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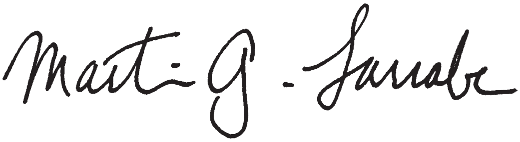

MARTIN GLOVER LARRABEE

January 25, 1910–June 16, 2003

BY DAVID R. BURT

BORN IN BOSTON AND educated at Harvard, Martin Larrabee showed signs of his New England background and upbringing throughout his long career. Mart was strong on character. He was hardworking, but not to excess, and persistent. Whatever he undertook was done thoroughly and properly. He did not believe in shortcuts; for instance, he disapproved of double publication of similar findings both in book chapters and in research papers, so that some of his students' thesis work appeared in print only as part of chapters in symposium volumes. He was generally serious, but also was kindly and knew how to have fun, with a dry, understated sense of humor. He enjoyed making and jury-rigging his own equipment, stayed in the lab as much as possible, and abhorred waste and sloppiness. He was a respected father figure and example to his graduate students and postdoctoral fellows. I was fortunate to be one of his students during and after his election to the National Academy of Sciences in 1969 and, after my graduation in 1972, to be one of his many friends.

His scientific contributions dealt mostly with miniscule bits of tissue, sympathetic ganglia from rats, chick embryos, and other organisms. (Rat ganglia weigh about a milligram.)

As a Ph.D. student with Detlev Bronk at the University of Pennsylvania, working with the cat stellate ganglion, he was the first to describe what was later called post-tetanic potentiation. In his later years, although nominally a biophysicist, he was mostly interested in metabolism and its relationship first to nerve activity and later to development. He thus helped to pioneer important areas of neurochemistry. He also took some side trips into other areas, including actions of general anesthetics, viruses and nerve growth factor, and pathways of signal transduction (not recognized as such at the time), making contributions in all of these areas as well.

FORMATIVE YEARS

Mart writes in his brief autobiography (1999), the source of most of this memoir, that he was already drawn to the concreteness of physics and mathematics in high school (Newton Country Day School), even though his father was a physician. Mart enjoyed building electric motors and radios in his spare time. He graduated as a physics major from Harvard College in 1932 after also considering engineering. During college he had spent a summer doing optics at Dartmouth and, more significantly, spent the summer of 1931 working with Keffer Hartline at the Marine Biological Laboratory in Woods Hole, Massachusetts. In that same summer Hartline first recorded from single fibers in the eye of the horseshoe crab. (Continuation of this work eventually earned him a Nobel Prize.) That summer and the next, Mart also worked with Baldwin Lucké (also of the University of Pennsylvania, but again working in Woods Hole) on the osmotic properties of Arbacia eggs. Mart's introduction of a diffraction method of measuring egg diameter helped gain him his first coauthorship (1935).

Initially attracted by the notice of a generous $300 scholarship in the fall of 1932, Mart entered graduate school at the University of Pennsylvania in the Johnson Foundation, which overlapped with the Biophysics Department. After several rotations, he was "adopted" by Detlev Bronk, the director, who introduced him to the study of sympathetic ganglia. (Their biophysical studies coincided with Feldberg's pharmacological studies of synaptic transmission in ganglia.) The advantages of this preparation include a relatively simple anatomy and physiology, easy accessibility, and a size, at least for rat and chick ganglia, small enough to be supplied adequately with oxygen and nutrients by simple diffusion. Mart was so convinced of these advantages that he stayed with ganglia for half a century when he resumed their study after the war.

His major finding during his thesis research with Bronk (1947) was that increasing numbers of ganglion cells were recruited to fire following a conditioning train of electrical stimuli (preganglionic nerve impulses). They termed this phenomenon "prolonged facilitation," but it was later renamed "post-tetanic potentiation." This early example of synaptic plasticity in the peripheral nervous system helped stimulate many studies of similar phenomena in the central nervous system. Some of these phenomena are now thought to underlie learning and memory.

Another piece of thesis research (1948), important at the time, helped to establish that conducted nerve action potentials and transmission across synapses are similarly sensitive to ischemia. This lack of oxygen and nutrients results from circulatory block, as in stroke. This demonstration was facilitated by the anatomy of cat stellate ganglia, which possessed both axons of passage and synapses. During this period he also contributed to some technical advances in electrophysiology.

Mart's doctorate was awarded in 1937, but he stayed on at the Johnson Foundation until Detlev Bronk was recruited to be the chair of physiology and biophysics at Cornell Medical School in New York City in 1940. At Cornell for one year he helped to teach physiology and helped to train a postdoctoral fellow, Clint Knowlton, who was working with pulmonary reflexes (1946). In 1941 Mart returned from Cornell to the Johnson Foundation when Detlev Bronk did.

The year 1941 also marked the country's entry into World War II, which helped to delay publication of much of Mart's earlier research and drastically shifted the focus of research at the Johnson Foundation and elsewhere. During the next four years Mart got to help with many projects connected to the war effort. One contribution in the area of respiratory physiology he relates (1999, p. 199) was to save the lives of three professors stuck in an improvised altitude chamber by taking over the controls from a high school student. His only publication from wartime research involved measurements of nerve regeneration (1948).

After the war Mart soon returned to the study of sympathetic ganglia; he worked with the first of his many international postdoctoral fellows, Jean Posternak, from Switzerland, whom he often visited in later years. Among other studies, they investigated the effects of general anesthetics on synaptic transmission through ganglia, contrasting the lower concentrations needed to block synapses with the higher ones needed to block axonal conduction (1952). This groundbreaking work still is cited in discussions of mechanisms of general anesthesia. Some of his other work at this time included the use of an oxygen electrode developed by Philip Davies. Inserted into cat stellate ganglia, it enabled estimation of their oxygen consumption and demonstration of an increase with electrical activity (1952). Thus began Mart's interest in the relationship between activity and metabolism, which he continued for many years.

Mart writes very fondly (1999, pp. 202-203) of his years in the Johnson Foundation with a paternalistic mentor. There he was privileged to work with a close-knit, friendly, and supportive group funded modestly but adequately by endowment and foundation money before the days of government largesse and competition for grants.

HOPKINS

Detlev Bronk became president of Johns Hopkins University on January 1, 1949. He brought with him Mart and most of the group who had earlier followed him to Cornell Medical School and back, founding the new Thomas C. Jenkins Department of Biophysics chaired by Keffer Hartline. Also included were some graduate students who later became Mart's fellow faculty members: Ted MacNichol and Frances Carlson. Mart found himself in temporary quarters in the medical school, in frequent contact with such luminaries as Vernon Mountcastle of physiology, Stephen Kuffler of ophthalmology, and David Bodian of anatomy, until he moved to the department's new building on the Homewood campus in 1953. Space there became available when Bronk moved again to become president of the Rockefeller Institute in New York City. Although he was invited to join Bronk, Hartline, Brink, and others who moved to Rockefeller, Mart elected to stay behind at Hopkins.

Meanwhile, his research had returned to general anesthesia, and in particular to the issue of whether anesthetics' actions on synaptic transmission were direct or indirect through block of metabolism. Working with Juan Garcia Ramos from Mexico and Edith Bulbring from England on rabbit ganglia, he showed that anesthetics blocked transmission at concentrations that did not affect oxygen consumption, whereas metabolic poisons blocked both in parallel (1952).

At about this time he started work with excised rat superior cervical sympathetic ganglia, enabling a variety of subsequent studies of the acute metabolic requirements of ganglionic transmission in terms of oxygen, glucose, and other nutrients. These studies helped form a foundation for understanding some of the early brain damage in strokes. Rat ganglia also supported a brief diversion into virology and observation of a puzzling pattern of ganglionic discharge brought on by infection with pseudorabies virus (1955). They also supported training of his first graduate student, Charles Edwards, who showed anesthetics to increase glucose uptake and lactate output (1955). Other students followed, including William Stekiel, Frank J. Brinley, and Paul Horowicz. Mart began to use radiotracer methods, and his lab was able to account completely for the metabolic products of labeled glucose (chiefly carbon dioxide and lactate) and to show that glucose metabolism did not account completely for resting oxygen uptake or for its increase with activity. Publications from this period include Horowicz and Larrabee (1958, 1962) and Larrabee et al. (1957). He became full professor of biophysics at Johns Hopkins in 1963.

A diversion into phospholipid metabolism was prompted by findings of Lowell and Mary Hokin. They reported that labeling of phosphatidyl inositol from inorganic phosphate could be increased by applying high concentrations of acetylcholine to sympathetic ganglia and other tissues. (Acetylcholine is the major neurotransmitter in ganglia.) Mart, working with Jack Klingman and William Leicht, was able to reproduce and extend these findings to natural activity under much more physiological conditions (1963, 1965). We in the lab in 1969, when Mart was elected to the National Academy of Sciences, speculated that these findings had helped to put him over the top for selection, even though nobody really knew then what the phenomenon meant.

At the time I was making my minor contribution by finding in my thesis research (1973) that ganglionic subcellular fractions with increased labeling of phosphatidyl inositol included synaptosomes, pinched off nerve terminals with adherent postsynaptic membrane fragments. Concurrently, a postdoctoral fellow from England, Godfrey L. White, was finding a lack of acute effect of activity on labeling of higher inositides. In hindsight, these and similar results most likely reflected the presence in ganglia of the phosphoinositide-phospholipase C signal transduction pathway.

Another area Mart explored was nerve growth factor (NGF), occasioned by the gift of some by Rita Levi-Montalcini, its discoverer, and brought into the lab by Giovanni Toschi from Rome in 1965. Graduate student Lester M. Partlow showed its dramatic effects on nerve outgrowth from chick sympathetic ganglia to be independent of synthesis of ribonucleic acid and protein (1971). Another student, David C. Halstead, studied effects (immunosympathectomy) of an antiserum to NGF. These and other early results with NGF foreshadowed discovery by others during the next 30 years of the key roles of neurotrophins (NGF and three others) on neuronal growth and maintenance in the brain and helped to stimulate Mart's later interest in development.

During this period Mart was treasurer of the new Society for Neuroscience (1970-1975). His other memberships included the American Physiological Society, the Biophysical Society, and the American Society for Neurochemistry. He was also awarded an honorary M.D. degree from the University of Lausanne in Switzerland in 1974.

Mart formally retired from Hopkins in 1975 upon reaching the age of 65 but was able to gain emeritus status, hold on to some research space, and maintain his research grant from the National Institutes of Health. This grant, titled "Metabolism and Function in Sympathetic Ganglia" and first awarded in 1954, was the only one Mart ever sought outside Hopkins. It was renewed over and over again to reach a total funding period of 43 years, one of the longest in NIH history. Working mostly on his own, Mart stayed in the lab for more than 20 years beyond his formal retirement and published 15 additional research papers. He maintained his interest in intermediary metabolism but turned from studying effects of activity in rat ganglia to studying development in chick ganglia, noting transitions in glucose utilization from anaerobic glycolysis (poor blood supply) to pentose cycle (supporting lipid synthesis) to conventional aerobic metabolism (1985, 1987). He started computer modeling in an effort to assess in detail the time course of partitioning of glucose carbons among the various pathways. This involved iteratively making assumptions about pools and fluxes, deriving corresponding equations, and embracing the new age of computers for the first time by trying to fit his data (1978, 1980, 1989). This was a lot to take on at an age when most have retired for real, but the challenge helped to keep him mentally young.

He also identified alanine as a major product of glucose metabolism besides lactate and that both were released to extracellular pools before being reabsorbed (1992). Finally, he established a preference of nervous tissue for lactate over glucose in fueling oxidative metabolism both in embryonic ganglia (1996) and, using calculations based on others' data, in brain (1996). Most surprisingly, his calculations suggested that blood lactate levels reached during intense exercise (20 mM) would supply about 60 percent of brain carbon dioxide output even in the presence of 5 mM glucose. (One is tempted to speculate about a relationship of these findings to recently-established beneficial effects of exercise on brain function.)

Before I consider briefly some other, more personal aspects of Mart's life, I would like to recall an episode that occurred during my time at Hopkins. Presumably because of Mart's care and thoroughness (nitpickiness?), he had been put in charge of distributing keys to departmental locks and of maintaining the lines feeding distilled water into departmental laboratories. On one April 1 (1966?) he entered the building to find a goldfish apparently swimming in one of the distilled water lines. He sputtered and fumed magnificently until it was pointed out to him that the glass tubing with the goldfish had been added in parallel to the actual distilled water line. He later accepted this student prank with typical good humor, although it did take him a while to cool down at the time.

FAMILY AND FUN

Mart was the son of Ralph Clinton Larrabee and Ada Perkins (Miller) Larrabee. He fathered one son, Benjamin Larrabee Scherer, in a first marriage to Sylvia Kimball and another, David Belcher Larrabee, in a second, much longer marriage to Barbara Belcher (more below). He wed his third wife, Sarah Galloway, two years after Barbara's death in 1996. Mart spent his final 10 years in a retirement community outside Baltimore, entered when Barbara became ill (and where he later met the widowed Sarah). He kept doing science for his first few years there, as noted above. After his marriage to Sarah, they got to spend several happy summers with family at her farm house in West Glover, Vermont.

Mart was a keen outdoorsman, maintaining an active interest in hiking, mountain climbing, and downhill skiing until he was well into his eighties. He inherited this from his father, who made time from his medical practice to pursue similar interests, in particular helping to construct a system of trails in the White Mountains of New Hampshire.

Mart writes (1999, p. 194) that he first met Barbara Belcher, later his wonderful wife for 53 years, at a mountain hut on one of these trails in 1936.

Beginning when I was a student, Mart undertook to emulate his father by building 30 miles of new trails in the nearby Gunpowder Falls State Park and Prettyboy Reservoir watershed, nominally under the auspices of the Sierra Club. (He also belonged to the Appalachian Mountain Club and Mountain Club of Maryland.) His volunteer laborers consisted mostly of departmental graduate students (and their spouses). He would go out the day before and lay string where we were to cut and mark the trails as we went along with painted baby food jar lids provided by his technician. We were motivated not only by our desire for a degree (the trail work actually was optional, even for students in his lab) but also by being outdoors in good company and most especially by delicious Sunday dinners provided afterward by Barbara. An ardent naturalist and birder, she sometimes accompanied us on the trail-cutting expeditions and provided us with nature lore. After I graduated and the trails were completed, Mart continued to organize occasional maintenance expeditions for many years, reuniting former students still in the area and recruiting new biophysics students. His endurance on these expeditions put some of us to shame, even though we were 30 to 40 years younger.

During their long and happy marriage, Mart and Barbara took many international trips, often doubled up with meetings, and especially favoring the mountains of Switzerland. They typically also spent several weeks in August on Monhegan Island in Maine. I twice got to house-sit at their lovely Baltimore County home while they were in Maine.

On these occasions, and at the dinners after trail cutting, I and my fellow students admired a piece of hydraulic engineering Mart had undertaken to feed water into a bird bath from the tank of his upstairs toilet. A long piece of thin plastic tubing dripped just fast enough to balance evaporation (and splashing by the birds).

Mart was survived by his wife, Sarah; his sons, Benjamin and David; and their families.

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