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SUSUMU HAGIWARA

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A Biographical Memoir by

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BORN IN YUBARI, Hokkaido, Japan, on November 6, 1922, the son of a school principal, Susumu Hagiwara went through public schools, graduating from high school in Mito, Honshu. Among the boyhood hobbies that persisted throughout his life were butterfly observation and collecting, begun with his father. He also enjoyed bird watching and painting. He was one of the select few admitted to the prestigious University of Tokyo. There he completed both his medical degree in 1946 and Ph.D. in physiology under Prof. T. Wakabayashi in 1951. During this period he was diagnosed with tuberculosis and had one lung removed, but he continued to write papers during his convalescence and recovered enough to live a surprisingly normal life.

In 1948 his first paper demonstrated that cicadas begin to sing at a certain level of light in the morning, delayed correspondingly on cloudy days. His thesis topic, the fluctuation of intervals in rhythmic excitation in frog stretch receptors, with comparisons to the intervals in human motor units during voluntary movement, foretold a lifelong bent toward comparative physiology. Already prolific, he published a substantial series of papers before 1953 on topics as diverse as the myogenic rhythm in cicada muscles (with A. Watanabe), the first penetration of Mauthner's neuron in fish (with I. Tasaki and A. Watanabe), and the statistical analysis of neuronal firing intervals. Each was a pioneering contribution; the last mentioned is often cited as a seminal study in the field now called neural computation that is rising rapidly in parallel with molecular neurobiology, the one more system oriented, the other more reductionist. Susumu Hagiwara cannot be pigeon-holed in one camp or the other.

One of the fascinations of this man's career is that a true hero of general physiology owes the essence of his fame to comparative studies, not in the usual sense that he spent his life on an unconventional favorable species but in sampling many species, far apart phylogenetically, upward of sixty different preparations in about as many species, from plants to humans, from clonal pituitary cells to leech neurons, from cicadas to barnacles, giant squid to bats, chirping birds to clam larvae, soft corals to mouse hybridoma cells, invertebrate eggs to cats. The motivation to search deliberately for unusual materials and to explore the world of species is an obvious thread throughout his work and more than a leitmotif. He learned early the lesson that even so basic an organelle as the cell membrane cannot be represented adequately by any one exemplar. He set out to broaden our view of nature's scope and range of available mechanisms.

Pretending to know nothing about zoology or botany, he asked his friends in that gentle, undemanding manner: "What kinds of eggs can we get? Where can one get amphioxus? Where is an example of a distributed synapse?" (The answer to the last is the sabellid polychaete giant, which he then took for study.) "If it's not too much trouble, is there any chance we could get some hummingbirds?" Procurement problems were a constant source of amazement and amusement. Susumu's antennae were tuned to the first hint of interesting material, as when Graham Hoyle discovered the giant muscle fibers in a North Pacific barnacle and later the simple photoreceptors in barnacles. Finding himself on the Great Barrier Reef or the Amazon River, Hagi could quickly find a remarkable species and bit of tissue in that species. To be sure, some preparations were suggested to him, but the notable feature was the instant sympathetic response and eagerness to try his iridectomy scissors and skillful fingers on it. Some preparations were not so delicate. It required 75-mm nails hammered into a hardwood plank to hold down a strong electric eel or *Gymnarchus*, both of which jerk each time they indulge in an air-breathing gulp.

If it needed another example, Hagiwara's life outstandingly illustrated how finding differences among species, preparations, or cell types can be a major source of insight into general physiology. This premier intracellular biophysicist must also be recognized as a neuroethologist. Not only is this true because of the implicit relevance of his membrane discoveries to species-characteristic behavior, but he was explicitly interested in uncovering the mechanisms of outstanding examples of natural behavior. How does a cicada sing? How does a hummingbird move its wings? What rules apply to interval distribution in a chirping bird's rhythm or the intervals between gulps in air-breathing loaches in the aquarium beside his hospital bed? These examples manifest his lifelong interest in animals as such.

At the time Hagiwara completed his Ph.D., Yasuji Katsuki (1905-94), head of the Department of Physiology of the Tokyo Medical and Dental University, was building a group that became the most fertile laboratory in sensory neurophysiology in the country. He was an international figure in auditory physiology who appreciated and himself indulged in many comparative studies, among diverse animals and various modalities. He recruited Hagiwara to his department in 1950 as his second in command and soon departed for a two-year stint abroad, including working periods in the laboratory of one of the authors (T.H.B.). During this early period at the TMDU, Hagiwara completed a series of studies on (1) the curious sonic muscle in certain cicadas that produce their summer buzzing sound by a myogenic rhythm, (2) the neuromuscular transmission in insects, (3) intracellular recording in Mauthner's neuron in catfish and insect muscle, and (4) a prescient paper on the effects of tetraethylammonium chloride on the muscle cell membrane.

When Katsuki returned, he promptly sent Hagiwara abroad for a similar two-year sequence of working visits to laboratories in Europe and the United States. Hagi spent such a period with Yngve Zotterman in Stockholm, participating in recording from the chorda tympani nerve of cats. He visited Sven Dijkgraaf in Utrecht; John Pringle, Alan Hodgkin, and Lord Adrian in Cambridge; and Ichiji Tasaki in Bethesda, Maryland. After six month at UCLA and three months at the Marine Biological Laboratory in Woods Hole with T.H.B. Hagiwara spent several months at the Johns Hopkins University working with Charles Edwards and Stephen Kuffler, several months in New York at Rockefeller University, and half a year at the National Institute of Neurological Diseases and Blindness in Bethesda with Tasaki. All this resulted in experience and papers on the physiology of taste in cats, cardiac ganglion pattern generators in lobsters, giant synapses in squid, stretch receptors in crayfish, and the electrical capacitance of muscle fiber membranes, among others.

He returned to Japan in 1957 and within two years rose to professor in the Second Department of Physiology in the Tokyo Medical and Dental University. He soon discovered that the expectations and obligation in this role were not for him and his chronic lung problem. He rejoined Bullock in Los Angeles in 1960 and by 1964 became completely independent, with his own laboratory and grants. During these years, while Hagi rapidly rose to the rank of research professor, eventually to overscale professor, we enjoyed many joint projects. Some brought distinguished Europeans such as Ladislav Tauc, Thomas Szabo, Hans Lissmann, and Per Enger, as well as accomplished and promising co-workers from Japan, including Hiromichi Morita, Koroku Negishi, Kenichi Naka, Shiko Chichibu, and Nobuo Suga. Besides continuing with previous preparations, Hagi and his co-workers began experiments on electroreceptors, polychaete giant synapses, and barnacle and hummingbird muscle. It was still possible to maintain active interest in both integrative and ion channel mechanisms, much to the benefit of both fields.

Hagi traveled during these years, visiting, for example, Hans Lissman in Cambridge, Alfred Fessard in Paris, and Angelique Arvanitaki in Monaco. From a hospital in Rome he wrote: "I was brought to this hospital unconscious from the hotel . . . acute pneumonia . . I lost all my weight. Since I did not have much weight, I am almost losing myself." He flew to Tokyo to recuperate, surprising his family and missing his symposium. This was not the first or the last episode of health problems during his trips, but it is significant that they did not stop him from traveling even to fairly remote places.

One notable trip was in March 1964 to the U.S.-Japan Joint Cooperative Program Symposium on Neurophysiology, for which the Japanese delegation, led by Yasuji Katsuki, included Tasunosuke Araki, Taro Furukawa, Kojiro Matsuda, Koichi Motokawa, Yutaka Omura, Masayasu Sato, Sadataka Takagi, Tsuneo Tomita, Koji Uchizono, and Akira Watanabe. The U.S. delegation, led by T. H. Bullock, included Michael

Bennett, Robert Galambos, Harry Grundfest, Susumu Hagiwara, Carlton Hunt, Stephen Kuffler, David Potter, Floyd Ratliff, and Walter Rosenblith. We mention the names because this influential meeting triggered a number of later projects and collaborations. We recall the visit Hagi, Mike Bennett, and Bullock made together, after the symposium, to the beautiful seaside resort of Shirahama. They asked the attendant in the public bath why it happened that they were the only bathers and were told that they were the only guests who were not newlyweds, bathing in private.

The very next month Hagi was off to the uncertainties of living and working in Belem, on the Amazon River, to do electric fish experiments with colleagues from UCLA and abroad. He did not do South America minimally but returned via Rio de Janeiro, Buenos Aires, and Santiago, apparently enjoying the sights and adventures, meeting scientists, and collecting butterflies.

In 1965 an invitation arrived from the Scripps Institution of Oceanography to be the first professor of neurobiology at the University of California at San Diego—quite independently of the new medical school, which was at the moment creating the first Department of Neurosciences. Hagi was recruited by the marine biology division of Scripps. Some credit is certainly due the late, great comparative physiologist, Prof. P. F. Scholander, on the faculty of that division and to the then-director of the UCLA Brain Research Institute, John D. French, who had persuaded the Scripps faculty to cosponsor with the institute a unique, and for many years jointly operated, marine neurobiology facility on the third floor of Scholander's new Physiological Research Laboratory. A popular hypothesis is that the marine biologists remembered the elegant electrophysiological demonstrations of functions of sense organs in fish by Yasuji Katsuki, Hagi's sponsor, and Yngve Zotterman from

Stockholm, Hagi's first foreign host, during their short visits years before. In the transition period, prior to moving to La Jolla, Hagi spent a period between May and August of 1965 as a visiting professor at the Collége de France and published several papers in French with Thomas Szabo.

With a group of postdoctoral associates, Hagiwara initiated the Marine Neurobiology Facility of Scripps and the Brain Research Institute. He enjoyed four years of idyllic existence and outstanding scientific creativity in La Jolla. The maiden voyage of the unique research vessel *Alpha Helix*, created by Scholander as an arm of the Physiological Research Laboratory and a national—really international—facility for comparative biochemistry and physiology in remote habitats, set off for the Great Barrier Reef in the spring of 1966. Hagi and Kunitaro Takahashi and chief scientist Bullock were among the ten scientists in the first three-month program. Many vignettes of that great experience crowd into memory. One was due to the chance that the three visited Bora Bora on the way to Australia and found that a fellow guest at the seaside hotel was the great astronomer Bart Bok, who took them to the end of the pier and gave a private lecture on the Milky Way and Southern Cross as an introduction to the South Pacific. As this expedition proved and many others subsequently confirmed, Hagi well exemplified the kind of bench scientist who could make good use of a few weeks in a laboratory at an exotic location.

Telling incidents shared by Hagi on the *Alpha Helix* Operation Billabong are recounted in a book by P. F. Scholander, *Enjoying a Life in Science* (University of Alaska Press, 1990). Susumu and "Pete" Scholander were kindred souls in their eagerness to explore the world of species and in their skill in finding specially favorable material for the study of fundamental problems, about half the time planned ahead of embarking on an expedition and half the time discovered among the species that had not been anticipated. His South American experience was enlarged in 1967 with a several-month trip to Chile, together with Alan Grinnell and Jared Diamond, to study synaptic mechanisms in giant squids at Monte Mar, the marine station near Valparaiso. A major storm aborted that project by driving the squid to other waters (for several years), but with customary ease Hagi found an ideal preparation in the muscle fibers of Chilean giant barnacles. Two years later he was off to New Guinea on an *Alpha Helix* expedition led by George Bartholomew, studying bats and collecting butterflies and carvings, again with Grinnell. A highlight of this trip was a stopover enroute at Marlon Brando's atoll off Tahiti. In 1973 Hagi was organizer and chief scientist of his own *Alpha Helix* expedition to the Great Barrier Reef, where he again worked with blue-spotted sting rays, as he had done in 1966 on the maiden expedition.

In 1969 he was enticed back to UCLA, a great loss to San Diego and gain for Los Angeles. He and his wife, Satoko, made an attractive home in West Los Angeles, decorated not only with his great butterfly collection, mounted birds, and New Guinea wood carvings but also scores of hanging plants and tanks with varieties of koi and tropical fish. In a short time he was named the Eleanor I. Leslie Professor of Neuroscience and enjoyed twenty happy and productive years at the Brain Research Institute and its Jerry Lewis Neuromuscular Research Center before succumbing in 1989 to an illness that demanded respiratory reserves he had lost nearly half a century before.

Whereas Hagiwara was best known for his contributions to membrane and channel biophysics, he made a wide variety of important contributions to systems physiology at the integrative level. His pioneering series of papers on the sound-producing muscle of cicadas started a pregnant line of research on its dynamics and neural control in England and the United States, showing that classical muscle physiology illuminates only a fraction of the properties of muscle that evolution has spun off. One of these studies was his own, in 1968, on the neuromuscular specialization in the wingbeat of hummingbirds. His analysis of sensory nerve impulse interval fluctuations is a standard reference point for a considerable later literature. He made major contributions to synaptic physiology and to the integrative mechanisms of the nine-celled cardiac ganglion of lobsters. He played a central role in the initial discovery of electroreceptors in weakly electric fish and in the further discoveries of multiple types of electroreceptors and nerve impulse codes.

Beginning in 1964 his concentration on ionic mechanisms in active membranes and especially on calcium channels became marked. After the great advance and wide acceptance of the Hodgkin-Huxley concept of the sodium and potassium ion basis of the nerve impulse in the squid giant axon membrane, Hagi asked himself four questions: (1) How widely can one apply the original sodium-potassium channel concept to electrical excitation among a variety of tissues in different animals? (2) What other voltage-gated membrane channels exist besides the original sodium and potassium channels? (3) What are the biological functions of those other channels? (4) How did the various ion channels evolve phylogenetically and how do they develop ontogenetically?

These questions led him to study preparations such as muscle fibers in barnacles, mussels, and amphioxus; eggs of starfish, annelids, and *Drosophila*; mudpuppy hair cells; crustacean photoreceptors; chromaffin cells in rats; lymphocytes and tumor cells in mice; seminiferous tubule cells; pituitary cells; left-handed snail cells; and human T cells. Only a vastly flexible expertise and a disciplined theoretical mindset could so successfully carry out the basic experiments, avoid dilettantism, and glean the harvest of general principles within natural diversity that Hagiwara did. He was a principal player during the years when the concept of one channel for each of two or three ions was gradually replaced by the understanding of a multitude of distinct channels for each ion, differing in proportions and distribution among cell types.

Hagiwara's name is particularly associated with calcium channels in cell membranes. Whereas the action potential had been adequately accounted for as a sodium spike for more than a decade, in 1964 Hagi and his colleagues recognized the calcium spike in an unlikely preparation—the normally nonspiking muscle fiber of a giant barnacle. For a time this spike was regarded as a curious anomaly—resistant to removal of external sodium but converted from nonspiking to a spiking cell by injecting sodium if its anion was a calcium binder like sulfate. He recounts, with characteristically self-deprecating humor, how, during this period when "the calcium channel was only found in miserable animals like crustaceans and was thought to play no important function in the human brain . . . I suffered tremendously from a minority [*sic*] complex," until time went by and calcium channels were found in a variety of tissues, including mammalian brains, and it became difficult to name an excitable tissue that does not possess calcium channels. He proposed the rule that sodium spikes are found where the function of the action potential is propagation of an impulse and calcium spikes are found where action potentials are coupled with effector functions such as contraction, secretion, transduction, transmission, and bioluminescence.

Bertil Hille, ten years ago, summarized: "Hagi [was] a research scientist of peerless distinction. . . . He is remembered as the champion who brought the calcium channel to its rightful respected place and in the process discovered blocking ions, flux saturation, inactivation dependent on internal calcium, and many other unanticipated phenomena." To a much higher degree than the sodium channel of the squid axon, the calcium channel does not obey the independence principle; the current (ion flux) is not linearly proportional to the external calcium concentration. The system becomes saturated, implying the existence of a limited number of carriers or charged membrane sites with which ions must interact in order to permeate the membranes. Hagiwara carefully distinguished between specific ionic binding sites and the general layer of charges forming the surface charge on the membrane. The permeability of the calcium channel to different cations was carefully dissected into its components, the binding constants for each ion and the relative mobility of each within the membrane. The binding sites were also characterized in terms of their affinities for different blocking cations. Hagi's discovery that intracellular calcium blocks calcium channels was the first clear demonstration of an important mechanism of calcium channel inactivation.

Hagiwara's analysis of calcium permeation in terms of binding affinities, dissociation constants, and screening potentials was probably the first application of the concept of enzyme kinetics to channel permeation mechanisms, and he pioneered what is now the generally accepted framework in which to interpret most ionic permeation and channel-blocking mechanisms. Studies of this nature make it possible ultimately to construct a physical model of a given channel and the factors governing the gating of permeability, selectivity of the channel, and mechanism of permeation. Through Hagiwara's research, our understanding of active calcium permeability mechanisms has advanced to the point that it is equivalent to our understanding of sodium permeability mechanisms and in many ways is much more important. In all cells studied to date, the voltage-dependent calcium flux properties are very similar to those shown by Hagiwara. His work thus laid a foundation for and provided invaluable guidance to everyone trying to understand the role of calcium in a wide variety of other important cell functions. In particular, these discoveries opened the way for new methods of treatment of various cardiac disorders, based on the rational use of external chemical messengers and calcium channel-blocking agents such as Verapamil, D-600, nifedipine, and others.

Hagiwara was one of the first to recognize and adopt the new technique of patch clamping when it was introduced and pioneered its application to the study of small mammalian cells whose membrane properties were previously almost completely unknown, such as pituitary cell lines and lymphocytes. His 1981 paper with L. Byerly on "Calcium channel" in the *Annual Reviews of Neuroscience* had been cited in 1,070 publications by 1992, making it the most cited paper in that journal up to that time.

Hagi never ran a large laboratory, but his co-workers were numerous. He was especially popular among young Japanese scientists experiencing their first visits abroad. His influence is conspicuous in the number of department chairpersons and prominent scientists who trained in his laboratory. He was an apparently relaxed, undemanding but inspiring leader. Particularly important to those who worked in his laboratory were the free-wheeling discussions of scientific ideas that took place at lunchtime each day. Hagi loved to talk science and to discuss the development of ideas and the role of personalities in science. Many feel that they learned more from these lunches than from their formal education in science. Hagi excelled at drawing out ideas from his students and remained deeply involved in their career development long after they left his laboratory. Those who experienced his formal lectures inform us that they were typically shorter than the allotted time and always crisp and rich in content, vivid and somewhat humorous, and delivered beautifully. This description reminds us of his writing style.

Hagi's ever-present gentle sense of humor is legendary. In the early 1960s the Brain Research Institute at UCLA was planning an outpost, the Marine Neurobiology Facility at the Scripps Institution of Oceanography of UCSD in La Jolla, which he was later recruited to head, as we recounted above. It was the top floor of a new building donated by the National Science Foundation. Hagi liked to tell how he sat in on a meeting with the site visiting committee. They asked about the obstacle of a hundred-odd miles between campuses and, according to Hagi, were told by Dr. French, the BRI director: "The San Diego Freeway starts a few blocks from the BRI and passes a few blocks from the SIO." This apparently was satisfactory and the grant was awarded, although the portions of the freeway constructed at the time ended about 10 miles south of UCLA and about as far north of San Diego. "Since that time I have been learning how neuropolitics works," said Hagi. He opened his talk at one meeting with these words: "It is a great honor to be selected as one of the speakers of this symposium. I am supposed to discuss my personal view of the brain. Unfortunately, I have not achieved enough sophistication to handle the problem philosophically. I hope I can reach such a level of sophistication while my own brain is still undeteriorated and viewable."

Shared experiences and warm memories of the authors extend well beyond Southern California. Traveling together in Japan, Hagi asked Bullock to ask for directions in the underground, since we got polite and helpful replies that way; when he asked, people were likely to say, curtly, "That way, as you should know!" Susumu brought out the best in others, including the Australian aborigine who speared sting rays on the coral reef for his studies of a special muscle. Joe, the giant aborigine, knew he needed undamaged tissue and asked Susumu, "Which side you want spear?" He was in no hurry to become a Californian and wrote in a letter quite some time after taking up residence in Los Angeles, "I am now learning how to drive but it is much more difficult than microelectrode penetration." In awe of the examination on American civics, Hagi delayed becoming a citizen for years after his wife breezed through her ceremony, but eventually (1971) screwed up his courage and did it.

Looking back over the record, it is plain that we cannot explain Hagi's unique success simply by his choice of species and interest in basic neuroethology. One major factor deserving notice is the sheer element of skill in many of Hagi's triumphs, manual and manipulative skill combined with patience. In addition, another factor can be inadequately termed ingenuity. This was nicely shown in his sandwich preparation of the barnacle muscle fiber membrane—from an opened fiber laid flat between holders that present the inside of the membrane to one chamber and the outside to another. Setups were never more complicated than they needed to be. He could develop a new preparation, do a set of experiments, and be on to something else, while others would still be thinking of where to begin. The common denominator of many clever holders for diverse preparations was simplicity. One often thought of the ultimate compliment: "Why didn't I think of that?"

A long list of firsts belong to Hagi's credit. To mention a few, he was the first to penetrate insect muscle, and the Mauthner's neuron of fish, and to apply the voltage clamp to the neuron soma. He introduced many species and preparations into physiology. With a succession of co-workers, he was the first to penetrate the squid giant synapse on both pre- and postsynaptic sides, close to the junction. Likewise, he and his associates succeeded in recording from inside the pacemaker and the follower cells of a miniature crustacean ganglion in the wall of the heart. This led to the first discovery of the subthreshold electronic influence of one neuron upon another, via very slow currents. Hagi and his co-workers found the specialized receptors that sense electric organ discharges from the same fish as well as from neighboring conspecifics. He was the first to make a barnacle muscle membrane spike, although this type of cell has probably not given a spike for hundreds of millions of years. He started the study of the statistical structure of spike interval trains in apparently stochastic series of motor units and sensory discharges—one of the early landmarks in neural computation.

Hagi had a direct impact on generations of students. He was a superior lecturer—speaking, as he wrote, in simple declarative sentences. Lucidity and a transparent organization of his exposition were characteristic. His talents in this department must have influenced many more people than were in his classrooms, since he was a successful lecturer at national meetings and at institutions he visited all over the world. Besides his formal teaching, Hagi profoundly shaped the lives of his many collaborators. His laboratory was always a hive of hard-working young investigators. We have no accurate count of them, but his bibliography shows about seventy coauthors.

Hagiwara's achievements were recognized by numerous awards. He was elected to membership in the American

Academy of Arts and Sciences in 1971. In 1976 he won the Kenneth Cole Award of the Biophysical Society. In 1978 he was elected to the National Academy of Sciences. In 1981 he was the Distinguished Lecturer of the Society of General Physiologists. This resulted in a seminal monograph titled *Ion Channels in Cell Membranes: Phylogenetic and Developmental Approaches* (1983). In 1983 a symposium volume was published in his honor (*The Physiology of Excitable Cells*, edited by A. D. Grinnell and W. J. Moody). In the same year he was awarded an honorary doctorate from the Université Pierre et Marie Curie in Paris. In 1984 he shared the Ralph Gerard Prize of the Society for Neuroscience with his long-time friend and colleague, T. H. Bullock. The National Institutes of Health indicated its confidence in Hagi's long-term productivity by giving him a seven-year Javits Neuroscience Investigator Award in 1987. He was honored posthumously by the Japanese government with the Order of the Rising Sun. Also posthumously, an international symposium was held in his memory in Okazaki, Japan, at the National Institute for Physiological Sciences and a book was published titled *Basic Neurobiology: Half a Century and Future*, edited by H. Ohmori and S. Ebashi (1991). In 1994 the Hagiwara Chair of Neurobiology was created at UCLA, with Francisco Bezanilla its first holder. Few, if any, neuroscientists have matched Hagi's record of fundamental contributions throughout the range of behavioral, integrative, cellular, and molecular neurobiology.

Hagiwara is survived by his wife and son. Among a large circle of friends across the world he was a special favorite, and an even larger circle of admirers and followers have benefited from his discoveries, insights, and elegant experimental foundations.

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