trial to be assembled. Remarkably, a few medical treatment experiments—we might call these clinical trial precursors—were right on the mark. In the 1780s, Benjamin Franklin's blindfold experiments used a control element. James Lind drew on comparative statistics in his study of several different treatments for scurvy. He found that consuming oranges and lemons was the most effective treatment for countering scurvy, although it was not known until much later that the condition resulted from a deficiency of vitamin C.²¹⁰

In the nineteenth century, growth in the areas of vital statistics and mathematical statistics contributed to ideas about comparison in studies of therapeutic methods. Still, other studies of the period did not go even this far. Some resulted in subjective and seemingly ludicrous claims of efficacy. In 1794, Benjamin Rush reported that his "bleeding" treatment was beneficial for patients with yellow fever. Even today there is no magic bullet for this disease, although it can be prevented with immunization.²¹¹ During the first decades of the twentieth century, testing of serums and drugs for infectious diseases illustrated a greater understanding of controls, randomization, and blinded assessment. Up until the middle of the twentieth century, medical experimenters had little real understanding of how to nullify the placebo effect using controls and randomization in comparative medical studies.²¹²

Randomization and controls were used in agricultural, industrial, and other types of experiments during the early twentieth century, but medicine was slow to catch up. RCT methodology, as used in medical trials, was pioneered by the British epidemiologist and statistician Austin Bradford Hill. In 1948, he and his colleagues published what is widely considered to be the first clinical trial conducted with a properly randomized control group. This landmark paper reported that when patients with pulmonary tuberculosis were treated with streptomycin, their survival rates improved and the size of tubercular lesions in their lungs decreased.²¹³

During the 1950s, Professor Hill wrote about concepts such as concurrent controls, the random allocation of patients to test groups, the definition of eligible patients, treatment schedules, objective evaluation of the result, and competent statistical analysis. Sir Austin Bradford Hill was knighted in 1961 and continued his research until his death in 1991. His publications helped the clinical research community understand that various control elements were essential to the success of a clinical trial. In the words of Dr. Stuart Pocock, a profes-

sor of medical statistics, only by incorporating these requirements could researchers hope to obtain “a truthful answer to a relevant medical issue.”²¹⁴ Still, acceptance of RCTs was slow to emerge in the United States.

NIH and Biostatistics

As medicine advanced in the mid-twentieth century and the number of available treatment options expanded, it became more important that adequate investigations be carried out to determine whether new therapeutics actually benefited the patient. NIH was at the forefront in developing randomized controlled clinical trials to do just that.

The National Cancer Institute sponsored RCTs that tested cancer treatments. NCI also stressed the importance of biostatistics for developing properly controlled trials. In the 1950s, NIH became a major center for biostatistics, attracting outstanding statisticians who developed new methodologies for applying statistical analysis to research in biology and medicine. This momentum began at NCI.

One of the first biostatisticians that NCI recruited was Harold Dorn, who in turn recruited a number of promising, young statisticians including Jerry Cornfield, Jacob Lieberman, Nathan Mantel, and Marvin Schneiderman. Dorn established a biometry group within NCI, the first of its kind at NIH. The group worked with laboratory researchers not only from NCI, but also with those from other institutes who needed statistical assistance. The statisticians pioneered new methodologies for evaluating potential treatments. For example, they worked with laboratory researchers to develop new techniques suitable to animal experiments, such as assessing the effect of anti-cancer drugs on the growth of experimental tumors implanted into mice. In the late 1940s and early 1950s, it was clear that the group under Dorn was, as Schneiderman recalls, “*the* statistical group in the Cancer Institute and at the time that meant it was *the* statistical group in all of NIH.”²¹⁵

In subsequent years, the members of this core group spun off to form or join biometry groups in other institutes. The number of institutes with biometry divisions gradually increased as biostatistics developed and statisticians nurtured disease-specific interests. Still, it took time for staff at different institutes to become convinced of the value of an in-house statistical group. In the mid-1950s, Cornfield, Dorn, and Lieberman moved out of NCI to form a free-standing biometrics branch at NIH. This group provided statistical services to NIH staff and helped establish new statistics groups in other institutes. By 1960 Dorn believed the group had accomplished its objectives along those lines and, accompanied by Cornfield, he moved to the National Heart Institute (NHI) to head its statistical program. The two men continued to play a leadership role in developing statistics programs at NIH; unfortunately, Dorn suddenly died two years later.

The critical mass of mathematical statisticians working together and the collective experience accrued in a variety of subjects made NIH a major center for biostatistics. A few of these up-and-coming biostatisticians were interested in clinical trials methodology as well as in epidemiology in general. Cornfield is credited with helping to build the theoretical foundation for methodological research in epidemiology and clinical trials. Samuel W. Greenhouse, Ph.D., whose career led him from the Cancer Institute to the Mental Health Institute and then to the Child Health and Human Development Institute, helped advance the theory and practice of clinical trials while researching mental health drug treatments. Fred Ederer, an important figure at NEI, helped develop clinical trials methodology during his 14 years at the NCI and NHI, before joining the National Eye Institute in 1971.²¹⁶

There was little interest in randomized trials at NIH in the 1950s and 1960s, except at the Cancer Institute and the Heart Institute.²¹⁷ In the mid-1950s, Congress gave a large appropriation to NCI to develop and test chemotherapeutic agents. The Cancer Chemotherapy National Service Center established seven multicenter groups, each composed of research institutions that simultaneously carried out RCTs of chemotherapeutic agents over the next decades throughout the United States. NCI used the ample congressional funding to organize regional statistical centers that were involved in the design, randomization, and data analysis aspects of the trials.²¹⁸ The trials and centers were funded and sustained primarily by renewable grants from NCI. The trials were generally of relatively short duration, as the researchers were looking for large responses to the particular intervention they were testing. Some of the NCI statisticians played an important role in the development of the methodologies for meeting the statistical challenges associated with these studies. Jerry Cornfield was involved in one of the first clinical trials dealing with the treatment of leukemia. The cancer chemotherapy trials fueled interest in clinical trials, shifting the momentum toward RCTs.²¹⁹

The Heart Institute also launched a series of randomized clinical trials. In contrast to the NCI model, the National Heart, Lung and Blood Institute (NHLBI) crafted each clinical trial individually to scientifically address a specific question. For example, NHLBI's first randomized trial, begun in 1951, compared three drugs in the treatment of rheumatic fever and the prevention of rheumatic heart disease. The Coronary Drug Project, begun in 1965, followed a specific design, used a large sample size, recruited its own cadre of patients (8,341), involved 53 clinics, and had a long follow-up period (15 years).²²⁰

Although NEI generally followed the model used by the NHLB, the institute was also influenced by the NCI cancer trials in setting up a series of centers to conduct clinical trials of AIDS drugs where rapid assessment was needed to keep pace with the rapid development of new therapies.

Resistance to RCTs

Despite increasing interest in RCTs, their acceptance was slow overall. For one thing, physicians generally resisted the concept of randomization. For example, Jerry Cornfield and Lincoln Moses, two outstanding biostatisticians, provided statistical analysis and guidance for a radiotherapy group treating lung cancer. During their interactions with this group, Cornfield and Moses found that the participating physicians did not readily accept the concept of randomization and its value in developing medical treatments.²²¹

The resistance was widespread. For physicians to admit to a patient that they did not know whether a particular treatment was helpful, of no value, or possibly harmful conflicted with medical education and practice. Medical training in general taught physicians to try any therapy that might appear beneficial as long as the physician felt no harm was being done. Advocates of RCTs pressed for a different sort of approach. To resort to randomly deciding whether a particular patient would receive the drug in question or a placebo contradicted this individualized approach to treatment. Many physicians also resisted the argument that statisticians must be included in an RCT from start to end—in designing the protocol, conducting the trial, and evaluating the results. To many physicians, this seemed too high a level of involvement. In general, many believed it was not appropriate for statisticians to declare whether a study was significant, especially because statisticians (as non-physicians) were reputedly ignorant of medical nuances. On the other hand, statisticians maintained that the physicians did not understand the statistical methods used in data analysis, and thus might not accept the implications deduced through these methods. Statisticians made it clear that the findings in an RCT were only valid when statistical analysis was done by a statistician; for example, in comparing the treated versus placebo groups (or the new treatment versus the standard treatment), only a statistician could determine whether the outcomes were significantly different. These prejudices widened the divide between the two groups.

The physicians were not alone in their skepticism. Some NIH scientists, too, did not understand the uses of statistics for laboratory and clinical research. Despite that NIH biostatisticians willingly provided assistance to the various institutes on a broad basis, many institute scientist-administrators did not grasp the value of creating a statistical group in their organization. Marvin Schneiderman recalls that one institute director became so intrigued by the collaboration between some of his investigators and NIH biostatisticians that he approached Cornfield about creating a statistics group. Thinking that Cornfield surely ranked low on the government's employee scale (as *only a statistician*), he was astonished to learn that Cornfield ranked near the top, indicative of a high skill and value level. Skepticism could be a problem even within NCI, where the biostatisticians were firmly ensconced. Schneiderman recalls being invited by an NCI laboratory chief to give a presentation to the staff about the activities of the NIH biostatisticians. For almost two hours they discussed

problems the laboratory researchers were having and whether the statisticians could help. As the meeting ended, the lab chief thanked Schneiderman effusively, but then said, in effect, “You know, what you guys are doing is quite interesting, but if it were really important, I would be doing it.”²²²

It was the occasional physician, highly respected by peers, who played an important role in convincing the medical profession that unless a planned clinical study included all the essential methodologies—randomization, masking (or ‘blinding’ in non-ophthalmic RCTs), avoidance of investigator bias, and statistical analysis of data—it was unlikely that the result would produce an unbiased answer.

In 1954, Michael Shimkin, M.D., was appointed to head NCI’s Biometry and Epidemiology Division. A productive laboratory researcher in experimental oncology throughout his career, Shimkin often served as an active consultant on randomized clinical trials. He was a forceful leader at NIH and well respected by cancer researchers. Shimkin favored the inclusion of statisticians in clinical research studies, and he exerted a positive influence on the overall acceptance of biostatistics in medicine. According to Fred Ederer, in an address at a cancer conference Shimkin made positive comments on the role of statisticians in clinical trials. While Shimkin pointed out that physicians might be annoyed by the proactive biostatistician, he had no doubt that statistics and biostatisticians were integral to clinical trials and, thus, key to developing efficacious medical treatments: “We have learned of the need for unequivocal definitions and criteria for meticulous experimental designs, of the requirement for randomized controls, and of the innumerable sources of bias that can be avoided by double-blind techniques, of the placebo effect to which the investigator is as liable as the subject, and of the annoying biostatistician who questions our plans, makes impossible demands, and finally doubts our interpretation of the results.”²²³

New government regulations also promoted and validated clinical research trials, no doubt helping to stem some of the skepticism. The Kefauver-Harris Amendment of 1962, building on the Pure Food and Drug Act of 1906, mandated that in order to obtain retail approval to sell a new drug sponsors must submit “adequate and well-controlled experiments by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.”²²⁴

NEI and Clinical Trials

Small Steps at NINDB

In the mid-1950s, the National Institute of Neurological Diseases and Blindness sponsored its first ophthalmic clinical trial, building on the work of Arnall Patz, M.D. A few years earlier Patz, as a young ophthalmology resident at Washington, D.C.’s Gallinger Hospital,

had undertaken the first modern RCT dealing with eye disease. The purpose of the study was to determine whether the high levels of oxygen commonly administered to premature infants in incubators caused retrolental fibroplasia (RLF), a potentially blinding condition. NINDB had initially turned down Patz's grant proposal as being unscientific but later approved the small study, which it jointly funded with the National Society for the Prevention of Blindness and the National Foundation for Eye Research. The results of this small RCT, only 65 cases, strongly implicated high incubator oxygen concentrations.²²⁵

These promising results served as a rational basis for undertaking a larger randomized clinical trial. Supported by NINDB and directed by V. Everett Kinsey, an ophthalmic biochemist, 75 ophthalmologists and pediatricians working in 18 hospitals were able to demonstrate that high concentrations of oxygen administered to premature infants in incubators did in fact cause the disease. Consequently, physicians as a common practice reduced the levels of oxygen administered to premature infants and the incidence of RLF dropped dramatically. For this work, Kinsey and Patz received the prestigious Albert Lasker Award for Clinical Medical Research in 1956, and Patz received the Presidential Medal of Freedom in 2004.²²⁶

The NINDB took another small step forward when it organized a Biometrics Branch. Irving Goldberg joined NINDB in 1957 as the assistant chief of the Biometrics Branch; Bernard Kroll joined NINDB in 1958 and served as head of the section on Systems Design and Procedures in the Perinatal Research Branch, Collaborative and Field Research; and Doris Sadowsky joined NINDB in 1959 as a mathematical statistician, having previously worked at NCI.²²⁷ The unit focused primarily on epidemiological data pertaining to amyotrophic lateral sclerosis (ALS) collected from the Island of Guam. It also helped organize and conduct the Collaborative Perinatal Study, a much-touted project that collected data on mothers and their newborns in hopes of determining the causes of mental retardation, cerebral palsy, and other congenital abnormalities of the brain.

In the early 1960s, NINDB attempted to recruit an epidemiologist to start an epidemiological program on visual impairment and blindness, a step that surely would have impacted efforts to sponsor other clinical trials in vision. The attempt failed, as too few epidemiologists thought there were opportunities in ophthalmic field research. Slowly that situation began to change.

Advances in the fields of clinical trials, biometry, and epidemiology resulted from the intertwining of their knowledge bases, resulting in a degree of mutual interdependence. During the 1950s and 1960s, epidemiology and clinical trials shared certain commonalities, particularly a reliance on statistical methods. Epidemiology was oriented toward establishing the risk factors for the development of disease. Using retrospective (case-control) studies, epidemiology examined associated risk factors in diseased patients compared to

healthy individuals who served as controls. Epidemiology also used prospective (cohort) studies, which closely tracked a large group of healthy individuals over many years, identified those who developed a disease, and then analyzed the risk factors leading to the disease. Clinical trials examined the effect of a specific diet, drug, or surgical procedure used as a treatment in order to determine whether it was beneficial, harmful, or without effect. Both epidemiological and clinical studies used statisticians to collect and analyze data. NIH statisticians played a seminal role in developing the statistical methodology of epidemiological studies, as well as advancing the use of statistics in clinical trials at NIH and throughout the United States. NEI actively encouraged this development.

NEI, Epidemiology, and Biostatistics

When Dr. Carl Kupfer joined NEI in 1970 as its first director, he knew it was important that NEI carry out clinical trials that use the appropriate scientific methodologies. It was not enough that researchers accept that trials must incorporate randomized controls and masking (or double blind) features; the proper design of solidly constructed clinical trials absolutely required quality statistical input.

Dr. Kupfer's appreciation for the importance of biostatistics and epidemiology for research stemmed from his experience as a student at the Johns Hopkins University Medical School from 1948 through 1952. Johns Hopkins was one of the few prestigious universities that taught a course integrating these subjects during this period. Dr. Kupfer provides an account of these experiences:

A course lasting eight weeks, three half-days weekly in biometry, was required of all first-year medical students. Being rather slow in mathematics, I was unable to complete all the problems assigned in the time available. However the application of statistics to formulate and solve medical problems left its imprint on me. When during my exit interview I met with Dr. Margaret Merrill, who was in charge of the course, I confessed that although I enjoyed the course and was impressed with the power of statistical analysis of complex medical diseases that enabled the physician to begin to understand the risk factors involved in the susceptibility of contracting a particular disease, I had not understood much of what had been presented. She smiled and said, "You must have an opportunity to teach in the course. That is the only way to understand statistics." Accordingly, I was a Laboratory Assistant in Biostatistics from 1953-1954 while in ophthalmology residency at the Wilmer Eye Institute and again in 1957-1958 upon returning to Hopkins after military service. I began to understand and appreciate the value of a strong biostatistics capability if one seriously contemplated a career in clinical research. At NEI, organizing a

research unit to conduct epidemiology studies and mount clinical trials was clearly a high priority.²²⁸

Kupfer also recalls that he was aware that many physicians held little regard for the value of epidemiology through the 1960s, despite the fact that it was gaining momentum as a discipline. Many prominent researchers discounted the use of epidemiology and clinical trials for medical practice. He recounts:

Upon returning to Johns Hopkins in 1957, I had the good fortune to meet Dr. Abraham Lilienfeld who had recently moved from the University of Buffalo School of Medicine to the Johns Hopkins University School of Hygiene and Public Health. He had just completed work on studying a chronic disease, cerebral palsy, by developing epidemiologic methods that could be applied to the study of chronic diseases. I made an appointment to see him with the question of trying to use these epidemiological methods to approach open angle glaucoma, one of the major chronic diseases facing the ophthalmologist. He proposed a case-control study as an initial effort and there followed several discussions to flesh out a protocol.

With this preliminary information in hand, I made an appointment with my supervisor—a physician and eminent researcher—and sketched out the details of a case-control study of glaucoma. After listening patiently for about 15 minutes, he interrupted to say that if I had enough time to do a study as I had proposed, he would find a research project that would make better use of my time.

My supervisor shared with others a perspective typical for that time: he was committed to fundamental laboratory research and considered epidemiology as overly time-consuming, too expensive, and not of the high caliber of laboratory research because of the formidable statistics required to control all the variables and compensate for bias that can creep in to such a study. Many physicians, and researchers, still disregarded the value of RCTs and the epidemiology approach for research as well as their importance for clinical medicine.²²⁹

In the 1950s and 1960s, two NIH institutes sponsored several epidemiologic case-control and cohort studies showing the relationships between certain factors and disease among specific populations or groups. In 1949, the National Heart Institute acquired from the U.S. Public Health Service the Framingham Heart Study Cohort, which laid out the risk

factors for heart disease. The study was carried out for several more decades and was still in existence when NEI was established.

At NCI Harold Dorn led a prospective cohort study that examined mortality rates among a group of veterans, both smokers and nonsmokers. Dorn's study followed two other cohort studies of smoking, one done in Britain, the other in the United States. All three studies found that cigarette smoking entailed nearly a 10-fold risk of developing lung cancer, a finding that had a strong impact on the U.S. Surgeon General's report on smoking and health, published in 1964.²³⁰

As additional case-control and cohort studies were done in topics other than lung cancer, and as the methodology was refined during the 1960s, the notion of proper statistical design became more accepted. Then, the problem became the lack of researchers who were properly trained in statistics and the scarcity of statisticians who specialized in medical statistics or biometrics.²³¹

Framingham Eye Study

One of the epidemiological research projects on which OBE embarked was the Framingham Eye Study. Under the direction of Dr. Kahn, this extramural study examined the eyes of the survivors of the original Framingham Heart Study Cohort, begun in 1948. The researchers had access to extensive laboratory and physical examination data as well as family history information. Twenty-five years after the original start date, Kahn arranged to have the surviving Framingham cohort given eye examinations. Carried out from 1973 to 1975, this was the first survey on the prevalence of visual disability and blindness in a well-defined population that had been followed for a prolonged period of time. This study took about two years to complete and coincided with NEI's first clinical trial.²³²

NEI and Randomized Clinical Trials

The NEI staff, under Dr. Kupfer's leadership, decided that it was important to fund clinical trials as well as fundamental, basic research, which previously had been the mainstay of NIH. NEI's commitment to fund clinical trials caused concern among many of its grantees who were engaged in both fundamental and clinical research in the laboratory. Some were not yet ready to embrace clinical trials as cutting edge science. "Fundamental" or "basic" research involves questions concerning basic biological and anatomical mechanisms. Located at one end of the research spectrum, fundamental research seeks to understand the mechanisms functioning in normal cells in order to identify what has gone wrong in diseased cells. Since this research is conducted in biological systems, it eventually plays an important role in the context of human health and disease, but that is not the immediate aim of the research. These researchers are concerned with mechanisms, and in ophthalmology ask such questions

as how the cornea maintains its clarity by existing in a state of deturgescence; what the metabolic activities and enzyme pathways are that maintain a normal lens clarity when the normal lens fibers are eventually devoid of the usual organelles; or what the metabolic interaction of the rods and cones of the retina is with the single layer of retinal pigment epithelium. Epidemiology and clinical trials are located at the other end of the research spectrum. They use knowledge about mechanisms (usually gained through fundamental research) to answer questions about the prevention and treatment of specific diseases.

In sponsoring clinical trials, some in the vision community felt that NEI was spuriously taking financial resources away from laboratory and clinical research. Yet, the important decision to fund RCTs was not made arbitrarily. NEI staff examined the entire spectrum of laboratory and clinical research for which the institute was responsible before deciding how to allocate the institute's limited resources. The institute's priorities were to concentrate on those areas in which health needs were the greatest and where there were the most opportunities for success in diagnosis and treatment. To be sure, the NEI managerial staff was sensitive to the concerns of the laboratory scientists in making such decisions. After all, the bench scientists comprised a major portion of the institute's constituency and provided a constant stream of knowledge about the eye and visual system, which was crucial to NEI's mission of bringing about improved diagnosis and treatment.

The American public and Congress were also part of NEI's constituency. They expected that the investment of large sums of money would yield major advances in the diagnosis and treatment of potentially blinding diseases of the eye and visual system. The NEI leadership believed that this could best be accomplished by having a strong clinical trials program. This would provide maximum opportunity to translate the advances in the laboratory to patient care.

Dr. Kupfer enlisted the expertise of all the top NEI managers in his quest to make clinical trials a major focus of the developing institute. The planning officer ensured that clinical trials were discussed as part of priority development in program planning. The executive officer made sure that budgets were developed with an eye toward major investments in these trials. The associate director for extramural programs and his staff were charged with developing mechanisms and ways to include clinical trials in all NEI grants and contracts programs. Finally, the information officer, who was responsible for public relations, developed public information material on the trials for wide dissemination. This approach was quite different from other institutes. Nevertheless, it provided maximum opportunity to translate the advances in the laboratory to the care of the patient.

First Study: Diabetic Retinopathy

The discontent of many of the laboratory and clinical researchers was noticeable in 1970 as Fred Ederer, the chief of the Clinical Trials Section in the OBE, helped organize the Diabetic Retinopathy Study—the first RCT to be conducted by NEI. Many years later, Dr. Bernard Becker, a member of the first National Advisory Eye Council at that time, recounted some of the problems.* Becker recalled how he had not initially been convinced that focusing on RCTs was a good idea. Like the laboratory researchers, he had feared that they would cut into the resources needed by other vital programs. He had been concerned about the costs of the planned Diabetic Retinopathy Study; though looking at the study retrospectively, he believed that the focus on RCTs proved to be the right decision:

Well, Carl Kupfer is responsible for that. I would have to say that I did not think that this was the most important thing to do. My theory was that it was terribly, terribly expensive and that using funds for trials was displacing many ROIs However, we were very interested There was considerable interest in diabetic retinopathy and treatment with photocoagulation. We hit upon this diabetic retinopathy study. I was part of the original planning on that with John Harris, but I really worried all the time about how expensive it would be—and it was. Carl Kupfer pushed for [the study], and I must say that he was entirely right. I mean that it generated the most exciting findings and it got the Eye Institute tremendous recognition But Carl was right and he pushed against many of us who said “that’s too expensive and we won’t be able to support other research.” Carl thought this was important and in a sense he was lucky, it paid off.²³³

In 1970, it was decided that the OBE should organize a fixed sample randomized controlled clinical trial in a disease with a long response time to treatment. It was determined that the area for the first major trial would focus on diabetic retinopathy, a condition in which the retina (the “seeing” part of the eye) undergoes hemorrhage from its blood vessels, with eventual destruction of the retina. Since about the mid-twentieth century, diabetic patients had received better medical care as a result of new knowledge of how to regulate the blood-sugar level; as a result, such patients were living longer. However, the longer diabetic patients lived, their chances of developing complications such as diabetic retinopathy increased significantly. Consequently, this disease of the retinal blood vessels had become one of the major causes of blindness and visual disability. In 1950, assessment of patients with the proliferative form (involving new retinal blood vessel formation and known as proliferative diabetic retinopathy, or PDR) indicated that about 50 percent of such patients would have serious visual disability in five years.²³⁴ This prediction was borne out. By the

early 1970s, PDR had become one of the leading causes—along with cataract, glaucoma, and macular degeneration—of new adult blindness in the United States. It was estimated that in America, 3,000 diabetics per year become blind (visual acuity 20/200 or less), with diabetic retinopathy as the sole cause or major component of blindness. In 1959, a procedure for the treatment of proliferative diabetic retinopathy called photocoagulation was introduced. Photocoagulation employed laser light with high heat and a very fine focus to either scatter hundreds of small burns throughout the peripheral retina, or occlude abnormal blood vessels that were bleeding and decreasing vision. The beneficial effect of the scatter technique appeared to be related to reducing the total amount of peripheral retinal tissue though the mechanism remains unclear. Occluding abnormal blood vessels near the macula (the site of best vision) prevents these vessels from leaking or bleeding, which if uncontrolled, causes destruction of adjacent macular tissue.

Although photocoagulation had quickly gained widespread use by the ophthalmic community, opinions were divided as to whether photocoagulation helped prevent severe visual loss from PDR. Some clinicians used photocoagulation routinely in patients with PDR and claimed good results, while some outstanding leaders in ophthalmology refused to allow photocoagulation to be used in their clinics, having observed serious complications from the procedure.²³⁵ Adequate evidence was lacking on the efficacy of the procedure—despite its widespread use on thousands of patients—because there had not been any rigorous studies following the basic principles of randomized controlled clinical trials and involving adequate numbers of patients. Out of a total of five small, controlled but non-randomized studies, two had shown favorable results; two had shown no benefit; and one had been noncommittal.²³⁶ While many treated patients showed improvement, other patients' conditions had not improved, or had actually worsened after treatment. It was thought that part of the problem in evaluating any treatment for PDR was that spontaneous remission could occur. Therefore, it was not clear whether improvement after treatment was actually related to the procedure or coincided with a spontaneous remission. With the increased prevalence of serious visual disability in patients with PDR, and the uncertainty of whether photocoagulation was beneficial or detrimental to reducing serious visual disability, NEI believed some action was essential.

In a recent interview, Dr. Rick Ferris recalled these concerns, describing how some clinicians accepted the value of a trial, while others did not:

[Some clinicians] felt very strongly that if treatment was effective, it would be best to demonstrate it by a carefully done clinical trial. I think the fact that Ed Norton, Arnall Patz, and some of the truly big names in retina that were advocating the study, even at a time when other people were saying that it was impossible to do a study on diabetic retinopathy because it was such a diverse disease, gave

the study the impetus necessary to make it successful. Critics were so focused on the severity and diversity of the disease that they thought it meant a trial was impossible. I think that actually showed the lack of understanding of the power of a randomized trial. The diversity across the two groups wasn't necessarily a bad thing, as it could be controlled for within the trial.²³⁷

NEI began planning the trial in 1971, and what emerged was a randomized, masked, controlled clinical trial called the Diabetic Retinopathy Study, which was designed to determine whether photocoagulation of the peripheral retina would slow down or prevent severe visual loss from proliferative diabetic retinopathy. As head of the Section on Clinical Trials of OBE, it fell to Dr. Ederer to help organize the DRS, along with Mathew Davis, M.D., who chaired the study, and Genell L. Knatterud, Ph.D., who directed the study's coordinating center. With his years of experience in biostatistics and clinical trials gained at the NCI and NHLBI, Ederer was well prepared to help get the study underway.

The DRS was the largest study undertaken to evaluate a new treatment for an eye disease since the 1950s cooperative study of the role of oxygen in retrolental fibroplasia. This RCT recruited and followed more than 1,700 patients with diabetic retinopathy at 15 medical centers for a five-year period; staff took retinal photographs every four months for documentation of the progress of the retinopathy. The photos were read in a masked manner at the Fundus (Retina) Photograph Reading Center in Madison, Wisconsin, according to a detailed protocol. A coordinating center monitored the progress, maintained ongoing quality control, and collected and analyzed the data for this multicenter study.

The DRS set up two components that had not been used much at NIH: a Data and Safety Monitoring Committee (DSMC) and a Policy Advisory Group (PAG). The DSMC, chaired by statistician Dr. Jerry Cornfield, was responsible for determining whether the study should continue, in the absence of harmful effects of treatment; be stopped when a statistically significant treatment was determined; or required a protocol change. The use of a DSMC was still a relatively new practice in clinical trials at this time. Following the example of the Heart Institute, NEI formed a PAG to monitor the clinical trial and ensure a rigorous design. The DRS set a useful precedent, illustrating how the data monitoring and policy oversight groups should and should not function.²³⁸

When the DRS began, it was widely publicized. Mailings were sent to practitioners specializing in ophthalmology and endocrinologists specializing in diabetes. In the design

of the trial and the preparation of a procedures manual, the following considerations were stressed:

1. The number of patients in the study had to be large enough so that the results had statistical validity.
2. A randomized concurrent control group had to be established. The DRS study created the ideal situation because the patient served as his own control since one eye was treated and the other eye was not.
3. Investigator bias was to be avoided by having the assessment of the results of treatment made in a masked evaluation; that is, those who evaluated the results of the treatment at the Fundus Photograph Reading Center were not the same persons who gave the treatment and did not know which eye received treatment.
4. All the procedures were highly standardized so that every investigator in the study followed exactly the same procedures of diagnosis, treatment technique, and assessment of the results so that no variables could be introduced to invalidate the study.
5. There would be competent biostatisticians and clinical researchers (those representing the DSMC) analyzing the results of the study at fixed intervals during the ongoing recruitment and treatment phase so that it could be determined as early as possible whether the study would be producing important information.
6. Major ethical considerations guided the design of the study. Photocoagulation was given to only one eye of each patient. By treating only one eye, each patient was to have the best chance of retaining vision in at least one eye. If it was found that photocoagulation was of no value, or even harmful, only one of the patient's eyes would have been subjected to treatment. If, on the other hand, treatment helped to preserve vision, each patient would have had the benefit of treatment in one eye.

Of course, this was NEI's first full-scale clinical trial, and there were bumps along the way. Dr. Ferris remembers that as the trial evolved most of the problems were related not so much to outcome but to the details of process—to the best ways of *doing* the study, such as determining the methods for measuring vision acuity in a research context and how to clearly define blindness itself. Ferris' site visits to the participating clinics offered a means of assessing the practicality of protocol methods and how well they were carried out. While some leading ophthalmologists did not want to participate in the study, others wanted to understand trials, this "new" type of clinical research. The University of Wisconsin's Matthew "Dinny" Davis, M.D., acted as DSMC chairman and was crucial to organizing and implementing the DRS and related trials. Like Carl Kupfer, Davis had a boundless interest in properly conducted randomized, controlled trials.²³⁹

The study went astonishingly well, and within two years began to show data indication that photocoagulation was highly beneficial. By September 30, 1975, after an average

of only 15 months of follow-up (range 0 to 38 months), a highly statistically significant finding was reported by the DSMC. The DSMC had evaluated several of the groups for the principal end point of the trial and considered the best end point to be visual acuity less than 5/200 at two or more consecutively completed follow-up visits four months apart. Using this end point, the treated eye had a 60 percent decrease in severe visual loss as compared to the untreated eye (Figure 1). However, there was a schism between the clinicians and biostatisticians over when to publish these findings. Some were anxious to publish these impressive results because a beneficial effect of this magnitude was rarely seen in clinical trials, while others thought it was too soon. However, some of the clinicians on the PAG, which was charged with scientific oversight of the study, “wanted to be sure that they had the right answer” and thought “that it was critically important to have an absolutely unequivocal result.” After spending so much money, they “could not afford to have the community saying” that the trial “had not proven the treatment benefit to everybody’s satisfaction.”²⁴⁰

It was up to the director to step up to the plate, assert sound leadership, and make a decision. There were several considerations. The protocol projected a follow-up totaling five years. By September 30, 1975, only 350 of the 1,732 enrolled patients had been followed for at least two years, and only 11 patients had been followed for three years. There was also the possibility that the treatment could produce a late-developing adverse effect.

To complicate matters further, a study just published in February 1975 reported findings of severe late complications of retinal photocoagulation.²⁴¹ Some PAG members were concerned that these complications could result in new cases of blindness, possibly reversing the initial beneficial effect. They argued for continuation of the study to its planned conclusion to allow evaluation of this possibility. The discussion was quite heated. Dr. Kupfer recounts how he reconciled the mixed messages he got from the DSMC and PAG:

I felt somewhat uncomfortable in rushing to print findings that were based on only two years of study. There were several issues to consider: What did the future hold? Would this impressive beneficial effect of treatment persist? Would the untreated eyes begin to have spontaneous remission, enduring for various lengths of time? Some members of both the DSMC and the PAG wanted a rapid decision and were clamoring for rapid publication; they thought that here the director was holding up critical information for thousands of diabetics with PDR. To obtain an independent opinion, Fred Ederer and I traveled to New York and visited Dr. Tom Chalmers, formerly the director of the NIH Clinical Center and then the dean of the Mount Sinai School of Medicine. Tom was an outstanding expert on clinical trials. After reviewing the protocols and data, he drew the conclusion that our clinical trial showed the extraordinary benefit of photocoagulation.

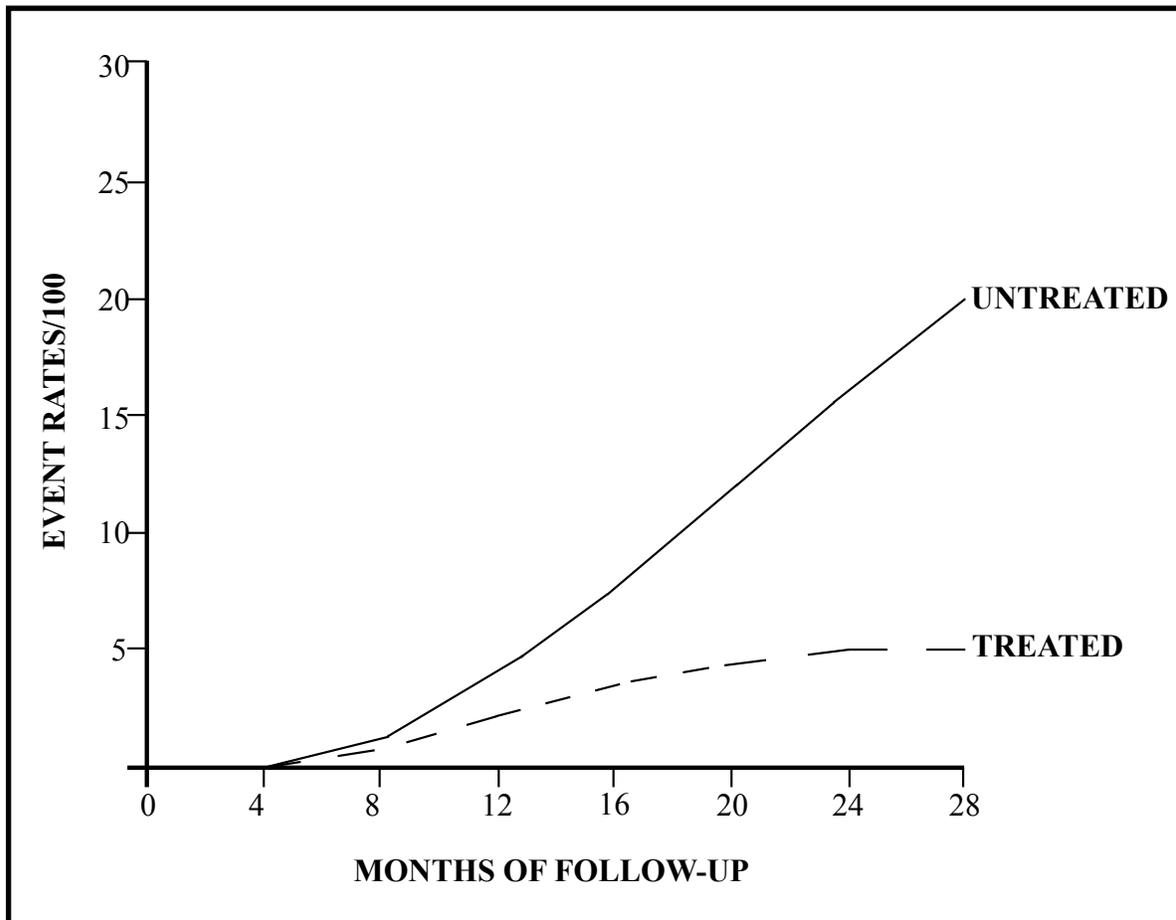
Fred advised me that I could not delay waiting another four months for the next examination of the patients in the two groups yet to be completed before making a decision. But suppose there was a reversal of the beneficial treatment in the treated eyes? In an effort to better understand what should be done, I suggested a hypothetical situation where, first, there was a late reversal of the beneficial treatment effect in treated eyes and second, suppose a significant improvement in untreated eyes developed after two years of follow-up as part of the natural history of the disease due to spontaneous remission. I asked Fred to analyze this worst-case scenario and determine what would be the outcome. Fred did not argue with me, realizing that I needed this information for my own peace of mind. He proceeded to develop quantitative estimates of the consequences of a postulated late harmful effect, taking into account estimates of the life expectancy of these patients and the negligible losses to follow-up. According to an NEI report, Ederer's calculations led to the conclusion that the substantial benefits gained in the first two years after treatment outweighed any delayed harmful effects that might occur over the next 20 years, even if the latter were severe.

So that I was absolutely certain about the significance of these findings, I asked Fred about the level of conviction. He replied, "There is no doubt whatsoever." Whereby Julian Morris, NEI's information officer and planning officer, cited a short phrase from Gilbert and Sullivan's *The Gondoliers*:

**Of that there is no manner of doubt-
No probable, possible, shadow of doubt-
No possible doubt whatever.**

This analysis convinced me that the early results had proven that photocoagulation was a scientifically valid treatment for PDR. I believed that this clinical trial would be recognized as one of the most successful clinical trials in the history of medicine for several reasons: it dealt with an important health question; the beneficial effect of treatment was enormous; the results were apparent after only two years of follow-up (probably due to the extra-large sample size); and sub-group analysis indicated which risk factors would respond most favorably to photocoagulation. Four-year follow-up data confirmed that photocoagulation treatment reduced the risk of severe visual loss by more than 50 percent.²⁴²

**(DRS Research Group.) Cumulative Event Rates of Visual Acuity
Less Than 5/200 at Two or More Visits for All Patients**



In the end, the study was very successful and well received. There was “general acceptance of the results,” according to Dr. Ferris, and the release of the results seemed to be “the fastest way to a consensus” about photocoagulation as a treatment.²⁴³

Dr. Kupfer strongly believed that it was NEI’s responsibility to publicly disseminate the study results. Julian Morris, head of NEI’s information office, had been intimately involved in the management of the DRS trial, especially at critical decision points, and he determined how, when, and where the results would be made public. The study personnel who conducted the RCT and the NEI staff shared the responsibility for disseminating information. Other top NEI managers were also part of these discussions. This approach of involving the upper-level managers in clinical trials would be expanded upon at NEI in later years.

Taking responsibility for dissemination of scientific findings was an important innovation. At the time of the DRS, many researchers and sponsoring institutions viewed their responsibility toward dissemination as simply to present scientific publications and presentations. Dr. Ferris explains that since the time of the DRS, “we have learned that

public dissemination of study results is a major responsibility.” Moreover, “It was important that we switched from just talking to clinicians to also talking to the public. If patients know about effective treatments, then they will talk to their doctors about them. We learned that it was important to let the public know the study results, and certainly now that is a major aspect of any major clinical trial.”²⁴⁴

Dr. Kupfer points to “a delightful and unexpected” side benefit arising from the trial and affecting the clinical community: “Those residents and fellows in the 15 clinical centers who had hands-on experience with this clinical trial became our most enthusiastic supporters for future clinical trials and tried to be involved in as many as possible.” With the support of this small, highly motivated group of experienced clinicians, the number of clinical trial research grant applications in several different diseases increased and several were approved for support by NEI.²⁴⁵

Two related NEI clinical trials followed the DRS trial: the Diabetic Retinopathy Vitrectomy Study (1976-1983), and the Early Treatment Diabetic Retinopathy Study (1979-1985). The OBE later estimated that if the 1985 recommendations based on these three clinical trials were followed by all diabetic patients with advanced diabetic retinopathy, they would have a 90 percent chance of maintaining vision after treatment, as compared to about 50 percent of the patients in 1950.²⁴⁶ This clearly put into perspective the power and effectiveness in providing a “truthful answer to a relevant medical issue,” Dr. Pocock’s dictum.²⁴⁷

NEI disseminated knowledge about clinical trials procedures and helped its research community gain familiarity about the methodologies involved. Dr. Kupfer was invited to speak at a meeting of the Association of University Professors of Ophthalmology (AUPO) slated for November 1973, in Washington, D.C. Dr. Kupfer suggested that instead of giving the talk himself, the staff of NEI’s Office of Biometry and Epidemiology present a workshop introducing and discussing the concept of RCTs and randomization. At the meeting, there was resistance by some of the AUPO clinicians who had completed previous studies without using randomization. It became apparent to Dr. Kupfer that teaching sessions would be helpful in conveying both the rationale and the mechanics of doing RCTs. Accordingly, the OBE taught a course lasting a few hours at the annual meetings of the American Academy of Ophthalmology. The course was later expanded to two-and-a-half days, with two additional outside researchers—familiar with clinical trials and statisticians—added to the OBE faculty. The longer course was offered just before the annual meetings of the Association for Research in Vision and Ophthalmology (ARVO). Each year about 60 clinicians with a few laboratory researchers and clinic coordinators of ongoing RCTs were enrolled. These participants took the first steps in learning about epidemiologic methodology and the conduct of clinical trials. The course, titled “Clinical Vision Research: Epidemiologic and Biostatistical Approaches,” was presented annually from 1980 to 1992 on 13 different occasions. Overall,

more than 700 ophthalmologists, optometrists, laboratory researchers, and clinic coordinators attended this course. This strategy of offering a course may never have convinced the older generation, but it appeared successful in training the new generation. Gradually, increasing numbers of clinicians became committed to RCTs and began to develop protocols on their own. Often, experts in RCTs provided assistance. Some of the trialists joined the teams planning protocols for ophthalmic RCTs, and they could play an important role in designing a trial. During these 13 years, the NEI supported several multicenter trials, and participants gained hands-on experience.

Clinical Trials Innovations

DSMC

In the mid 1970s, the numbers of clinical trials supported by NIH increased and received greater attention. Donald S. Fredrickson, M.D., NIH director from 1975 through 1981, requested that a special NIH clinical trials committee be formed from various NIH components. This committee, which included Fred Ederer from NEI's Office of Biometry and Epidemiology, was charged with the task of developing a basic set of guidelines that would apply to all NIH-supported clinical trials, especially those supported by a grant rather than a contract or the grant-contract combination. The new guidelines proposed by the committee included a requirement for a DSMC to be incorporated into the clinical trial organization at the grantee institution. Its role would be to examine the accumulating study data periodically (for instance, yearly or semiannually) and decide whether the study should be continued as planned, continued with protocol changes, or discontinued. With this arrangement, the DSMC would have responsibility for quality control and the authority to notify the appropriate NIH institute of any quality lapses.

Cooperative Agreements

To facilitate clinical trial proposals submitted by the community, NEI introduced the Cooperative Agreement, an innovation that allowed RCTs to be funded by a line item in the budget. Although this support was technically neither a grant nor a contract, it had elements of each: it had the grant aspect of an investigator receiving the funds approved by NEI on the advice of the study section review, and it had the contract aspect in that an NEI staff member participated in all the decisions regarding the conduct of the trial to help maintain the highest standards of RCT methodology.

As a grant mechanism, the Cooperative Agreement facilitated a novel administrative relationship between the grantee institutions and NEI. It provided support for the conduct of the entire clinical trial—as long as the grantee adhered to the protocol. It also allowed

NEI staff to closely monitor progress and the assessment of data analysis by the coordinating center. This arrangement differed from the traditional arrangement because in the past, the grantee institution had complete autonomy in conducting the research for the duration of the grant period, and it supplied the NIH grantor organization with a short progress report only once a year.

The Cooperative Agreement ensured NEI's full participation in all aspects of the clinical trial, with the goal of ensuring quality research. The arrangement was mutually beneficial. For instance, if the investigator in charge of the clinical trial found additional funds were needed, the NEI staffer assigned to this trial would convey the request to the NEI director and provide a knowledgeable assessment of whether additional funds were justified. Dr. Kupfer and the NEI clinical trials staff would discuss the situation and make a decision whether or not to supply additional financial help. Aware of the escalating costs of doing clinical research, Kupfer was usually sympathetic to such requests. It was not so easy to continue funding, however, if the investigator proposed a change to the trial protocol, for then the DSMC as well as NEI had to give approval. The NEI director, the clinical trials staff, and the DSMC had the responsibility as well as complete authority to adjudicate any major changes in the conduct of the trial.

Staffing a New Clinical Research Branch

The number of RCTs submitted by the extramural community to NEI for review and funding gradually increased during the 1970s and 1980s. NEI increased its clinical trials budget considerably over the period of 1985 to 1989; Congress added \$12.5 million in 1985 and earmarked additional funds for trials in 1987. By 1990, NEI was using the cooperative clinical research grant category as its main funding mechanism for clinical trials, which had increased to almost \$20 million in Fiscal Year 1990 from zero in 1985.²⁴⁸ To keep apace with funding, it was necessary to have a reasonably sized unit of individuals knowledgeable in the management, conduct, and quality assessment of the results of clinical trials as data became available. In 1987, NEI created the Collaborative Clinical Vision Research Branch to manage extramural vision research programs, especially clinical trials supported through cooperative agreement grants. Dr. Kupfer met with this group in their office once a month, bringing with him NEI's top staff, including the deputy director, the executive officer, and the information officer. All of the new branch staff had expertise in both clinical trials and epidemiology. They monitored all ongoing trials and handled concerns such as poor adherence to protocol.

By the 1990s, NEI was sponsoring more than a dozen trials simultaneously and various problems emerged, not surprisingly. Dr. Kupfer often called upon the OBE staff to provide advice concerning the conduct of a particular clinical trial. This was particularly im-

portant in view of the tremendous public health implications of clinical trial results. No other vision research activity had such an immediate and major impact on the treatment of disease of the visual system. Therefore, NEI had to “get it right” before the results were released to the public.

Defining a Clinical Trials Methodology

In 1978 Larry Rand and Carl Kupfer published an article describing the rationale and methodology of a well-conducted controlled scientific clinical trial. The piece discussed how a multicenter RCT could be successfully carried out.²⁴⁹ Although this publication dealt with a specific trial concerning diabetic retinopathy, the methodology and design had clear applications to RCTs more broadly.

First of all, Rand and Kupfer maintained, the trial must follow the principles of the scientific method from start to finish. To establish that it was possible to improve the outcome of a disease by a specific therapy such as drug administration, surgical intervention, nutritional changes, or radiation, special attention to the design of the study was required and should be described in a study protocol. A design should also fulfill ethical and organizational as well as scientific requirements so that a trial could be conducted efficiently and according to plan. Successful protocol design depended on the skill of the principal investigator in charge of the daily conduct of the trial, as well as each investigator at the other clinics involved in the study.

The article also described what Rand and Kupfer considered the essential characteristics of a well-conducted, controlled, randomized multicenter clinical trial in order to ensure a reliable outcome free from bias. The protocol must:

1. Describe the purpose of the trial and what hypotheses are being tested.
2. Describe the trial design and provide the details in a written protocol.
3. Calculate the number of patients required for the treated as well as nontreated groups or the standard treatment (if one exists) versus the new treatment. The sample size must be large enough to ensure statistically meaningful data.
4. Describe how the control group will be chosen and the method of randomization.
5. Set up a coordinating center to organize the collection and analysis of the data and to conduct site visits of the participating clinics. The center must have a staff, including statisticians, coordinators, and administrators, who are thoroughly familiar with the protocol and able to analyze the data using appropriate statistics and tests of hypothesis, which will lead to conclusions that are substantiated by the data analysis and be accepted for publication by a peer-reviewed journal.
6. Establish a group of expert physicians, statisticians, and ethicists who are not directly involved in the clinical trial and who assess the progress of the trial every 12 months,

or more frequently if indicated. (At NEI, this group was the DSMC.) This group had the responsibility of allowing a change in protocol, stopping part or all the study if harmful effects of the treatment become apparent, or stopping the study if the new treatment was proven to be statistically and clinically superior to the standard treatment or no treatment. In this last case, it was essential to assess the clinical implication of the statistical conclusion. If the treatment was shown to be statistically better, but clinically the slight improvement was either not meaningful to the patient and the course of the disease or was accompanied by an increased morbidity associated with the treatment, then a clear assessment needed to be presented, taking into account all aspects of the treatment effect. If the clinical trial was financially supported by an institute, then it was highly desirable to have an institute representative with clinical-trial experience be a member of the DSMC. This presupposes that the institute has one or more such staff persons, as well as a strong biometry and clinical-trial unit that can be called upon to consult on ongoing clinical trials.

Costs and Benefits

The number of RCTs submitted by the extramural community to NEI for review and funding gradually increased. Between 1976—when the two-year DRS results were published—and 2000, NEI supported a total of 60 trials, some still ongoing, others completed. They dealt with all aspects of the visual system and eye diseases, including studies on retinopathy of prematurity, age-related macular degeneration and related retinal diseases, glaucoma, visual processing, strabismus and amblyopia, ocular infections, and other ocular conditions such as corneal transplantation, ocular melanoma, and myopia. Major changes in treatment often resulted from these trials.

In Fiscal Year 2000, NEI spent about \$36 million for clinical trials support. In comparison, NEI funded approximately 1,316 aid research grants, including research project grants (RPGs) and career, cooperative clinical research, and other awards for a total of approximately \$374 million, including indirect costs. The total Fiscal Year 2000 NEI budget was more than \$450 million. The success rate was 42 percent, which represents the percentage of total new RPG applications funded, and was the second-highest success rate for paying approved grants among all the institutes at NIH. Because of NEI's commitment to giving grants to individual scientists (known as investigator-initiated research grants) rather than to large consortia, NEI could and did maintain one of the highest success rates (funding 42 percent of approved grants), while at the same time investing heavily in clinical trials.

NEI's commitment to clinical trials was exemplified in its budget. NEI had the largest percentage—namely 10 percent—of its total research budget committed to clinical trials. This was second only to the National Cancer Institute, which in Fiscal Year 1986 had 14.5 percent of its total budget devoted to RCTs.²⁵⁰

In the end, the benefits produced by the trials are simply not quantifiable. The returns went well beyond proving the efficaciousness of a specific treatment to supplying all sorts of information on the interaction between bodily mechanisms and disease. Before clinical trials were accepted, skeptics—and probably many converts as well—did not really understand at that time how much could be learned about disease pathology. Rick Ferris summarized this aspect succinctly:

I think that one of the big lessons in ophthalmology that was learned was how valuable the natural history information is to understanding a disease process. So, when we talk about justifying the cost of the trials, we have to keep in mind we learn much more from them than whether treatment A is better than treatment B.²⁵¹

In a recent interview, Steve Ryan, M.D., professor of ophthalmology at the Doheny Eye Institute (USC School of Medicine), also emphasized the importance of NEI's clinical trials: "From my perspective, as long as vision research was in the NINDB, clinical trials in ophthalmology never got the attention they deserved." The National Eye Institute, he continued, "truly changed how we in the retina community thought about diagnosis and treatment, with your emphasis on clinical trials and, for example, the great success of the diabetic retinopathy study. These NEI trials made us read the literature far more critically. Practice patterns changed."²⁵²

* * *

In a presentation to the New York Academy of Medicine in 1968, Dr. Donald S. Fredrickson discussed clinical trials in a lecture titled, "The Field Trial: Some Thoughts on the Indispensable Ordeal." He made several astute observations:

Field trials are indispensable. They will continue to be an ordeal. They lack glamour, they strain our resources and patience, and they protract the moment of truth to excruciating limits. Still, they are among the most challenging tests of our skills. I have no doubt that when the problem is well chosen, the study is appropriately designed, and that when all the populations concerned are made aware of the route and the goal, the reward can be commensurate with the effort. If, in major medical dilemmas, the alternative is to pay the cost of perpetual uncertainty, have we really any choice?²⁵³

His conclusions were quite prescient in light of NEI's own success with clinical trials over the next 35-plus years.

Problems with Trials

By Dr. Carl Kupfer

As might be expected during the course of 70 clinical trials over a 30-year period, there were several occasions when the integrity of the process was challenged on political, managerial, or quasi-scientific grounds. Below is a sampling of those I experienced during my tenure as NEI director.

When Congress meets the Executive Branch – Prospective Evaluation of Radial Keratotomy (PERK) Study

There are about 11 million Americans who have myopia (are near-sighted) that can be corrected with glasses or contact lenses. An early surgical procedure designed to correct the problem of myopia involved incisions made in the cornea to cause it to flatten and thus reduce the myopia. The procedure was introduced in Japan in the 1940s and 1950s by Drs. T. Sato and K. Akiyama. They made incisions in both the anterior and posterior surface of the cornea; the posterior incisions, primarily, caused damage to the cornea. The procedure was later adapted in the Soviet Union by Drs. Svyatoslav N. Fyodorov and Valery V. Durnev, who made between 8 and 16 radial incisions to the anterior corneal surface, sparing a small central area. This surgical procedure became known as radial keratotomy or RK. Introduced in the United States in 1978, it slowly gained in popularity. At first only a few ophthalmic surgeons performed the procedure, but as interest in RK increased more surgeons were being asked by their myopic patients if they could do the operation. Dr. Fyodorov came to the United States, and during his press conference at the Soviet Embassy announced that the time had come for the near-sighted to throw away their glasses. As public and professional interest expanded so, too, did concern over the lack of any scientific assessment of the long-term safety and efficacy of RK. In 1980, a group of ophthalmic surgeons proposed to NEI a multicenter clinical trial to evaluate the potential benefits and risks of RK. The group was encouraged to develop such a clinical trial—later to be known as the Prospective Evaluation of Radial Keratotomy or (PERK) Study.

Not too long afterward, I received a telephone request from a congressman from North Carolina: Would I be so kind as to come and meet with him to discuss NEI and research priorities the following day? Of course I agreed, and at the appointed time I walked into the congressman's office, expecting to meet with him alone. To my surprise, I was introduced to two ophthalmic surgeons active in RK surgery who were well known by reputation. The meeting proceeded to unfold in a most curious way. The congress-

man proudly related to me that he had undergone RK and now had better than 20/20 vision without glasses or contact lenses. He said that these two ophthalmic surgeons, who had apprised him of NEI's plans to mount a clinical trial to determine the safety and efficacy of RK, had performed several hundred cases and concluded that RK was both safe and effective. They could see no reason for NEI to repeat their findings. The congressman was convinced that the cost to conduct such a clinical trial—\$2 to \$3 million over a five-year period—would be a waste of taxpayer's money. The purpose of the meeting was to persuade me to cancel any plans to support a clinical trial of RK.

The two surgeons, with the congressman's backing, then proposed a conference where patients who had been operated upon would testify about their experience, and other surgeons using the RK procedure could present the knowledge they had gained. Of course, I knew that this would be, in government parlance, the traditional "dog and pony show." I was prepared then and there to say that since there was no scientific assessment of this surgical procedure, NEI would proceed in the usual manner to fund a well-designed clinical trial. This study would provide the American taxpayers with the information needed to make an informed decision about the surgery. But Congress rightfully demands respect, and when a member suggests doing something, it is wise to seek advice. All NEI top management participated in developing strategy and science options to deal with this threat. Dr. Dan Seigel weighed in on clinical evaluation, Ed McManus considered political strategy, Ron Geller, director of Extramural Programs, considered grant options, and Julian Morris reviewed public relations options. Ultimately, NEI hosted a "conference" presenting half-a-dozen ophthalmic surgeons practicing RK and some of their RK patients. Meeting in Wilson Hall on the third floor of NIH's Building 1, the surgeons provided firsthand testimony about the safety and success of RK. The patients bore witness to the improvement to their eyesight by reading a visual acuity chart. Some performed well without any optical correction for myopia. What was memorable, however, was when a weeping young lady who had difficulty reading the easiest (20/20) line of letters was admonished by her surgeon to try harder!

Having satisfied the congressman's request for NEI to hear from the surgeons and patients themselves, I enlisted the help of probably the most outstanding ophthalmologist in North Carolina at that time, Dr. Samuel MacPherson, the director of the MacPherson Eye Clinic. He met with the Carolina congressman, and in a most diplomatic manner, convinced him to

allow the clinical trial to proceed if it was of high caliber. MacPherson reasoned that the study might very well confirm the congressman's contention that RK was safe and effective, adding luster to the congressman's record. He could highlight his efforts on behalf of not only his constituents, but for all North Carolina citizens. The congressman was neutralized, but the resistance of the RK surgeons remained.

We gained another supporter. The National Advisory Eye Council (NAEC) learned that NEI was considering supporting a clinical trial of RK and voted unanimously to alert the chairperson of the NIH Visual Sciences, a study section of the NIH Division of Research Grants. In the meeting minutes the NAEC stated that RK was still an experimental procedure and its safety and efficacy should be determined in the usual way (i.e., a clinical trial). This position was restated at the NAEC meeting of September 21, 1981.²⁵⁴

In the meantime, the multicenter clinical trial proposal went through the usual peer review process, received a high priority, and was approved by the NAEC. A Cooperative Agreement and funding was put in place, and the study slated to begin in April 1981. Much to our surprise, several ophthalmic surgeons who were already performing the RK procedure filed a lawsuit against me, NEI's other senior staff, members of the NAEC, and the American Academy of Ophthalmology. Once known, the names of the surgeons participating in the trial were promptly added to the lawsuit. Interestingly, the plaintiffs objected to the word *experimental*, which appeared in the deliberations of the NAEC in 1979 and again in 1981.²⁵⁵ The plaintiffs wanted to substitute the word *investigational*. The NAEC refused, and the lawsuit continued. Government lawyers from the U.S. Department of Justice argued that government employees carrying out their duties as mandated in congressional legislation could not be sued. Ed McManus had known this before the trial was started and had talked with NIH lawyers. We felt we were on solid ground. Obviously, the NEI staff members were government employees, but so were the NAEC members—even though they only attended meetings a few days each year. The participating surgeons bore the full brunt of the lawsuit, with the legal and financial burden placed squarely on them. NEI realized that if this load was not relieved in some way, in the future, surgeons would avoid participating in clinical research. It was particularly important to help as the surgeons participating in the clinical trial had voluntarily agreed not to charge for the surgery on patients enrolled in the trial. Exercising a rarely used option, NEI contributed unexpended funds to the surgeons' legal defense; these

funds would have ordinarily been returned to the U.S. Treasury at the end of a fiscal year. This helped considerably, and it also established the precedent that NEI would protect participating physicians in clinical trials if the circumstances warranted.²⁵⁶

Although clinical trial data was generated by the one-year post-operative follow-ups, the goal was to find long-term information on safety and efficacy. Hence, PERK continued for 10 years. The results indicated that RK can reduce but not completely eliminate the need for spectacles or contact lenses for distance vision, that patients might gradually become far-sighted and need reading glasses after the age of 40, and that the operation was reasonably safe. As a post-script, the North Carolina congressman lost his reelection soon after the clinical trial began.

Were clinical trials supported by all ophthalmologists?

In November 1986, the Collaborative Ocular Melanoma Study (COMS) began in 43 clinics throughout the United States and Canada. For almost 100 years, the standard treatment for choroidal melanoma (melanoma in the back of the eye) was removal of the eye (enucleation). More recently, there had been increased interest in treating the tumor with radiation therapy, possibly saving the eye and perhaps some vision. However, the survival rate of patients following treatment with radiation as compared to enucleation of the eye containing the tumor was unknown. There was mounting enthusiasm in the ophthalmologic community to have a randomized controlled clinical trial follow a large number of choroidal melanoma patients for several years, comparing enucleation and radiation to determine relative success in increasing survival.

There were only about 1,800 new cases each year of choroidal melanoma in the United States and Canada. Ambitiously, the plan was to recruit about 900 patients each year and reach the estimated sample size of 2,300 patients, randomized, in about three years. An attempt was made to recruit every clinic, especially those in large population centers, which were equipped to participate in such a study. Only a few ophthalmic surgeons specialized in the treatment of choroidal melanoma with radiation, and they saw as many as 50 percent or more of all such patients. Unfortunately, they believed that they already had the answer to the question of the efficacy of radiation versus enucleation: radiation not only preserved the eye and hence sight, but radiation was as good or perhaps even better than enucleation since there was some

suggestion in the literature that the surgical procedure itself might inadvertently spread tumor cells from the eye to other parts of the body.²⁵⁷ Although this small group of surgeons collectively had experience with large numbers of patients, analysis of their data was retrospective and nonrandomized. Despite this criticism, they considered the proposed clinical trial to be unnecessary. In an effort to encourage the surgeons who specialized in the radiation treatment of choroidal melanoma to participate in the trial, Drs. Stuart Fine and Bradley Straatsma led a number of information sessions at the American Academy of Ophthalmology and ARVO meetings in 1983 and 1984. It became crystal clear that none of them wanted to participate. In a last effort, NEI convened a meeting in December 1984, inviting about 60 potential participants in the melanoma clinical trial, including the aforementioned ocular surgeons. They attended, but walked out during the middle of the meeting to demonstrate their opposition. There was a great deal of anger in the room after this staged walkout. One of the ophthalmologists who was planning on participating actively in the upcoming trial stood up and charged them with bad behavior, declaring “they are not your patients, they are our patients and we refer them to you for the best possible care, and we believe that the best care is enrolling those patients in a randomized trial.” In September 1986, the annual meeting of the Retina Society was held in Colorado Springs. Dr. Stuart Fine gave a 10-minute presentation of the COMS, followed by a 45-minute open discussion with the audience. Drs. Fine and Straatsma adjourned to the lobby where they were approached by one of the melanoma specialists who opined that the COMS was unethical. Dr. Straatsma responded quickly and forcefully. Unconvinced, a handful of surgeons mounted a boycott of the trial by not referring patients.²⁵⁸

Without the cooperation of this small group of ophthalmologists and their referrals of patients to the study, it took 12 years of strenuous efforts at all of the participating clinics in the United States and Canada to recruit the necessary number of patients. Even then, the final number still fell short because the participating COMS surgeons could no longer sustain the effort of recruitment. The study then focused on follow-up.

The results of the COMS were published in 2001 (15 years after the commencement of the trial) and clearly demonstrated that the five-year survival rates for radiation and enucleation were about the same, 82 percent. When compared to the immediate loss of vision with enucleation, those eyes treated with radiation lost vision gradually, with 63 percent having visual acuity of

20/200 or worse by three years after treatment. Some of these eyes became painful enough to warrant enucleation. Dr. Bradley Straatsma, professor and founding director of the Jules Stein Eye Institute at UCLA and a participating surgeon in the COMS, recently commented on the COMS:

I think the perseverance of the NEI in supporting the Collaborative Ocular Melanoma Study should clearly be put on the record. Without that, we would still be in doubt about whether it was important to treat the eye and have it remain in place or simply surgically remove the eye. And it took tremendous courage—first, for the investigators to carry out the project, and second for the NEI to support it to the point where we can now say conclusively that in the study period of 10 years following completion of treatment, there is no difference in the outcome following plaque therapy or enucleation of the eye for a medium-sized melanoma. This is an enormous accomplishment that could never have been done with any mechanism other than NEI support.²⁵⁹

In the end, it is important for the community of ophthalmologists to want to support randomized controlled clinical trials. If individual doctors do not want to participate actively, then the best direction for them to take is to remain quiet, skeptical, not interfere with the trial, wait until the study is completed, and encourage open discussion from all sides.

Collaboration between private industry and the federal government: The Sorbinil Retinopathy Trial

In the decades of the 1960s and 1970s, the enzyme aldose reductase (AR) was studied intensively in diabetic cataract and other diabetic complications in experimental animals. Of particular interest was the implication that the major pathology underlying diabetic retinopathy involved the selective loss of intramural pericyte (mural) cells lining the capillary vessels of the retina. The loss was thought to be related to the presence of the enzyme AR in the mural cells. This enzyme converted the high level of glucose that diffused readily into the mural cells. The glucose within the mural cell was then converted to sorbitol and fructose, sugar alcohols that were unable to diffuse out of the mural cells in diabetic animals. With the accumulation and entrapment of the sugar alcohols within the mural cells, water flowed into the cell, down along an osmotic gradient, and the cell burst and died. The mural cells were thought to control the flow of blood through the capillary bed, and with their loss the capillaries dilated and underwent proliferation of the remaining endothelial cells, which lined the capillaries and caused the formation of

capillary aneurisms. With an attempt to continue to provide oxygen and nutrients to the retina, new vessels sprouted from the remaining capillaries. However, these new capillaries did not have mural cells and tended to be quite friable so that they leaked blood and were prone to hemorrhage, causing the long-term occurrence of retinal detachment and destruction of the retina. These changes were well documented in animal experiments. In the animal models, these destructive changes to the retina were decreased through the inhibition of aldose reductase.²⁶⁰

A hypothesis generated from the animal studies was put forward suggesting an AR inhibitor (ARI) may prevent, delay, or stop the development or progression of diabetic retinopathy in diabetic patients. From NEI's experience with previous clinical trials involving diabetic patients, a quantitative measurement of the number of aneurisms had been developed by reading stereo-photographs of the retina and comparing the aneurism counts over time. All photographs were read in a masked fashion by the central Fundus Photograph Reading Center, according to a defined protocol. With the animal results in mind, Pfizer, Inc. developed an ARI called sorbinil, which was to be studied in a clinical trial jointly with NEI. The trial began recruitment in 1983, and was stopped briefly in 1986 by the FDA because of serious hypersensitivity reactions in several patients. Both NEI and Pfizer successfully petitioned the FDA, and treatment resumed using a titrated-dosage schedule that 497 patients completed over a 42-month period. With respect to the retina, the number of microaneurysms increased at a slightly slower rate in the sorbinil group than in the placebo group. The differences became statistically significant at 21 and 30 months. However, about 7 percent of the patients receiving sorbinil developed a hypersensitivity reaction in the first three months. It was decided that in view of the adverse hypersensitivity reactions, chronic administration of sorbinil over many years was not clinically feasible. We are still waiting for an ARI that is highly effective and does not cause any serious adverse effects. Additionally, the ability to transfer laboratory experience to the patient still remains an important goal.

The unique collaboration between private industry and the federal government was important, although laborious to work out. As in previous cases, all of NEI's top management was brought into the decision-making process on whether the trials should continue and how to proceed with this study. Jin Kinoshita discussed the basic science developed by the NEI, Dan Seigel outlined the clinical trial, Ed McManus filled in the management

picture and political nuances, and Ron Geller, the director of the Extramural Program, provided personnel support to the Data and Safety Monitoring Committee. Both NEI and Pfizer wanted complete control of the study, which in turn made the negotiations quite difficult. Finally, under the direction of McManus, a deal was struck that kept the scientific requirements that Seigel, Geller, and Kupfer thought absolutely necessary. NEI and Pfizer shared in the design, funding, and oversight of a multicenter randomized clinical trial. Pfizer provided the medication and funded 10 of the 11 participating clinics, including the Data Coordinating Center and the Fundus Photograph Reading Center. NEI funded the Data and Safety Monitoring Committee (which included a Pfizer representative) and its own participating intramural clinic. Both sponsoring parties were pleased with the cooperation and worked hard to overcome all obstacles. In a biennial report, the NIH director referred to the collaboration between NEI and Pfizer as the “first such partnership between an NIH component and a pharmaceutical company in conducting a clinical trial.” Mr. McManus received the highest honor award, the Distinguished Service Award from the Department of Health and Human Services for “outstanding management skills in negotiating the organizational, financial and policy aspects of an innovative collaborative multimillion dollar agreement with a major pharmaceutical company to test a new drug as a treatment for complications of diabetes.”²⁶¹ This award demonstrated that others farther up the chain of management in the government respected NEI’s innovation in management of NIH programs. Overall, this experience with industry served NEI well in preparing for subsequent collaborative trials.

If it’s new, is it better?

Non-arteritic ischemic optic neuropathy (NAION) is the most common cause of acute optic nerve disease in the elderly, causing severe and permanent visual loss. Through the early 1990s, there was no proven treatment for this condition, nor any way to prevent or reduce the possibility of involvement of the second eye. With this clinical backdrop, a new surgical procedure called optic nerve decompression surgery (ONDS) was introduced in the early 1990s, based upon the unproven assumption that NAION was caused by impaired blood flow to the optic nerve and that decompression surgery would restore vision by alleviating pressure surrounding the optic nerve. Within a short period of time, ONDS was on its way to becoming the standard of care. To their credit, a number of surgeons who performed this procedure sought NEI’s assistance in designing a randomized clinical trial to evaluate

the safety and efficacy of the operation. Twenty-four clinical centers recruited 420 patients. Within two years of the start of the Ischemic Optic Neuropathy Decompression Trial (IONDT), the Data and Safety Monitoring Committee recommended stopping further recruitment into the trial. NEI issued a clinic alert (to some 25,000 ophthalmologists and neurologists) reporting the findings that surgery was not as effective as careful follow-up in recovering some vision improvement and that surgery appeared to be harmful. It was recommended that ONDS not be used in cases of NAION. Whereas the rates of improvement for untreated eyes had previously been estimated to range from 0 to 33 percent (without any supportive data), the IONDT presented data on its untreated control group showing that spontaneous recovery of useful vision occurred in about 43 percent of untreated patients. Only 23 percent of the surgically treated ONDS group had recovery of useful vision. This meant that it was likely that almost half of the patients who had operations, if left alone, would likely have had some recovery of useful vision.

Consequently, this meant that many patients were harmed by the surgery in that they had lost the chance of recovering some useful vision. As a result of the IONDT, costly and ineffective surgery was abandoned as a treatment for NAION.

In the absence of clinical trial data, should “standard of care” treatment of serious eye disease be evaluated for safety and efficacy even after decades of use?

Optic neuritis is an inflammatory disease of the optic nerve that usually affects young adults and is more common among women than men. Optic neuritis can also be associated with multiple sclerosis. The Optic Neuritis Treatment Trial (ONTT) was organized to assess the beneficial and adverse effects of the standard treatment for this condition in most cases—oral corticosteroids. This treatment had been used for about 50 years, and yet an RCT had never been conducted. Some physicians strongly recommended no treatment, since the majority of these cases cleared up spontaneously with or without treatment. These differing approaches were partly a result of the absence of clinical trial data to demonstrate effectiveness of corticosteroids. But even if vision returned to 20/20, often there were abnormalities in color vision and visual field, among other problems. Since optic neuritis was associated with multiple sclerosis, an effort was made to identify risk factors for the development of multiple sclerosis in patients with optic neuritis. Patients with an acute onset of unilateral optic neuritis, along with other symptoms, were

randomized to one of three treatment groups: oral prednisone for 14 days, intravenous methyl prednisolone for 3 days followed by oral prednisone for 11 days, and oral placebo for 14 days. The oral prednisone and placebo groups were double masked (neither patient nor doctor knew which treatment was administered) while the intravenous methyl prednisolone group was single masked (only the patients did not know what treatment they were receiving).

The results showed that treatment with standard-dose oral prednisone alone did not improve the visual outcome and was associated with an increased rate of new attacks of optic neuritis. Therefore, it was recommended that this treatment be avoided. This was a clear example where a so-called standard treatment that had never been proven effective was removed from the list of treatments. The treated group receiving intravenous methyl prednisolone recovered vision more rapidly, but the drug did not provide any long-term benefit to vision. Although the group without any treatment (the placebo group) had a slow improvement to 20/20 or near 20/20 vision for up to one year, some patients still had symptomatic deficits in vision. This study is ongoing to determine the long-term relationship between optic neuritis and multiple sclerosis.

Randomized Clinical Trials: The key to ending controversy—the Effects of Light Reduction on Retinopathy of Prematurity

Previous reports on the use of light reduction on the eyes of preterm infants in the nursery have produced conflicting results with respect to the incidence of retinopathy of prematurity (ROP). An article in the *New England Journal of Medicine* in 1985 reopened the entire issue by reporting that light could contribute to the development of ROP. This sparked public interest, especially among parents of children with ROP, and articles appeared in the lay press suggesting that an important contributing factor to the development of ROP (i.e., high levels of ambient light) may have been overlooked. A review of this paper and others indicated that the studies all suffered from one or more of the following limitations: lack of randomization (e.g., the use of historical controls); small numbers of infants at high risk for ROP; unmasked or uncertified examiners; lack of standardized examination protocols or methods of disease classification; and poorly controlled or unmeasured techniques of light reduction.²⁶²

As a result, NEI felt it was essential that this question be answered properly, with a randomized clinical trial appropriately named the Effects of

Light Reduction on Retinopathy of Prematurity. A prospective randomized multicenter study of 409 premature infants with birth weights less than 1,251 grams was begun, and the infants were randomized to typical nursery lighting or reduced light from opaque goggles worn within 24 hours after birth until four weeks after birth, or 31 weeks post-conceptual age, whichever was longer. The goggles reduced visible light exposure by 97 percent and ultraviolet light exposure by 100 percent. Upon removal of the goggles, ophthalmologists masked to the treatment assessed the infants for ROP at least biweekly, for up to 13 weeks. It was concluded that a reduction in ambient-light exposure does not alter the incidence of retinopathy of prematurity. It appears that this well-designed randomized clinical trial has answered the question.²⁶³

Chapter 7

National Eye Health Education Program

The effort to establish eye health education programs at NEI began in the 1980s, a period ripe for such a development. “This was a time, historically, when people started thinking about prevention,” and “there was almost a blossoming . . . of interest in prevention and education,” according to Terry Lierman, an NIH administrative officer who later became a senior Senate staffer and a political consultant. The National Eye Health Education Program (NEHEP) was among the first programs of its kind at NIH.²⁶⁴

The push for a national education program pertaining to eye health initially came from a pharmaceutical company interested in making more people aware of the problems of eye disease and the drug treatments available for one eye disease in particular, glaucoma. This company retained the premier biomedical research lobbying firm in Washington, D.C., to encourage NEI to establish an eye health education program that would spread the message that glaucoma could be controlled by drug treatments.²⁶⁵ The proponents believed that support from NEI’s top management was essential in order to convince Congress to pass legislation acquiring long-term funding for such a program.

For their own reasons, the NEI management team of Carl Kupfer, Edward McManus, and Julian Morris were receptive to the idea of mounting eye health education programs. As the second Reagan presidential administration came to an end, the NIH budgets were shrinking and Congress was becoming increasingly conservative and frugal with government expenditures. At the same time, the vision research ideas that merited grant aid were growing by leaps and bounds, a result of NEI shoring up the ophthalmic research field the previous decade and a half. The politics of NIH was also changing in that the capability to secure increases in appropriations was no longer based solely on the connections of a few prominent ophthalmologists with well-placed senators or representatives, but also on how strongly the general public—or at least how strongly large advocacy groups—perceived the need. At that time the richest institutes, Cancer and Heart, were getting even richer because of the high profile of the diseases—the leading causes of death—that they studied, and the small institutes such as NEI were having to compete harder to gain public recognition and financial support.

The NEI leadership was interested in initiating an eye health education and awareness program as a way to attain more recognition for NEI's research programs, as well as improve the potential for transferring clinical research results to the public. As a side benefit of such a campaign, institute leaders hoped, Congress would raise the appropriations for eye research in recognition that NEI-supported clinical research was improving Americans' eye care and health. Promoting eye care services that resulted from publicly financed NEI-supported research might demonstrate to the public and remind Congress that investments in research programs were worthwhile because they resulted in products that could be used to treat eye diseases. The NEI leadership believed that a public eye health education program would boost the institute, propelling it into the headlines and thus increasing public awareness.

NEI cautiously explored public eye health education as an expansion of its traditional public information and public inquiries program. The Cancer Institute and the National Heart, Lung and Blood Institute were already supporting extensive public health education programs in their respective disease areas. Suggested preventive measures, such as those for lowering blood pressure and reducing the risk of heart attacks and stroke, had resulted from research directly supported by NHLBI.

While the NEI leadership saw the value in these education programs, they feared the programs would be too costly and cut into the funds available for its overall research program. Moreover, the NEI leadership thought it wise policy, in general, to refrain from actively launching an education program until definitive research results had been demonstrated. For this reason, NEI was hesitant to sponsor a program in glaucoma. For example, one of several approved drugs, topical Timolol (produced by the Merck pharmaceutical company), had been approved for glaucoma treatment by the FDA in 1978, but it had not been subjected to extensive NEI-managed clinical trials.²⁶⁶

Still, the institute's leadership indicated that it might be willing to launch an education program if the first eye disease to be addressed was diabetic retinopathy, which was highly prevalent. The institute had supported two definitive clinical trials that tested treatments for this condition; the studies found that appropriately timed laser treatment could prevent blindness in more than 90 percent of the patients with this affliction.²⁶⁷ Furthermore, NEI-supported research demonstrated that more than 50 percent of those known to have diabetic retinopathy did not receive the laser treatment—even after the potential success of this intervention was widely publicized through normal channels of communication. Clearly, this was an obvious target of opportunity for a proactive public awareness campaign.

NEI reached an agreement with the lobbyist and his client promoting glaucoma treatments: NEI would respond favorably to congressional interest in an eye health education program that included both diabetic eye disease and glaucoma. One participant remembers thinking that this move “was kind of revolutionary as far as NIH was concerned, because

traditionally the basis of NIH has been test tubes, laboratories, laboratories, laboratories.”²⁶⁸ NEI still had concerns about glaucoma by the time the legislation was proposed, but there were approved FDA drugs to treat this disease on the market along with other promising treatments in the pipeline. The Senate Appropriations Subcommittee of the Committee on the Department of Health Education and Welfare included the funding for this education program in its annual appropriation bill for NIH; the program then survived conference with the House and became law in 1988. The National Eye Health Education Program began with a congressional appropriation of \$3 million to launch the program.

NEI hired Ms. Judith Stein, a specialist in public health information who had extensive experience in the National Cancer Institute’s communication and education programs and had worked at the Bascom Palmer Eye Institute, University of Miami Medical School. Stein was indeed a fortunate choice and a lucky recruitment since there were only a few experienced information specialists with knowledge of health education at NIH or even in the public health service at that time. NEI also had on staff Julian Morris, an unusually gifted government executive who was very knowledgeable about DHEW communication and eye health education activities. He was in charge of NEI’s public information activities, which included the traditional activities of answering public inquiries and writing speeches and public announcements about eye diseases and research activities. He also handled press relations, and although NEI press conferences were infrequent, he saw to it that they were carried out under regular NIH public information protocols. Morris had also assumed the chief of program planning duties at the institute and mastered those activities, although he had never received formal training in this area. He was an outstanding writer, innovative thinker, and master of analysis. Later, Ms. Rosemary (Rosie) Janiszewski, a well-trained health education expert, joined NEI to administer the program.

Morris and Stein, the officials responsible for implementing and developing NEHEP, sought the assistance of Michael White, who helped run the NHLBI health education programs. NHLBI had conducted several health education programs, and its high blood pressure programs and cholesterol-lowering program had been particularly successful. White provided valuable advice about launching and conducting educational campaigns, which the institute readily adopted.

Many challenges had to be overcome before the education program could be implemented. There was no consensus within the broader vision research and eye care communities or within NIH leadership about the need for NEI to launch such eye health education programs. This lack of broad support made it difficult to move forward smoothly, unlike during the institute’s earlier strategic planning initiatives when most of the interested parties were in agreement.

Proponents maintained that NEHEP represented an unusual opportunity to raise the institute's image, which was necessary if NEI was to sustain the same—or higher—levels of Congressional financial support. Julian Morris argued that health education programs were a natural extension of NIH research programs, especially because they brought the results of NIH research to the “bedside.”

Despite the validity of these arguments, some groups were concerned that the effort had been initiated by only a few key NEI leaders and an outside interest group. Moreover, some top scientist-managers at other NIH institutes were reluctant to endorse the notion of extending the mission of an institute beyond that of supporting biomedical research. This attitude was evident, for example, at the National Institute of Diabetes and Digestive and Kidney Diseases (NDDIK),* which had a diabetes control and prevention program that dealt primarily with service delivery rather than education. Much of the diabetic health education functions had already been assumed by the Centers for Disease Control and Prevention (CDC).²⁶⁹ Not until 1997 would the National Diabetes Education Program (NDEP) be established in cooperation with CDC and other public and private partners.²⁷⁰

Dr. Bradley Straatsma, who chaired the first NAEC committee on the educational program, remembers that there was initially a lot of negative feeling and skepticism that lasted for a few years. Some considered public education inappropriate and counterproductive for a research institute. Others voiced concerns about potential government control or interference with ongoing educational activities sponsored by nonprofit organizations.²⁷¹

The National Cancer Institute and the National Heart, Lung and Blood Institute had taken the traditional legislative route to developing their education programs. The authorizing statutes for each institute contained the foundation for these activities. Building on this foundation, the two institutes achieved new program authority for health education efforts by obtaining additional legislation. Though Byzantine, this public process, with its public hearings, congressional-committee oversight, and proposal negotiation, allowed the various interests involved to vet the proposals and provided interested parties opportunity for input and testimony. Historically, this was the traditional mechanism for expanding an institute's functions and adding or deleting programs in a variety of areas.

NEI's approach to finding support for the education program was unique, and the result was probably for better rather than worse. The NEI staff added health education programs legally but through the legislative backdoor, allowing for very limited input from outsiders. NEI management wanted to avoid a lengthy legislative process since it was concerned that this process could open the door to a variety of unexpected outcomes, some of which could be highly undesirable. Instead, to validate the education mission, NEI relied

* NDDIK has gone through multiple organizational and name changes since it first started as the National Institute of Arthritis and Metabolic Diseases (NIAMD) under the 1950 Omnibus Medical Research Act.

upon a phrase in the authorizing legislation mandating that the institute look after the “special health problems and requirements of the blind.”²⁷² This, along with the legislative force of language from the annual appropriations bill, was deemed sufficient by NEI management and other executive branch officials to proceed with the program. Congressional players responsible for reviewing the implementing language in their authorizing and appropriation bills also accepted this rationale.

To dispel the negativity, NEI stressed coordination and collaboration with the other organizations involved in eye activity, rather than trying to dominate the field.²⁷³ Based on previous implementation campaigns and the advice from Mike White and others, NEI held a conference as the first step in promoting NEHEP and solidifying support for it. The first National Eye Health Education Conference was held in March 1989, and all of the major organizational players in the eye research field were invited to attend and help lay the groundwork for the coordination and development of NEHEP. This offered a means of developing consensus, especially if all of the potential stakeholders participated fully in the early development of NEHEP’s operations. The major organizations, 35 in all, were represented at this meeting, including the American Academy of Ophthalmology (AAO), the American Optometric Association (AOA), and the National Society to Prevent Blindness (NSPB). These three entities had the biggest stake in eye health education activities at the time. A complicating factor emerged at the meeting: members of AOA and AAO had been engaged in disputes over professional turf and practice issues for several years. This could have had a direct impact on the outcome of NEHEP. In particular, the controversy revolved around the question of whether the educational literature should refer to optometry or ophthalmology, or even both. After much discussion, the conference participants finally agreed to use the vague term *eye care professional* in the NEHEP publicity campaigns to describe the specialist that prospective patients should consult.²⁷⁴ Still, the competition between medical doctors and the optometrists cast a shadow over the conference.

Another problem involved the NSPB (later called Prevent Blindness America), one of the oldest voluntary public health organizations in the country. The NSPB believed that it should lead and carry out the eye health education program; after all, its representatives argued, the organization already had a modest program in place devoted to educating the public about preventing eye injuries in the workplace and protecting children with visual disabilities. The NSPB representatives privately suggested to NEI management that the institute could simply provide grant support to NSPB, who would carry out the education program.²⁷⁵ Obviously, this would have gutted the NEHEP program and used up most of the limited funding available. Moreover, to conduct a campaign that was national in scope would require tremendous effort on the part of many groups not just one; therefore, it did not

seem a viable alternative. Also, that course would have taken the program away from the direct control of NEI.

Despite the time and labor involved in hammering out agreements, the conference was nevertheless useful as a vehicle for airing different points of view. By the end of the meeting, the conferees reached a general consensus that much more effort was required to bring the problems of eye health and eye care to the attention of the American public, that now was the time to do something about it, and that NEHEP was the most appropriate vehicle.

Hindsight might suggest that a legislative process of public hearings on the proposal might have afforded the interested parties more opportunity to participate in the program's development upfront, mitigating some of the early conflicts that arose at the conferences—but that might have come at too high a cost in terms of loss of control and timing. Moreover, the process NEI chose allowed face-to-face negotiations that, in the end, probably achieved more than a traditional approach would have.

Other strategies were developed to ensure inclusiveness. In order to guide the program and ensure input from stakeholder organizations most affected by NEHEP, such as AAO, AOA, and NSPB, NEI established a planning committee to oversee the program. A partnership organization was also formalized, establishing as charter members the 35 organizations attending the first conference. It was determined that the planning committee would carry out NEHEP's agenda. The planning committee was chaired by Dr. Bradley Straatsma, UCLA School of Medicine, who had served NEI well in a variety of capacities, most notably as the chairman of the first National Advisory Eye Council's Program Planning Committee.

The NEHEP Planning Committee was established as a panel of the Vision Research Program Planning Subcommittee of the NAEC, and was made up of 11 members. This structure helped bring NEHEP into the mainstream of policy development at NEI and vice versa. The members represented several disciplines, including optometry, ophthalmology, health communications, and eye care education. The planning committee had four main objectives:

- 1) Prioritize programs
- 2) Provide implementation and evaluation advice
- 3) Find ways for the NEHEP to expand and meet its goals
- 4) Ensure that its members would work together for the common interest.

This last objective was most important, especially regarding finding a way for the optometrists and ophthalmologists to work together on NEHEP activities. The leaders of these two professions were represented on the planning committee and actively worked toward this end.²⁷⁶

The NEHEP conferences were held biannually. After the first conference, the planning committee reviewed NEHEP staff activities, especially those related to selecting a contractor to help formulate messages for the two programs and developing an agenda and participant list for the second conference.

The institute held its second NEHEP National Conference February 28 to March 1, 1991. More than 37 member organizations and 68 attendees participated. Relying on the managerial skills of NEHEP's in-house leaders Judith Stein and Rosie Janiszewski, NEI pursued a careful, step-by-step, rigorous planning process for developing an agenda of action for review by the participants of this second conference. The chosen contractor and NEHEP staff from NEI were experts in social marketing, a form of marketing that emphasized communication programs aimed at changing behavior, in this case, health behavior. Social marketing was widely used by NHLBI in its high blood pressure education programs. NEI formed two task forces, operating under the purview of the planning committee, to select the messages and strategies dealing with each of the two targets: glaucoma and diabetic eye disease. Each task force was staffed with some of the best subject-matter specialists in the United States who provided in-depth advice on how best to tailor the program. Additionally, NEI retained the consulting firm Uilisac Productions to provide professional marketing support and help formulate program messages that would resonate with target audiences. Uilisac experts presented their ideas at the second conference, proposing the unifying theme "Don't Lose Sight of Glaucoma." They described the principal elements of the communication campaigns such as public service announcements, print media advertisements, and community eye health education kits.²⁷⁷ The organizational representatives in attendance then had a chance to critique these proposed materials and later articulate how they thought their organizations might use them and distribute them to the community. The conferees made a variety of recommendations regarding the materials, most of which were adopted. One of the most valuable suggestions emerging from this conference was that NEHEP should publish a newsletter to facilitate the interactions of participating organizations and to inform the public about ongoing activities and plans for the future.

NEI followed this suggestion, and started the newsletter *Outlook*, which continues to be published regularly. NEI and the NEHEP consultants borrowed heavily from the example of other efficacious health education techniques used at NCI and NHLBI. Thus, NEI developed a national electronic bibliographic database of printed and audiovisual eye health education materials. The other two institutes had found such a database—in their respective health subjects—indispensable. While the federal government already had a computerized bibliographic database that included many separate sections on various health topics, it contained only limited information on topics related to vision and eye health. As NEHEP got started, it was decided that such a tool, free to users, would be helpful to organizations

participating in the new eye health education program. Eye health materials were catalogued into a database. This allowed partnership members, interested health professionals, and the general public to have easy access to the materials through an online computer subscription, usually maintained by a library or health institution.

The NEHEP collaborators relied on painstaking analysis and forethought in developing the national campaigns for health education in diabetic eye diseases and glaucoma. They tested various education materials, an expensive and time-consuming activity, for the approval of the conferees. Using focus groups, they tested which audiences should be targeted and whether radio or print media was a better communication channel for transmitting messages.

NEI-supported research had previously identified two prominent information gaps regarding diabetic eye disease. First, many people with diabetes were not aware that eye disease could be a major complication of diabetes. Second, health professionals did not have the eye health education materials required to inform and explain diabetic eye disease to the public. The focus groups tested methods for overcoming these gaps. Initially, family members of diabetics were thought to be the prime candidates for relaying messages about vision complications caused by diabetes. The focus group tests showed, however, that for various reasons family members believed they should not take on the task of delivering this message. They already interacted with diabetics in their family about diet, exercise, medication, and other issues, and that seemed enough responsibility. Instead, health care professionals, such as primary care physicians and pharmacists, seemed to be the best communication channel. It was thought that these professionals were in a key position to educate diabetics to seek dilated eye examinations. They were chosen as the target audience to receive diabetic eye disease messages.²⁷⁸

At one point, the NEHEP Planning Committee centered on the recommendation made by retinal disease experts (highly regarded academic research ophthalmologists) that only a comprehensive eye examination through a dilated pupil was acceptable for diagnosing diabetic eye disease. Some felt this might be a problem for many optometrists who were not used to dilating eyes since they generally focused on evaluating refractive problems. Yet, optometrists in some locales were already allowed to dilate eyes according to state law.²⁷⁹ This recommendation was accepted by both optometry and ophthalmology professionals in the advisory group. Eventually, continuing education courses about diagnosing diabetic eye disease through dilation were developed and conducted by the different professional organizations.

After the second NEHEP conference, organized ophthalmology professionals expressed concerns about the diabetic eye disease aspects of the eye health education program. The executive vice president of AAO asked for a special meeting with top NEI staff to discuss concerns about implementing the program. AAO wanted to be certain that a sufficient

number of its members were trained to do specialized retinal eye examinations. NEI agreed, and a longer timetable was created to implement the program. Another concern that emerged was the lack of a base of intervention research, or what might also be called applied research, pertaining to glaucoma and diabetic retinopathy; this type of research examined specific eye health education options and predicted different outcomes. While focus groups provided insight on alternative approaches to delivering education programs that could change human behavior, NEI, given its research orientation, preferred to ascertain the best methodologies through extensive applied research. As a compromise it was decided to conduct research on services implementation after the health education program itself was launched. NEI competed and awarded three grants for applied health services research on how best to organize and deliver education programs in glaucoma and diabetic retinopathy. These projects were expected to take several years and when completed, the results would be assimilated into the overall educational program already in progress. It was understood that this was not an optimal approach, and that it would have been better to develop the applied research base before embarking on the program. There was already a preponderance of scientific evidence that treatments worked for glaucoma and diabetic retinopathy, though, so it was decided that starting sooner rather than later would help prevent as much blindness as possible.

Lions *SightFirst* Program

Several partnership organizations participated heavily in the education program, probably none more than Lions Clubs International. Carl Kupfer and Ed McManus were already advising the Lions on their worldwide program in blindness prevention called *SightFirst*, which focused on blindness in developing countries (see International Initiatives in Chapter 8). Such collaboration seemed to be mutually beneficial. The NEI leadership believed that the Lions' participation in community-based eye health education programs in the United States would be helpful—the Lions' leadership thought that adding a U.S. component to their efforts would assist in securing a greater “buy-in” by Lions members and facilitate fund-raising among its local clubs. Judy Stein and Rosie Janiszewski assisted the Lions in developing a manual to help local Lions Clubs participate as NEHEP partners in U.S. communities. At that time, there were about 1.5 million Lions members in the United States in more than 400 clubs, so the NEHEP staff considered this an exciting opportunity to gain messengers who would help spread educational messages.

Early on, information emanating from the initial NEHEP work indicated that a national survey of the public's knowledge, attitudes, and practices regarding eye health and eye disease would be useful, indeed essential, to further develop the program. A survey would establish a baseline for any evaluation efforts and would measure the success of the program in years to come. It would help to know what Americans already knew about diabetes and glaucoma in order to determine how effective the education programs were over time. If NEI

launched the survey, it would need to secure approval from the U.S. Office of Management and Budget. But if NEI acted only as a minor financial partner, no such approval was required, so NEI asked the Lions to collaborate on this activity. The Lions provided a *SightFirst* grant of \$50,000 that allowed a national survey to go forward. The survey generated much useful information that guided NEHEP efforts over the next several years.

Additionally, the Lions *SightFirst* campaign participated broadly as an NEHEP partner, both nationally and locally through its clubs. The Lions enlisted comedian Steve Allen, actresses Brooke Shields and Jane Meadows, and Surgeon General C. Everett Koop to produce public service announcements delivered on radio and television channels all around the country. This campaign stressed the importance of dilated eye examinations for people at risk for glaucoma and diabetic retinopathy. The Lions local clubs also distributed many glaucoma and diabetic retinopathy educational kits at local health fairs and other venues.²⁸⁰ Other partners, such as the American Diabetes Association, the service sorority Delta Gamma, the philanthropic group The Links, Inc., and the National Association of Retail Druggists (NARD) (representing 40,000 independent retail pharmacies), also enthusiastically joined in with the eye health education campaign. NEHEP held a star-studded launch in Washington, D.C., in December 1991, accompanied by a national press conference estimated to have reached 46 million Americans.²⁸¹

As the NEHEP program developed, there were several high-risk populations selected for targeted campaigns, including African-Americans for glaucoma and Hispanics for diabetic eye disease. NEI had found through its social marketing research that diabetes was a major and expanding problem among Hispanics, but few in that community knew much about the disease, let alone its impact on vision. Diabetic retinopathy was the leading cause of blindness among working-age adults at that time, and 1 in 10 Hispanics had diabetes. It was an especially difficult challenge to address this population because there were several ethnic subgroups, each with distinct cultural attributes. According to NEI focus group research, many Hispanics did not trust doctors who were not Hispanic. It was also difficult to persuade individuals to follow the dietary advice necessary to control diabetes and its complications.

To address these challenges, the NEHEP designated a special ad hoc group for work on Hispanic outreach efforts. This group, made up of experts in Hispanic health care, recommended relying on the broadcast media as the primary source to deliver eye health messages to Hispanics. It also recommended using community organizations as channels of communication for eye health messages. Heeding this advice, NEI tailored services for this critical at-risk audience. In response to the need for specialized programs, NEI unveiled a special outreach program in October 1995 called *Ojo Con Su Vision!* (Watch Out for Your Vision!), developed to educate Hispanics on the risk of eye disease. The program successfully reached about 75 million people through an intensive media campaign.²⁸²

The *VISION* Exhibit

By 1992, nearly 25 years after the creation of NEI, NEHEP was moving full steam ahead. To reach an even wider audience, Julian Morris and Judith Stein developed the concept of a traveling exhibit that would celebrate the institute's 25th anniversary and at the same time educate large audiences by appearing in several major metropolitan areas. It would be hosted by NEHEP partners or major NEI grantee institutions, such as local departments of ophthalmology or optometry, or independent eye research institutes. This was to be the first such traveling exhibit sponsored by an NIH component, and many thought that a specific congressional appropriation was required. NEI, however, simply informed Congress that it would fund the exhibit development and travel costs as part of its ongoing programs. This turned out to be sufficient.

The director of NEI asked that the staffs of NEHEP and the NEI Health Communications Office oversee and manage the exhibit. This was a unique project for them because the exhibit was not, per se, a basic element of the NEHEP program, but it did serve the complementary purpose of highlighting the achievements of NEI and its publicly funded eye and vision research. The exhibit was called *VISION* and took up 2,000 square feet, the size of a medium-sized house. Additionally, it had 52 panels featuring various aspects of vision and discussing NEI-supported results that were helping to protect sight from disease. There were 10 interactive modules providing viewers with a hands-on experience. They demonstrated the various facets of vision such as how light gets focused by the eye, how we perceive color and motion, and how visual information gets processed by the brain. The world-famous Exploratorium Museum in San Francisco developed the modules. The exhibit also contained interesting artifacts such as antique eyeglasses and eyeglasses of the “rich and famous,” including those that had belonged to singer John Denver, President George H. W. Bush, and the popular Miss Piggy, a character from the television show *The Muppets*.

The traveling exhibit premiered at the Exploratorium in October 1993 and stayed for two months before moving on. It was a hit everywhere. In Chicago alone more than 30,000 people were estimated to have visited the exhibit during its two-month stay at the Museum of Science and Industry, the second-most-visited science museum in the United States. The director of design resources there remarked on the exhibit's widespread appeal: “Vision appeals to a variety of visitors You might see a school group, a family with small kids, and an older couple in the exhibit, all at the same time.”²⁸³ The exhibit's Chicago opening coincided with the annual meeting of the American Academy of Ophthalmology, also held in the city. The local organizing committee, composed of NEHEP partners and NEI grantee organizations, arranged to have Michigan Avenue, which might be termed Chicago's “Main Street,” lined with banners advertising the exhibit.

Over a span of 10 years, the *VISION* exhibit reached hundreds of thousands of people in 30 different locations. In the last few years of its run, the anniversary aspect of the exhibit was downplayed and banners announcing the exhibit simply referred to a “Celebration of Vision Research.”

VISION was a galvanizing force that allowed those interested and deeply involved in eye health and eye research to work together at the local level to raise the American public’s awareness of eye disease and the specific preventive steps that could be taken for particular eye problems. Along the way, the public also learned about NEI’s research contributions and how institute support for eye research helped to alleviate, in a cost-effective manner, blinding and disabling eye diseases. Finally, the exhibit educated people about the benefits of treating certain eye diseases and hopefully influenced some to seek treatment.

The vision arena had come a long way since the 1960s when there was no federal organization focused solely on vision, not much private funding supporting eye research, and no practical way to bring the results of research to the American public.

Some of the community coalitions that had been assembled to manage the local productions of *VISION* continued to function in one fashion or another after the exhibit left a particular city. At the suggestion of Ed McManus, Stein organized departments of ophthalmology, departments of optometry, the American Academy of Ophthalmology, and a few individual eye research institutes that had participated in local exhibit events. The group met once a year to develop and report on common agendas for national eye health education and advocacy for the coming year. One main objective was to ensure that the results of NEI clinical trials and laboratory research were reported widely and accurately. The National Alliance for Eye and Vision Research (NAEVR), an umbrella political advocacy organization created by NEI fans, developed and taught courses on advocacy to help increase its federal funding in the legislative process. These efforts helped solidify a cohesive coalition of eye care professional groups—one that was ready to carry forth the NEHEP message.

A separate network for optometry departments and optometry schools, colleges, and the American Academy of Optometry was also developed on a different track. In a brilliant stroke of marketing and management, Judy Stein and her staff brought together the sometimes competitive optometry and ophthalmology groups into one umbrella network that worked well together for several years on NEHEP and other eye health advocacy and education issues.²⁸⁴

The *VISION* exhibit was significant for reasons beyond just educating the American public about eye diseases and the cost effectiveness of taxpayers’ investments in eye and vision research. It served as a vehicle for NEI to demonstrate its leadership to local audiences. NEI’s budget was providing tens of millions of dollars to the eye research commu-

nity by the mid 1990s; indeed, NEI was giving millions of dollars in research funds to many individual departments, covering both ophthalmology and optometry. By cultivating cooperation through the exhibit, NEI was able to help frame or at least influence the agenda of NEI grantee organizations. Although not widely known, these same organizations had developed local resources for fund-raising and advocacy at the community levels, primarily dealing with local issues, and had the capability to take on additional tasks and responsibilities. This probably also decreased the incidence of congressional earmarks requiring funding for a specific eye research center or optometry in a specific district.

In the end, the leadership and marketing expertise demonstrated by Judith Stein, Jean Horrigan (an NEI staffer hired to work on the exhibit), and the other NEHEP contributors was unprecedented. They were able to produce results never before demonstrated by any other NIH institute.

Healthy People 2000

While NEI managers showed prescience in a number of policy matters, there were a few cases in which they did not assume as strong a leadership role as they might and perhaps should have. This included the U.S. government's national health campaign called *Healthy People 2000*, an HHS* preventive health initiative aimed at improving the health of Americans by the year 2000. In the monograph that served as the guiding manual for this program, every major disease area had its own chapter. The monograph, however, lumped together some diseases that its authors considered minor. The description of eye disease prevention was subsumed under a single grouping of chronic diseases. This gave eye disease a much less prominent place in the agenda than NEI considered ideal. A strong effort from NEI might have led to a more powerful presentation.

NEI's leadership was reluctant to assign multiple staff members to initiatives such as the *Healthy People 2000* campaign because they saw such work as secondary to the core mission of supporting eye and vision research. The NEI leaders had boldly but with great forethought expanded into eye health education only because they viewed it as a direct extension of this core mission.

NEI was also seriously understaffed and staffing resources were historically the most difficult asset to secure in the federal government. NEI had already moved into the prevention arena with its NEHEP program and was making plans to celebrate the institute's 25th anniversary. Further, although usually a team player at the NIH level, NEI's top staff always held the Public Health Service and HHS leadership at arm's-length. The leadership at HHS and its predecessors had often been overtly political in their orientation, as well as short-sighted in their approach to problems, being primarily focused on the biannual election cycle.

* The Department of Health and Human Services was formerly known as the Department of Health, Education and Welfare. It was renamed in 1979 when a separate Department of Education was created.

And of course, what was good policy for one administration might be anathema to the next. Distracted by politics, the HHS leadership found it difficult to develop solid, viable policies that made sense for the long term and that served all the constituent institutions and agencies under the agency's umbrella. Furthermore, the federal government was prone to severe bureaucratic micromanagement. The NIH institutes and NEI, for the most part, were able to avoid political quagmires because they received their funding from a specifically budgeted line item. NEI and the other institutes jealously guarded this most important prerogative and encouraged the establishment of their own significant advocacy/lobbying networks, such as NAEVR, to perpetuate control. To be involved with a different group of well-meaning—but too often misguided—preventive health advocates at the department level was something that NIH—and especially—NEI approached warily.

It would have been difficult to predict that C. Everett Koop, a pediatric surgeon and the U.S. Surgeon General in charge of this effort, would become one of the most effective health-education spokesmen of modern times, and that *Healthy People 2000* would be such a rounding success. In the early press reports of his nomination for this position, Koop was described as a famous surgeon and physician—not as a captivating speaker and preventive medicine advocate or pioneer. Some NEHEP partners tried to encourage NEI to play a more active role in *Healthy People 2000*, reasoning that this was a government program and NEI was the only federal player that could really coordinate eye care activities. Although the campaign required a lead federal agency, NEI was not ready to assume a labor-intensive effort. In the end, NEI did not actively participate in the process, and eye health issues indeed received a less prominent focus than they deserved.

Still, the NEHEP staff participated on a minor level in this new important health education initiative. Judy Stein garnered a speaking assignment for NEI at one of the HHS kick-off events conducted by the American Medical Association. The meeting had more than 1,000 physicians in attendance, and the NEHEP staff was allowed to distribute many of its educational materials and information kits at this meeting, making a respectable showing for NEI.

Healthy People 2010

In the follow up to the *Healthy People 2000* campaign, NEI received a second opportunity to become a major player in setting the national health agenda. HHS organized a new campaign aimed at setting health goals for 2010. Among the NEHEP partners, Prevent Blindness America (PBA) was especially vocal in encouraging NEI to assume a leadership role for the new campaign. Participating, it was thought, might enable NEI to successfully make the case that eye care and vision were important enough to be a major element of this federal initiative. NEI explored the options. After much negotiating with the Public Health Service, the objectives from NEHEP were accepted as a major component of *Healthy People*

2010, although they were combined with information concerning hearing problems. The vision community did not believe this combination was the optimum solution; nevertheless, this seemed a good beginning and a major victory for those advocating the importance of eye disease.

Many policy people in the eye care community came to believe that having eye disease emphasized by *Healthy People 2010* would help persuade state and local health officials that eye disease was indeed important and worthy of their support. Additionally, some felt that Medicaid and Medicare reimbursement for vision-related treatments could be influenced if eyes and vision were part of the *Healthy People* prevention efforts. NEI leadership also believed that the campaign held great promise for persuading the public to support increased federal appropriations for the institute. For example, one of the 10 vision objectives included in the *Healthy People 2010* report was to increase the number of people receiving vision rehabilitative services and devices when they suffered from low vision. This, of course, provided a great boost to the fledgling NEHEP programs concerning low vision education. Ken Tuck, M.D., past president of the American Academy of Ophthalmology, said in an interview in *Outlook* that the vision community “can be proud that measurable eye health objectives are prominent on the Nation’s health agenda for the first time.”²⁸⁵

The NEHEP partnership became a powerful political force with several organizations leading the way, namely Prevent Blindness America, the American Academy of Ophthalmology, and the American Optometric Association, all working as a team to develop objectives that should be included in the federal initiatives. Together, they successfully convinced PHS and HHS that eye care and preventive eye health strategies should be included in the *Healthy People 2010* campaign.

Fourth NEHEP Conference

By the fourth NEHEP conference held in San Antonio in March 1997, the partnership among NEHEP members was mature, vigorous, and fully participatory. Conference attendees held several important discussions that would have a positive impact on the program. NEI’s Rick Ferris discussed the new Healthcare Effectiveness Data and Information Set (HEDIS), a tool created by a nonprofit organization to assess the quality of care and service of Health Plan providers. A major goal of NEHEP was to encourage providers to increase the number of diabetics having regular dilated exams. This was accomplished.

Proposals concerning a National Diabetes Month for November and a Glaucoma Awareness Month for January were well received by the participants. Since then, these designations have generally been accepted. As many as 22 partner organizations have joined together to conduct information campaigns on diabetic eye disease alone in a single year.²⁸⁶

Low Vision Education Program

The problem of low vision had been a growing concern for NEI over the years, and several workshops had been held to discuss potential NEHEP programming in this area. According to the NEHEP newsletter, “Low vision is defined as a visual impairment, not correctable by standard glasses or contact lenses, that interferes with an individual’s ability to perform activities of daily living.”²⁸⁷ It is common in older people and often caused by age-related macular degeneration and other eye disease problems that resulted in partial loss of vision.

At the fourth conference, a proposal from the planning group on low vision education was presented and reviewed at a special meeting attended by over 20 representatives (half) of the NEHEP partnership. The planning group gave a vote of confidence to the proposed plan, and after slight modification based on partner input, NEI moved ahead with the program.²⁸⁸

Low vision was now recognized as the important problem it was. NEHEP, supported by NEI, established a planning committee for designing an educational program. NEHEP subsequently launched the National Low Vision Education Program in October 1999, with a kick-off event at the National Press Club in Washington, D.C. This was the first major eye health education component to be added to the existing NEHEP programs.

Low vision was becoming a greater eye health problem as the population aged; 1 in 8 Americans were 65 or older, and the baby boomers would join these ranks in the next several years. Aging was associated with an increase in eye disease, especially age-related macular degeneration, and these numbers dictated the need for a program in this area. The director of NEI was concerned about any education effort, because even though researchers had found promise in the use of drug, laser, and surgical treatments, at that time there were no proven treatments for macular degeneration. Furthermore, low vision therapies, with their use of highly specialized assistive devices, had not yet been adequately validated by applied research or clinical trials. In addition, the at-risk patient population was very difficult to approach with rehabilitation efforts because many felt that their vision loss was just a part of growing old. Undaunted, NEHEP, with the strong collaboration of major partners such as the American Foundation for the Blind and Lions Club International, forged ahead with the program. Assisted by an expert panel, the NEHEP partners concluded that well-trained professionals who were educated in using low vision equipment (such as magnifiers and hand-held scanners) could significantly aid patients with low vision. With training, people with low vision could often maintain their ability to live independently. Certainly, visual rehabilitation could enhance the quality of life of many patients with low vision.

As the director of NEHEP, Rosemary Janiszewski led the organization through an intricate maze of professional groups representing ophthalmologists, optometrists, social

workers, and others. She did an outstanding job, performing a delicate balancing act with the help of NEI's director and deputy director. This area of care was perhaps even more complicated than regular eye care because of the different types of specialists providing low vision services. The program was based upon a national media campaign through print, television, and radio public service announcements, directed at the people most likely to have low vision and their families. The campaign was similar to the programs launched in glaucoma and diabetic eye disease. In consulting with some of the best centers for low vision rehabilitation in the United States, NEHEP staff learned that the number of patients with low vision being served represented only a small fraction of those who could benefit from treatment. Many individuals with low vision were not aware that they could be helped. As a result of this information, campaigns were also directed at professional providers such as ophthalmologists to help raise patient awareness that rehabilitation resources were available within local communities. NEHEP produced and distributed educational materials on low vision to its many partners around the country.²⁸⁹

Low Vision Exhibit

Buoyed by its success with the *VISION* exhibit and the cooperation of the many partners who had sponsored it, NEI developed a highly specialized second exhibit focused on low vision. It was launched in April 2001, and by the end of 2002 had traveled to 32 cities in 14 states. NEHEP staff entered the exhibit into a national competition sponsored by the International Council of Shopping Centers, and was selected as one of the winners. As a result, the exhibit was shown at shopping malls around the country. NEI developed two similar traveling exhibits geared toward low vision, dubbed the "National Eye Site Tour," each containing similar major features:

- Colorful kiosks aimed at all audiences, from the young to senior citizens.
- Interactive multimedia touch screens programmed to educate people about low vision.
- A display of aids and services to assist those with low vision.
- Information on local services and resources for low vision.²⁹⁰

In addition to the exhibits, NEI developed a special website for NEHEP programs, adding a section on low vision to raise awareness that help was available. Several partner organizations stepped forward to play a major role in making the early phase of the low vision education program a success. The American Foundation for the Blind and the National Association for Visually Handicapped (NAUH) were among those offering innovative approaches to reach this underserved population. Finally, to address a growing segment of the afflicted population, the low vision education materials were translated into Spanish to reach the aging Hispanic population. In NEI's 1999 *Outlook* report, Janiszewski summed up the

goals of the low vision NEHEP program: “Loss of vision can be frightening [and] while there may not be anything medically that can be done for people with low vision, their quality of life can be greatly improved. The Low Vision Public Education Program seeks to emphasize that just because people don’t see as well as they did before, they don’t have to lose their independence.”²⁹¹

Five-Year and Ten-Year NEHEP Evaluations

Unlike many federal programs, NEHEP committed early on to conducting in-depth periodic program and management evaluations of its activities. NEI commissioned these evaluations as part of its good management practices; outside contractors, with significant help from partner organizations, performed the evaluations. At the five-year evaluation point in 1997, NEHEP was cooperating with 53 member organizations made up of private, nonprofit, government, and professional organizations. These groups were composed of members and individuals who were serving or had targeted many of the at-risk groups being addressed by NEHEP initiatives in diabetic eye disease and glaucoma. Many used NEHEP educational materials and most supplemented these items with their own publications and services. A contractor interviewed 35 of the 53 partners, and all spoke positively about the benefits of being a NEHEP member.

In summary those interviewed stated the following:

- The partnership had encouraged the public and professional groups involved to report eye care as a major health concern.
- NEHEP served as a catalyst that helped members better collaborate.
- The partnership activities had a broader impact by encouraging other organizations outside the partnership to join in with the partnership’s eye care education activities.

NEHEP, according to the membership survey, met the needs of almost two-thirds of the members surveyed. Of those surveyed, 76 percent found the three NEHEP vision education kits on glaucoma, diabetic eye disease, and low vision to be “very useful” and rated them 4.5 (on a scale of 1 to 5) for their utility. The evaluation also found that more than 8,000 public service announcements developed by NEHEP aired on national and cable television in 1992, with 31,270 airings in 1994. From January 1992 to December 1996, more than 1,323 articles discussing NEHEP programs appeared in newspapers and magazines. The evaluators concluded that print media coverage of eye health information had grown significantly over the life of the program, with diabetic eye disease coverage increasing nearly five times and glaucoma coverage three times.²⁹² Clearly, at the five-year point, NEHEP had been shown to be remarkably successful and to have potential for providing spill-over publicity for showing the importance of all eye concerns and the need for increased funding for NEI-supported vision research.

The 10-year evaluation in 2002 of NEHEP, performed by the American Research Institute, was more expansive than the five-year evaluation and included interviews with 58 of the 63 member organizations. The goal was to examine how effective the program had been in reaching audiences in the three target areas: glaucoma, diabetic eye disease, and low vision. This evaluation generally concluded that NEHEP had been very successful in almost all areas:

- 72 percent of the representatives and 63 percent of the executives and representatives reported that NEHEP partnership has increased their organization's capacity to serve their target audience.
- 90 percent of partners reported that their organization had benefited from the association with NEHEP and NEI.
- 91 percent reported that NEHEP has been responsive to their organization's needs.
- 91 percent would recommend becoming a NEHEP member to others.²⁹³

On a less positive note, the evaluation showed that some of the founding NEHEP partners were less likely than later partners to recommend to newcomers that they join NEHEP. Follow-up steps were suggested by the evaluators to find out more about this negative attitude, but it likely stems back to the early competition between major professional and voluntary organizations in the field. It probably also related to some partners' belief that NEI should pass any eye health education funding on to them rather than running the program itself. They thought they had better a standing in the community, and with more funding they could do the job required. However, the fact that many Americans knew little about eye disease and eye health was reflected in the NEHEP survey conducted in 1991. NEI saw this as a good reason for trying a new eye health education strategy and running the program itself.

* * *

NEI had warily moved into what was, for the institute, a new frontier of eye health education. The path was full of pitfalls. NEHEP went beyond the boundaries of basic and applied biomedical research. However, by continuing its emphasis on (1) using and emphasizing good management practices in carrying out its program, (2) stressing program-planning approaches with heavy involvement of affected parties, and (3) selecting high-quality staff, the institute developed a program to be proud of. NEHEP, with a staff of five and modest financial resources, revolutionized the way in which Americans regarded eye disease as a major health problem.

Chapter 8

International Health Initiatives

Introduction

In the mid 1970s, NEI embarked on a new set of activities in the field of international health. The institute assumed a proactive role in applying and sharing expertise to others around the globe. What role could be more appropriate for NEI than using its research capabilities to reduce avoidable blindness among the millions of men, women, and children throughout the world?

As awareness of eye disease increased, blindness and visual disorders came to be understood as pervasive global problems. International activities dedicated to the alleviation of eye-related disease expanded. An emerging network of governmental, professional, and philanthropic groups, such as the World Health Organization and the member organizations of the International Agency for the Prevention of Blindness (IAPB), collaborated on new public health programs designed to help prevent eye disease. NEI, with its span of research capabilities, staff, and financial resources, supported this network along several fronts, including its commitment to a research program that would advance knowledge about the pathology of blinding eye diseases prevalent in developing countries. In addition to building up the scientific and medical knowledge underpinning new public health initiatives, NEI developed methods for efficiently disseminating applied research findings in ways suited to the socioeconomic realities of developing nations. The science of operations research provided the means for doing so. NEI also incorporated epidemiological approaches into research so as to uncover social, cultural, economic, and other environmental factors that affected eye treatments. NEI pushed at the boundaries of medico-scientific analysis, maintaining that it was important to evaluate treatments in a methodological way. NEI's most important and innovative activities in the international sector were in three vision research areas: cataract, blinding malnutrition, and refractive error. And finally, NEI developed an international exchange program.

The Overburden of Avoidable Blindness

During the three-and-a-half decades of NEI's international work, four major eye diseases that were considered treatable or preventable affected large numbers of people

throughout the developing world: age-related cataract, trachoma, onchocerciasis (river blindness), and blinding malnutrition caused by vitamin A deficiency. Cataract affected people living in the United States and other industrialized countries, but these populations typically had access to treatment. The other three conditions were found primarily in nonindustrialized impoverished regions. Large numbers also suffered from visual disability simply because they did not have corrective eyeglasses. NEI and its advocacy partners focused on cataract, blinding malnutrition, and vision correction because other philanthropic-professional collaborations were already implementing trachoma and onchocerciasis prevention programs.

First-hand Observation

As NEI's director, Dr. Kupfer had the opportunity to experience first hand the harshness of visual disability among impoverished populations. Blindness exacted a terrible toll, especially in cases where it could be prevented with proper treatment. At the invitation of the Pan American Association of Ophthalmology, Dr. Kupfer traveled to numerous Caribbean and South American countries in July and August of 1975 to informally assess levels of visual disability and the state of care. Serving as a consultant to the Pan American Health Organization (PAHO) and IAPB, he visited local health facilities, performed examinations in outpatient clinics, and consulted with local ophthalmologists. There was a high prevalence of visual disability throughout Latin America and the Caribbean, and Dr. Kupfer found that "glaucoma seemed to be the leading cause of blindness and visual disability in the Caribbean Islands of Barbados and St. Lucia, while cataract was a major cause throughout all of South America."²⁹⁴

Kupfer encountered a growing desire among the international medical community for action, and specialists were eager to learn about new methods of treatment. "It was impressive to see the ophthalmologic community in many of these countries formulating residency programs, organizing Basic Science courses, and coming to meetings in the United States, especially the American Academy of Ophthalmology annual meeting," recalls Kupfer.²⁹⁵

Increasingly aware of the global impact of eye disease, Dr. Kupfer realized just how important prevention activities were, but also recognized the obstacles:

As I became more involved in international activities, I began to realize the stark difference in eye health care within developed countries as opposed to ophthalmic treatment in less developed areas. In modernized countries such as the United States, there were successful treatments for preventable eye problems. There were programs available to the general populace, often funded by the government, for treating cataract cases with surgery and refractive errors with spectacle correction. However, in large countries

like China and India (which had populations in excess of 1 billion) and smaller, less populated countries, blindness and visual disability from cataract and refractive errors were often not treated. The impoverished general population lacked appropriate medical facilities and could not afford the relatively high cost of surgery or corrective spectacles. Many even found it difficult to take time away from work. I heard over and over again, “If I don’t work today, I don’t eat today.”²⁹⁶

Dr. Kupfer’s experiences in Latin America and interactions with various international organizations profoundly shaped his outlook. It became clear to him and his NEI colleagues that the public health community at large could benefit from applied research; the institute’s staff and affiliated researchers could help develop and improve methods for preventing and treating specific eye diseases affecting impoverished populations abroad. Public health advocates of all stripes needed better solutions to the logistical problems involved in taking eye care to the rural poor in undeveloped regions; they also needed scientifically informed methods for overcoming obstacles such as costs and prevailing socioeconomic conditions and cultural attitudes that militated against success. Over the next 30 years, NEI helped the public health community meet many of these requirements.

Organizing for International Action

In the mid 1970s, international nonprofit organizations began to devote more resources to alleviating vision disabilities and preventing blindness. By then, NEI was well established, and these groups were aware of its stellar work and growing reputation. NEI was in a position to provide assistance.

WHO

One of the most important international agencies that NEI worked with was the World Health Organization (WHO), a specialized United Nations agency that acted as a coordinating authority on international public health matters. From its inception, WHO has provided assistance, guidance, and funding to member countries for establishing and implementing disease control programs.

In the early 1970s, the organizations that collaborated with WHO became increasingly interested in blindness prevention worldwide. WHO convened the Study Group on the Prevention of Blindness to assess the magnitude of the problem and more clearly define the terms *visual impairment* and *blindness* for an international audience. In 1972, WHO systematically inventoried the available data on blindness and reported that there were between 10 and 15 million blind people in the world. In 1975, the World Health Assembly (WHO’s

governing body) adopted a resolution urging the establishment of initiatives against diseases causing blindness.

Dr. Kupfer humorously recounts how the initiative almost did not get passed:

At the 25th World Health Assembly in Geneva in 1975, the Indian delegation proposed a resolution to establish within WHO a global program for the prevention of blindness. The draft resolution had been developed by the secretariat of the WHO and the Government of India, with the full support of its Prime Minister, Mrs. Indira Gandhi. At the appropriate time during the general debate of the assembly, the chairman stated, “I understand that the delegation from India will now propose a resolution.” Nothing happened. The chairman repeated the introduction. The head of the Indian delegation, presumably suffering from jet lag, was fast asleep in his chair. Fortunately, the delegate seated next to him prodded him in the ribs. The Indian delegate immediately rose to his feet and with perfect composure proposed the resolution, which was then unanimously accepted.²⁹⁷

The resolution resulted in the WHO Programme for the Prevention of Blindness, officially established in 1978. WHO member countries contributed funds supporting activities for reducing the prevalence of blindness caused by cataract, trachoma, blinding malnutrition, and onchocerciasis, the diseases that were most problematic on a global scale. To get the program off the ground, WHO initiated a number of task-force meetings on specific issues, including data on blindness, manpower development, the economics of blindness prevention, primary eye care, and program development for individual countries.

Dr. Kupfer, representing NEI, was closely involved with WHO's new program. To him, participating in international health organizations seemed appropriate; it dovetailed with the interests of President Jimmy Carter's administration, which had made it a priority to encourage American international health activities worldwide.²⁹⁸ Kupfer attended WHO's 1978 World Health Assembly in Geneva as a member of the U.S. delegation. He then was appointed to the new WHO Program Advisory Group (WHO-PAG) on the Prevention of Blindness, established in 1979. Composed of a rotating membership of about half-a-dozen leaders from international nongovernmental organizations (NGOs) and academic institutions, the WHO-PAG advised WHO on the direction and content of its blindness prevention program.

IAPB

NEI worked closely with another organization, the International Agency for the Prevention of Blindness. IAPB was established in January 1975 under the strong leadership

of Britain's Sir John Wilson, a leading public health advocate. Blind since boyhood, Wilson, in his capacity as the director of the Royal Commonwealth Society for the Blind, encouraged the international community to intensify its focus on the problem of global blindness. As a result, IAPB was organized.

IAPB formed an umbrella organization representing various nongovernmental organizations such as Christoffel Blindenmission (CBM), the International Eye Foundation (IEF), and the Royal Commonwealth Society for the Blind (RCSB), later renamed Sight Savers International (SSI).²⁹⁹ IAPB supported the WHO program, encouraging countries to participate in WHO activities and establish national programs. A network of professional associations, nonprofit groups, and medical, educational, and research institutions, together with IAPB mounted a cooperative universal offensive to drastically reduce the "overburden of avoidable blindness," a phrase coined by Professor Barrie R. Jones (University of London) at the first IAPB General Assembly.³⁰⁰ IAPB, through its members, supported health education, mobile eye care services, eye hospitals and clinics, and training for service providers. On a global scale, IAPB continues to disseminate information on successful approaches to eye care delivery, on increasing public awareness, and on pooling resources among nations.

NEI supported this work, with Dr. Kupfer serving as president of IAPB from 1982 to 1990. NEI staff assisted the organization by providing expertise and advice on various NGO eye health projects. Kupfer recalls the importance of the work of IAPB and its leader:

I met Sir John Wilson, the leading force behind the creation of the IAPB, in 1975 at the first meeting of the executive board of the IAPB in Puerto Rico. We discussed how I might participate in the IAPB. Sir John offered me the chairmanship of the IAPB Priorities and Projects Committee (PPC), which I accepted. The PPC's responsibility was to prioritize projects used to support fund-raising campaigns by the NGOs that were IAPB members. My committee's first priority was to organize national prevention of blindness committees in as many countries as possible. These committees would mobilize resources and increase public awareness and implement health care strategies to reduce the world's avoidable blindness. Since the WHO could not act unless requested to do so by a member country, it was hoped that the national committees would encourage their governments to ask WHO to take action on the need for research to improve health care, treatment, and prevention of blindness and visual disability.

As a committee chairman, and later as IAPB president, I interacted continuously with Sir John. There is no doubt that the creation of the IAPB, by bringing together organized ophthalmology

(International Association for the Prevention of Blindness), the leading blindness organization (World Council for the Welfare of the Blind) and the NGOs, was directly attributable to the Herculean efforts of Sir John Wilson. Under his leadership, the IAPB played an increasingly effective role in coordinating the activities of almost all of the nongovernmental organizations, so that the blindness prevention organizations spoke with one voice. The founder and organizer, Wilson, was the spirit of the IAPB until the end of the century.³⁰¹

World Health Day

Another component of increasing global health consciousness has involved designating a certain day as devoted to a particular health issue. Since 1950, World Health Day has been celebrated on the 7th of April annually to mark the founding of WHO, and each year WHO selects a theme highlighting a priority area of concern. Communities around the world recognize the day and slate activities designed to raise awareness.

With so many possible health issues to choose from, any single problem gets a turn in the spotlight only sporadically. For World Health Day, April 7, 1976, the theme was “Foresight Prevents Blindness.” Not since 1962 had World Health Day been devoted to the prevention of blindness, partly because there had been a lack of media interest. Every effort was made to generate interest for the 1976 event. NEI collaborated with other government agencies, WHO, and the U.S. National Society for the Prevention of Blindness to publicize the theme. NEI staff drafted a message for President Gerald Ford that was televised nationally. They also prepared a feature article on the six leading causes of preventable or correctable blindness: cataract, glaucoma, eye injuries, trachoma, onchocerciasis, and keratomalacia. A mix-up occurred in Malaysia where posters were printed backwards, stating “Blindness Prevents Foresight.” This was certainly not the message that the participating organizations were trying to get across!

The theme “Foresight Prevents Blindness” conveyed the message that actions could be taken to preclude the onset of some eye problems. World Health Day encouraged people to become more aware of the problem of blindness throughout the world, to learn more about its causes, and to become educated about what might be done. The theme also encompassed the notion that preventive research was another aspect of foresight, and that increasing resources dedicated to research in blinding eye disease was necessary for stemming this public health problem.

Measuring Magnitude and Cause

Consciousness-raising events, while valuable, could only go so far in remedying problems. For new blindness initiatives to succeed, the world needed to understand just how extensive was the problem of blindness. WHO formed the Task Force on Data on Blindness to compile data on visual problems and provide numbers on the blind and visually impaired worldwide. The task force used two different definitions of blindness accepted at that time; having less than 6/60 [20/200] vision, considered to interfere with being economically self-sufficient, and having less than 3/60 [20/400] vision, which was thought to result in social deprivation.* The task force in 1978 estimated that there were 28 to 42 million blind people in the world, depending on which definition was used. Even with such large totals, the task force probably underestimated the problem because the numbers only reported the “best corrected vision” achieved; this included, for example, wearing eyeglasses to correct a refractive error. For a long time, there had been the prejudice that refractive error was not justifiably included as a problem of blindness and disability. Carl Kupfer, Leon Ellwein, and Ed McManus helped convince WHO that refractive error must be included as part of the definition of eye disease.³⁰² Now, WHO reports blindness and visual disability not as best-corrected visual acuity, but rather in terms of *presenting* visual acuity (i.e., the uncorrected visual acuity with which an individual is living). Presenting visual acuity takes into account eye diseases (such as age-related cataract, glaucoma, macular degeneration, trachoma, and onchocerciasis) *as well as* correction problems, such as the lack of appropriate eyeglasses after cataract surgery and broken or lost glasses. When these adjustments are made, the real impact that visual impairment and blindness have in the world becomes apparent. Taken together as a group, eye diseases/conditions ranked number nine on the WHO global burden of disease scale in 2003.³⁰³

The global burden of disease calculation is expressed in disability adjusted life years (DALYs) and incorporates life years lost to mortality, which is not usually associated with blindness, as well as loss in quality of life associated with morbidity. In this context, it is worth remembering that the large percentage of blindness occurring throughout the developing world today is either preventable or treatable with current knowledge.

More information was needed on the regional scope of blinding diseases. The first General Assembly of IAPB, held in Oxford, England, in 1978, focused on this issue. IAPB

* Visual acuity is measured by starting with a fixed distance of the patient from a chart (usually 20 feet or 6 meters) and measuring the fraction consisting of the numerator (the distance from the chart) divided by the denominator (size of the letter that can be seen at that distance). If the visual angle subtended by the denominator at 20 feet or 6 meters is the same as the numerator, the patient would have “normal vision” (i.e., 20/20 or 6/6 vision). However, if the patient has decreased visual acuity, it is necessary to have the denominator be a larger letter than 20 feet or 6 meters. If the patient can only see a denominator letter that a person with normal vision can see at 200 feet or 60 meters, then the patient’s vision is measured as 20/200 or 6/60. That means the patient must be 20 feet away from the chart to read the letter that a person with 20/20 or 6/6 vision can see at 200 feet or 60 meters. The vision would be recorded as 20/200 or 6/60.

hosted a three-day conference for 170 attendees representing national committees from 44 nations. The meeting focused on identifying the major causes of blindness on a regional basis (e.g., blinding malnutrition in Southeast Asia, river blindness in Africa), developing strategies to stimulate intra- and inter-governmental action, and increasing blindness-prevention activities in relation to regional needs. Among the speakers was Professor Edward Maumenee, one of the major personalities who had helped to establish NEI. He addressed the assembly with an optimistic presentation on “The Role of the Ophthalmologist in Global Action to Prevent Blindness.”³⁰⁴

Dr. Kupfer followed with a presentation titled, “Tomorrow’s Blind Population,” which contrasted to Dr. Maumenee’s hopeful and upbeat talk. Kupfer recalls:

I described how population statistics from several sources indicated that the total U.S. population would increase less than 50 percent between 1970 and 2030. In contrast, the numbers of those over the age of 55 years would increase 123 percent, and those over age 85 years would increase by an astounding 300 percent. Calculations of the estimated prevalence of cataract, age-related macular degeneration, glaucoma, and diabetic retinopathy between 1970 and 2030 in men and women age 55 years and over would likely exceed 160 percent for each disease, a number much greater than the rate of population growth for that age group. With respect to the developing countries, population growth would triple between 1970 and 2025. Diseases, infections, malnutrition, filarial disease, and ocular accidents, all leading causes of blindness and not age-related, would be even greater factors in causing blindness. Even more disturbing was the finding that the number of people in these developing nations aged 55 and over would increase fivefold by the year 2025 and those causes of blindness that are age-related would increase as much or even more. I concluded this dismal picture with a call to action, saying, “There can be no doubt that the time for concerted remedial action on the part of all the world’s nations is at hand. Only by pooling our resources, expertise, and energies can we hope to slow, much less to reverse, these very disturbing trends.” After I finished my presentation, there was an intermission for refreshments. Dr. Maumenee approached me shaking his head and said that my talk was the most depressing piece of news he had ever heard. Why couldn’t I say something a little more optimistic! With that comment, I knew he had been listening. Probably, it was at that moment that he committed himself to redouble his effort to promote activities for the prevention of blindness worldwide.³⁰⁵

NEI and International Research

NEI assisted with the new global campaign, fronted by WHO and IAPB, to combat avoidable blindness. The institute dedicated resources to three types of eye problems important for international health: age-related cataract, blinding malnutrition, and uncorrected refractive error in children. NEI staff provided advice and expertise on prevention initiatives and provided financial support for project activities and staff.* NEI made important contributions in research and training, supporting a number of field research trials.** Leon Ellwein, Ph.D., took the lead in the design and conduct of projects on which NEI collaborated with WHO. Dr. Ellwein, with varied training in engineering, operations research, and management, had expert knowledge on the conduct of clinical trials, disease risk assessment, and other types of medical projects. He had served as a consultant, medical school professor, and dean before joining NEI full-time in 1991. Ellwein and the NEI staff created innovative public health eye programs, advancing the notion that treatments must be properly evaluated to assess their true value before being implemented in fieldwork. They introduced epidemiologic methodology to international organizations. Through it all, NEI staff insisted that field prevention programs must be scientifically based.

Cataract

Age-related cataract was the major cause of blindness throughout the world, despite the fact that a safe and effective treatment for restoring vision was available. NEI staff thought that careful epidemiologic analysis was necessary for determining the best ways of providing low or no-cost surgical treatments that were also highly successful in restoring sight (as evaluated by measuring vision some weeks after surgery). They also needed to know how to overcome socio-cultural resistance to treatment.

Cataract-free Zones

To accomplish these objectives, NEI helped develop and implement cataract surgery outreach initiatives along the lines of what was known as the *cataract-free zone*. This term was popularized by Perugu Siva Reddy, M.D., chief of the Sarojini Devi Eye Hospital in Hyderabad, India, who mobilized traveling eye camps that visited rural populations. A cataract-free zone encompassed the notion of providing patients within a residential area with access to eye examinations and low-cost surgery to remove cataracts. Key to the concept was taking ameliorative care to populations rather than waiting until patients showed up at clinics.

* Under a contractual relationship with WHO, NEI supported a small portion of the personnel staff at the headquarters in Geneva.

** NEI dedicated a part of its limited resources to the WHO Program for the Prevention of Blindness, and entered into a contract with WHO on September 30, 1979, to fund joint research personnel and projects in three areas of research.

This strategy was geared toward needy populations who would not, or could not, afford to visit a clinic.

Dr. Reddy continued the tradition of traveling eye camps, in place since the early part of the nineteenth century when Indian and British medical practitioners had worked to bring eye care to needy rural populations. Reddy's work, of course, employed more current knowledge and was more highly organized; he was accompanied by a cadre of good surgeons, and the eye camps visited villages on a regular basis. Dr. Kupfer explains:

Reddy followed a set procedure: announcements were sent to rural villages, and on the designated day those villagers who were blind or visually impaired assembled in a building or tent to be examined. The prospective patients would pass through a number of stations for measurement of vision, refraction, intra-ocular pressure check, and ophthalmoscopic examination. Visually impaired villagers who likely had cataracts were given the option of having surgery that afternoon or the next day in a makeshift operating room. Those who came forward had the cataract removed (via the intracapsular cataract extraction method). Following the surgeries, most of the medical team departed but left behind a small group to look after the patients during the few days of convalescence. Upon discharge, each patient received aphakic spectacles to replace the patients' lenses removed at surgery.³⁰⁶

South American Demonstration Projects

NEI and collaborating organizations wanted to organize a cataract-free zone demonstration project along the lines of Reddy's eye camps, but NEI staff believed this type of public health work, proactive as it was, needed improvement. Participants would need to know the prevalence of blindness in the patient population, have adequate facilities for performing surgery, and be able to schedule extended follow-up for patients. NEI, the Pan American Association of Ophthalmology (PAAO), and Helen Keller International (HKI) jointly sponsored a meeting at NIH in April 1986 to develop a program. South American ophthalmologists, officials of the Pan American Health Organization, staff of HKI, and experts in operations research and cataract-intervention programs attended the meeting.

The planners focused on developing an approach that would attract large numbers of cataract patients. Based on lessons learned from previous public health projects like Reddy's, the planners knew that it would be difficult to attract advanced cataract patients to the hospital for surgery. Some patients would not commit to the required multiple visits or would have no one to accompany them, which was a necessity. The project would also have to counteract cultural resistance: many poorer South Americans believed that it was natural

for the aged to go blind as part of the course of life and that there was no alternative. The program also had to suit the socioeconomic conditions of the project area. Although the cost of surgery was modest by U.S. standards, it was still beyond the means of many. Medical and surgical care would have to be available at low or no cost and still be of high quality. Pre-surgical diagnoses would also have to be comprehensive in order to cull unsuitable candidates, such as those with preexisting retinal pathology; otherwise dissatisfied patients—whose surgeries had not succeeded because of preexisting conditions—might actively discourage others from getting treatment.³⁰⁷

To develop a workable strategy, planners looked to the principles of *operations research*, a managerial tool advanced by the U.S. military in World War II, and coming into vogue among large organizations by the early 1970s. Operations research applied theory to practice in order to optimize results. An applied field, operations research used scientific methods such as mathematical modeling and statistics to inform decision makers about potential problems so as to maximize performance. The notion was that the best possible solution to a problem could be determined by a scientific analysis grounded in mathematics, logistics, and other social science fields.

Two cataract-free zone demonstration projects were initiated in South America, each in a delimited geographic area with a restricted population, with the objective of reducing the level of cataract blindness to an absolute minimum within a specified short period of time. Helen Keller International and other organizations funded the two projects and organized the fieldwork; NEI designed the study and oversaw the data collection, data analysis, and preparation of the resulting publications.

The projects were carried out in Chimbote, Peru, and Campinas, Brazil, two cities that were considered to be underserved and presumed to have a high prevalence of cataract blindness. Some of the local ophthalmologists were initially concerned that Campinas was not a good choice because it had a university with a strong department of ophthalmology and a medical school attached to a good hospital; thus, they thought, it would be difficult if not impossible to find anyone blind from cataract who had not undergone cataract surgery.³⁰⁸ However, Dr. Reddy's work in India had forcefully demonstrated that waiting for blind or visually impaired patients to show up at a clinic was not a good approach for detecting these individuals in the community. There would be plenty of patients needing help. Indeed, the results of the project showed that there was an undetected cataract blindness problem in both areas.

In planning the studies, participants took into account certain factors they felt that international cataract work had in the past overlooked. It has been estimated that over his professional career as a cataract surgeon, Reddy performed 250,000 cataract operations.³⁰⁹ Yet, the prevalence of blindness in his patient population was unknown; surgery was

carried out in a temporary makeshift operating room, and extended follow-up was absent. In the end, the success of the operations was not known. Reddy's projects had failed to measure how many villagers, blind from cataract, had not come forward, nor had they measured patients' final *walking around vision*, a term referring to the long-term visual outcome of the patient after surgery. Walking around vision depended on several factors, including the success of the surgical operation, the absence of other causes for decreased vision such as glaucoma or retinal disease, the onset of late complications from the surgery, such as retinal detachment, glaucoma, or infection, and whether the patient had lost or broken the aphakic spectacles given to them after surgery. In short, a cataract operation did not automatically translate into restored vision. To simply state the numbers of cataract operations accomplished does not signify that those patients gained improved eyesight with cataract surgery. Hard evidence is required to demonstrate the connection between surgery and restored vision. So much effort and energy had been expended on identifying patients with blinding cataract and performing the 250,000 surgeries, and the results remained unknown.

The South American demonstration projects involved an outreach program: a mass publicity campaign was followed by a survey in which ophthalmologists and associated healthcare workers made door-to-door visits. People 50 years of age or older were asked to participate in an in-house vision acuity screening test. If visual acuity was less than 20/200, the patient was retested at a community health post. Outpatient surgery was offered to those patients whose vision problem was considered to result from cataract. Intracapsular surgery was performed in Chimbote, while extracapsular surgery was employed in Campinas. Visual acuity was tested three weeks post surgery, and an additional four to eight months post surgery in Campinas. Only two-thirds of those seen came forward for surgery. Eighty percent of operated cases had a postoperative visual acuity above 20/200. It was concluded that those not improving after surgery had other causes of poor vision, such as macular degeneration, chorioretinopathy, or another undetermined etiology.³¹⁰ The survey offered figures on the prevalence of cataract in those over 50 years of age. This statistic could be used to deduce the proportion of the cataract blind that would agree to surgery, and which incentives should be offered to encourage more patients to seek surgery. Additional house-to-house surveys were completed to determine "surgical coverage," that is, those who chose to have surgery out of the total eligible (calculated by dividing the number of surgical cases by the number of surgical cases plus unoperated cataract), and the visual outcome of those having the operation. At each stage, mathematical assessment and simple statistics were used to identify areas for improvement and the degree of success. The demonstration projects also provided low or no-cost surgery, and transportation was provided to and from local hospitals. In addition, staff provided extensive postoperative evaluations of vision. The publication detailing the study and its outcome was published in 1990.

These two demonstration projects served as a turning point: first, they underscored the magnitude of blinding cataract in areas thought to be free of this problem, and second, they provided practical knowledge about how a cataract-free zone program could be organized to provide high-quality care and surgery at low or no cost for large numbers of patients. The demonstrations marked a clear departure from the cataract-free zone projects in India. Among the key changes were: determining the prevalence of blindness as a result of cataract rather than other causes (accomplished through door-to-door visits and screening examinations); performing cataract surgery under sterile and well-equipped operating room conditions in a local hospital to improve surgical outcome while still charging a nominal amount or nothing for surgery; and follow-up to measure the success of the surgeries.

Francisco Contreras Campos, M.D., in Peru, and Newton Kara-José, M.D., in Brazil, were both heavily involved in the cataract-free zone experiment. They appreciated the need to go out into the community to locate those blinded from cataracts, bring them to a hospital facility, perform the surgery without charge, and return them to their homes with appropriate spectacles. The projects in Peru and Brazil supplied lessons from which ophthalmologists in other regions could learn.

Lions Clubs

In the early 1990s, Lions Clubs International provided major impetus to implementing cataract-free zones. Lions International approached NEI about sponsoring projects that could be accomplished worldwide, were oriented to sight restoration, could involve local Lions Clubs, and would be successful in having a major impact on reducing blindness and visual disability. The NEI staff suggested that the Lions focus on the conquest of cataract, and this immediately caught their imagination. Lions International began a fund-raising campaign. Ultimately, about \$212 million was raised by the Lions for this program, which was oriented toward eye care service projects in countries lacking resources.

Through the Lions *SightFirst* campaign, Lions International provided funds to local Lions Clubs collaborating with local ophthalmologists to begin a community-based program to deliver free surgery to the cataract blind. The *SightFirst* program began in the early 1990s and played a major role in South America. The goal was to eradicate cataract blindness along the lines of the earlier cataract-free zone demonstration projects in Peru and Brazil. The lessons learned from the two cataract-free zone campaigns in South America informed the Lions *SightFirst* cataract projects worldwide. Many local Lions Clubs in South American cities were keen on participating in cataract-free zone activities and provided services such as transporting patients to and from the hospital and assisting with personal needs and hygiene.

This model spread quickly to countries in Southeast Asia, Africa, and the Far East, with appropriate modifications to fit the local circumstances.

SightFirst convened a small advisory board composed of Professor Akira Nakajima, Dr. Carl Kupfer, Dr. Bjorn Thylefors (the WHO representative), and Lions members. The *SightFirst* projects represented a true partnership between the Lions, local participants, and NEI. While the collaborative spirit that developed among all of the participants was important, it is fair to say that without NEI's involvement in the development of the cataract-free zone model, the *SightFirst* cataract program in South America would not have been as successful. Nonetheless, efforts were made to have the local ophthalmologists and Lions receive the accolades; NEI stayed in the background.

As the Lions *SightFirst* projects were phased out, the universities in São Paulo (under Dr. Belfort) and Campinas (under Dr. Kara-José), along with the Brazilian Council of Ophthalmology, convinced Brazil's Minister of Health to provide financial support for the National Cataract Program. This program continues today through government support.³¹¹

NEI and Evaluating Success

Dr. Bjorn Thylefors, director of the WHO Programme for the Prevention of Blindness, discussed worldwide prevention of cataract blindness at the IAPB Fourth General Assembly, held at Nairobi, Kenya, in 1990. He underscored the importance of knowing, during the course of a project, how much progress was being made toward attaining practical, real solutions and objectives. In his keynote address, Thylefors stressed the need to "include an obligatory component of monitoring and evaluation in all national programs, in order to demonstrate success or failure, and to analyze constraints in program procedures." The "options for evaluation mechanisms, as worked out by the WHO Programme, should be considered and adapted to local needs Obviously, cost effectiveness has to be borne in mind when setting up evaluation schemes, but any sustainable program should reliably document results and achievements."³¹²

ICCE versus ECCE

One of the most critical and challenging projects conducted at the Aravind Eye Hospital demonstrated the value of Thylefors' principle about the necessity of evaluating efficacy. NEI, in cooperation with WHO, sponsored a randomized controlled clinical trial comparing two types of cataract surgery: (1) the intracapsular cataract extraction (ICCE), accompanied by fitting the patient with aphakic spectacles, and (2) the extracapsular cataract extraction (ECCE) method, combined with the implanting of an intraocular lens (IOL).

ICCE, already employed for more than 100 years, consisted of removing the natural lens from the eye once it had become opaque, thus preventing light from reaching the retina. The operated eye did not have an artificial lens inserted and the patient was fitted with a pair of aphakic spectacles.

With ECCE, most of the opaque lens was removed and an artificial IOL was implanted in the operated eye. The idea of replacing the natural lens with an artificial one dated to 1949, when a British ophthalmologist, Harold Ridley, placed an artificial lens in the eye at the location where the natural lens had been removed because of cataract. Although the Ridley lens—as the type of lens he used became known—was successful in some of the cases, there were enough complications to discourage further implantation of this type of lens. Nonetheless, the idea became popular, and by 1969 there were several other types of artificial lenses available on the market. By about 1980, artificial lenses had been improved considerably in terms of size, lightness, and tolerance by the eye, and the surgical procedure (called *pseudophakia*) to place the lens correctly in the eye was improved. The ECCE and IOL implant became the standard procedure in the majority of patients operated on in the industrial world.

The ICCE operation had its advantages: it was relatively easy to perform both quickly and successfully, and it did not require the added expense of an IOL (about \$50 to \$100). Instead, for only a few dollars, the patient could be fitted with a pair of aphakic eyeglasses to compensate for the removal of the natural lens. The disadvantages were related to the fact that aphakic correction of one eye produced a large discrepancy in image size between the two eyes (one aphakic and the other still with the natural lens having reasonably good vision). This situation was intolerable for the patient. Unilateral cataract surgery using this method was of no benefit, especially for individuals still gainfully employed.

Thus, if ICCE was used, there was a critical need to have the cataracts from both eyes removed—only then could aphakic spectacles provide adequate vision to both eyes. Yet, surgeons were reluctant to operate on both eyes at the same time because an infection in one eye could affect both eyes. There was always a possibility that the lens capsule that was not removed might become opaque and the patient would need another minor operative procedure three to four years later to make an opening in the lens capsule. This opacity occurred in about 10 to 20 percent of patients having this procedure. Few patients wanted to return for a second operation. If the first operation was successful, they were unhappy with the distortion caused by the thick aphakic spectacles. This period of adjustment was often interpreted by the patient as an unsuccessful outcome of the surgery. It was also necessary for good vision that the patient be given aphakic spectacles soon after surgery, and it was important that the spectacles be kept in good condition without scratches or bent frames.

The ICCE surgical procedure persisted as the operation of choice in countries such as India, but ECCE slowly gained in use, along with improvements pertaining to operation and eye structure issues, in cataract blindness programs.³¹³ As of 1992, an IOL was placed in less than 10 percent of the patients.³¹⁴ Data on the type of cataract operation in India indicated that from 1992 to 1995, the number of Indian ophthalmologists switching to ECCE/IOL increased from 20 to 33 percent, while the number of ICCE procedures decreased from 56 to 43 percent. The number of ECCE performed without an IOL stayed constant at 21 percent.³¹⁵ It should be noted that the vast majority of the operative procedures using ECCE/IOL were in the private sector.

By the 1980s, it was apparent that the ECCE/IOL procedure had the advantage of usually producing a good visual result. In competent hands, the patient might not need spectacles if vision without them was satisfactory for his or her needs. The disadvantage was that it involved a more challenging operative procedure that required the practitioner to relearn cataract surgical techniques; so, courses were given to teach the ECCE/IOL technique. Also, an IOL had to be purchased, though inexpensive, high-quality IOLs soon became available for about \$10.

Meanwhile, the debate continued. Some of the organizations supporting cataract surgery in the developing world were more comfortable continuing with the traditional safe, quick, and relatively easy-to-perform ICCE operation, while other organizations wanted to try to achieve better results for the patient. Reliable data comparing the safety and efficacy of these two procedures was nonexistent. The only answer was to conduct a randomized clinical trial comparing the two procedures.

NEI turned to the Aravind Eye Hospital in Madurai, India, where ECCE/IOL had been used for several years. With assistance from the NEI staff, a study was designed with all the necessary built-in quality controls. The senior ophthalmologists at Aravind agreed to conduct the trial, which began in 1995 with financial support from NEI and WHO. There were 3,400 patients who participated in the trial. Half were randomly assigned to receive ICCE with aphakic spectacle correction, while the other half received ECCE/IOL with spectacle correction, if needed. An international group of six ophthalmologists and biostatisticians, well-versed in clinical trials methodology, were chosen by NEI and convened as the Data and Safety Monitoring Committee. Of particular significance for this study was the development and inclusion of a quality-of-life questionnaire, administered to all the patients.³¹⁶ The results indicated that the best corrected vision following surgery performed by senior ophthalmic surgeons was slightly better when using the ECCE/IOL technique; more importantly, the data showed that the post-surgery quality of life was vastly better for those in the IOL group.³¹⁷ Following this study, the ECCE/IOL technique slowly squeezed out the ICCE surgery and was accepted universally as the standard of care.

National Studies

NEI, in collaboration with WHO, began a series of projects evaluating national programs designed to document the prevalence of cataract blindness in adults and the outcomes of cataract surgery. These studies were in line with Dr. Thylefors' 1990 talk on the need to evaluate and monitor national eye programs that left such a lasting impression on clinicians and NEI staff. There was growing concern about the efficacy of national cataract surgery programs, particularly in Nepal and India, where increasing numbers of cataract operations were performed through various NGOs without measuring the visual outcome. There was concern about China, too, which continually reported low cataract surgery rates. The governments in these countries welcomed nonprofits that sponsored and funded cataract surgery. While the NGOs usually excelled in mobilizing political will and resources, there was concern in some quarters that some NGO programs exclusively emphasized the number of eyes operated on instead of reporting the number of eyes in which vision had been successfully restored or improved.

NEI decided to support studies on the prevalence of blindness and the outcome of cataract surgery. To determine the number of eyes in which vision had been successfully restored or improved, the visual acuity of a sampling of patients was measured after surgery. Cataract surgery outcomes were measured clinically in terms of presenting visual acuity and from the patient's vision-related quality-of-life perspective as assessed by questionnaire responses. The results of these epidemiological research studies carried out in Nepal, China, and India are briefly summarized below; a more detailed description, including the estimated costs of program services, can be found in published papers.

Fortunately, NEI had available data for comparison that could be used in the Nepal evaluation projects. In 1981, a carefully constructed National Blindness Survey had been conducted in Nepal by the nonprofit organization SEVA (a Sanskrit word meaning "service"), which showed that 3.77 percent of the Nepalese population over the age of 45 years were bilaterally blind (less than 3/60). This survey had led to the establishment of a national eye care program for the control and prevention of blindness, begun in 1982. By the end of 1994, an estimated 140,000 surgeries (primarily cataract) had been performed through the national eye care program.

The NEI/WHO evaluation initiative in Nepal assessed whether there had been a reduction in the prevalence of the cataract blind in two representative rural areas of Nepal following surgical cataract procedures. The NEI/WHO project surveyed people ages 45 years and older from Nepal's Lumbini and Bheri zones using cluster sampling; those counted in a door-to-door survey were examined, and 5.3 percent of those examined were determined to be blind, defined as presenting visual acuity of less than 6/60 bilaterally. The principal

cause was cataract in at least one eye in 78 percent of cases. The surgical coverage was approximately 42 percent.

The study showed that the prevalence of blindness decreased slightly from that estimated in 1981 and that cataract surgical coverage increased somewhat, but none of these changes were statistically significant. Accordingly, the blindness prevalence in Nepal in the area studied was still quite high by the time the study was completed—and no doubt, still is.³¹⁸

The scores from the visual function and quality-of-life questionnaires correlated with visual acuity, so that as visual acuity improved, the scores from the visual function and quality-of-life questionnaires also improved. The survey indicated that the principal causes of vision impairment or blindness in operated eyes were surgical complications, macular degeneration, optic atrophy, and glaucoma. Whether some of these conditions predated the surgery was not amenable to analysis at the time.³¹⁹

What was learned from this Nepal study? It was apparent that the postoperative visual outcome was quite disappointing. It is true that substantial improvement in vision occurs if refractive error is corrected, particularly in aphakics without spectacles. However, the outcome that must be dealt with is the presenting vision of the patient. This is the “real world” visual acuity as experienced by the patient after cataract surgery. Sight restoration not only includes the surgery but also the correction of any refractive error with glasses. Without refractive correction, it is all too easy for the patient to ascribe poor vision to a failure of cataract surgery. In addition, careful screening of prospective surgical patients for preexisting causes of decreased vision, such as glaucoma, macular degeneration, and other retinal degenerative conditions, would make those patients ineligible for cataract surgery. According to the vision function and quality-of-life assessment, the patients recognized quite clearly when surgery had failed and their vision had not improved to a level where daily activities could be pursued.³²⁰ The resulting disappointment could have an enormous impact on whether there were enough “satisfied customers” receiving cataract surgery to spread the word that this procedure was successful. Unsatisfied customers sway prospective patients for cataract surgery to forgo the operation. Improving cataract surgery outcomes and keeping costs to a minimum might ensure adequate patient satisfaction.

Similar NEI/WHO-sponsored studies using identical protocols were conducted in China in two different locales. The data from two counties, Shunyi County near Beijing, and Doumen County near Guangzhou, were similar to each other in prevalence of blindness (4.3%).³²¹ The studies showed that patients from these two counties, as well as from a subsequent study in Hong Kong, were not receiving the full sight-restoring potential expected from modern-day cataract surgery.³²²

In India, cataract surgery had been in place on a wide scale for several decades. The NEI/WHO studies in India were able to access earlier national data for comparison purposes. A few prior surveys measuring the prevalence of cataract problems had provided the Indian government with a rough basis for understanding the scope of the problem. The NEI/WHO-sponsored surveys in the 1990s, however, emphasized the importance of outcomes, something that had not been addressed at all in the earlier Indian Government surveys. Moreover, the quality control of the later studies by NEI/WHO was more rigorous. These 1990 studies, funded and managed by NEI/WHO, with the World Bank contributing some funds, were carried out in specific districts and used the same survey protocols developed by NEI and used in Nepal and China. To ensure complete enumeration of study subjects and a high response to the eye examinations, surveyors went door-to-door identifying everyone over the age of 50. It was important to ensure that individuals participate in the study by having the eye examination. If a large enough cross-section of individuals with and without problems did not show up for the exam, it was difficult to interpret and generalize the data. With the earlier studies sponsored by India's Government, the extent to which the people examined were truly representative and selected with minimum self bias was unclear.³²³ The evaluation studies in Nepal, China, and India clearly documented the need for better planning of surgical programs, with attention to the training of the surgeons, selection of cases, and careful operative procedures. Even with best correction, the visual acuity in cataract-operated eyes was poor. It is apparent from the studies cited above that the concept of presenting vision is important in assessing visual outcomes in both prevalence surveys as well as surgery outcome. Best-corrected vision is only acceptable as an outcome if, in point of fact, the refractive error has been corrected and the person wears the corrective equipment.

Summarizing the results of the outcomes of cataract surgery conducted in Nepal, China, and India, the potential improvement to a level of 6/12 vision following cataract surgery was as good as 90 percent under the best of conditions. ECCE/IOL was found superior to ICCE in safety, visual acuity restoration, and visual function/quality-of-life (VF/QOL) outcomes. Blindness (due to cataract) varied considerably between countries, and continued to be a significant public health problem among the elderly in many areas—especially among women and the uneducated. Cataract surgery outcomes, both visual acuity and VF/QOL, were frequently below what was achievable.

Implementing the Epidemiological Approach

One of the most successful operations research projects in the delivery of cataract surgery was conducted by the Aravind Eye Hospital in Madurai, India. The study is a good example of how the epidemiological approach was put to use in fieldwork. This NEI-funded project took place during the late 1980s, under the direction of G. Venkataswamy,

the hospital director, working in conjunction with the University of Michigan. The goal was to develop a solution for overcoming patients' reluctance to undergo surgery, a problem Venkataswamy and his team of ophthalmologists had confronted with their mobile eye camp work. Often, too many villagers with blinding cataract refused surgery despite being offered free transportation to and from Aravind Eye Hospital. Venkataswamy wanted more people to have the surgery done at the base hospital in Madurai.

U.S. and Indian scientists with expertise in operations research, health education, and epidemiology developed a study that looked at ways to reduce various socio-cultural, economic, and logistical barriers to cataract surgery among India's rural blind. Educational and motivational activities, aimed at increasing both awareness and acceptance of cataract surgery, were evaluated in a probability sample of 100 villages, including (1) house-to-house visits by a patient who had successful cataract surgery (referred to as an aphakic motivator), (2) house-to-house visits by eye health workers, (3) visits by a screening van to a central location in a village, and (4) health-education campaigns conducted at weekly marketplaces. To determine the effect of economic subsidies on surgical acceptance rates, each of these activities was tested with two different incentive combinations: free travel, food, surgery, and eyeglasses were offered to half the study subjects, and free surgery and eyeglasses to the other half. Aravind Eye Hospital already practiced a policy of not charging for the operation if the patient could not afford it. In general, about 50 percent of the patients operated on at Aravind paid no fee. The surgery was financed from paying patients. Percentage reductions in the backlog of cataract-blind patients, and increases in surgical coverage were used to measure the effectiveness of the different strategies.

The analysis of the data suggested that the screening van and the aphakic motivator intervention, along with the full economic incentives, were most successful in bringing cataract-blind patients to cataract surgery. The aphakic motivator was more effective than the screening van, but it was also more costly. The study results, published in 1991, have been used to guide the development of more cost-effective programs at Aravind and elsewhere for reducing cataract problems.³²⁴

Age-related cataract epidemiological studies in India and Barbados

Two other studies dealt with epidemiological research. The first example is a case-control study of factors affecting the development of age-related cataract. It was conducted jointly by the scientists and members of the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India. In a hospital-based case-control study of 1,441 patients with age-related cataract and 549 controls, the association between types of cataract—nuclear, cortical, posterior subcapsular, and mixed types—and a number of physiologic, behavioral, environmental, and biochemical variables were studied.

There appeared to be an increased risk of cataract with lower educational achievement and decreased cloud cover at place of residence (for all types of cataract); the use of aspirin less than once a month (for posterior subcapsular and mixed cataract); high blood pressure (for nuclear and mixed cataract); use of cheaper cooking fuels (for cortical, nuclear, and mixed cataract); and lower levels of an antioxidant index based on red blood cell levels of glutathione peroxidase and glucose-6-phosphate dehydrogenase and plasma levels of ascorbic acid and vitamin E (for posterior subcapsular and mixed cataract). The risks were statistically different for different cataract types, a finding that emphasized the need to investigate the epidemiology of specific types of cataracts.³²⁵

The last example of epidemiological research is a study of the prevalence and incidence data of age-related cataract in Barbados. It involved risk-factor analysis in patients with glaucoma, age-related macular degeneration, and diabetic retinopathy. NEI and Dr. Carl Kupfer had been developing the basis for a working relationship with the Government of Barbados when Dr. Kupfer visited the country in 1978. At the request of the Pan American Health Organization (PAHO), Kupfer gathered information on the major causes of blindness and visual disability throughout the Caribbean. In visiting the hospitals and clinics of several islands, he saw a large number of blind and visually disabled patients. Cataract seemed to be the major cause of poor vision. On the islands visited, the best facility appeared to be the Queen Elizabeth Hospital in Barbados, which also had several well-trained and competent ophthalmologists in attendance. In the ensuing years (from 1978 to 1985), Kupfer maintained contact with the Minister of Health of Barbados and met with him during annual visits to the PAHO headquarters in Washington, D.C. The Minister was interested in surveying the blind in Barbados to determine prevalence and possible risk factors for cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration. This offered a unique opportunity to determine the prevalence and incidence of major eye diseases in a population of predominantly African origin. The resulting Barbados Eye Study was an exceedingly productive and scientifically outstanding collaboration between the Ministry of Health of Barbados and NEI. The study was begun in 1985 and ended in 2003, and the principal investigator was M. Cristina Leske, M.D., M.P.H., from the University of New York at Stony Brook.

Barbados was an excellent site for such a study because the demographic data on all Barbadians born on the island during the last 75 years was available. The population was stable and Barbadians did not change residence often. They rarely left the island; if they did, they usually returned in a relatively short period of time. They were also motivated to keep their appointments at the hospital. Data on birth date, sex, and residence on the island was available. The data gathered on the predominantly Afro-Caribbean population was generalizable to other groups of African origin, such as the African-American population; thus, the

study also produced some of the first data on age-related cataract, glaucoma, diabetic retinopathy, and macular degeneration pertaining to African-Americans.

Blinding Malnutrition and Vitamin A Deficiency

The second area of research, at the other end of the age spectrum, was blinding malnutrition affecting infants and young children, a problem in the non-industrialized world.

Dr. Kupfer joined the International Vitamin A Consultative Group (IVACG) when it was formed in 1975 by the United States Agency for International Development (USAID) to advise countries on vitamin A supplementation. This group examined the high prevalence of vitamin A deficiency among children ages one through six years, primarily in countries of Asia, the Middle East, Africa, and South America. Vitamin A deficiency among children was serious and could lead to death in the first few years of life. The rate of mortality was estimated to be approximately 50 percent among children who had vitamin A deficiency in those regions. Additionally, vitamin A deficiency, when accompanied by malnutrition, can cause blindness resulting from keratomalacia, a softening of the cornea (usually bilateral) leading to opacification and perforation of the cornea.

The interventions most commonly employed in the 1960s and 1970s were the distribution of a concentrated vitamin A supplement to children in the form of capsules or a syrup (the primary form used in India), or foods such as sugar fortified with vitamin A (used in Guatemala). From a medical viewpoint, it was not yet fully understood whether these were the best preventative approaches. More research was needed to answer questions such as what was the interdependence of protein supplementation and vitamin A utilization; the optimal dosage of vitamin A to increase blood levels of vitamin A; the most effective approach to increasing retinol-binding protein in the serum of malnourished children; and the possible role of collagenase (an enzyme causing softening of the cornea) in keratomalacia, resulting from vitamin A deficiency.

In view of the importance of these questions, the NEI staff examined whether there were sufficient high-priority research opportunities related to ocular manifestations of vitamin A deficiency. Furthermore, they explored the possibility of setting up a collaborative research facility to investigate vitamin A deficiency-related problems, such as diagnosing the condition early-on, the treatment of young malnourished children, and preventing the onset of diarrhea and weight loss potentially leading to blindness and death.

Blinding malnutrition, primarily related to vitamin A deficiency, and the impact of improving an individual's overall health, became the second area (after cataract) of NEI international collaborative research. NEI sponsored a workshop on preventing blinding

malnutrition, held at NIH in October 1976. A major outcome was the designation of the National Institute of Nutrition (NIN) in Hyderabad, India, as a Collaborative Clinical Research Centre for the Prevention of Blindness. The patients were Indian children with vitamin A deficiency, and both Indian scientists and American scientists collaborated on a number of projects. The American Government contributed dollar funds through the USAID office in India to purchase the research instrumentation needed for the projects. The Indian Government supported the clinical and field research on children enrolled in the projects designed to reduce both blinding malnutrition and death among the children ages one through six years.

Dr. Kupfer describes the participation of USAID:

It was fortuitous that I met one of the USAID representatives working in India while I was visiting the Science Attaché at the American Embassy in Delhi. We struck up a conversation. The USAID representative opined that he was under pressure to fund some activities that were more humanitarian in nature than building roads and bridges. I casually mentioned our efforts to combat blinding malnutrition among poor Indian children. Plans were underway for the NEI, in conjunction with the Indian Government, to support the Collaborative Research Center in conducting research to combat this blinding eye disease. Although we had funding from the Indian Government for salaries and local expenses, we fell short of dollars to purchase necessary equipment to conduct the research. He asked how much we needed and I swallowed hard and said 3 million dollars. He said that would be perfect because that was the remaining amount of money he had to invest. That is how the USAID, by purchasing the necessary research equipment needed for these projects, became a partner in this most important enterprise.³²⁶

The NEI relied on the advice of a consultant, Dr. Barbara Underwood, a senior researcher in vitamin A biochemistry with many years of fieldwork in countries around the world. Underwood joined the NEI staff in late 1982, after teaching and conducting research at the University of Maryland, Columbia University, Penn State, and MIT. She became assistant director for international activities, helping to conduct an international program to combat blindness, particularly blinding malnutrition, primarily in India. Underwood retired from NEI in 1998 as one of the world's foremost authorities in nutrition and the biochemical aspects of vitamin A.³²⁷

The American and Indian Governments signed a Memorandum of Understanding at NIH in 1982. Studies on vitamin A and its relationship to blinding malnutrition in children soon commenced at NIN in Hyderabad, with the financial support of USAID.

Dr. Underwood coordinated the scientific projects, which were implemented by the American and Indian scientists. The planned projects focused on developing strategies for early detection of xerophthalmia (night blindness and drying of the conjunctiva and cornea), detection and treatment of keratomalacia (softening and perforation of the cornea), and improvement of nutrition to help prevent morbidity, loss of vision, and death from vitamin A deficiency. At a meeting in Hyderabad, NEI scientific staff and NIN researchers prepared research proposals in the format of an NIH research grant application. The proposals were sent for review through the NEI Visual Science Study Section, where they received a high and “payable” priority. Although NEI was not funding the studies, having the plans critiqued by an impartial study section assured that the collaborative research projects would be of high quality. NEI then turned to the Fogarty Center at NIH, which had authority to disperse unused PL 480 funds. As part of the PL 480 program, the U.S. Government in the 1950s purchased surplus American foodstuffs for distribution to the poor in India, as well as other countries, in order to prevent massive nutritional insufficiency and death. India became more self-sufficient in the 1970s and 1980s, and PL 480 funds no longer needed for food were made available for other health-related activities, including research. PL 480 funds paid for part of the joint ophthalmic NEI/India projects at the Collaborative Research Center in Hyderabad. By about 1982, the Hyderabad Centre had completed equipping the laboratories and training the personnel that would conduct the laboratory and clinical research studies.

One of the first collaborative studies conducted at NIN investigated the effect that diarrhea might have on absorption of a large oral dose of vitamin A supplement. The results showed that despite the presence of diarrhea, more than 90 percent of the dose, given with oral rehydration fluids or water, was absorbed. This was an important finding because undernourished children with diarrhea are frequently vitamin A deficient, but there was a tendency to withhold vitamin A prophylaxis until they had recovered from diarrhea. For a severely deficient child, this could rapidly precipitate xerophthalmia, followed by keratomalacia.³²⁸

Since measles was thought to be an additional risk factor for keratomalacia and possible blindness, a study of slum children was undertaken to look at the relationship between measles, malnutrition, and the occurrence of blindness. One of the significant findings was that serum level of vitamin A is significantly depressed during the acute phase of measles, but returns to the normal homeostatic level after eight weeks of recovery. Evaluating vitamin A status from serum levels during an infection, therefore, may not always provide a true picture of vitamin A levels in the blood. This observation has been repeatedly demonstrated, emphasizing the need for more reliable means of assessing vitamin A status during acute or chronic infections. One such measure, dubbed the Relative Dose Response (RDR) test, was developed in Dr. Underwood’s laboratory. It provides an indirect measure of critically depleted liver stores of vitamin A before the serum level declines to levels diagnostic of deficiency.

A follow-on study conducted at Hyderabad showed that clinical symptoms of vitamin A deficiency appeared to be associated with hyperproliferation of the conjunctival goblet cells, whether or not there was a superimposed measles infection.³²⁹ This was an additional, easily detected sign of vitamin A deficiency. A subsequent methodological study at Aravind Eye Hospital in Madurai, India, was done to determine which staining technique for revealing conjunctival goblet cells obtained by impression cytology provided the best reproducibility for vitamin A status assessment under field conditions.³³⁰

Dr. Underwood's responsibilities at NEI included working with scientists outside of India in the effort to prevent blinding malnutrition. One of the first large field tests using the RDR assessment tool was carried out in collaboration with scientists in Recife, Brazil. The results were reported in 1984. The vitamin A status was assessed using the RDR test before and after 20, 120, and 180 days following a 200,000 IU dose of vitamin A. Low serum levels (under 200µg/L) were invariably associated with an elevated RDR, which indirectly indicated depressed liver stores; whereas, higher values (between 200-400 µg/L) were not consistently predictive of a positive RDR. All elevated (20% or higher) RDR levels reverted to normal following supplementation indicating liver stores restored above the critical level of depletion. The study concluded that the RDR test was more predictive of marginal liver stores when serum values were in the range of 200-400 µg/L, than was the serum value alone. This suggested that RDR could better identify children in a marginal state of deficiency than could a serum level, and that the test could also be used to evaluate the effectiveness of intervention programs when serum values were in a range above 200µg/L that could not be interpreted with any confidence.³³¹

Further evaluation of data from the Brazilian study compared children who unexpectedly became infected with chickenpox during the course of the six-month follow up to a single, large vitamin A supplement. The six-month RDR assessment revealed that 74 percent of the children who had the chickenpox infection tested RDR-positive, compared to only 10 percent of those not infected. This study was the first to quantitatively document how an infection accelerates the rate of depletion of vitamin A liver stores.³³² This emphasized the importance of public health interventions to control infections in conjunction with vitamin A intervention programs.

Probably the most important collaborative field study done was with the Indian scientists at the Aravind Eye Hospital. The result was a surprise to everyone. Mortality was reduced more than 50 percent just by providing a small weekly dose of vitamin A equivalent to the recommended dietary intake. The programmatic significance was that a decrease in mortality was realized at an intake level potentially obtainable through food and did not require a massive dose supplement. In fact, the effect noted by the frequent low-dose administration exceeded the effect found in any of the other randomized, controlled trials that used a single

massive dose (200,000 IUs), given at four to six month intervals. Subsequent studies found similar advantages of frequent small doses over large doses given to hospitalized sick children. The excuse for not pursuing this as a public health strategy was the logistics involved in providing the supplement weekly versus at four to six month intervals.³³³ In spite of the remarkable effects on mortality observed in this study, it was not possible to demonstrate the impact of the weekly dose on the incidence of diarrhea or respiratory infections. In addition, no improvement in the growth of the child could be shown.

The studies suggested that neither frequent contacts nor vitamin A alone could solve health and nutrition problems reflected in morbidity and the wasting away of children living in deprived environments. It takes a more holistic approach incorporating social and public health programs that improve the environment and social context to make a significant difference in morbidity.

In summary, much new and valuable information came from the collaboration of scientists from NEI, India, and other countries where blinding malnutrition is a significant health problem. More needs to be done before blinding malnutrition disappears. It is hoped that the groundwork has been laid and research will continue, as well as collaboration with WHO and other NGOs.

Refractive Error in Children

The third area of international research began in the early 1990s, when NEI assumed a role in determining the prevalence of childhood refractive error and the consequences when this problem was left uncorrected.

The *SightFirst* program in Latin America showed that for each person needing cataract surgery to restore vision, there were two individuals requiring refractive correction to provide good eyesight. Refractive error was the most common visual disability in children. As a result, a multi-country study was planned to examine this issue. NEI, collaborating with WHO, provided contract support, designed the protocol, visited ongoing field-research activities, analyzed data, and helped report the findings. These studies focused on the prevalence of refractive errors and visual impairment in school-aged children from different ethnic origins and cultural settings. The areas studied were the Mechi zone in Nepal,³³⁴ the Shunyi district in China,³³⁵ and the La Florida district of Santiago, Chile.³³⁶ Because all three studies shared a common protocol, the direct comparison of data among the studies was straightforward. The data showed that among children ages 5 to 15 years, refractive error was the major cause of decreased vision and few of the studied children wore glasses; refractive error, however, could be easily corrected with glasses, resulting in improved vision. Thus, lack of refractive error correction was a significant public health problem, easily remedied, but mainly ignored.

Another interesting and provocative finding pertained to the prevalence of myopia in these three ethnically and culturally different populations. At one end of the spectrum, China had almost 45 percent myopia by age 15 years; Chile was somewhat less, at 15 percent, while Nepal had only about 1 percent at age 15 years. These findings are being investigated further to seek explanations for these wide differences, with additional studies planned for China, India, Malaysia, and South Africa.

In general, it is apparent that reduced vision because of refractive error in school-aged children varies considerably among countries and between rural and urban settings. Uncorrected myopia in school-aged children is a growing public health problem. In some settings, two-thirds of those who could benefit from spectacles are without them.

Exchange Programs and Support for International Researchers

In the mid 1970s, NEI, in an effort to further expand its research base, began to develop training programs for young investigators and exchange programs for collaborative research among senior investigators. In 1966, Dr. Jin Kinoshita, a rising star in ophthalmic biochemistry at Harvard's Howe Laboratory of Ophthalmology, met Professor Akira Nakajima of the Juntendo Medical School in Tokyo at a symposium on the Biochemistry of the Eye held in Tutsing, Germany. They became friends. Kinoshita consulted with Nakajima about ophthalmic biochemists in Japan who might want to spend time at Howe Laboratory. Nakajima suggested Dr. Kabasawa, an ophthalmologist working in ophthalmic biochemistry, and Dr. Okisaka, who was working in experimental pathology. Both Japanese scientists joined the Howe Laboratory in 1971 to gain additional research experience. When Kinoshita and Toichiro Kuwabara moved to the NEI intramural program in 1972, the two Japanese scientists moved with them. They were among the first foreign vision scientists studying at NEI.

This initial arrangement was informal and allowed the investigators to pursue their research interests with the help and guidance of Kinoshita and Kuwabara. It gave rise to the desire to have a more formal structure. The resulting exchange program between Japanese and American vision scientists was one of the most successful collaborations in the visual science area. In 1975, Professor Akira Nakajima from the Juntendo University Department of Ophthalmology and Professor Mizukawa from the Osaka University Department of Ophthalmology, invited Dr. Kupfer, Dr. Kinoshita, and Dr. Kuwabara to visit Japan with the intent of arranging a formal agreement for the exchange of senior vision scientists between NEI and the Japanese Ministry of Health and Welfare. The latter, however, was unable to accommodate such a program at that time. Dr. Kupfer sought the advice of the U.S. Embassy in Tokyo. The embassy staff was most helpful and arranged an agreement between NEI and the Japan Society for the Promotion of Science (JSPS), a quasi-governmental organization

affiliated with the Japanese Ministry of Education. Theodore Cooper, M.D., assistant secretary for health at DHEW, and Dr. Seiji Kayak, president of the JSPS, jointly announced the agreement in 1976. The program provided for the exchange of well-established Japanese and American scientists pursuing research on blinding and disabling eye diseases. The terms of the governing Memorandum of Understanding allowed two exchanges—one long and one short—per year. Through this program, Japanese and American laboratory and clinical investigators began to collaborate on important areas of vision research. This was the first formal agreement for such a scientific exchange in the area of vision research between the United States and any foreign country. Initially covering a three-year period, the exchange program ended 15 years later in 1991 (see Appendix B).

In 1976, Professor Nakajima and Dr. Kinoshita (who by that time was the scientific director of the NEI IM program) discussed the possibility of having a second program for younger, less senior researchers. The notion was to have promising young Japanese ophthalmologists who already had some research experience join the intramural program at NEI for two to three years to acquire further research experience. Upon their return to Japan, the expectation was that these individuals would eventually obtain academic positions in a university ophthalmology department and provide leadership to the next generation of Japanese ophthalmologists. They would assume the responsibility of conducting research, training ophthalmologists, and providing treatment to patients with visual disabilities. The program officially began in 1976, and the last candidate left NEI in 1995. The program and its cadre of researchers enjoyed a high level of success. Thirty-two out of 55 ophthalmologists (58%) returned to academic ophthalmology and currently hold academic appointments as assistant (9), associate (9), or full professor (14). Nine (16%) work in hospitals as ophthalmologists, and 14 (25%) are in private practice. Through the efforts of Nakajima in Japan and Kinoshita and Kuwabara at NEI, this program had a major impact in providing research training to a large segment of the generation that now guides Japan's substantial program in vision research.

Through the years, individual scientists from several countries, including Great Britain, Italy, Sweden, Australia, and New Zealand, have applied for research grants from NEI and were successful. For a foreign national to receive a research grant, the proposal must have an outstanding rating; the grant is restricted to a maximum of three years with the opportunity of renewal for another three years, and indirect (overhead) costs cannot be provided. Scientists abroad, funded by NEI, account for only a small amount of the total extramural funding.

In addition to exchange programs, NEI also fostered the spread of knowledge among the international community by encouraging grants to vision researchers from other countries. Dr. Kupfer recalls:

On one of my trips to Hyderabad, India, in the early 1990s, I met Professor Dorairajan Balasubramanian (known as Balu to his friends), the director of the prestigious Centre for Cellular and Molecular Biology in Hyderabad. Dr. Balasubramanian inquired about spending a year at NEI in the intramural laboratories to continue research on the eye lens. That was easily arranged, and the staff at NEI was quickly impressed with his competence as a researcher. In a casual conversation, I asked him why he never applied to the NIH for grant support, as was done by a few foreign nationals. I was fully aware that there were some collaborative research grants between laboratories in the United States and India, but they usually were submitted by the American side and the principal investigator was almost always an American. He said he would consider that idea. Soon after, an RO1 grant proposal listing Balu as the principal investigator was submitted to the NIH, assigned to the NEI, peer reviewed by the Study Section, and given a high priority. The grant was funded in 1995 for three years (the time limit for foreign grants). The subject of this RO1 grant was, “The Origin, Structure, and Role of Pigments in Human Eye Lens.” Balu was the third Indian scientist listed as principal investigator to receive an RO1 grant from the NIH, and we were proud that it was NEI that funded this grant.³³⁷

* * *

NEI, with minimal resources, played an important role in international activities by (1) advising the major worldwide delivery programs of eye services; (2) developing and advising U.S. policy on an international eye care program; (3) influencing major international organizations, such as WHO, by encouraging their involvement and support of eye care programs; (4) encouraging one of the largest world NGOs, Lions Clubs International, to become a major patron of the Prevention of Blindness program worldwide; and finally, (5) expanding the international pool of vision researchers involved in the support and conduct of eye research worldwide.

On December 16, 2004, WHO announced that the global rates of cataract, vitamin A deficiency, and other avoidable eye diseases had decreased.³³⁸ Surely, NEI’s work was in part responsible. Indeed, a WHO representative recently described the long collaboration between NEI and WHO as “outstanding, leading to the development of most of the currently recommended strategies and their subsequent monitoring.”³³⁹

Dr. Kupfer’s presentation as the outgoing president of IAPB at the Fourth General Assembly in 1990 continues to provide a fitting description of the importance of international work:

In summary, let us remind ourselves of the need to keep three thoughts in mind. First, [we must] set priorities on allocation of scarce resources. It is better to do a few projects well, in utilizing resources effectively and efficiently, than to spread the same resources over many projects in a limited and inadequate manner. Secondly, we must continually be concerned with the quality of the outcome of the project; this outcome should represent excellence in achieving stated objectives, whether it be in fully restoring vision to the cataract blind or preventing blinding malnutrition. Evaluation will tell us whether we have delivered a quality service with constituent satisfaction. We should not settle for less. Finally, and most important, we must at all times maintain a customer-oriented service mentality. In a sense, the blind are like hostages. They are held hostage to their disability and are held hostage to those of us who can make them see again. They have few, if any, options in their quest for a better life.

Accordingly, we must be especially conscious of the humanitarian aspect of our actions. This feeling for humanity must pervade our thinking, our planning, and our actions.^{340*}

* In 1988, Dr. Kupfer became the Acting Director of the Fogarty International Center at the invitation of the NIH Director, Dr. James Wyngaarden. Dr. Kupfer stipulated that Ed McManus join him. During their seven months there, the two organized a program planning group that served as sub-committee of the center's Advisory Board. This group led several of the institutes on campus toward a new and expanded direction regarding international health activities.

Appendix A: Abbreviations

AAO	American Academy of Ophthalmology
ACRF	Ambulatory Care Research Facility
AFB	American Foundation for the Blind
ALS	Amyotrophic lateral sclerosis
AOA	American Optometric Association
AR	Aldose reductase enzyme
ARVO	Association for Research in Vision and Ophthalmology
AUPO	Association of University Professors of Ophthalmology
CD	Clinical Director
CDC	Center for Disease Control and Prevention
CBM	Christoffel Blinden Mission
COMS	Collaborative Ocular Melanoma Study
CRAC	Clinical Research Advisory Committee
D-AL	Democrat from Alabama
DALY	Disability Adjusted Life Years
DHEW	Department of Health, Education and Welfare
DDIR	Deputy Director of NIH Intramural Research
D-PA	Democrat from Pennsylvania
DRG	Division of Research Grants
D-RI	Democrat from Rhode Island
DRS	Diabetic Retinopathy Study
DRRF	Division of Research Resources and Facilities
DSMC	Data and Safety Monitoring Committee
D-WVA	Democrat from West Virginia
ECCE	Extracapsular Cataract Extraction

EM	Extramural
ETDRS	Early Treatment of Diabetic Retinopathy Study
FASEB	Federated American Societies for Experimental Biology
GPRA	The Government Performance and Results Act
HEDIS	Health Plan Employer Data and Information Set
HKI	Helen Keller International
IAPB	International Agency for the Prevention of Blindness
ICCE	Intracapsular Cataract Extraction
IEF	International Eye Foundation
IM	Intramural
IOL	Intraocular Lens
IONDT	Ischemic Optic Neuropathy Decompression Trial
IRB	Institutional Review Board
IVACG	International Vitamin A Consultative Group
JSPS	Japan Society for the Promotion of Science
MCA	Music Corporation of America
MRA	Model Reporting Area
NAEC	National Advisory Eye Council
NAEVR	National Alliance for Eye and Vision Research
NAION	Non-Arthritic Ischemic Optic Neuropathy
NARD	National Association of Retail Druggists
NAS	National Academy of Science
NAVH	National Association for Visually Handicapped
NCI	National Cancer Institute
NDDIK	National Institute of Diabetes and Digestive and Kidney Diseases
NDEP	National Diabetes Education Program
NEI	National Eye Institute
NEHEP	National Eye Health Education Program

NGO	Non-Governmental Organization
NHI	National Heart Institute
NHLBI	National Heart, Lung and Blood Institute
NIAMD	National Institute of Arthritis and Metabolic Diseases
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINDB	National Institute of Neurological Diseases and Blindness
NINDS	National Institute of Neurological Diseases and Stroke
NLM	National Library of Medicine
NSPB/PBA	National Society for the Prevention of Blindness (Prevent Blindness America)
OBE	Office of Biometry and Epidemiology
OMB	Office of Management and Budget
ONDS	Optic nerve decompression surgery
ONTT	Optic Neuritis Treatment Trial
PAAO	Pan-American Association of Ophthalmology
PAG	Policy Advisory Group
PAHO	Pan-American Health Organization
PBA	Prevent Blindness America
PDR	Proliferative Diabetic Retinopathy
PHS	Public Health Service
PERK	Prospective Evaluation of Radial Keratotomy Study
PPBS	Planning, Programming, Budgeting Systems
PPC	IAPB Priorities and Projects Committee
RCSB	Royal Commonwealth Society for the Blind
RCT	Randomized controlled clinical trial
RDR	Relative Dose Response

RLF	Retrolental Fibroplasias
RPB	Research to Prevent Blindness
RPG	Research Project Grants
ROP	(pre-threshold) Retinopathy of Prematurity
SD	Scientific Director (of an NIH Institute)
SSI	Sight Savers International
USAID	United States Aid for International Development
VF/QOL	Visual Function/Quality of Life Outcomes
WHO	World Health Organization
WHO-PAG	WHO Program Advisory Group

Appendix B: US-JSPS Scientific Exchange Program Participants

Table 1 — Japanese Scientists to USA

Name of Japanese Researcher	Institution	Institution Visited
Tohru Yoshizawa	Prof. of Biophysics, Kyoto University	Princeton University
Makoto Tamai	Lecturer, Dept. of Ophthal., Tohoku University	Univ. of California
Motohiko Murakami	Prof. of Physiology, Keio University	Yale University
Kanjiro Masuda	Lecturer, Dept. of Ophthal., University of Tokyo	Yale University
Mitsuo Ikeda	Prof. Tokyo Technical Univ.	Univ. of California, San Diego
Naohiro Ishii	Asst. Prof., Nagoya Technical Univ.	Univ. of California, Los Angeles
Masao Tachibana	Asst. Prof., Nagoya Technical Univ.	Harvard University
Kouroku Negishi	Prof of Physiology, Kanazawa Univ.	New York University
Mototsugu Saishin	Asst. Prof., Nara Medical College	Johns Hopkins University

Name of Japanese Researcher	Institution	Institution Visited
Eichi Yamada	Prof. of Anatomy, Univ. of Tokyo	National Eye Institute
Manazbu Mochizuki	Assoc. Prof. of Ophthal., Univ. of Tokyo	Yale University
Yozo Nishimura	Assoc. Prof. of physiology, Keio University	Yale University
Motokazu Itoi	Prof. Of Ophthal., Kyoto Prefectural Med. College	Eye Bank Sys. & Corneal Disease
Akira Urayama Shigeaki Ohno Kanjiro Masuda Tsuyoshi Sakane Kimihiro Nakae Akira Nakajima Yoshiro Fukuda Mitsuko Kogure	Professor Akita University Assoc. Prof., University of Tokyo Assoc. Prof., University of Tokyo Assoc. Prof., Shimane Medical College Assoc. Prof., Dokkyo Medical College Professor, Juntendo University Professor, Juntendo University Assoc. Prof., Tokyo Women's Medical College	Workshop on Cause and Treatment of Behcet Disease
Jiro Usukura	Research Fellow, University of Tokyo	Jules Stein Eye Institute

Name of Japanese Researcher	Institution	Institution Visited
Hiroshi Uozato Motokazu Itoi	Research Fellow, Nara Medical School Prof. of Ophthal., Kyoto Prefectural Med. College	Johns Hopkins University
Keiji Uchikawa	Research Fellow, Tokyo Technological Univ.	California University
Naoyuki Usaka	Assoc. Prof., Otte University	Penna. State University
Makoto Higuchi	Research Fellow, Hokkaido University	National Eye Institute
Mizuo Matsui	Prof. of Ophthal., Nihon University	University of Illinois
Takayuki Murakoshi	Research Fellow, Tokyo Medical & Dental Univ.	Rockefeller University
Akira Nakajima Yutaka Inaba Takeo Juji Manabu Mochizuki Shigeaki Ohno Ko Okumura Kazunori Onoe Masahiko Usui	Prof. of Ophthal, Juntendo University Prof. of Hygiene Juntendo University Prof. of Immunology, Univ. of Tokyo Assoc. Prof., Univ. of Tokyo Assoc. Prof. of Ophthal., Hokkaido University Prof. of Immunology, Juntendo University Prof. of Immunology, Hokkaido University Prof. of Ophthal, Tokyo Medical College	US-Japan Workshop on Ocular Immunology (Hawaii)

Name of Japanese Researcher	Institution	Institution Visited
W. H. Miller	Professor, Yale University	Prof. Junichi Toyota, St. Marianne Medical School
H. Shichi	NEI, Laboratory of Vision Research	Prof. Toru Yoshizawa, Kyoto University

American Scientists to Visit Japan by Agreement

Name of Researcher	Institution	Institution Visited
D. J. Hamasaki	Assoc. Prof. Univ. of Illinois	Prof. Toru Yoshizawa, Kyoto University
T. G. Ebrey	Assoc. Prof. Univ. of Illinois	Prof. Kyoji Tasaki, Tohoku University
L. K. Li	Research Fellow, Columbia Univ.	Prof. Kenshi Sato, Tokyo Science University
H. G. Wagner	Sr. Research Fellow, NEI	Prof. Kosuke Watanabe, Tokyo Women's Medical College
V. N. Reddy	Prof., Oakland University	Prof. Shuzo Iwata, Meijo University
E. L. Kean	Prof, Case Western Reserve Univ.	Prof. Yo Kibata, Kobe University
R. D. Freeman	Prof. University of California	Assoc. Prof. Chuji Tsumoto, Kanazawa University
L. J. Takemoto	Research Fellow, Kansas State Univ.	Prof. Shuzo Iwata, Meijo University
R. Siminoff	Prof. Temple University	Prof. Kenichi Naka, Okazaki
J. E. Dowling	Prof. Harvard University	Prof. Kenichi Naka, Okazaki
T. Kuwabara	Chief, Lab of Ocular Pathology, NEI	Prof. Akira Nakajima, Juntendo University
G. Inana	Chief, Molecular Science, NEI	Prof. Akira Nakajima, Juntendo University

Name of Researcher	Institution	Institution Visited
J. H. Kinoshita	Scientific Director, Intramural, NEI	Prof. Shuzo Iwata, Meijo University
R. B. Nussenblatt	Chief, Ocular Immunology, NEI	Assoc. Prof. Manabu Mochizuki, University of Texas
M. Alpern	Prof. Michigan University	Assoc. Prof. Kenji Kitahara, Jikei Medical College
J. J. Wolken	Prof., Carnegie Mellon University	Prof. Kyoji Tasaki, Tohoku University
T. R. Sherer	Prof., Oregon Health Sci. University	Prof. Ko Murachi, Kyoto University
US Participants: Carl Kupfer, MD R. B. Nussenblatt, MD Jin Kinoshita, PhD T. Kuwabara, MD E. McManus A. S. Fauchi, MD	N.I.H.	Workshop on Etiology and Treatment of Behcet Disease

Appendix C: Interviews

Conducted by Ed McManus and Carl Kupfer

Angle, Joanne, Executive Director, Association for Research in Vision and Ophthalmology,
May 18, 2006, Rockville, MD

Becker, Bernard, August 4, 2004, St. Louis, MO

Berlage, Nancy, March 12, 2005, Bethesda, MD

Berlage, Nancy, October 15, 2005, Bethesda, MD

Berson, Eliot, April 30, 2006, Association for Research in Vision and Ophthalmology Annual
Meeting in Fort Lauderdale, FL

Chen, Philip, December 21, 2005, Bethesda MD

Davis, Michael, December 16, 2005, Bethesda, MD

Dowling, John, November 5, 2004, Boston, MA

Dowling, John, May 3, 2006, Association for Research in Vision and Ophthalmology Annual
Meeting in Fort Lauderdale, FL

Ederer, Fred, August 2, 2005, Bethesda, MD

Ellwein, Leon, March 20, 2005, Bethesda, MD

Enoch, Jay, May 2, 2006, Association for Research in Vision and Ophthalmology Annual
Meeting in Fort Lauderdale, FL

Ferris, Frederick, December 2, 2004, Bethesda, MD

Ferris, Frederick, December 20, 2005, Bethesda, MD

Goldstein, Murray, September 2, 2004, Bethesda, MD

Hill, Gill, August 30, 2004, Bethesda, MD

Kaufman, Herbert, March 15, 2005, New Orleans, LA.

Kennedy, Thomas, August 30, 2004, Bethesda MD

Kinoshita, Jin, April 2005, Bethesda MD

Levinthal, Carl, August 4, 2004, Bethesda, MD

Lierman, Terry, December 14, 2005, Bethesda, MD

McLaughlin, Jack, July 18, 2005, Bethesda, MD

Nakajima, Akira, August 9, 2005, Bethesda, MD

O'Brien, Paul J., May 16, 2005, Bethesda, MD

Raub, William, May 18, 2006, Bethesda, MD

Ryan, Steven, April 30, 2006, Association for Research in Vision and Ophthalmology Annual Meeting in Fort Lauderdale, FL

Schepens, Charles, November 7, 2004, Bethesda, MD

Sears, Marvin, August 30, 2004, telephone interview

Sherman, John, July 26, 2004, Bethesda, MD

Stein, Judith & Janisewski, Rosemary, March 14, 2005, Bethesda, MD

Straatsma, Bradley, April 20, 2005, UCLA at Los Angeles, CA

Venkataswamy, Govindappa, May 11, 2004, Bethesda, MD

Weeks, David, January 25, 2005, Association of University Professors of Ophthalmology Meeting, Phoenix, AZ

Appendix D:

National Advisory Eye Council Members

Name	Date of Service	Institution
Adams, Anthony B.	02/10/1997 - 11/30/2000	University of California, Berkeley
Anderson, Douglas R.	01/18/1983 - 02/28/1987	University of Miami School of Medicine, Florida
Atkins, Marian C.	10/28/1975 - 10/31/1979	Cincinnati, Ohio
Bauer, Catherine B.	10/01/1971 - 09/30/1973	St. Marys, Pennsylvania
Becker, Bernard	02/17/1969 - 09/30/1973	Washington University, St. Louis, Missouri
Beebe, David C.	07/20/1995 - 11/30/1998	Uniformed Services University of the Health Sciences, Bethesda, Maryland
Berman, Bernard	12/14/1984 - 10/31/1988	National Retinitis Pigmentosa Foundation
Blodi, Frederick C.	03/18/1984 - 10/31/1984	University of Iowa Hospitals, Iowa City, Iowa
Blount, Wilbur C.	03/18/1991 - 11/30/1993	Columbus, Ohio

Name	Date of Service	Institution
Bok, Dean	01/31/1999 - 11/30/2002	University of California, Los Angeles
Brown, Kenneth T.	03/06/1978 - 10/31/1981	University of California, San Francisco
Brubaker, Richard E.	01/31/1987 - 10/31/1997	Mayo Clinic, Rochester, Minnesota
Burnside, Mary Beth	11/02/1991 - 09/28/1994	University of California, Berkeley
Carreon, Reynaldo J.	11/02/1970 - 09- 30/1974	Pan American Medical Center, Los Angeles, California
Cepko, Constance L.	12/01/1997 - 11/30/2001	Harvard Medical School, Boston, Massachusetts
Chan, Tony Q.	10/28/1975 - 10/31/1979	Albuquerque, New Mexico
Chandler, John W.	01/06/1989 - 12/31/1992	University of Wisconsin, Madison
Christensen, Jerry L.	01/24/1977 - 10/31/1980	University of Missouri, St. Louis School of Optometry
Cleary, Patricia A.	01/31/1999 - 11/30/2002	Georgetown, University, Washington, D.C.
Cleveland, Patrick H. (Ex-Officio)	06/01/1987 - 01/01/1994	Veterans Affairs Medical Center, San Diego, California
Cloud, Sanford Jr.	12/01/1997 - 05/22/2000	The National Conference
Cogan, David G.	02/01/1969 - 01/31/1972	Harvard Medical School, Boston, Massachusetts
Conner, William C.	11/09/1981 - 10/31/1985	Health Hearing Group, Ft. Worth, Texas

Name	Date of Service	Institution
Constantine-Paton, Martha C.	12/05/1999 - 11/30/2003	Massachusetts Institute of Technology, Cambridge, Massachusetts
Culver, James F. (Ex-Officio)	04/28/1969 - 04/18/1973	Office of the Surgeon General, USAF, Washington, DC
Cyert, Lynn	04/24/1992 - 11/30/1995	Northeastern State University, Oklahoma
Dauphin, Sue	01/26/1996 - 11/30/1997	National Sjögren's Syndrome Association
David, Nobel J.	03/17/1969 - 05/02/1980	Veterans Administration Hospital, Miami, Florida
Dowling, John E.	12/02/1985 - 10/31/1989	Harvard University, Boston, Massachusetts
Duane, Thomas D.	03/07/1978 - 10/31/1981	Wills Eye Hospital, Philadelphia, Pennsylvania
Dunbar, Florence	10/25/1972 - 09/30/1976	Chicago, Illinois
Enoch, Jay M.	02/25/1975 - 09/30/1976, 12/20/1980 - 10/31/1984	University of California, Berkeley
Enroth-Cugell, Christina E.	12/03/1979 - 10/31/1983	Northwestern University, Evanston, Illinois
Farmer, James	12/02/1979 - 10/31/1983	Coalition of American Public Employees, Washington, DC
Faye, Eleanor E.	01/27/1984 - 10/31/1987	New York Association for the Blind, New York, New York
Felix, Jeanette S.	01/20/1993 - 11/30/1996	Foundation Fighting Blindness

Name	Date of Service	Institution
Ferree, John W.	02/14/1969 - 01/01/1970	National Society for the Prevention of Blindness
Fisher, Marian R.	07/16/1995 - 11/30/1998	University of Wisconsin, Madison
Flynn, John T.	12/01/1987 - 11/30/1991	University of Miami Medical School, Florida
Flynn, William J. (Ex-Officio)	12/01/1997 - 02/10/2000	Lackland Air Force Base, Texas
Fry, Glenn A	03/01/1969 - 09/30/1973	Ohio State University College of Optometry, Columbus
Gilbert, Helen H.	01/02/1971 - 09/30/1974	Washington, DC
Grant, Morton W.	1/13/1973 - 10/31/1977	Harvard Medical School, Boston, Massachusetts
Gund, Gordon	01/09/1981 - 10/31/1984	National Retinitis Pigmentosa Foundation
Guyton, David L.	04/24/1992 - 11/30/1995	Johns Hopkins School of Medicine, Baltimore, Maryland
Harris, John E.	02/07/1969 - 01/31/1972, 02/25/1975 - 10/31/1978	University of Minnesota, Minneapolis
Hartline, H. Keffer	03/14/1969 - 09/30/1973	Rockefeller University, New York, New York
Hatchell, Diane L. (Ex-Officio)	05/30/1994 - 11/30/1998	Veterans Affairs Hospital, Durham, North Carolina
Heath, Gordon G.	01/21/1977 - 10/31/1980	University of Indiana, Bloomington

Name	Date of Service	Institution
Hellner, Richard T.	02/05/1997 - 11/30/2000	Prevent Blindness America
Hernandez, M. Rosario	06/07/1999 - 11/30/2002	Washington University School of Medicine, St. Louis, Missouri
Higginbotham, Eve J.	07/18/1995 - 11/30/1998	University of Maryland School of Medicine, Baltimore
Hill, Richard M.	11/01/1982 - 02/28/1987	Ohio State University, Columbus
Hillis, Argye	06/25/1991 - 11/30/1994	Scott & White Memorial Hospital, Temple, Texas
Holmes, Sadako S.	05/06/1992 - 11/30/1995	National Black Nurses Association
Horwitz, Joseph	05/14/1991 - 11/30/1994	University of California Los Angeles School of Medicine
Hubel, David H.	01/24/1996 - 11/30/1999	Harvard University School
Jameson-Hurvich, Dorothea	12/17/1984 - 01/31/1989	University of Pennsylvania, Philadelphia
Jampolsky, Arthur	01/31/1984 - 10/31/1987	Smith Kettlewell Institute, San Francisco, California
Kaufman, Herbert E.	11/01/1978 - 10/31/1982, 01/20/1993 - 11/30/1996	Louisiana State University Eye Center, New Orleans
Kaufman, Paul L.	03/18/1991 - 11/30/1994	University of Wisconsin, Madison
Kinsey, V. Everett	02/01/1969 - 09/30/1970	Oakland University, Rochester, Michigan

Name	Date of Service	Institution
Knight, Millicent L.	01/24/1996 - 11/30/1999	North Shore Eye Center, Evanston, Illinois
Krajczar, Norma F.	11/21/1979 - 10/31/1983	New Jersey Commission for the Blind and Visually Impaired, Newark, New Jersey
Laties, Alan M.	01/31/1979 - 10/31/1982	University of Pennsylvania School of Medicine, Philadelphia
Legge, Gordon E.	12/05/1999 - 11/30/2003	University of Minnesota, Minneapolis
Leske, M. Cristina	02/16/1987 - 10/31/1990	State University of New York, Stony Brook
Liddicoat, Douglas A.	01/26/1984 - 10/31/1987	Watsonville, California
Lolley, Richard N. (Ex-Officio)	08/20/1979 - 10/10/1984	Veterans Administration Medical Center, Sepulveda, California
Lurie, Erwin J.	02/11/1988 - 11/30/1991	Juvenile Diabetes Foundation of America
Maumenee, A. Edward	02/17/1969 - 06/09/1970, 02/25/1975 - 10/31/1978	Johns Hopkins Hospital, Baltimore, Maryland
Mazur, David O.	01/09/1994 - 11/30/1997	National Naval Research and Medical Center, Bethesda, Maryland
Morgan, Meredith	02/07/1969 - 01/31/1971	University of California, Berkeley
Mountcatle Jr., Vernon B.	01/21/1971 - 09/30/1974	Johns Hopkins School of Medicine, Baltimore, Maryland
Nakayama, Ken	09/15/1995 - 11/30/1997	Harvard University, Cambridge, Massachusetts

Name	Date of Service	Institution
Nesburn, Anthony	02/05/1997 - 11/30/2000	Cedars Sinai Hospital, Los Angeles, California
Newell, Frank B.	12/06/1971 - 09/30/1975	University of Chicago, Pritzker School of Medicine, Illinois
Norton, Edward W. D.	03/03/1978 - 10/31/1981	University of Miami, School of Medicine, Miami, Florida
O'Connor, G. Richard	11/12/1973 - 10/31/1977	Proctor Foundation, University
Petrauskas, Raymond R. (Ex-Officio)	05/08/1974 - 09/20/1979	Andrews Air Force Base, USAF, Maryland
Polse, Kenneth A.	01/21/1987 - 10/31/1990	University of California, Berkeley
Powell, C. Clayton	12/04/1971 - 09/3/1975	Atlanta, Georgia
Rabb, Maurice F.	12/18/1990 - 11/30/1993	Chicago, Illinois
Reddy, Venkat N.	11/01/1982 - 02/27/1987	Oakland University, Rochester, Michigan
Riggs Lorrin A.	02/02/1977 - 10/31/1980	Brown University, Providence, Rhode Island
Ryan, Ralph W.	02/03/1979 - 10/31/1982	Morgantown, West Virginia
Ryan, Stephen J.	01/22/1982 - 10/31/1985	Doheny Eye Institute, University of Southern California, Los Angeles, California
Schepens, Charles L.	11/21/1973 - 10/31/1988	The Retina Foundation, Boston, Massachusetts
Schultz, Richard O.	12/19/1984 - 10/31/1988	Medical College of Wisconsin, Milwaukee

Name	Date of Service	Institution
Shipp, Melvin D.	01/10/1989 - 12/31/1992	University of Alabama, Birmingham
Shovlin, Joseph P.	01/25/1993 - 11/30/1996	Northeastern Eye Institute, Scranton, Pennsylvania
Smelser, George K.	02/07/1969 - 01/31/1972	Columbia University, New York, New York
Soni, P. Sarita	12/05/1999 - 11/30/2003	Indiana University, Bloomington
Sparks, David L.	01/10/1989 - 12/31/1992	Baylor College of Medicine, Houston, Texas
Sperling, Harry G.	10/28/1975 - 10/31/1979	University of Texas, Houston
Spivey, Bruce E.	12/01/1987 - 11/30/1991	Pacific Presbyterian Medical Center, San Francisco, California
Stein, Jules	02/07/1969 - 01/31/1971	Universal City, California
Steinberg, Roy H.	07/17/1995 - 07/26/1997	University of California, San Francisco
Straatsma, Bradley R.	12/10/1989 - 10/31/1989, 11/02/1972 - 09/30/1976	Jules Stein Eye Institute, University of California, Los Angeles
Sutphin, John E.	10/09/1991 - 01/10/1994	Naval Hospital, San Diego, California
Swan, Kenneth C.	02/07/1969 - 01/31/1971	University of Oregon Medical School, Portland, Oregon
Takemoto, Larry J.	01/31/1999 - 11/30/2002	University of Kansas, Lawrence , Kansas

Name	Date of Service	Institution
Tredici, Col. Thomas J. (Ex-Officio)	12/10/1979 - 04/01/1991	Brooks Air Force Base, San Antonio, Texas
Weeks, David F.	12/27/1985 - 10/31/1989	Research to Prevent Blindness
Wiesel, Torsten N.	01/29/1981 - 10/31/1985	Harvard Medical School, Boston, Massachusetts
Worthen, David M.	10/11/1984 - 05/31/1987	Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland
Young, Tommie A.	02/25/1975 - 10/31/1978	North Carolina Agricultural and Technical State University, Greensboro
Zadnik, Karla	12/03/2000 - 11/30/2004	Ohio State University, Columbus, Ohio
Zarbin, Marco A.	12/01/1998 - current	New Jersey VA Hospital, Newark
Zee, David S.	01/23/1996 -11/30/1999	Johns Hopkins Hospital, Baltimore, Maryland

Endnotes

Note on Citation Format: The references below use a mix of historical and scientific citation formats, according to the type of source. For the reader's convenience, throughout the text we often placed notes within sentences or at the end of sentences rather than at paragraph-end, the usual practice for historical works. The text's heavy reliance on oral histories, anecdotal materials, and scientific data, place a heavy premium on the reader being able to easily identify the source of the information. Thus, we refrained from using *ibid* or *idem*. A shortened form of citation for publications is used where there is little chance for confusion. A shortened citation for interviews is used in the notes; a full bibliographical listing of interviews follows.

Note on Cited Collections: In the endnotes, NEI Files refer to the historical collection in the possession of the National Eye Institute, Bethesda, Maryland. The Carl Kupfer and Edward McManus Memoir Files contain personal writings, e-mails, and dictations, and remain in the possession of the authors. Interviews are currently in the possession of the National Eye Institute.

¹ V. Reddy and D. Cogan, "In Memoriam, Dr. Everett Kinsey," *Investigative Ophthalmology & Visual Science* Jan 1979, vol. 18, no. 1, pp. 1-2.

² Goldstein interview, p. 7.

³ For developments, see Daniel M. Albert, *Dates in Ophthalmology: A Chronological Record of Progress in Ophthalmology over the Last Millennium* (New York: Parthenon Publishing Group, 2002).

⁴ On PHS mandate, see Annual Report of the Surgeon General of the Public Health Service, 1912, p. 9. For background, see website of Office of the Public Health Service Historian at http://lhncbc.nlm.nih.gov/apdb/phsHistory/resources/phs_hist/pub_phs05.html

⁵ Victoria A. Harden, "A Short History of the National Institutes of Health," NIH History Office website, at <http://history.nih.gov/exhibits/history/index.html>.

⁶ Ruth R. Harris, "A Brief History of the National Eye Institute," *Government Publications Review*, vol. 12 (1985), p. 429; Frank W. Newell, "The Origins of the National Eye Institute, 1933-1968," in *The History of Ophthalmology*, Daniel M. Albert and Diane D. Edwards, eds., (Cambridge, MA: Blackwell Science, 1996), p. 314; Newell, Frank W. (1995). *The Origins of the National Eye Institute 1933-1968: The Fifth Charles B. Snyder Lecture*. *Documenta Ophthalmologica* 89:127-144. On the growth of NIH, see Shannon, James A. (July 1976). *Federal support of Biomedical Sciences: Development and academic impact*.

Journal of Medical Education 51(7), part 2, p. 10. For budget numbers see Harden, "A Short History of the National Institutes of Health," NIH History Office.

⁷ See "Biographical Information," and "Mary Lasker and the Growth of the National Institutes of Health," in *The Mary Lasker Papers, Profiles in Science*, National Library of Medicine, at <http://profiles.nlm.nih.gov/TL/>

⁸ See "Introduction" to Finding Aid to the Jacob M. Ulmer Papers, 1949-1969 relating to the promotion and funding of research to prevent blindness, National Library of Medicine, National Institutes of Health: <http://www.nlm.nih.gov/hmd/manuscripts/ead/ulmer.html>.

⁹ Harris, "A Brief History of the National Eye Institute," pp. 429-30, quoting Kingsley, as found in W. Michael Havenar, *To Make You See* (New York Vantage Press, 1973), pp. 45-46: "J. Donald Kingsley, acting administrator for the Federal Security Agency, then the parent agency of the NIH, explained, 'We are gravely concerned lest the trend toward separate research establishments for more and more specific disease entities undermine the effectiveness of the research program as a whole.'"

¹⁰ "Mary Lasker and the Growth of the National Institutes of Health," p. 2, *The Mary Lasker Papers, Profiles in Science*, National Library of Medicine, National Institutes of Health, at <http://profiles.nlm.nih.gov/TL/>

¹¹ Harris, "A Brief History of the National Eye Institute," p. 430.

¹² Harris, "A Brief History of the National Eye Institute," p. 430; Lewis P. Rowland, MD, *NINDS at 50: An Incomplete History Celebrating the Fiftieth Anniversary of the National Institute of Neurological Disorders and Stroke* (Bethesda, MD: NINDS, 2002), p. 17; Newell, "The Origins of the National Eye Institute, 1933-1968," in *The History of Ophthalmology*, pp. 314-316; "Mildred Moser Weisenfeld, 1921-1997," *Arch Ophthalmol* 1998; 116:401.

¹³ B. Furman, *A Profile of the United States Public Health Service 1798-1948*, (Washington, D.C.: United States Government Printing Office, 1971), p. 450; Rowland, *NINDS at 50*, pp. 11, 16-17.

¹⁴ Ruth Harris, "A Brief History of the National Eye Institute," p. 432.

¹⁵ Ruth Harris, "A Brief History of the National Eye Institute," pp. 431-32.

¹⁶ Ruth Harris, "A Brief History of the National Eye Institute," p. 431.

¹⁷ This according to Ruth Harris, "A Brief History of the National Eye Institute," p. 433.

¹⁸ This percentage according to Newell, "The Origins of the National Eye Institute, 1933-1968," in *The History of Ophthalmology*, p. 317. Newell does not cite a reference for this information. Rep. Fred B. Rooney states that "15% was allocated for eye research in 1967," in *Hearings to Establish NEI*, U.S. Congress, House Committee on Interstate and Foreign

Commerce, Nov. 1, 1967, p. 10, according to Harris, "A Brief History of the National Eye Institute," p. 445, Appendices, A and B, Tables of Appropriations.

¹⁹ Becker interview, p. 6.

²⁰ Newell, "The Origins of the National Eye Institute," *2 Documenta Ophthalmologica*, p. 140.

²¹ Becker interview, p. 6.

²² Dowling interview, pp. 9-10.

²³ Ruth Harris, "A Brief History of the National Eye Institute," p. 443.

²⁴ Steven Podos, "On Presentation of the Proctor Medal of the Association for Research in Vision and Ophthalmology to Bernard Becker," *Invest Ophthalmol Vis Sci* (Oct 1980): 1150-52.

²⁵ Robert B. Welch, MD, "Alfred Edward Maumenee, Jr., MD," *Trans Am Ophthalmol Soc.* 1998; 96: 9-12; Ruth Harris, "A Brief History of the National Eye Institute," p. 433.

²⁶ On Maumenee's friendship with Sen. Hill, see Ryan interview, p. 3.

²⁷ Becker interview, p. 19.

²⁸ "Eulogy for Dr. David Cogan delivered by Shirley Wray to the American Neurological Association, October 18, 1993," *Journal of Neuro-Ophthalmol*, vol. 14, no. 1, 1994; Robert B. Welch, MD, "Alfred Edward Maumenee, Jr., MD," *Trans Am Ophthalmol Soc.* 1998; 96: 9-12 (quote), p. 59.

²⁹ Phillips Thygeson, MD, "On the Presentation of the Proctor Medal of the Association for Research in Ophthalmology to Michael J. Hogan," *Investigative Ophthalmology & Visual Science*, vol. 2, no. 5 (1963): 410-11; University of California (System) Academic Senate 1977, "University of California: In Memoriam: Michael John Hogan, Ophthalmology: San Francisco," May 1977, at <http://oac.cdlib.org/>.

³⁰ Peter R. Egbert, MD, "Frank Counsel Winter, MD (1922-2004)" *Arch Ophthalmol* 2004;122:1734-1735; "2004 Obituaries," Stanford University Medical Center Alumni Association website, <http://med.stanford.edu/alumni/obits/winter2004.html>.

³¹ "Obituary John Milton McLean, 1909-1968," *Brit J Ophthal* (1968) 52: 575-76.

³² Newell, "The Origins of the National Eye Institute, 1933-1968," in *The History of Ophthalmology*, pp. 318-19.

³³ David Glendenning Cogan, the Howe Laboratory of Ophthalmology at Harvard Medical School, the Massachusetts Eye and Ear Infirmiry, and the National Eye Institute An interview conducted by Sally Smith Hughes, 1990 (The Foundation of the American Academy of Ophthalmology, Regional Oral History Office, University of California—Berkeley), p. 130. This was even before a separate institute was considered, according to Cogan.

³⁴ Newell, “The Origins of the National Eye Institute, 1933-1968,” in *The History of Ophthalmology*, p. 318. “Stein Eye Institute Established at UCLA,” *Los Angeles Times*, 16 Mar 1962.

³⁵ Becker interview, p. 17.

³⁶ Newell, “The Origins of the National Eye Institute, 1933-1968,” in *The History of Ophthalmology*, p. 318; Weeks interview, p. 9.

³⁷ Weeks interview, p. 1.

³⁸ “Interview of Bernard Becker, M.D., 19 Oct 1990,” by Marion Hunt, 19 Oct 1990, pp. 13, 17, OH 061, Bernard Becker Medical Library, Washington University School of Medicine, St. Louis, Missouri.

³⁹ Goldstein interview, pp. 8-9.

⁴⁰ Goldstein interview, p. 8.

⁴¹ Becker interview, p. 8

⁴² “Permanent Subcommittee is Formed by NINDB to Review Eye Research,” *The NIH Record*, 25 Jul 1967.

⁴³ Enoch interview, pp. 1-9.

⁴⁴ Newell, “The Origins of the National Eye Institute, 1933-1968,” in *The History of Ophthalmology*, p. 319; See also A. Edward Maumenee, MD, The Wilmer Ophthalmological Institute at the Johns Hopkins University and the Stanford Medical School, An interview conducted by Sally Smith Hughes, 1990 (The Foundation of the American Academy of Ophthalmology, San Francisco, Regional Oral History Office, University of California at Berkeley), pp. 179-180. Also see Ryan interview, p. 2.

⁴⁵ Maumenee Interview Conducted by Sally Smith Hughes, p. 181.

⁴⁶ Kaufman interview, pp. 3, 7.

⁴⁷ Becker interview, p. 18.

⁴⁸ Materials for RPB Writer's seminar, Arlington, VA, including: press advance for 7 Nov 1965; Text of remarks by Jules Stein, 6 Nov 1965; and Highlights of Public Opinion Survey Conducted for RPB, 5/15/1965, Ulmer Papers, National Library of Medicine.

⁴⁹ Duane interview, pp. 97-99.

⁵⁰ See "Announcements," *Investigative Ophthalmology*, vol. 3, no. 4 (Aug 1964): 480. Thomas D. Duane, *Ophthalmic Research: USA—A Comprehensive National Survey of Eye Research* (n.p.: RPB, 1965).

⁵¹ Lawrence A. Zupan interview, p. 457, "Interviews Conducted by Sally Smith Hughes, Ph.D.," in *The Foundation of the American Academy of Ophthalmology, and Regional Oral History Office, The Bancroft Library University of California Berkeley, The American Academy of Ophthalmology and Otolaryngology: Oral History Recollections of Past and Present Leaders*, 1998, at http://digitalassets.lib.berkeley.edu/roho/ucb/text/ophthalmology_amer_assoc.pdf *he History of Ophthalmology*.

⁵² Newell, "The Origins of the National Eye Institute, 1933-1968," in *The History of Ophthalmology*, p. 319. See also The Gallup Organization, Inc., "Public knowledge and attitudes concerning blindness—a survey sponsored by Research to Prevent Blindness," Inc., New York, October 1965, unpublished data.

⁵³ See McManus statements in Kaufman interview, p. 6.

⁵⁴ Newell, "The Origins of the National Eye Institute, 1933-1968," in *The History of Ophthalmology*, p. 318.

⁵⁵ Harris, "A Brief History of the National Eye Institute," p. 434

⁵⁶ Weeks interview for quote; see also Kaufman interview p. 5.

⁵⁷ Harris, "A Brief History of the National Eye Institute," p. 435.

⁵⁸ Letter John Gardner (Secretary DHEW) to Harley Staggers (Chairman, House Committee on Interstate and Foreign Commerce), 31 Oct 1967, in NEI Files.

⁵⁹ Harris, "A Brief History of the National Eye Institute," p. 435; "Statement by William H. Stewart, M.D., Surgeon General U.S. Public Health Service, Department of Health Education and Welfare, before the Subcommittee on Public Health and Welfare, Committee on Interstate and Foreign Commerce, House of Representatives, Washington, D.C., October 31, 1967," p. 8, Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶⁰ Kaufman interview, p. 4.

⁶¹ “Statement of Ralph W. Ryan, M.D., of the American Association of Ophthalmology, on Establishment of a National Eye Institute” Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶² Kaufman interview, 15 Mar 2005, p. 4; see also “Statement of Herbert E. Kaufman, M.D., Professor and Chairman, Department of Ophthalmology, University of Florida, Gainesville, Florida, to Interstate and Foreign Commerce Committee of the House of Representatives, 1 Nov 1967 on H.R. 12843 and related bills to establish a National Eye Institute,” Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶³ “Statement of A. Edward Maumenee, M.D., Professor of Ophthalmology, Johns Hopkins University School of Medicine and Director, Wilmer Eye Institute, Johns Hopkins Hospital, to Interstate and Foreign Commerce Committee of the House of Representatives, 1 Nov 1967 on H.R. 12843 and related bills to establish a National Eye Institute,” quote on p. 5, Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶⁴ “Statement of David G. Cogan, MD, Professor and Chairman, Department of Ophthalmology, Harvard Medical School, to Interstate and Foreign Commerce Committee of the House of Representatives, 1 Nov 1967 on H.R. 12843 and related bills to establish a National Eye Institute,” pp. 4, 5, 7., Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶⁵ “Statement of Michael J. Hogan, MD, Chairman, Department of Ophthalmology, UC Medical School, San Francisco, to Interstate and Foreign Commerce Committee of the House of Representatives, 1 Nov 1967 on H.R. 12843 and related bills to establish a National Eye Institute,” pp. 5, Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶⁶ “Statement of Frank W. Newell, MD, Professor and Chairman, Division of Ophthalmology, University of Chicago, to Interstate and Foreign Commerce Committee of the House of Representatives, 1 Nov 1967 on H.R. 12843 and related bills to establish a National Eye Institute,” quote p. 4, Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶⁷ “Statement of Thomas D. Duane, MD, Professor and Head, Department of Ophthalmology, Jefferson Medical College Hospital, Philadelphia, Pennsylvania, to Interstate and Foreign Commerce Committee of the House of Representatives, 1 Nov 1967 on H.R. 12843 and related bills to establish a National Eye Institute,” pp. 5, 8, Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶⁸ “Statement of Bradley R. Straatsma, MD, Director of Jules Stein Eye Clinic, Professor and Chief, Division of Ophthalmology, UCLA School of Medicine, Los Angeles, California, to Interstate and Foreign Commerce Committee of the House of Representatives, 1 Nov 1967 on H.R. 12843 and related bills to establish a National Eye Institute,” pp. 2, 4, Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁶⁹ “Statement of Jules Stein, [to Interstate and Foreign Commerce Committee of the House of Representatives, 1 Nov 1967 on H.R. 12843 and related bills to establish a National Eye Institute], Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁷⁰ Newell, “The Origins of the National Eye Institute, 1933-1968,” in *The History of Ophthalmology*, p. 320. See also, “Statement Presented by John F. Nagle, Chief, Washington Office, National Federation of the Blind, in Public Hearings Conducted by the Subcommittee on Public Health and Welfare, Committee on Interstate and Foreign Commerce, House of Representatives, in Support of H.R. 10780, November 1, 1967,” Typewritten document in Folder labeled House Hearings 1960-1969, NINDB, in NEI Files.

⁷¹ Harris, “A Brief History of the National Eye Institute,” p. 436.

⁷² Blodi, *History of the National Eye Institute*, p. 425.

⁷³ Kaufman interview, p. 4.

⁷⁴ Helen Keller’s Speech, 1925 International Convention Cedar Point, Ohio USA, June 30, 1925, Lions Clubs International, at http://www.lionsclubs.org/EN/content/lions_history_hkspeech.html.

⁷⁵ Newell, “The Origins of the National Eye Institute, 1933-1968,” in *The History of Ophthalmology*, p. 320; Weeks interview, pp. 24-25, 36.

⁷⁶ Weeks interview, p. 19; Newell, “The Origins of the National Eye Institute, 1933-1968,” in *The History of Ophthalmology*, pp. 311, 320.

⁷⁷ NIH Legislative Highlights, 19 Aug 1968, NEI Files.

⁷⁸ Newell, “The Origins of the National Eye Institute, 1933-1968,” in *The History of Ophthalmology*, p. 320; Goldstein interview, see statements by Kupfer, McManus, and Goldstein, p. 8; Weeks interview, p. 18; Dowling interview, p. 5; Levinthal interview, p. 2.

⁷⁹ Harris, “A Brief History of the National Eye Institute,” pp. 438-439.

⁸⁰ Becker interview, p. 8. See also Sherman interview, pp. 5-6.

⁸¹ Announcement, “Dr. Carl Kupfer, First Director of National Eye Institute,” *Investigative Ophthalmology*, Oct 1969, p. 562.

⁸² Carl Kupfer Memoir File.

⁸³ Carl Kupfer Memoir File.

⁸⁴ Hill interview, p. 25.

⁸⁵ E-mail Carl Kupfer to Nancy Berlage, 3 Aug 2007.

⁸⁶ E-mail Carl Kupfer to Nancy Berlage, 2 Aug 2007; see also Carl Kupfer, "Looking Back on 25 Years at the NEI: A Research and Management Philosophy," *Investigative Ophthalmology and Visual Science* (Feb 1994) vol. 35, no. 2, pp. 323-24.

⁸⁷ E-mail Ed McManus to Nancy Berlage, 1 Aug 2007.

⁸⁸ E-mail Ed McManus to Nancy Berlage, 1 Aug 2007.

⁸⁹ Title 42 USC Sec 284a.

⁹⁰ 42 USC 284a, section 406 of the PHS Act, as amended. The council is governed by the provisions of the Federal Advisory Committee Act, as amended (5 USC Appendix 2), which sets forth standards for the formation and use of advisory committees. See <http://www.nei.nih.gov/about/naec/charter.asp>.

⁹¹ See NEI website, <http://www.nei.nih.gov/about/naec/history.asp>.

⁹² Kupfer, McManus, Berlage interview, p. 23 (McManus quote).

⁹³ Ryan interview, pp. 6-8.

⁹⁴ Straatsma interview, p. 12.

⁹⁵ Dowling interview, p. 17.

⁹⁶ Jack W. Carlson, "The Status and the Next Steps for Planning, Programming, Budgeting," in *The Analysis and Evaluation of Public Expenditures: The PPB System*, a compendium of papers submitted to the Subcommittee on Economy in Government of the Joint Economic Committee, Congress of the United States, 91st Cong, 1st sess, vol. 2, 1969, pp. 613-14.

⁹⁷ Virginia McMurtry, "Performance Management and Budgeting in the Federal Government: Brief History and Recent Developments," CRS Report for Congress, Congressional Research Service, Library of Congress, Washington, D.C., 16 Mar 2005, p. 2.

⁹⁸ Dorothy Rice, "Estimating the Cost of Illness in Health Economic Series," Public Health Service Publication, no. 947-6, series 6 (Washington, D.C.: U.S. Govt. Printing Office, 1966), p. iii. On PPBS and HEW, see also William Gorham, "Sharpening the Knife that Cuts the Public Pie," *Public Administration Review*, vol. 28, no. 3 (May/Jun 1968), pp. 236-41.

⁹⁹ McMurtry, "Performance Management and Budgeting in the Federal Government."

¹⁰⁰ Dowling interview, 5 Nov 2004, p. 2.

¹⁰¹ Kennedy interview, 3 Aug 2004, part 2, p. 18.

- ¹⁰² McManus and Berlage interview, 12 Mar 2005, p. 8. See Edward H. McManus, *Allocating Resources for Biomedical Research* (Master's Thesis, University of Wisconsin-Madison, June 1970), p. 16.
- ¹⁰³ On the demise of PPBS as a formal structure, see Stanley B. Botner, "PPB Under Nixon," *Public Administration Review*, vol. 32, no. 3 (May/Jun 1972), pp. 254-55.
- ¹⁰⁴ McManus, Kupfer, and Berlage interview, 15 Jan 2005, pp. 1-2, 6, 10 (Kupfer quote, 2, 4); for a discussion of across the board cuts and NEI's refusal to do this, see Dowling interview, p. 12.
- ¹⁰⁵ Dowling interview, p. 4.
- ¹⁰⁶ Minutes of the NAEC, Executive Session, 20 Nov 1973, p. 3.
- ¹⁰⁷ William Proxmire, "Foreword . . . PPB, The Agencies and the Congress," in *The Analysis and Evaluation of Public Expenditures: The PPB System*, U.S. Congress Joint Economic Committee, Compendium of Papers Submitted to Sub Committee on Economy in Government, 91st Cong, 1st sess, vol. 1, p. vi-vii.
- ¹⁰⁸ Quote by McManus, telephone conference call McManus, Berlage, and Kupfer, 11 Jun 2007.
- ¹⁰⁹ List of first council members and professional affiliation, April 3, 4, 1969.
- ¹¹⁰ Minutes of NAEC Meeting, Mar 1972, p. 4.
- ¹¹¹ Minutes of NAEC Meeting, 25 Jun 1974, p. 6.
- ¹¹² Section 452 of the Public Health Service Act (42 USC 289J).
- ¹¹³ National Advisory Eye Council Charter Establishing NEI 1973, p. 2, at www.nei.nih.gov/about/naec/charter.asp.
- ¹¹⁴ Minutes of the NAEC Meeting, Jun 1978, p. 6.
- ¹¹⁵ *Vision Research a National Plan (1983-1987)*. Support for Vision Research, US Dept. of Health and Human Services, Public Health Service, NIH, vol. 3, NIH Publications No. 83-2447, p. 3.
- ¹¹⁶ Straatsma interview, pp. 7-8.
- ¹¹⁷ McManus, Kupfer, and Berlage interview, p. 22.
- ¹¹⁸ Minutes of the NAEC, Executive Session, Nov 1973, p. 4.
- ¹¹⁹ Dowling interview, see McManus comment, p. 10.

¹²⁰ National Advisory Eye Council, Vision Research Program Planning, vol. 1. Introduction, Program Summary, and Recommendations; vol. 2, Research Program Analysis. DHEW Publications Nos. (NIH) 75-664 and 75-665, April 1975.

¹²¹ National Advisory Eye Council Interim Report (1976). Support for Vision Research, US Dept. of Health and Human Services, Public Health Service, NIH, NIH Publications No. 76-1098; see p. xi.

¹²² See for example, Dorothy Rice, "Estimating the Cost of Illness," Health Economics Series, no. 6, DHEW Pub. No. (PHS) 947-6 (Rockville, MD: U.S. Department of Health, Education and Welfare, 1966), p. iii.

¹²³ Vision Research: A National Plan: 1978-1982, The 1977 Report of the National Advisory Eye Council, US Dept. of Health, Education and Welfare, Public Health Service, NIH, vol. 2, Panel Report, p. 124; National Research Council of the National Academies, Advancing the National's Health Needs: NIH Research Training Programs (Washington, D.C.: The National Academies Press, 2005), at <http://grants.nih.gov/training/outcomes.htm>.

¹²⁴ Vision Research: A National Plan: 1978-1982. The 1977 Report of the National Advisory Eye Council, vol. 2, Panel reports, US Dept. of Health and Human Services, Public Health Service, NIH, NIH Publications No. 76-1098, pp. 138-145.

¹²⁵ Vision Research: A National Plan: 1978-1982, vol. 2, p. 146.

¹²⁶ Between 1969 and 2007, the Society for Neuroscience grew to nearly 37,000 members and is the world's largest organization of scientists devoted to the study of the brain. During this period, there were 39 Presidents of the Society for Neuroscience of whom 9 (23%) were supported in their research by the NEI.

¹²⁷ The 1983 Report of the National Advisory Eye Council, vol. 1. Vision Research: A National Plan (1983-1987), US Dept. of Health and Human Services, Public Health Service, NIH, NIH Publications No. 83-2470, p. 5.

¹²⁸ The 1983 Report of the National Advisory Eye Council, vol. 1, p. 5.

¹²⁹ Exec Summary Vision Research: A National Plan, 1983-1987, US Dept. of Health and Human Services, Public Health Service, NIH, NIH Publications No. 82-2470, n.d., p. 3.

¹³⁰ Exec Summary Vision Research: A National Plan, 1983-1987, p. 4.

¹³¹ Exec Summary Vision Research: A National Plan, 1983-1987, p. 3.

¹³² Exec Summary Vision Research: A National Plan, 1983-1987, p. 11.

¹³³ Davis interview, p. 5.

¹³⁴ Minutes of the NAEC Meeting, 30-31 Jan 1984, pp. 6-7.

¹³⁵ Biennial Report of the National Institutes of Health: Report of the NIH Director (June 1989), vol. 1, 1987-1988, US Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH Pub. No. 89-2912, p. 5.

¹³⁶ Davis interview, p. 19.

¹³⁷ Davis interview, p. 20.

¹³⁸ Vision Research: A National Plan 1994-1998. A report of the National Advisory Eye Council, National Institutes of Health, National Eye Institute, p. 1.

¹³⁹ Vision Research: A National Plan 1994-1998, p. 8.

¹⁴⁰ Vision Research: A National Plan 1994-1998, p. 6.

¹⁴¹ Vision Research: A National Plan 1994-1998, p. 3.

¹⁴² Vision Research: A National Plan 1994-1998. p. 7.

¹⁴³ Government Performance Results Act of 1993, Office of Management and Budget, retrieved from <http://www.whitehouse.gov/omb/mgmt-gpra/gplaw2m.html>.

¹⁴⁴ Vision Research: A National Plan 1999-2000. A Report of the National Advisory Eye Council, US Department of Health and Human Services, National Institutes of Health, National Eye Institute, p. v.

¹⁴⁵ Vision Research: A National Plan 1999-2000, p. xviii.

¹⁴⁶ Vision Research: A National Plan 1999-2000, p. xix (quote), xx.

¹⁴⁷ Kennedy interview, 30 Aug 2004, pp. 17-18.

¹⁴⁸ The 1983 Report of the National Advisory Eye Council, vol. 1. Vision Research: A National Plan (1983-1987), US Dept. of Health and Human Services, Public Health Service, NIH, NIH Publications No. 83-2470, p. 6.

¹⁴⁹ Dowling interview, 5 Nov 2004, p. 2.

¹⁵⁰ McLaughlin interview, p. 5.

¹⁵¹ Davis interview, pp. 24-25.

¹⁵² Hart left in 1953, and Ryan resigned in 1955. See “Statement of Ralph W. Ryan, M.D., of the American Association of Ophthalmology, on Establishment of a National Eye Institute,” Typewritten document in Folder labeled House Hearings 1960-1969, NINDB; Statement of Ralph W. Ryan to the Interstate and Foreign Commerce Committee of the House of Representatives, November 1, 1967, on H.R. 12843 and related bills to establish a National

Eye Institute, as reported in the AJO 64: No. 6 Dec 1967, pp. 1219-1220. See also Blodi, Frederick C., "The History of the National Eye Institute," AJO (1993) vol. 115, pp. 420-425.

¹⁵³ Who's Who in NINDB, Biographical Sketches of the Scientific and Administrative Staff (NINDB, 1966), q.v. "Dr. Ludwig von Sallman"; Ingrid Farreras, "Ophthalmology Branch, NINDB" in Ingrid G. Farreras, Caroline Hannaway, and Victoria A. Harden, eds., *Mind, Brain, Body, and Behavior: Foundations of Neuroscience and Behavioral Research at the National Institutes of Health* (Washington, DC: IOS Press, 2004), pp. 121-124. For a list of staff members see, Appendix B, "Ophthalmology Branch, NINDB," p. 320.

¹⁵⁴ Blodi, "The History of the National Eye Institute," AJO, 422.

¹⁵⁵ Berson interview, pp. 2-3, 6-7 (quotes).

¹⁵⁶ Kaufman interview, pp. 1-2.

¹⁵⁷ Harris, "Brief History of the National Eye Institute," p. 432.

¹⁵⁸ O'Brien interview, p. 2.

¹⁵⁹ O'Brien interview, p. 4; see also Berson interview on the small space available for animal research, pp. 7-8.

¹⁶⁰ Carl Kupfer Memoir File.

¹⁶¹ Carl Kupfer Memoir File; also see e-mail Carl Kupfer to Nancy Berlage, 22 Aug 2007.

¹⁶² Memo, Director NINDB, NIH, through Director NIH, to Dr. Milton Silverman, DHEW, 26 Sept 1966; see Table 1.

¹⁶³ Harris, "A Brief History of the National Eye Institute," p. 433.

¹⁶⁴ Rowland, NINDS at 50, p. 123.

¹⁶⁵ Harris, "A Brief History of the National Eye Institute," p. 433.

¹⁶⁶ O'Brien interview, p. 8.

¹⁶⁷ O'Brien interview, pp. 7-8, for quotes. For Kupfer recollections, see Carl Kupfer Memoir File.

¹⁶⁸ E-mail Carl Kupfer to Nancy Berlage, 22 Aug 2007.

¹⁶⁹ Carl Kupfer Memoir File.

¹⁷⁰ Kinoshita interview, p. 4.

¹⁷¹ Kaiser-Kupfer M, Caruso RC, Valle D, Reed GF: Use of an arginine-restricted diet to slow progression of visual loss in patients with gyrate atrophy. *Arch Ophthalmol* 122: 982-984, 2004.

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¹⁷⁴ “The National Institute of Neurological Diseases and Blindness Program in Diseases of the Eye, Disorders of the Visions, and Blindness,” Office of Program Analysis Report No. 13, 10 Jul 1967, p. 10. See also Anderson, PH, Model Reporting Area, *J Am Optom Assoc.* 1969 Aug; 40(8), pp. 803-5.

¹⁷⁵ Minutes of Meeting of the National Advisory Neurological Diseases and Blindness Council, 22-23 Jun 1967.

¹⁷⁶ Minutes of NAEC Meeting, 26 & 27 Jun 1969, Appendix II, p. 3.

¹⁷⁷ Linda Huss, “NEI’s Roy Milton Retires after 27 Years of Federal Service,” *NIH Record*, 2 Jul 1996, p. 11; Linda Huss, “NEI Mourns Statistician Marvin Podger,” *NIH Record*, 26 Jan 1999.

¹⁷⁸ Ferris interview, p. 1; e-mail Rick Ferris to Nancy Berlage, 2 Apr 2007.

¹⁷⁹ Kinoshita interview, p. 10.

¹⁸⁰ Kinoshita interview, p. 3.

¹⁸¹ For more on Dr. Kinoshita’s background and personality see David G. Cogan, “On the Presentation of the Friedenwald Award to Dr. Kinoshita,” vol. 4, no. 5, pp. 780-81.

¹⁸² McManus comments in Kinoshita interview, pp. 7-8.

¹⁸³ As described by Carl Kupfer.

¹⁸⁴ For general information on the Blue Ribbon Panel, see the NIH intramural program website at <http://www1.od.nih.gov/OIR/sourcebook/sci-review/blue-ribbon.htm>.

¹⁸⁵ For clinical center, see <http://clinicalcenter.nih.gov/about/welcome/history.shtml>.

¹⁸⁶ Type 1-2-5 grants definitions are in “Activity codes, Organizational codes and Definitions used in the Extramural Programs,” September 1992 NIH Manual Issuance 410163042.

- ¹⁸⁷ On the reduction decision, see e-mail Carl Kupfer to Nancy Berlage, 14 Aug 2007.
- ¹⁸⁸ For a description of the current RO1 grant mechanism, see <http://grants.nih.gov/grants/funding/RO1.htm>.
- ¹⁸⁹ Edward McManus Memoir File.
- ¹⁹⁰ Vision Research: A National Plan, 1994-1998, p. 376.
- ¹⁹¹ Carl Kupfer Memoir File.
- ¹⁹² Strategic Plan In Vision Research Vision Research: A National Plan, 1978-1982, p. 14.
- ¹⁹³ McLaughlin interview, p. 7.
- ¹⁹⁴ 1983-87 NAEC Plan, p. 63.
- ¹⁹⁵ Carl Kupfer Memoir File.
- ¹⁹⁶ Weeks interview, pp. 32, 141.
- ¹⁹⁷ Carl Kupfer Memoir File.
- ¹⁹⁸ Carl Kupfer Memoir File.
- ¹⁹⁹ Kupfer, C. The National Eye Institute. *AJO* 74:1020, 1972.
- ²⁰⁰ Vision Research: A National Plan 1978-82, Vision Research Training, p. 445-448 .
- ²⁰¹ Vision Research: A National Plan 1978-82, Vision Research Training, p. 447.
- ²⁰² Table 5, Vision Research a National Plan Summary Volume, 1978-82, pg. 42.
- ²⁰³ Vision Research a National Plan Summary Volume, 1978-1982, p. 42.
- ²⁰⁴ Vision Research A National Plan, 1978-82, Vision Research Training, p. 448.
- ²⁰⁵ Vision Research A National Plan, 1978-82, Vision Research Training, p. 60.
- ²⁰⁶ Vision Research A National Plan, 1978-82, Vision Research Training, p. 60-61.
- ²⁰⁷ Vision Research A National Plan: 1983-1987, vol. one, The 1983 Report of the National Advisory Eye Council, pg. 60.
- ²⁰⁸ Arthur K. Shapiro and Elaine Shapiro, *The Powerful Placebo: From Ancient Priest to Modern Physician* (Baltimore, MD: Johns Hopkins University Press, 2000) p. 228.
- ²⁰⁹ Lilienfeld AM, "Ceteris paribus: The evolution of the clinical trial," *Bulletin of the History of Medicine* 56 (1982):1-18.

²¹⁰ Kaptchuk TJ, “Intentional Ignorance: A History of Blind Assessment and Placebo Controls in Medicine,” *Bull History of Medicine* 72 (3) (Fall 1998), 396; Lilienfeld AM, “Ceteris paribus” 4-5; James Lind, *A Treatise of the Scurvy* (Edinburgh: Sands Murray & Cochran, 1753).

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²¹² Lilienfeld AM, “Ceteris paribus.”

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²¹⁵ Simon RM, “A Conversation with Marvin A. Schneiderman,” *Statistical Science* 12 (2) (1997): 100.

²¹⁶ Green SB, “A Conversation with Fred Ederer,” *Statistical Science* 1997, 12 (2) (1997), 127. For more on Cornfield’s contributions, see Fred Ederer, “Jerome Cornfield’s Contributions to the Conduct of Clinical Trials,” *Biometrics*, vol. 38, no. 1; “A Memorial Symposium in Honor of Jerome Cornfield,” *Proceedings of “Current Topics in Biostatistics and Epidemiology* (Mar 1982), pp. 25-32.

²¹⁷ For background on clinical trials at NIH, see Ederer interview, pp. 4-5.

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²²¹ Green, “A Conversation with Fred Ederer,” p. 128.

²²² For both anecdotes, see Simon, “A Conversation with Marvin A. Schneiderman,” pp. 101-102.

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²⁶⁹ Stein and Janiszewski interview, pp. 4-6.

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