Exploring the Nervous System

With Electronic Tools, An Institutional Base, A Network of Scientists

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Explorers of the Nervous System:
With Electronics, An Institutional Base, A Network of Scientists

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PREFACE

This book is not an authoritative or a comprehensive history of neuroscience. The author is not a professional scientist or historian. He was a biomedical engineer who worked with neurologists and neuroscientists for more than 50 years at Columbia Medical School, Sloan Kettering Cancer Research Institute and Rockefeller University. He might qualify as an informed layman writing a memoir of association with famous neuroscientists, particularly those he worked with during 48 years at the Rockefeller.

His first boss from 1947–1951 with whom he wrote his first scientific paper was Paul Hoefer MD Ph.D., a refugee from Hitler's Germany, Director of the EEG Department, a clinical and research facility at Columbia Medical School. With Hoefer he not only did clinical and engineering studies on frequency analysis of the EEG, but also studied neurophysiology and repeated Gasser's classic experiments on the frog sciatic nerve.

During those years he was often a member of the staff in the neurological surgery operating room running an EEG machine with electrodes placed on the exposed surface of the brain during operations. He was able to observe the surgeon placing electrodes on the exposed brain of the patient. Electrical stimulation of the motor and sensory areas of the brain by the surgeon was routinely used to locate such areas. The patient was awake under local anesthesia and could respond by stating how and where he felt the stimulus or by involuntary movement. The surgeon used this information to avoid damaging these vital areas in surgery to remove brain tumors or scar tissue sources of epileptic seizures. During this period the author worked evenings in Harry Grundfest's physiology lab maintaining electronic equipment that Grundfest had designed based on Toennies pioneering work for Gasser, the Director of the Rockefeller Institute, where both Grundfest and Toennies had worked in the late 1930's.

Following the years at Columbia, the author worked on radiological physics electronic instrumentation first at a New York City Department of Hospitals X-Ray and Radiology Instrumentation Lab as a senior physicist and later as a pre and post-doctoral fellow in the Physics Department at Sloan Kettering Institute.

His doctoral thesis done at Sloan Kettering for a Polytechnic Institute of Brooklyn, Electrical Engineering D.E.E. degree concerned a mathematical model for the uptake of radioactive isotopes in different assumed compartmental parts of the body such as the circulatory system or the thyroid gland.

In 1957 he started work at Rockefeller University becoming Head of the Laboratory of Electronics as an Assistant Professor in 1958, retiring as an Emeritus Associate Professor in 1990 and continuing to work on his own projects such as this book until the present.

In the course of these 48 years at Rockefeller he met and worked for most of the neuroscience professors and their students mentioned in the book. The Electronics Laboratory, which he headed, was concerned with designing and maintaining appropriate electronic and later computer equipment to be used in electrophysiological research. He worked for and with the Nobelist Herbert Gasser and spent 20 years in daily contact with H. Keffer Hartline, consulted with Thorsten Wiesel, and knew personally, worked with, or had studied seriously the work of everyone highlighted in this book. It has been fun and a labor of love.

The table of contents of the book speaks for itself, mainly the accomplishments and of some of the movers and shakers of 20th century neuroscience. The first two chapters outline the origin of the Rockefeller Institute and the highlights of neuroscience in the 19th century. The remainder of the book is mainly devoted to the role of scientists connected with the Rockefeller Institute/University with the exception of the 5th chapter devoted to the British Nobelists. A few other outsiders had connections with the scientific network. Until the advent of genetically manipulated microorganisms and mice, the preeminent technologies that drove neuroscience were microelectrodes, electronics and its offspring digital computers.

One of the background themes of this account is the preeminent role of technology, mathematics and the physical sciences. This knowledge in the hands of creative biologists played a significant role during World War 2 in expanding knowledge of radar and in peace that of the nervous system. This contribution was often augmented by their mastery of the tools of their trade and its widespread communication through their social network.

INTRODUCTION

This book is not primarily a description of the current state of scientific knowledge of the nervous system. The author tells the story of the highlights of progress during the last 100 years by detailing the experiments of some of its most accomplished scientists. The major theme of this book is the historical roots of the progress of neuroscience in the 20th century. It is our claim that this progress has its origin not only in a unique group of talented individuals who sought answers to specific questions about the structure and functions of the nervous system but on their support from their education, the institutions which provided it and by the societal and technological culture in which they flourished.

The industrial revolution which emerged from the Middle Ages generated a need for new tools and technology. This sparked progress in the sciences of physics, chemistry and mathematics as well as biology. Leeuwenhock's microscope made possible Cajal's findings in neuroanatomy. Faraday and Maxwell made possible Einthoven's galvanometer. Electrical stimulation of nerves and Helmholtz's measurement of conduction velocity made possible Sherrington's study of the neural anatomy of reflexes and Adrian's study of sensation. Gasser was the first to use a vacuum tube amplifier and a cathode ray oscilloscope to obtain the waveform of a compound nerve and to find the complex of individual single nerve's waveform. With dissection, microscope studies and mathematical reasoning he was able to determine the relation between nerve diameter, conduction velocity and function. Hodgkin and Huxley used Gerard's microelectrode and World War 2 advances in electronics and radioactive isotopes to determine the electrophysiology of the nerve cell.

The unraveling of the genome would not have been possible without the personal computer and the advances in electronics and automation that made it possible. These advances made possible genetic cloning and knockout genes which have led to broad new advances in the cellular biology of the nerve cell, which we shall discuss in terms of the leaders in this research.

But Nobel prize winners in all these areas were nurtured by great Universities and Research Institutions such as the Rockefeller Institute for Medical Research. They were also given a push by a network of preceding generations of scientists. Hodgkin's mentor Lord Adrian sent him to Gasser where he had a chance to test his own innovative ideas not only with Gasser but also to learn with Curtis and Cole at Woods Hole, with Gerard in Chicago, Erlanger in St. Louis, and to learn more skill with Toennies in the use of electronics in Gasser's lab in New York.

We use the research accomplishments of about 30 individual scientists spanning the 20th century in neuroscience to illustrate our theme, and to examine their research contributions. About one-half of them spent a significant part of their career at the Rockefeller Institute that Detlev Bronk transformed into a University. The 100 year history of the Rockefeller University provides a glimpse of the institutional base which provided support to the winners of 20% of the 100 Nobel Prize awards in the 20th century in Medicine or Physiology and 20 % of those prizes were related to neuroscience. In last half century this University has trained over 900 Ph. D. students, two of whom became Nobelists, dozens of the students later became members of the US National Academy of Science, many more are now prominent full Professors in other Universities. Currently. there are more than 100 Ph. D. candidates and more than 600 post graduate associates at Rockefeller. We will devote a chapter to the careers of 6 former students who are prominent researchers in neuroscience.

The author felt it appropriate to discuss the founding of the Rockefeller Institute as illustrative of how it attained its role as a major research institute in biology and medicine and how it began nurturing the growth of science and scientists. It is also instructive to outline the growth of neurobiology in the 18th and 19th centuries setting the background for the more dramatic growth in the 20th century. As a matter of tracing the role of the University we will follow Gasser's legacy through 4 generations to the present.

Another important theme is the generations of mentors and students. Adrian and Gasser mentored Hodgkin. Hodgkin mentored Gadsby. A.V.Hill mentored Bernard Katz who mentored Bert Sakmann. Frank Brink was mentored by Detlev Bronk. In turn Brink mentored the student Charles Stevens who mentored Erwin Neher. Without drawing a chart showing what every graduate student in science knows well that it matters greatly who is your mentor not only because it helps you get a faculty appointment but it matters because of what you can learn from a leading scientist. Our account will feature mentors and students who became mentors and focus on a sequence of contributions to leading areas in neuroscience.

The role of World War 2 was a leading factor in accelerating progress in neuroscience as well as in the physical sciences, electronics and computers. Many of the scientists that we shall treat became radar officers during the war. Both at Harwell in England and the MIT Radiation Labs in the US young scientists who became prominent later in life became expert in electronics. Others worked on computers and codes or as Grundfest did developed electronic instruments for medical applications to treat wounded soldiers or worked on biological and chemical agents that might be used as weapons.

The themes of technological advances, individual talents and insights, education and experience in the physical, chemical and mathematical sciences, and in the use of technology, a secure institutional base, and communication and support from the network of scientists these are the seeds and nutrients of scientific progress both in the cell biology as well as for progress in the study of the structures and functionality of the nervous system. Those individuals who have followed this path have been in the forefront of this last century's phenomenal growth in neuroscience. This book aims at telling the story of the contributions of a representative sample of this elite and its history.

EXPLORING THE NERVOUS SYSTEM

With electronic tools, an institutional base and support from a network of scientists

CHAPTER 1

Introduction, the Institutional Base

On a journey of exploration we need to know the origins of the journey, the equipment used, and the supporting institutions. Since neuroscience is a worldwide venture involving many countries and sponsors, we will rely mainly on our own experience as representative of the whole. The second chapter will give the historical background. This account will survey the period from the late 18^{th} century until the beginning of the 20^{th} century. In succeeding chapters we will introduce leading figures, their associates and many students that became leaders along with their mentors. The remainder of this account will carry us through the 20^{th} century. We begin:

In the crowded spaces and hustle of New York City's East Side there exists a beautifully landscaped 5-block area overlooking the river. It is a veritable calm oasis. A canopy of 100-year-old tall trees overlooks verdant lawns and marble walks. Through them one can see a few not too tall modern buildings at the south end, flanking ivy covered old buildings. Relatively few people walk, savoring the peacefulness of the scene.

Here some of the most distinguished scientists of the 20th century spent part of their lives. Twenty-one of them won Nobel Prizes. Others won many other awards such as membership in the National Academy of Science and Honorary Degrees. This place is now known as the Rockefeller University, formerly The Rockefeller Institute for Medical Research. Besides research by senior scientists, it has in residence about 100 graduate students and about 600 hundred-post doctoral associates. The University gives Ph.D. degrees, about 30 per year mainly in Medical and Biological sciences. There are 5 to 15 or more students each year entering a joint Ph.D. and MD program with Cornell Medical School, a block uptown. Harvard, Stanford, Cambridge or the Sorbonne might just as easily have accepted these graduate students. They follow no prescribed curriculum but work as junior partners of their professors. The post docs are one step ahead of the students in their work toward a successful career.

Our story is about the origin here and continuing influence this place has on the knowledge of the structure and functions of the nervous system. This area of science was first called Neurophysiology; now Neuroscience is a more popular name. To properly appreciate what has been accomplished at the Rockefeller University, one has to look into the history of this branch of Medicine. Part of this story concerns the origins and growth of the Rockefeller Institute itself.

The emergence of this institution in the United States along with others of a similar nature abroad has to be evaluated in the light of profound changes in the quality of life in the countries that were most deeply affected by the industrial revolution.

The period from the end of the Civil War in America in 1865 to the end of the 19th century was "the best of times, the worst of times"(Dickens). Along with the emergence of people with great wealth, there was abject poverty, malnutrition and disease. (Corner 1964)[1]. The center of gravity of the population was shifting from small independent farms to the cities.

Many farmers' unmarried daughters had already gone to work in the Lancaster textile mills, and their siblings seeking other factory work in the growing cities often followed them. Railroads and telegraph lines were moving coast to coast and across the land, followed by telephone and oil pipelines. The factories of the industrial revolution had created the need for many inventions; one such was the steam engine needed to pump water out of the English coal mines (Schneirla 1942)[2].

The problems of public health and medicine were diverse and difficult. Some of these problems were already being solved in Europe by a growth in scientific knowledge through laboratory investigation. Other diseases proved less curable, either because of crowding and poor water, milk and sanitation, or because their prevention or treatment needed a deeper scientific knowledge.

In Europe during the 19th century significant experimental research in physics, chemistry and medical science had already occurred. These developments were mirrored in the mechanistic philosophy of Rene Descartes, along with the biological writings of Darwin, as well as the philosophical views of Herbert Spencer and Huxley[3]. These led, at first, to naïve attempts to view the body as a machine and to reduce physiology to chemistry. The saving grace was that such medical explanations could be subject to laboratory testing.

As a result of earlier medical research, it was now possible to consider the heart as a pump and measure heart rate and blood pressure. One could test the contents of the stomach for acidity. Galvani's discovery of electric currents that could stimulate nerves and muscles showed that physics was relevant to the study of physiology.

As the 19th century ended more precise applications of basic scientific knowledge to biology and medicine were made. Moreover, the technology created by inventive scientists became more widely available. Among these legacies from the past was Leeuwenhoek's microscope. The development of lathes and milling machines made it possible to improve the microscope by the precision grinding of lenses. Other intricate machines were introduced not only in factories for the production of goods, but for use in scientific research. Einthoven's string galvanometer, the induction coil, electrical motors and generators led to a variety of test equipment for generating and measuring electric currents and voltages.

The Rockefeller Institute for Medical Research was planned and founded in the period from 1897 to 1906. Part of the stimulus for this venture was the fact that the level of available medical and preventative health care in the United States was inadequate. Many of the medical schools in the United States were little more than trade schools, lacking any real commitment to scientific medical education in any subject other than anatomy. In 1900 the survival rate for babies in the first five years of life was as low as 50% in some parts of the country and not much higher elsewhere.

Infectious diseases, such as typhoid fever, tuberculosis and diphtheria, were the most obvious problem. European laboratories were already making dramatic progress in this area. Koch in Germany, Pasteur in France, and Kiyosha Shiga in Japan identified the microorganisms causing diseases. Vaccines and antitoxins producing immunity to these diseases followed closely the identification of their causative agents.

In Europe and Japan there was already a history of private and governmental support of scientific research. The Royal Society as a medium for lecture and discussions was founded in the 17^{th} century. The Medici Academie in Florence, and the Paris Academy of Science followed it. In the 19^{th} century there were established in Germany, the research laboratories at Gottingen, and at the University of Berlin. Koch's laboratory at the Imperial Health Office in Berlin, the Russian Institute for Experimental Medicine, and privately financed institutes for Pasteur, Lister and Emil Ludwig were opened. New York City and Rochester had initiated government financed health offices headed by competent medical authorities such as Theobald Smith.

In 1897 John D. Rockefeller Sr. had all but retired from his oil business and with the help of Frederick Gates, a Baptist Minister, who had an uncommonly good business sense, was trying to give away substantial portions of his $250,000,000 fortune. Gates had won Rockefeller's trust by his skill in managing some of Rockefeller's investments as well as his philanthropy.

Gates, as a young pastor had become very skeptical of the average physician's medical skill or training. A medical student whom he had known as a child recommended to him Osler's "Principles and Practice of Medicine." Reading this book from cover to cover while on vacation during the summer of 1897, Gates developed the idea that "medicine could hardly hope to become a science until medical research could be endowed and qualified men could devote themselves to uninterrupted study and investigation on an ample salary, entirely independent of medical practice."[4] When Gates returned from his vacation he dictated a memorandum to Rockefeller advocating the establishment of such an institute for medical research.

Meanwhile JDR Jr. had joined his father's staff as a chief confidante and advisor. He was a keen advocate of the idea, which was investigated and thought about by both of the Rockefellers for the next three years, while their agents investigated comparable institutions in Europe.

JDR's son recollected years later that his father's interest in the project had been strengthened in December 1900 by the untimely death of his first grandson, Jack McCormack, who died in infancy from scarlet fever. The attending doctor had admitted that there was nothing he could do to treat the disease.

JDR Jr. sounded out a prominent pediatrician L. Emmett Holt, his fellow parishioner at the First Avenue Baptist Church, when they spent a few hours together on a train in November 1900. "Holt made the point that the recent success of diphtheria antitoxin was not a chance discovery but the result of deliberate laboratory work in which fundamental biological principles had been applied."[5] At a subsequent dinner meeting at the home of Dr. Emmett Holt with Dr. Christian Herter, JDR Jr. communicated his father's decision to go ahead with the project. JDR Sr. had pledged an initial sum of $20,000 a year for 10 years.

Holt was to become Professor of Pediatrics at Columbia College of Physicians and Surgeons. Herter had worked with William Welch, Dean at Johns Hopkins University Medical School. Herter was a Professor of Pathological Chemistry at Bellevue, and later Professor of Pharmacology at Columbia. He had set up a research laboratory in biochemistry, pharmacology and bacteriology with his own private funds.

Holt and Herter suggested that the Rockefeller Institute should have a board of trustees which might include William Welch, Hermann Briggs, Mitchell Prudden of New York, Theobald Smith of Harvard, and Simon Flexner. Dean Welch was regarded as the preeminent figure in American Medicine. During his tenure many of the most influential doctors in America studied at John Hopkins. This is where Herbert Spencer Gasser, the second Director of Rockefeller Institute studied.

Welch was also noted for his informal style. As Head of the Trustees until 1917, he would not hire a secretary, and filed his notes on the meetings of the trustees on all the chairs and tables of his bachelor apartment. About twenty years later, Simon Flexner then Director of the Institute had to travel to Welch's apartment to retrieve these documents along with the correspondence for The Journal of Experimental Medicine, which Welch had edited.

Briggs was head of the NYC Department of Public Health set up during the cholera epidemic of 1892. Prudden had introduced the use of the diphtheria antitoxin in the U.S.A. Smith headed the Massachusetts Board of Health and Flexner was Professor of Pharmacology at the University of Pennsylvania.

Welch, Holt, Herter, Briggs and Prudden met in a hotel room at the annual meeting of the Association of American Physicians in Washington, April 30 to May 2, 1901 to set up the Institute. Flexner was included on June 14. They planned eventually to set up a small laboratory under direction of the trustees. They had assurances from JDR Jr. that although his father's interest was more humane than scientific, he would not allow his desire for practical results to influence the direction of the organization.

They hoped to persuade Theobald Smith to be director at an annual salary of $5000. While both Columbia and the University of Chicago tried to appropriate the Institute, the trustees thought at first to set up the Institute as a Laboratory in the NYC Board of Health. Both Rockefellers, father and son, vetoed all of these propositions, because they wanted members of the Institute to be completely independent and free to make their own agendas of work. The trustees also voted against any initial teaching role.

In lieu of trying to set up a Laboratory immediately, they decided to start functioning by providing grants in aid for promising young investigators. Welch, as Editor of the Journal of Experimental Medicine, knew many young men who were heads of laboratories at Harvard, Pennsylvania, Western Reserve, Chicago, Michigan and Stanford, whose work might be facilitated by grants.

In 1901–1902, the trustees authorized 23 grants budgeted at $250 to $1500 totaling expenditures of $13,200 in bacteriology, immunology and biochemistry from scientists from 9 American cities and 2 from Germany. In 1902–1903 the total was $14,450. Briggs proposed a study of the NY milk supply budgeted at $7,000 to pay the salaries of a bacteriologist and inspector of dairies, tenement houses and children's hospitals and to provide laboratory supplies and animals for testing. The final report presented by Park of the NYC Health Department and Holt found that both the milk sold to tenement houses and that served at children's hospitals from cans in hot weather, had a shockingly higher bacteria count than the milk distributed in sealed containers by charitable organizations. This report led to sensational accounts in the Sun, Journal and Herald, New York City newspapers.

In January 1902, Andrew Carnegie gave the trustees of the Carnegie Institute of Washington 10 million dollars for the "advancement of knowledge and the improvement of mankind"[6]. This competitive organization strengthened John D. Rockefeller's resolve to increase his support for the Institute project.

By this time the trustees had worked out a plan to establish a laboratory with an annual budget of $137,640. JDR Jr. appealed to his father for $5 million in capital funds. JDR Sr. offered $1 million for now and a willingness to consider more an unspecified time later.

Smith had declined the offer of the directorship. Flexner was elected Director of the Institute on October 25, 1902 at a salary of $10,000 per year. Rockefeller bought the Schmerhorn farm from the Estate of the owner for $650,000 in May 1903. The property stretched from Avenue A (York Avenue) to Exterior Street (now FDR Drive) from 64th street to 68th street. The Rockefeller Institute directors bought the norther eastern 1/3 of the property. After an appraisal, the Board gave Rockefeller senior $137,425 of his $1 million grant to purchase that part of the property in its own name. The New York State Legislature then passed legislation closing first 66th, then later 64, 65 and 66th street from York Avenue to the river.

It cost the Institute $276,000 to build the first building, Founders Hall, which included an Animal housing facility and a powerhouse. Ground breaking occurred in July 1904.

The Institute's first three decades were marked by an emphasis on research in pharmacology, pathology and bacteriology in connection with the need to counter the devastation brought about by infectious diseases. In 1905 New York City was struck by an outbreak of cerebrospinal