NATIONAL ACADEMY OF SCIENCES

HARRY GRUNDFEST

1904—1983

A Biographical Memoir by

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NATIONAL ACADEMIES PRESS
WASHINGTON D.C.

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January 10, 1904–October 10, 1983

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HARRY GRUNDFEST'S CONTRIBUTIONS to (and his influence on) the field of neurophysiology were extensive, touching all corners of the field, providing inspiration and direction to more than 100 young scientists, and proposing mechanisms for how membrane electrical events determine cellular processes. These include conduction and excitation in nerve fibers, chemical and electrical signalling between excitable cells, and excitation-contraction coupling.

Considering the breadth of his contributions and the well over 500 publications describing many of them, it is difficult within an introductory paragraph or two to select what may be considered the overriding contributions. For this reason I emphasize that the following is my personal selection and clearly others may have a different point of view.

A concept that he put forth and that evolved over numerous publications was the heterogeneity of cellular membranes and the role this attribute of membranes plays in determining cellular activities. Initially his interpretation of current-clamp data led to the proposal that cell membranes are a composite of two types of membranes, electrically excitable and electrically inexcitable. This concept gave rise to the view that membranes are mosaic structures in which different regions of the bounding cell membrane possess varying amounts of a given type of ionic conductance. This concept of the bounding membrane was incorporated into models to describe synaptic, secretory, and contractile signalling processes.

The mosaic structure of membranes has been well substantiated by present-day techniques, which allow for biochemical identification and separation of various segments of cell membranes and classification of the ion channel types associated with them. Examples are the tubular system in muscle and synaptosomal fraction of nerve cells.

Another and equally important contribution was his establishment of a laboratory and training program, based on his philosophy, that taught and inspired a large number of scientists whose names and research are well known by those in the field of neuro/electrophysiology.

Harry Grundfest was born on January 10, 1904, in Minsk, Russia. His father Aaron, a rabbi, and mother Gertrude had four children, three boys and one girl, before coming to this country in September 1913. Harry graduated from high school in Kearny, New Jersey, in 1921 and then entered Columbia College where he received his A.B. degree in 1925, M.A. in 1926, and his Ph.D. in zoology and physiology in 1930. The parents emphasized the value of a higher education and consequently both brothers became medical doctors and his sister a biologist.

In January 1926 he married Rose Danzig, who became recognized as a fine artist and sculptress. They had one child, daughter Brooke, who maintained the family tradition, receiving her Ph.D. degree in anthropology.

SCIENTIFIC CAREER (1929-1954)

Harry's fellowship years were spent at the laboratory of biophysics at Columbia University (National Research Council, 1929-30) and the Johnson Foundation for Medical Physics at the University of Pennsylvania (National Research Council and Johnson Fellow, 1930-32).

His research during these early years was concerned with the excitatory processes of the visual system (spectral sensitivity of sunfish), nerve-muscle complex, and muscle. His first instructorship began at Swarthmore College (1932-33) and continued in the Department of Physiology at Cornell University Medical School through 1935. Here he laid the foundation for the classical studies with H. S. Gasser by publishing several papers on the excitatory properties of nerve bundles and their compound action potentials.

Much of his research during the first part of his tenure at the Rockefeller Institute (1935-45) was done in collaboration with H. S. Gasser. Their work was a milestone in neurophysiology, determining for the first time the different nerve fiber types whose action potentials compose the compound spike of nerve bundles, and describing the relationship between nerve fiber diameter and conduction velocity.

World War II temporarily changed the course of Harry's research. At the time he was national secretary of the American Association of Scientific Workers. In this capacity he wrote an article titled "Science in the War" that appeared in the *Weekly Science Page*, Science Service, Washington, D.C. He backed his words in this article by taking a leave of absence from Rockefeller to spend several years working on government projects. The research was done at two sites, the Climatic Research Unit at Fort Monmouth Signal Laboratories and the Wound Ballistic Unit at Princeton University. This work dealing with nerve regeneration and wound damage to the peripheral and central nervous system was mainly described in restricted reports, but some of this material was published in biological journals.

At the end of the war Harry returned to his alma mater to stay for the remainder of his career. Promotions came rapidly from research associate, Department of Neurology (1945), to assistant professor (1947) and associate professor of neurology (1949). Much of his research during this period was done in collaboration with David Nachmansohn and concerned the role of acetylcholine (Ach) in excitation and conduction in nerve and muscle.

The view that Ach was directly involved in the excitation and conduction processes was held by Nachmansohn throughout his career. While this concept received support from their collaborative research, subsequent findings by Harry as well as many other neurophysiologists were incompatible with this proposed role for Ach.

Harry's activities beyond research during this period included membership on the advisory committee for planning the biology building for the Weizmann Institute and chairperson of the medical advisory board of the Hebrew University and Hadassah (1950-54). He traveled to Israel in 1950 to deal with matters concerning the organization of the medical center. Subsequent planned trips had to be cancelled due to the government's denial of his passport renewal. The latter was a product of the "dark ages" era for our country, which was under the influence of Senator Joseph McCarthy and his supporters.

In 1953 Harry was summoned to appear before the McCarthy Committee. He testified that he was not a communist, but he refused to discuss other affiliations, political views, and those of friends and colleagues by invoking the first, fifth, and sixth amendments to the Constitution. Research continued throughout the McCarthy era in spite of the government's withdrawal of funds and lack of support from some faculty members and previous collaborators. Without the strong backing of Houston Merritt, who was both chairperson of the Department of Neurology and dean of the medical school at the time, he might not have survived the unwarranted persecution with his university position intact.

PURPURA YEARS (1954-1961)

Research activities were not diminished in spite of the obstacles placed in Harry's path by the government and some factions in the medical school. In fact, research on electrocortical phenomena was pursued at a rapid pace and, as a consequence, numerous publications appeared during this period. Over forty papers were published by Grundfest, Purpura, and colleagues between 1955 and 1961. This prolificacy was predictable for it was a product of the collaboration of two individuals with comparable enthusiasm and drive for deciphering the basis of the electrical activity monitored topically from cerebral and cerebellar cortices.

Both Harry and Dominick Purpura shared the belief that the dominant contribution to the cortical electrical activity was from excitatory and inhibitory postsynaptic potentials (e.p.s.p. and i.p.s.p.) at the level of the dendrites, a belief that was well supported by research findings in subsequent years. Part of their approach, described by Harry in a number of review articles, was based on the view that neurons in the mammalian central nervous system (CNS) have the same basic properties as peripheral junctional systems that are more readily characterized in lower animals. Furthermore, an axiom of this theorem is that the complexity of the CNS is not due to special properties of the neurons, but results from the multiplicity of cells and their interconnections.

Another contribution of the Grundfest-Purpura era was the mode in which they used pharmacological agents to obtain information about the system under investigation. This approach laid some of the foundation stones for present day neuropharmacology. Agents like ω-amino and ω-guanidino compounds were viewed as having specific synaptic activities and thus were used (in particular GABA) as tools to dissect electrical signals composed of i.p.s.p. and e.p.s.p. This work provided the impetus for investigating the action of these compounds on the crustacean neuromuscular junctions (n.m.j.). This research, which led to the conclusion that GABA was the transmitter for the inhibitory n.m.j., was done in part by myself under Harry's guidance during my tenure as a Grass Fellow at the Marine Biological Laboratories in Woods Hole, Massachusetts, in 1958. I joined the laboratory as a postdoctoral fellow the following year and stayed on as a member of the department for the remainder of Harry's career.

KRAMER BUILDING YEARS (1961-1976)

The McCarthy Committee hearings and the black list were behind him and the renaissance in neurophysiology at Columbia College of Physicians and Surgeons began. Space in the medical center was limited and, with the increase in personnel following reinstatement of government funds, additional facilities were needed. This was attained by renting the upper story of a building located one block east of the medical center and owned by Kramer Medical Supply Company. The latter's offices and business were on the ground floor of the building.

While housed in the Kramer Building about eighty postdoctoral fellows and four predoctoral fellows worked, trained, and completed requirements for Ph.D. degrees. Most of these fellows were from foreign countries, including Argentina, Brazil, Colombia, England, Israel, Japan, Mexico, Poland, Russia, Scotland, Switzerland, Venezuela, and Yugoslavia. Colleagues who were familiar with this international make-up of the laboratory often referred to the second floor as an annex of the United Nations.

Harry's design of the floor space in many ways reflected his philosophy regarding the teaching and training of young scientists. Eight research rooms surrounded a large central area that contained the following prioritized items: a full wall-length blackboard, a library containing most of the current biological journals, and an H-shaped arrangement of tables and chairs.

This spatial arrangement of the laboratories around the central room maximized interactions amongst the fellows and was not a favorable design for encouraging timidity. The blackboard was occupied most of the time. New findings, schemes, and equivalent membrane circuits were chalked across the board. Discussions about interpretations arose and debates ensued. These debates frequently carried over to the lunch period when most of the fellows assembled around the tables. This central area also served as a seminar room for more formal presentations by visiting scientists.

On some occasions science was not on the lunch menu and politics and philosophy were on tap. In view of the international make-up of the group, U.S. foreign policies were a subject commonly discussed. While Harry did not hesitate to initiate or join in ongoing discussions and debates (science or other subjects), he more frequently orchestrated them.

Before leaving this subject it is necessary to comment about the lunch scenes in the central room. Something that never failed to draw the attention of new members and first-time visitors was the placement of several gallon jars on the center table just before the lunch period. The contents could be properly prepared only by a special store located somewhere on the lower east side of Manhattan. The contents, called barrel-cured Kosher sour dill pickles, were delivered by the store at regular intervals. A special pickle fund (money from private industry, not government funds) provided these items for all who wished to partake in lunch at Kramer's. This specialty of the house was not part of Harry's teaching philosophy; rather, as some said, it was his attempt to lose weight (the only food he consumed at lunch). I personally believe the latter was an excuse and the real basis for this practice was Harry's great love for properly prepared pickles. Purpura prefers to call this phase of Harry's career the Great Pickle Period.

During the Great Pickle Period the number of researchers at a given time ranged from fifteen to twenty-five. Keeping the group supplied with adequate electrophysiological equipment was a demanding job.[1] To this end, Harry enlarged his medical electronics facility, which was not located in the Kramer Building, but occupied space in the recently built Black Building, a part of the medical school complex. This space housed one of the best medical electronic laboratories in neurophysiology. George Katz and Ernie Amatniek, electronic engineers, were household names in the field. Amatniek's tenure ended shortly after the Kramer period began and Katz headed the lab throughout the remainder of Harry's career.

While fulfilling all the demands for equipment design and construction, Katz, under Harry's advisorship, completed his requirement for his Ph.D. degree in physiology (1964). With part of his time now devoted to biological research, Katz had his responsibilities in the electronic area alleviated by the addition of two more engineers, Sidney Steinberg and Daniel Benamy, as well as three associates.

Harry's input in the development of electrophysiological equipment was significant as one might gather by noting his name on the membership list of the American Institute of Electrical Engineers and the Institute of Radio Engineers, as well as publications dealing with the design of D.C. amplifiers. Another demand placed on the engineering division that required a fair bit of ingenuity was the design of twenty to thirty research setups to be highly portable.

Every year towards the end of May, two large moving vans appeared in front of the Black and Kramer buildings to move the research equipment to the Marine Biological Laboratories in Woods Hole. The yearly pilgrimage to Woods Hole was considered by Harry to be a major part of his training program. Neurophysiology was at its pinnacle in the 1960s and electrophysiological research at the Marine Biological Laboratories was highly competitive and carried out at a fever pitch.

The experience for the trainees was heightened by Harry's seminar series held on Monday nights. The tempo of these meetings was on the same level as that of the research and these meetings became known as the Monday Night Fights. The moderator was referred to affectionately by some as Papa Bear, a title that I believe was bestowed upon him by Ellen Grass, president of the neurophysiology Grass fellowship program at the laboratories. The list of speakers for the Monday Night Fights included some of the finest scientists in the field. A few names that will be familiar to most include A. Hodgkin, A. Huxley, I. Tasaki, K. C. Cole, S. Kuffler, and H. Huxley. The latter four speakers were regular summer residents and trainees were able to interact with them on a frequent and informal basis.

Research in the early part of the Kramer Building period, as it was for all periods in Harry's career, made use of numerous types of excitable cells from a wide variety of animals and tissues. Marine fish, primarily but not exclusively electric, provided a source of electroplaques as well as secretory, sensory, and neuronal cells. Axonal studies used squid, crayfish, and lobsters. Insects, frogs, lobsters, crayfish, and fish provided neuromuscular and muscle preparations.

The problems under investigation were as diverse as the preparations described above and for this reason it is difficult to designate areas of research with specific years in this period of Harry's career. There was, however, an emphasis on structure-function studies between 1960 and 1970. The roots for the latter began to grow rapidly after Michael V. L. Bennett joined the laboratory of neurophysiology in 1957. A few years after Harry introduced Bennett to electric fish and electroplaques (*Scientific American,* October 1960), the tempo of research on these preparations reached a peak. Interest in the field was also heightened by the publication of numerous papers dealing with the electrophysiological and structural properties of electroplaques by Harry, Mike, and colleagues.

An outgrowth of this work, in which Mike Bennett was also the primary investigator, was the study on the properties of cell-cell junctions. Both electrotonic and chemical synapses were investigated using electrophysiological and morphological approaches. The latter involved extensive electron microscopic investigations of both types of junctions, mainly in preparations from fish. This aspect of the work was carried out by George Pappas, a member of the Department of Anatomy and a longtime collaborator. These studies identified and classified cell-cell junctions, determined the mode of signalling between the cells, and emphasized the physiological significance of electrotonic junctions.

Structure-function studies on single muscle fibers also began during this period. The focus of these investigations was on the role played by transverse tubules, diads, and triads in the excitation-contraction-coupling (ECC) process. This work was initiated shortly after Lucien Girardier came to work[2] with Harry. Collaboration with Philip W. Brandt (then an assistant professor and currently a full professor in the Department of Anatomy) provided the essential electron microscopic skills. This, however, was only one of Brandt's skills.

Brandt's other skills made him a primary contributor to the numerous research projects on muscle in the subsequent years. Initiation of this work represented a rekindling of Harry's earlier interest in muscle[3] and it laid the foundation for the final phase of his career in which muscle physiology was dominant (1970-83). However, to reiterate, with Harry's broad interests and knowledge, a single theme cannot be assigned to any segment of his career. To further emphasize this point, the titles of three papers that he authored and that were published in 1975 are listed: "History of the Synapse as a Morphological and Functional Structure," "Physiology of Electrogenic Excitable Membranes," and "The Role for Elementary Properties of Sensory Receptors in Transduction and Coding Information."

A finding that strongly supported Harry's view that cell membranes are a mosaic of ion permeabilities was the observed change in light scattering by single muscle fibers subjected to conditions that cause an outward movement of chloride ions. The change in light scattering was due to localized and osmotically induced swellings (accumulation of salt within a restricted volume) along specific portions of the transverse tubular system (diads). Since the degree of swelling and light scattering was found to be a function of the magnitude of chloride efflux or the intensity of an inward current applied through an intracellular electrode (filled with a chloride salt), the tubular membranes forming the diads with the cisterna of the sarcoplasmic reticulum must contain a predominance of chloride channels. This was the first demonstration of the heterogeneity of ion channel distribution in cell membranes that merely required a cell and the use of a microscope. This finding gave rise to the channeled current proposal for the ECC processes. That is, the flow of current through the anion-permselective membranes at the diadic junctions will cause local accumulation and depletion of given ions within the gap-junction volume and the ionic change serves as a signal for Ca release from the sarcoplasmic reticulum. This study led to the investigation of the steps following the release of Ca that are involved in the regulation of the interaction between actin and myosin.

A systematic study of the role played by Mg, ATP, Ca, and MgATP in regulation of contraction in skinned muscle fibers ensued. This work showed that force developed in the absence of Ca as MgATP was increased from zero (rigor state) to a maximum at ~3.0 μM (50 percent of the force-generating capability of the fiber) and then declined to a minimal level (~10 μM). These data led to an empirical formulation describing force generation in which the contractile proteins could exist in one of three states: rigor (zero MgATP), force generating (single bound MgATP), and inhibited (two bound MgATP). By assuming that Ca can only interact with the rigor and single bound MgATP state, the antagonistic effects of Ca and MgATP over a wide range of concentrations (encompassing the physiological levels) could be accurately predicted. Since a quantitative model of force generation has not been developed, this treatment is the only available means for predicting force as a function of MgATP and Ca concentrations.

I cannot end this brief description of Harry's scientific contributions without commenting about his teaching and guidance of those who were fortunate enough to have worked with him. In all the letters written by those who worked with him for his *festschrift* in 1972 and his memorial in 1983 there was a common sentiment expressed regarding the time spent with him. This was most elegantly stated in a letter to me from Dominick Purpura, who at the time was unable to leave Stanford University to attend the memorial at Columbia University's College of Physicians and Surgeons:

> To paraphrase Oster, there are those present who will feel, and no exaggeration when I say, that to have know Harry Grundfest was, in the deepest and truest sense of the phrase, a liberal education. Whatever way my days decline, I felt and feel, tho' left alone, his being working in mine own: The footsteps of his life in mine. . . . Tho' much is taken, much abides.

HONORS AND AWARDS

Besides his membership in the National Academy of Sciences, Grundfest was an elected member of the Physiological Society of London and the Japanese Physiological Society. He was an honorary member of the Czechoslovak Medical Society.

He was awarded the degree of doctor honoris causa by the University of Geneva in Switzerland and he received the Claude Bernard Medal of the Sorbonne, as well as the Physicians and Surgeons Distinguished Service Award from Columbia University.

Of particular note was the award he received from the Japanese government. The Order of the Rising Sun is the highest award given to foreigners and seldom is bestowed on U.S. scientists. His recognition by the Japanese physiologists is well evidenced by the more than twenty postdoctoral fellows who traveled to this country to work with him.

NOTES

1. Readers unfamiliar with this period in electrophysiology would not be aware of the sparsity of commercially available equipment that was adequate for the needs of the researchers.

2. In the collection of letters for Harry's *festschrift* Lucien Girardier recalled how he soon learned after joining the laboratory that young scientists came to work with him rather than under him.

3. H. Grundfest. Summation of two subliminal stimuli in single muscle fibers. *Am. J. Physiol.* 105:42.

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