The year 1987 marks the 100th anniversary of the founding of the parent institution of the United States Public Health Service—The Hygienic Laboratory of the U.S. Marine Hospital Service, at Staten Island, New York.

To mark the occasion, and in recognition of the remarkable contribution that the National Institutes of Health (NIH) in general, and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) in particular, have made to the advancement of neuroscience, the Journal is pleased to publish the following essay by Dr. Donald Tower, Director-Emeritus of NINCDS.

In publishing this short essay, the Journal wishes to acknowledge also the contributions of the other NIH Institutes that have generously supported, and continue to contribute to work in neuroscience, together with the National Science Foundation and several other U.S. government and voluntary health agencies too numerous to mention individually. Without this support, neuroscience in the United States would not have become such a vigorous and exciting intellectual discipline, nor would this Journal exist.

W. Maxwell Cowan, Editor-in-Chief

The Impact of the NINCDS on the Neurosciences: An Essay Written for the Centennial of the NIH

Donald B. Tower

Director-Emeritus, NINCDS, NIH, Bethesda, Maryland

This essay, written as a contribution to the June 1987 participation by the NINCDS in the celebration of the centennial of the NIH (dated from the founding of the Hygienic Laboratory at Staten Island in 1887), discusses the impact of the NINDB/NINCDS on the neurosciences. Contrasts are drawn with the status of basic and clinical neurosciences in the late 19th century and prior to 1950, when the NINDB was established. This impact has involved its role as advocate and focal point for the support of research and research training in the neurosciences; the training of research and academic personnel and the funding of research projects, both significant factors in the postwar proliferation of methods and technologies; and the catalyzing of the steady progress in scientific knowledge, as reflected in examples from various facets of the programs of the neurological institute, in a continuum from the very basic and fundamental to the very clinical and pathological neurosciences.

The U.S. National Institutes of Health (NIH) are customarily thought of as post-World War II institutions, yet their origins reach back to 1887 with the establishment of the Hygienic Lab-

oratory at the Staten Island, New York, hospital of the U.S. Marine Hospital Service (the forerunner of the U.S. Public Health Service). The mission of the Hygienic Laboratory was primarily the control of infectious and nutritional disorders. Within four years of its founding, the Laboratory was moved to downtown Washington, D.C., where it remained until the opening of the NIH campus in suburban Bethesda, Maryland, in 1938. By that time, the name of the Laboratory had been changed to the National Institute [*singular*] of Health as a result of legislation passed by the U.S. Congress in 1930. After the move of the NIH to the Bethesda campus, increasing pressure from professional and lay groups resulted in the proliferation of the research divisions of the NIH over the next several decades into the familiar array of present-day institutes. Of particular relevance here are the mental health institute (NIMH) established by Congressional authorization in 1949 and the neurological institute (then the NINDB), fashioned in part from the resources of the NIMH by Congressional authorization in 1950. Thus, their major impact on the neurosciences has really occurred since 1950.

Yet even at the time of the founding of the Hygienic Laboratory a century ago, many of today's major neurological problems had been described clinically and pathologically, and significant contributions to the knowledge of the structure and function of the nervous system were already in progress. Parkinson's disease had been described by James Parkinson in 1817, localized pathologically to the substantia nigra, and treated with belladonna alkaloids (by 1879). Guillaume Duchenne had described the muscular dystrophies, in 1861 and 1872, and their hereditary nature was recognized in 1891. Huntington's disease was known well before its definitive description in 1872 by George Huntington, who emphasized its hereditary nature, its onset in adulthood, and its tendency to dementia. Myasthenia gravis was described by Samuel Wilks at this same period (in 1877), and treatment with physostigmine had been tried in 1895.

Correspondence should be addressed to Office of Director, NINCDS, Building 31, Rm. 8A52, National Institutes of Health, Bethesda, MD 20892.

This essay was written at the behest of the Director of the NINCDS and the Editor of *The Journal of Neuroscience* as part of the celebration by the NINCDS of the centennial of the NIH.

NEI: National Eye Institute

NIAID: National Institute of Allergy and Infectious Diseases

NIH: National Institutes of Health

NIMH: National Institute of Mental Health

NINDB: National Institute of Neurological Diseases and Blindness (established in 1950; name changed to NINDS in 1968 when the NEI was formed)

NINDS: National Institute of Neurological Diseases and Stroke (new name for the NINDB after 1968, until 1975 when name changed to NINCDS)

NINCDS: National Institute of Neurological and Communicative Disorders and Stroke (new name for the NINDB/NINDS after 1975)

0270-6474/87/071601-06\$02.00/0

The epilepsies, known since the time of Hippocrates, were put by J. Hughlings Jackson (in 1870 and later) into the modern context of excessive discharges of neurons characteristic of the gray-matter areas of origin and spread of the discharges. Treatment with bromides had already been introduced by Locock in 1857, and studies of the electrical excitability of cerebral cortex by Fritsch and Hitzig (1870) and by Ferrier (1873) were contemporaneous with Jackson's clinical studies. Even surgical excision for focal seizures was tried by Horsley in 1886. The EEG was anticipated by Richard Caton's recording of electrical activity from rabbit brain in 1875.

Such clinical observations were complemented by numerous experimental studies. For example, in 1849 Claude Bernard described the effects of curare on neuromuscular preparations. Thudichum carried out his extensive analyses of the chemical composition of human brain, published just three years before the establishment of the Hygienic Laboratory. At the turn of the century several investigators attempted to measure cerebral blood flow and metabolism in the dog (Hill and Nabarro in 1895; Jensen in 1904; and Alexander et al. in 1912) but failed to correct adequately for extracerebral fractions. In the years after 1889, Santiago Ramón y Cajal developed metallic stains that permitted him to provide a modern-day delineation of the histology of neurons and glia. And in the early decades of the 20th century, Hans Winterstein reported a striking series of observations on the frog spinal cord–nerve–muscle preparation that correlated stimulation, metabolic events, and actions of various drugs. These selected examples illustrate how active neuroscientific research was in the late 19th and early 20th centuries.

Why then did these clinical and experimental studies—and the many others like them—not engender the rapid progression of basic and clinical neurosciences so familiar to us today? Perhaps the most important reason was that there was no focal point and no effective advocacy until the National Institute of Neurological Diseases and Blindness (NINDB) became operational after 1950. The Institute's first director, the late Pearce Bailey, recalled that neurological medicine and research had long been regarded as appendages of psychiatry under the umbrella of neuropsychiatry, a term used by the military in both world wars. Most academic neurological units were subsidiary to either psychiatric or internal medicine services. At the end of World War II there were only 32 residency positions in neurology available in the U.S. The low ebb to which North American neurology had fallen was reversed to a considerable extent by two training and research groups: the Montreal Neurological Institute under Wilder Penfield, Herbert Jasper, and their colleagues; and the neurological program of the U.S. Veterans Administration (VA), with Pearce Bailey as the first chief (1946–50) of VA neurology. Residency training programs within VA hospitals or at university hospitals of adjacent medical schools were resurrected, and an advisory committee drawn primarily from the American Neurological Association and the newly organized American Academy of Neurology was set up to further academic neurology and to assure better patient care.

With such developments came demands for a national institute for neurological research at the NIH (an idea originally propounded much earlier by Harvey Cushing in World War I). Strong pressures arose from the early group of voluntary (lay) health agencies, notably the National Multiple Sclerosis (MS) Society, the Muscular Dystrophy Association (MDA), the National Epilepsy League, and United Cerebral Palsy (UCP). How-

ever, unlike the cancer and heart groups, these agencies did not initially urge a single institute but proposed separate institutes for each of the many neurological disorders. Nevertheless, what began as the National Multiple Sclerosis Act, introduced by Senator Tobey of New Hampshire, was eventually modified into a bill sponsored by Tobey and Senator O'Mahoney of Wyoming to create the NINDB within the U.S. Public Health Service with responsibility for support of research and training across the whole spectrum of neurological and sensory disorders.

The creation of the neurological institute in 1950 did not automatically initiate a wave of activity because, despite authority for research and training programs, no new funds were appropriated until 1953—the monies before then coming as transfers of active grants previously supported by other institutes, for example, the NIMH. Indeed, the intramural basic laboratory research program of the new NINDB was originally administered as a joint NIMH–NINDB program under Seymour Kety and his successors, until its division into two separate programs in 1960. One of the early problems was getting the message to Congress, since testimony from the various voluntary health agencies tended to be fragmentary and contradictory. To remedy this situation, colleagues from both professional and lay organizations met together in 1952 to form the National Committee for Research in Neurological Disorders (NCRND). This committee has continued to function to the present day as the now collective voice for nearly 100 professional and voluntary health agencies and as the principal advocate for the neurological institute and its programs before the public, especially the U.S. Congress. Consequently, a concerted program could be advocated, with the neurological institute as its focal point. Other federal agencies—like the NIMH, the eye institute (NEI), established in 1968, the National Science Foundation (NSF), established in 1950, and the many VA hospital laboratories and clinics—as well as those voluntary health agencies with fellowship and research grant programs (the MS Society, the MDA, and others) all have contributed. But the bulk of support for clinical and basic neuroscience (more than two-thirds of the total) has come from the neurological institute. Thus, the first impact of the neurological institute on the neurosciences can be appreciated from its role as advocate and focal point for the support of research and training in the neurosciences.

Since World War II biomedical research in general has benefited from the extensive proliferation of methodologies and technologies, with the neurosciences sharing therein in many ways. Often the methods or techniques already existed, some of them for decades. For example, chromatography can be traced to Mikhail Tswett, who in 1906 separated plant pigments on calcium carbonate columns. Adaptations to paper and to modern support agents and their commercial availability and instrumentation have made chromatographic techniques standard tools in most laboratories. The use of radioactive tracers was pioneered by Georg Hevesey, who in 1923 showed that thorium B, a radioactive isotope of lead, was handled by living plants in a manner identical to that for stable lead. The nuclear industry growing up after World War II has provided both the commercial availability of varieties of isotopes, as well as the instrumentation with which to monitor and analyze them. As early as 1907 Ross Harrison had cultured embryonic cells (including neurons), and in the 1930s Ernst Ruska developed a practical electron microscope, but these technologies had to await the adaptations of the post-World War II period to become the

familiar laboratory tools of today. Consider also the accessibility today of reagent biochemicals, toxins, and preparations from exotic species (like squid, electric eel, and *Aplysia*).

Some outright revolutions have occurred, such as the shifts from the vacuum tube to the transistor (introduced in 1947) and now (after 1957) to the semiconductor silicon chip and integrated microcircuitry—remarkable developments that provide the compact computers and microprocessors for the many research applications of today. There are many other examples, especially in the fields of immunology and molecular genetics and in the development of new imaging techniques, e.g., computed tomography and positron emission tomography (PET) and magnetic resonance imaging.

In many cases these technological advances originated commercially; yet the biomedical research community and funding agencies like the NIH were integral parts of the process. For it was the demand, the market provided by the latter, that encouraged and underwrote much of the commercial research and development. This consumer role does not belong exclusively to the biomedical research community, but that community was obviously a significant factor.

The two major impacts of the neurological institute upon the neurosciences have been in training research and academic (teaching) personnel and in funding fundamental and clinical research projects. Within 25 years after the establishment of the NINDB, the number of neurological residency positions in the U.S. had increased from 32 to more than 700. In that same period, nearly 15,000 research fellowships and traineeships (including a relatively small but significant number in the NINDB Intramural Program) had been supported. And the NINDB/NINCDS funding for research in the neurosciences had risen from a modest \$1.25 million in 1953 to nearly \$300 million in 1983, with budgetary increases during the 1950s and 1960s of 20–25% yearly. By comparison, support for neuroscience research and training in Canada and in Britain remained proportionately smaller at one-third or less of the U.S. level when expressed on the basis of population. These few statistics illustrate, on the one hand, the effectiveness of the NINDB/NINCDS as a focal point and advocate in securing support for the funding of research and training in the neurosciences and, on the other hand, the creation of a significant cadre of scientists and institutions with needs for the many new methods and technologies. Surely, however, the most important impacts have been on sustaining the steady progress of scientific knowledge itself—impacts that reflect the several facets of programs of the neurological institute. A few examples chosen at random must suffice here.

When the NINDB was established in 1950 there were available in clinical practice three established anticonvulsant drugs—phenobarbital, diphenylhydantoin (phenytoin), and trimethadione—with overall efficacies in terms of seizure control of less than 50%. The quality of life for patients with epilepsy left much to be desired. Subsequent extensive research efforts have uncovered many new transmitter agents (like GABA, dopamine, and glutamate) and new membrane mechanisms (receptors, ion channels, second messengers, etc.). The NINDB inaugurated a special epilepsy branch and program, headed initially by J. Kiffin Penry, from which emerged several major advances: the first new anticonvulsant drugs to reach the U.S. marketplace in 16 years (the benzodiazepines, carbamazepine, and valproate) and the practical technology for monitoring blood levels of anticonvulsant drugs in order to correlate circulating drug levels with

clinical response. Screening programs continue with the goal of identifying novel new anticonvulsants. Clinical seizure control has now risen to 85–90%, and the great majority of epileptic patients have been enabled to rejoin society. The problems of epilepsy are by no means solved, but the pressures to improve clinical management have generated many valuable insights into the relevant neurochemical, neurophysiological, and neuropharmacological mechanisms.

After a century and a half, the mystery of Parkinson's disease was suddenly dissipated when the depletion of dopamine in the substantia nigra was demonstrated. Attempts at replacement therapy soon succeeded with the use of L-DOPA alone or in combination with a peripheral decarboxylase inhibitor (such as Carbidopa or Sinemet). Despite dramatic improvements in the quality of life conferred on most patients by such therapy, not all the problems of Parkinson's disease have been solved, especially with respect to the side effects of therapy, progression of the disease, and the complicating dementia. New drugs like bromocriptine and congeners are being sought, and investigators now have available to them the first animal model for Parkinson's disease—an extraordinary development in itself. The agent, MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), was discovered as a result of its accidental production during attempted synthesis of methadone (for treatment of heroin addiction) and the development of severe Parkinson-like symptoms following accidental or purposeful contact. Subsequent studies have revealed the metabolic conversion of MPTP in brain into the active toxic intermediate by the action of monoamine oxidase B and the accumulation of the active metabolite via the dopamine uptake system into cells of the substantia nigra. Each of these steps can be blocked by the monoamine oxidase B inhibitor Pargyline or by an inhibitor of dopamine uptake, respectively. Almost serendipitously, the opportunity to mount major assaults on the persisting problems of Parkinson's disease seems to be at hand. One such approach has been the trial, in experimental animals and in patients, of brain transplants containing dopaminergic neurons intended to serve as surrogate sources of dopamine.

Myasthenia gravis provides another example. By the time that the NINDB came into existence this disorder was well understood clinically as a disorder of neuromuscular transmission (analogous to curarization), treatable with neostigmine and occasionally thymectomy, and probably classifiable as an autoimmune disorder. Yet the precise nature of the problem eluded everyone until experiments designed to immunize rabbits with purified acetylcholine receptor protein produced experimental myasthenia. Further investigations demonstrated the presence in human patients of circulating antibodies to the acetylcholine receptor protein and the passive transfer of the disorder. As a result, there is now an animal model for the disease; the occurrence of myasthenia in newborn infants from myasthenic mothers can be accounted for; and the efficacy of adrenocorticotropin or prednisone and the role of the thymus with respect to the immune system are understandable. One dramatic derivative of these studies has been the use of immunological probes to isolate in pure state the acetylcholine receptor, to delineate its molecular structure and protein sequences, and to elucidate the functionally controlled conformational changes of the central ion channel that accompany reception of the transmitter and the modulation of its action by agonists or antagonists. Sufficient data have already been accumulated to permit computer-modeling experiments.

The study of neuromuscular and muscle disorders has been a major research initiative of the NINDB Intramural Program, inaugurated by its first Clinical Director, the late G. Milton Shy, and his colleagues. Their techniques of muscle biopsy and examination by histochemical and electron-microscopic procedures yielded new insights, led to the discovery of new diseases, and served to train a whole generation of clinical investigators now dispersed throughout the country. One of the more refractory neuromuscular problems has been the elucidation of the precise nature of the sex-linked hereditary disorder Duchenne muscular dystrophy. All the answers are not yet in, but by the use of molecular genetic techniques and cDNA probes, it has been possible for a new generation of investigators to localize the gene involved in Duchenne muscular dystrophy to the short arm of the X-chromosome at position Xp21, very close to the centromere. In time it should be possible to isolate the gene itself, so that the gene product may be determined and the cause of the clinical disorder deduced. Meanwhile, current DNA probes have been used with good diagnostic accuracy, especially for prenatal evaluation of fetuses at risk.

Another hereditary disorder, the autosomal dominant Huntington's disease (HD), has begun to yield to the onslaught of modern molecular genetic techniques. In 1979, at the urging of the Congressionally mandated National Commission on Huntington's Disease and Related Disorders, the NINCDS organized, in collaboration with several nonfederal institutions, a combined epidemiological and genetic study of a very large collection of HD families in remote villages on Lake Maracaibo, Venezuela. The evidence indicated that HD had probably been introduced there centuries ago by a European sailor and that as a result of extensive intermarrying in these isolated villages there were now many cases, often the offspring of parents who both were afflicted (i.e., double dose). From the studies of this patient cohort it has been possible to localize the gene involved in HD to the short arm of chromosome 4, with a linkage within 2 centimorgans to the A haplotype of the marker G8. Once again, applications to diagnosis, screening, isolation of the gene, specification of its product, and delineation of the precise defect responsible for this hereditary disorder now seem within reach.

Among the more than 500 genetically determined disorders of the nervous system, a number of the autosomal-recessive disorders are now well understood. The sphingolipid storage diseases—including Tay-Sachs, Niemann-Pick, Gaucher's and Fabry's diseases—have been demonstrated each to result from the deletion or alteration of a gene specifying in each case a specific enzyme involved in the degradation of the sphingolipid characteristically found to accumulate in neurons and/or other tissue cells in these disorders. Investigations led primarily by Roscoe Brady and colleagues in the NINDB/NINCDS Intramural Program have characterized these lipid storage diseases as disorders of lysosomal hydrolases. These workers have identified the respective missing or attenuated enzymes, developed diagnostic and screening tests (for carriers and for fetuses at risk), and not only purified and isolated the human enzymes but undertaken enzyme replacement therapy on a limited scale, with some promising results. Even though such therapeutic heroics may eventually defer to gene repair or replacement techniques, these studies have been remarkable among those studies in recent years that have addressed seemingly hopeless and desperate clinical problems and have provided not only an understanding of their nature but the means of addressing prevention and therapy.

The vulnerability of the human nervous system during the nine months of gestation and the perinatal period prompted the NINDB to embark in the late 1950s on one of its most ambitious programs. The Collaborative Perinatal Study, conceived by Pearce Bailey and originally headed by Richard Masland (later the second director of the NINDB), involved some 54,000 mothers and their 60,000 offspring, who were studied over the next decade. The study aimed to address the major problems of cerebral palsy, developmental disabilities, mental retardation, and the high mortality and morbidity of infants in the perinatal period. An early dividend was the introduction in 1963 of the Guthrie test (an assay for blood phenylalanine) suitable for mass screening for newborn phenylketonuria—a procedure that proved very effective in preventing new untreated cases and the once inevitable mental retardation.

Another example comes from the 1964 epidemic of rubella (German measles) that totaled 1.8 million cases in the U.S., including 6000 pregnant mothers enrolled in the NINDB Collaborative Perinatal Study. The consequent abnormalities in those babies include microcephaly, eye lesions, deafness, cardiac malformations, and mental retardation, thus establishing the devastating effects of congenital rubella. Several groups of investigators, including John Sever and colleagues in the NINDB Infectious Diseases Branch, quickly isolated the rubella virus so that an effective vaccine could be developed; this was marketed by 1969. With the protection so afforded, no such epidemic disaster need recur. The group under Sever has made a number of other contributions, notably the demonstration of the role of the measles virus in the disabling fatal brain disorder subacute sclerosing panencephalitis.

Contemporaneously, the NINDB laboratory headed by Carleton Gajdusek and Clarence J. Gibbs, Jr. was immersed in trying to fathom the mystery of *kuru*, a CNS disorder characterized by shaking, progressive motor disability, dementia, and death and restricted to the Fore people of the highlands of Papua-New Guinea. The Australian health officer Vincent Gigas and Gajdusek described this disorder in 1957. Initially it was thought to be a hereditary or toxic disorder, but examination of brain specimens suggested to William Hadlow (of the NIAID Rocky Mt. Laboratory) and Igor Klatzo (of the NINDB Intramural Program) that the neuronal and astrocytic lesions resembled closely those found characteristically in the transmissible disorder of sheep known as scrapie and in the human degenerative CNS disorder Creutzfeldt-Jakob disease (CJD). Accordingly, Gajdusek and Gibbs set out to ascertain whether *kuru* was transmissible by inoculating samples of *kuru* brains intracerebrally into chimpanzees. Successful transmission was first demonstrated 22 and 30 months after inoculation, and subsequent studies reduced the incubation period to an average of 11 months (in contrast to the 8.5 year incubation period in the rhesus monkey). Eventually, these workers achieved transmission of *kuru*, scrapie, and CJD to mice, hamsters, and other common mammals. Besides the most unusual properties of these slow or latent viral agents, these observations represented an astounding and revolutionary discovery, that neurological disorders previously considered to be chronically degenerative in nature were actually transmissible. For these investigations Gajdusek won the Nobel Prize for Physiology or Medicine in 1976, and the work has stimulated much additional study to ascertain the precise nature of the transmissible agents and the extent to which this phenomenon may apply to the chronic degenerative (and even iatrogenic) disorders of the nervous system.

The foregoing examples have barely sampled the large body of investigations and findings, and these examples have deliberately emphasized clinical relevance and correlations. Ultimately, it is the disorders of the human nervous system that pose the problems and demand solutions, and the impact of the neurological institute is inevitably felt in such contexts. Nevertheless, the funding of training and of research grants, contracts, and collaborative studies and the like clearly creates a continuum from the very basic and fundamental to the very clinical and applied. The study of epilepsy has probably taught us more about the structure and function of the nervous system than would have been possible under most other rubrics. So it is that there are many facets to this neuroscience continuum. For example, the late William Windle working at the NINDB convinced research scientists and clinicians alike that, contrary to long-standing dogma, CNS axons could indeed regenerate. His stubborn conviction engendered a host of subsequent studies on the mechanisms and agents involved in central regeneration and on the means for attacking such clinical problems as paraplegia, multiple sclerosis, and stroke in which central connections have degenerated or been severed.

Such studies remind us of many related areas of research: growth and trophic factors, axonal transport, and neurotransmitter and neuromodulatory agents. When the NINDB began there were only 2 established neurotransmitters, acetylcholine and norepinephrine; now there are several more conventional transmitters—e.g., GABA, dopamine, serotonin, and glutamate—as well as a growing number of neuropeptides and neurohormones that serve to modulate the transmission of impulses across synapses. Moreover, there is increased attention to the study of receptors for such agents, where much of the plasticity of the nervous system may reside. The voltage-clamp technique pioneered by the late Kenneth Cole in the NINDB Intramural Program for studies on axonal conduction has been borrowed by many others; and the application of the more recent patch-clamp method to the analysis of ion channels has revolutionized the study of neuronal membranes and opened up the way for understanding the mechanisms of action of the second messengers initiated by activated surface receptors.

At the other end of the spectrum, so to speak, increasing attention has been given to integrated regional and total cerebral functions, as studied by the various imaging techniques. Despite some inherent technical limitations, such procedures have provided much new information about seizures, stroke, multiple sclerosis, Alzheimer's disease, dyslexia, and other disorders. An important aspect of such studies deals with the sensory inputs and the central processing required to store and respond appropriately to these inputs, as exemplified by research on pain, consciousness (and coma), memory, cognition, and speech. In this regard there are such disparate examples as auditory prostheses (cochlear implants) for deafness and the many studies on the memory deficits and dementia of Alzheimer's disease.

As new approaches to clinical problems have come on-line, the NINCDS has stood ready to help in their evaluation and application. A good recent example is the multicenter collaborative evaluation of the efficacy of the microsurgical procedure of extracranial-to-intracranial arterial anastomosis to bypass an area of insufficient or occluded blood supply with the intent of alleviating transient ischemic attacks and preventing incipient strokes. Some 65 clinics worldwide collaborated in this study of 1377 patients; although funded by the NINCDS, this program was supervised and administered by local investigators. After

an evaluation period of 5 years, the data were analyzed by an independent committee, which reached the clear conclusion that the surgical anastomotic procedures conferred no significant benefits over conventional, conservative neurological management of such patients. In other situations the NINCDS may utilize a consensus panel, as in the recent evaluation of the value of plasmapheresis in treating presumed autoimmune disorders like Guillain-Barré syndrome, acute myasthenic crises, MS, and amyotrophic lateral sclerosis (ALS). The panel of outside experts viewed the procedure as effective for the first 2 problems, of possible benefit in MS, and not useful for ALS.

On a number of occasions the neurological institute has extended its impact beyond the United States, albeit to a modest degree. In its early years, the NINDB funded a few foreign research grants, in concert with other NIH institutes. For Western Europe in the early post-World War II period, this support from the NINDB helped to revitalize distinguished neuroscience laboratories and to give European neurosciences a needed boost until support from their own research councils could begin. Funding for Canadian, Latin American, and other foreign groups also was provided. Counterpart or PL-480 funds in countries such as Poland, Yugoslavia, Israel, and India were restricted to the support of studies that would benefit American neuroscience and technology, but the local foreign laboratory usually benefited as well from such NINDB-sponsored projects. For example, the NINDB contract with David Shapiro's laboratory in Israel provided for supplies of pure radioisotopically labeled synthetic sphingolipid substrates used in the diagnostic and screening assays for the various sphingolipid storage diseases, as carried out in Brady's laboratory at the NINDB, on a worldwide basis for some years. More recently, the NINCDS has supported activities of the International Brain Research Organization and the World Federation of Neurology and has collaborated in the neuroscience center program of the World Health Organization. With the increasing budgetary constraints and foreign-exchange problems of recent years, the foreign programs of the NIH have been concentrated under the aegis of the Fogarty International Center at the NIH, and the NINCDS has supported its share of fellowships, scholar awards, and the like.

In an account of this sort it is not possible to provide detailed documentation, to acknowledge all contributors, or, indeed, to be comprehensive. And like Newton's Third Law of Motion, the impact of the neurological institute on the basic and clinical neurosciences has been reciprocated by impact on the institute from the community. Thus, the perception of the need for greater emphasis on research in Alzheimer's disease came from concerned neuroscientists in the community, which generated, in the mid-1970s, two NIH conferences sponsored jointly by the NINCDS, the NIMH, and the National Institute of Aging; together these conferences have provided much of the stimulus for further research activity. Additionally, the NINCDS provided expertise in bringing together various local and regional groups to form a single national voluntary agency for Alzheimer's disease. To cite another example, the development of positron emission tomographic (PET) scanning occasioned a conference called by the NINCDS at which expert advice was sought from the scientific community and was later weighed with the institute's national advisory council before the PET research center program was undertaken. Over the years many workshops, conferences, symposia, commissions, and, since 1970, the Society for Neuroscience have been utilized to achieve interfaces between community and institute on a wide variety

of issues and initiatives. What has transpired is exemplified in the foregoing selected accounts, with no pretense of assigning credit precisely but simply to provide a feel for the climate that has prevailed.

In characterizing the impact of the neurological institute upon the neurosciences (and vice versa), one might apply such descriptors as cascade, facilitation, recruitment, amplification, stimulus, reinforcement, modulation, and even inhibition. Recently, Lewis Thomas wrote that we should anticipate discoveries matching the great conquests of infectious diseases in the previous generations, particularly in the field of neurobiology. And he insisted that "medicine needs more research." What has taken place in the neurosciences since World War II and the establishment of the neurological institute has been a true scientific revolution, like that which occurred in the 17th century. Today we stand on the threshold, gazing at a neuroscience horizon that has suddenly been greatly widened. Our situation is comparable to that of the 17th century scientists who gazed into the newly invented microscopes and telescopes that revealed the expanded horizons of the microworld of nature within and the macroworld of the planetary system without to which

they could apply the newly conceived scientific method. In like manner, the concepts and technologies of neuroscience reveal expanding vistas of opportunities for understanding the nervous system and for the mastery of its disorders. The community and the NINCDS are surely equal to the challenge.

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