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HERBERT SPENCER GASSER

1888—1963

A Biographical Memoir by

MERRILL W. CHASE AND CARLTON C. HUNT

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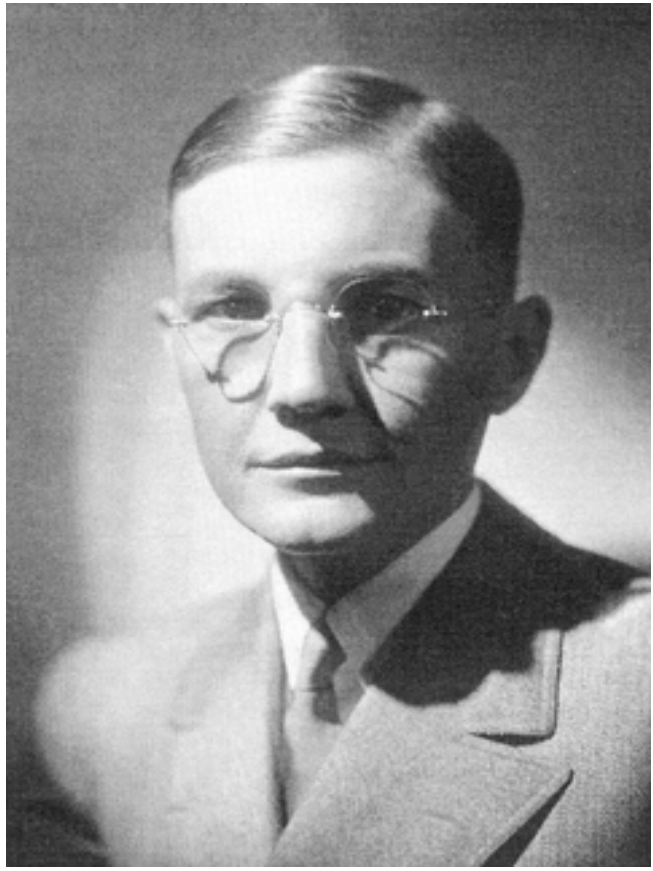

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Hubert S. Coen

HERBERT SPENCER GASSER

July 5, 1888–May 11, 1963

BY MERRILL W. CHASE AND CARLTON C. HUNT

HERBERT GASSER was a major scientific figure. An outstanding physiologist, he was a pioneer in the field of neurophysiology. In addition, as Director of the Rockefeller Institute for Medical Research from 1935 until 1953, he exercised an important national and international influence on science. This long-overdue memoir has been written almost thirty years after his death. We both knew him at the Rockefeller Institute and have had access to extensive archival material. Though our information about his early years is limited, Gasser's autobiography (1964), written characteristically with great reserve and in the third person, contains much of interest.

ORIGINS AND EARLY YEARS IN WISCONSIN

Herbert Gasser was born in 1888 in Platteville, a small town in southwestern Wisconsin. His father, Herman, was an immigrant from the Tyrol, who, after working as a pharmacist, studied medicine and became a practicing physician. His mother, Jane Elizabeth Griswold Gasser, came from a family of early Connecticut settlers. The given names of their first child, Herbert Spencer, stemmed from his father's perusal of books by Wallace, Darwin, and Spencer after

local newspapers attacked the concept of evolution. There were two younger siblings, a sister and a brother.

Gasser recalled his youth in Platteville: ". . .excursions into the countryside, fishing in the summer and skating in winter. There were few distractions, no cinema or radio, and travel was by horse and buggy. Children had to find their own amusement." Reading was of great importance to him. He also built furniture, taking pleasure in benchwork. Fine craftsmanship remained a lifelong interest. Young Gasser had a simple box Kodak camera that he supplemented with much "improvised equipment." As he remembered: "This experience later turned out to be a good training for a physiologist."

In accordance with his father's wishes, Gasser studied at the state normal school in Platteville. A year was lost because of an unspecified but serious illness; he graduated in 1907. Gasser wished to continue studies in engineering, but his father preferred that he enter medical school. Gasser was not attracted to a country doctor's life. He wanted further education but felt medical training was too great a price to pay. At last, he and his father struck a compromise that he later considered a turning point in his life: "The university would be allowed if no specialization were to take place." Gasser attended the University of Wisconsin at Madison, receiving a bachelor's degree in 1910 and, in the next year, a master's degree. At Wisconsin he took some medical school courses. He wrote about himself: "That is how it came about that his introduction to physiology was through a lecture course given by Prof. Joseph Erlanger before the latter's departure to Washington University in St. Louis. Erlanger was a beautifully clear lecturer, but the subject matter he presented differed so widely from what was anticipated that it amounted to a revelation. Gasser listened to the lectures with bewilderment and felt he was getting

only a feeble grasp of their content. He had no realization that Erlanger was aware of his attendance."

Gasser remained at the university as an assistant in biochemistry, meanwhile completing his preclinical subjects, and then was appointed an instructor in physiology. As a student at Wisconsin, Gasser was involved in several studies with Loevenhart, an imaginative chemist, on the effects of oxygen want and with Meek on the responses of the heart to exercise.

At the medical school in Wisconsin, there were young faculty who were enthusiastic about research and Gasser came to realize that "medical science could be considered a discipline in its own right. In this light medicine appeared in a form which Gasser found acceptable." Because Wisconsin had only a two-year school, Gasser had to complete his medical education at another school, and he wisely chose Johns Hopkins. It apparently required some persuasion to get his father's consent, and the costs were a considerable strain.

JOHNS HOPKINS

The Johns Hopkins medical curriculum provided for elective time; Gasser utilized this for study in physiology. Professor William Howell suggested that he work on mechanisms of blood clotting, studies that he did not complete until after leaving Baltimore. Howell confirmed Gasser's results. Gasser was pleased that this independent work had been successful, but it was not a field of long-term interest to him.

When Gasser received his M.D. in 1915, Howell offered him a position in physiology, but Gasser did not feel free to accept it and returned to Wisconsin where Loevenhart appointed him as an instructor in pharmacology. As he wrote: "The salary was higher and the location was adapted to

helping in the support of a younger sister and brother at the University of Wisconsin."

ST. LOUIS (1916-31)

A year later Gasser had an opportunity to return to physiology. Joseph Erlanger invited him to take a position in his new department at the recently reorganized Washington University School of Medicine in St. Louis. In the spring of 1917 the United States entered the First World War. Gasser worked with Erlanger on problems related to the war effort, investigating wound shock and publishing eight papers on this topic. In the summer of 1918 he joined Loevenhart at a chemical warfare station at American University in Washington, D.C., and worked on Lewisite. At the war's end he returned to St. Louis, in December 1918. At this time he had no clear research direction but had some interest in the nervous system. There were discussions in the department about the problem of recording nerve activity, and Gasser was aware of the need for a new and innovative technical approach.

A classmate from Johns Hopkins, H. S. Newcomer, who had a background in physics, had constructed a three-stage amplifier using thermionic valves. He visited St. Louis, where he and Gasser tried using this amplifier in conjunction with a string galvanometer to record impulses in the phrenic nerve. While the amplification was sufficient to detect the nerve action potentials with the string galvanometer, the latter was too slow to record the fast potential changes with fidelity.

A recording device with sufficient speed did exist, the cathode ray or Braun tube, in which a beam of electrons was deflected by potentials applied to pairs of vertical or horizontal plates. Bernstein had mentioned its possible use for the recording of rapid nerve potential changes in his

book on "Electrobiologie" in 1912. But there was a problem of sensitivity. As Gasser wrote: "In the old Braun tubes, cathode beams were composed of high velocity electrons wrenched from cold cathodes by high voltages. There was still a large gap between the sizes of the potentials needed to deflect them and those which could be produced through the augmentation of a nerve action potential with the aid of the new amplification. Then there occurred an event crucial in its significance."

This crucial event occurred in 1920, when both the Physical Society and the American Physiological Society happened to meet at the same time in Chicago. Professor Horatio Williams, of Columbia, told Gasser there would be a paper read at the Physical Society meeting that would interest him. J. B. Johnson of Western Electric Laboratories was describing a modification of the Braun tube with a heated cathode, allowing the tube to be operated at lower voltages and thus increasing its sensitivity. Newcomer's amplifier had enough gain for the modified Braun tube to record nerve potentials. It was following this development that Erlanger joined Gasser in the studies on nerve potentials. Their first attempt to acquire a cathode ray tube met with resistance from Western Electric, which refused to sell them one. Undaunted, they made a tube by coating a phosphor inside an Erlenmeyer flask. Western Electric subsequently relented and sold them a tube.

To provide for triggering of sweeps of the cathode ray oscillograph and for stimuli to be delivered to the nerve, much ancillary apparatus had to be constructed. This was done largely with mechanical devices. Condenser discharges were applied to the plates deflecting the beam horizontally for the time axis, while vertical deflection was produced by the amplified nerve signal. Records were obtained by holding film on the tube face in the dark room and repeating

the sweeps until a sufficient exposure was obtained. To minimize vibration, the apparatus was mounted in a basement laboratory on a foundation separate from that of the building. Nonetheless, passing streetcars often disturbed the delicate recordings. The images were blurred, and careful correction had to be made for the nonlinearities in horizontal and vertical deflections. In spite of technical difficulties, in shortly over a year Erlanger and Gasser were ready to publish a first paper on the nerve potentials recorded with the oscillograph. Writing some forty years later, Gasser recalled: "The most difficult step in opening up a new field had been taken. Ever afterward, Gasser never had any doubt about the direction he would follow."

It was evident from these earliest studies that the action potential recorded from the frog sciatic nerve was compound in nature (i.e., it resulted from the summation of potential changes in many individual axons). But the characteristics of the action potentials in the individual axons were not known. Much remained to be done.

In 1921 Gasser was made head of the Department of Pharmacology at Washington University, a position he held until 1931. The pharmacology position was accepted with some misgivings and with the stipulation that he would be free to follow his own line of research. Gasser's interest in pharmacology probably stemmed from the influence of Loevenhart. Later, Gasser described taking the chair at Washington University as his "final excursion into Pharmacology." Already, Gasser had come to view himself primarily as a physiologist.

Shortly after Gasser became professor of pharmacology, Abraham Flexner visited the Executive Faculty and, referring to his boyish appearance, asked: "What have you been doing making freshmen Professors?" Soon thereafter Flexner indicated that the General Education Board of the Rockefeller

Foundation would support an extended stay in Europe, for him to gain further experience in pharmacology and to better his knowledge of foreign languages. Gasser had already planned to attend the International Physiological Congress in Edinburgh; there he delivered a paper on the new electrophysiological technique and met with European physiologists. Gasser was soon elected to membership in the Physiological Society of Great Britain (1924).

Exploitation of the new oscillographic technique had barely begun when Gasser began his sojourn abroad, which was extended to a second year. He first worked on muscle with A. V. Hill at University College, London. They published a long paper on the dynamics of muscular contraction; and, in another paper with Hartree, Gasser found that the mechanical and thermal responses of muscle were inseparable. He then went to Straub's laboratory in Munich and, following that, to Louis Lapique in Paris.

Lapique was well-known for his work on nerve and muscle excitation and for his ideas about "chronaxie," an indirect measure of the speed of voltage change of the tissue to an applied current pulse. When Gasser showed his records of compound action potentials to Lapique, "he suggested forthwith that the velocity differences might be associated with the sizes of the fibers." His visit with Lapique was the only one during the European trip that had direct relevance to Gasser's long-range interests and led to a special publication.

Gasser next went to Henry Dale's laboratory. They studied the development of increased sensitivity of muscle to nicotine and acetylcholine following denervation. Doing no further work on muscle, he later wrote an important review on the subject of muscle contracture (1930).

Back in St. Louis, Gasser resumed studies on peripheral nerve with Erlanger. George Bishop had joined in the ef-

fort and brought to the group a considerable array of skills, both practical and theoretical. His knowledge of physics was extensive, and he was very helpful in designing the recording conditions so as to avoid artifacts. In 1924 a paper titled "The Compound Nature of the Action Current in Nerve as Disclosed by the Cathode Ray Oscillograph" was authored by Erlanger and Gasser "with the collaboration in some of the experiments of George H. Bishop." This important paper was a milestone in the development of knowledge about the physiology of peripheral nerve. No less than eight further papers carried Bishop as a joint author.

The excised sciatic nerve of the bullfrog was the principal experimental subject, mounted in a closed humidified chamber on an array of electrodes for stimulation and recording. One recording electrode was placed at the cut end of the nerve, the other some distance centrally, and the potential difference between the two was recorded. With such extracellular recording, impulses arriving at the electrode located on the intact nerve produced a negative deflection.

To provide a quantitative understanding of the action potential recorded from the multiaxonal nerve at different distances from the site of stimulation, it was necessary to know the number and sizes of the axons in the nerve, the form of the action potential in the individual axon, the speed of conduction of the action potential in different axons and its relation to axonal diameter. It would later be found that after-potentials also had to be taken into account.

Gasser was particularly interested in reconstructing the "compound" action potential by summing the predicted potential changes in all the individual axons of the bullfrog nerve, at a particular conduction distance, and comparing this with the recorded action potential. This approach proved

to be very useful and one that Gasser used for his entire research career. From cross sections of the nerve, the numbers of axons (nerve fibers) of various sizes were counted, the action potential of each size group was approximated by a triangular waveform of depolarization, the group of axons of a given size being assumed to have a constant conduction velocity that was proportional to their diameter. Only the myelinated axons of bullfrog peripheral nerve, the so-called A fibers, were studied in their early work. When recording near the cathode, where all the axons were stimulated at the same instant, the action potential had a simple form, the axon potentials in all the axons being nearly synchronous. But with increasing conduction distance the difference in the time of arrival of the action potentials in the fastest and slowest axons increased progressively. The successive elevations in the potential record were produced by axons conducting progressively more slowly; the deflections were called alpha, beta, gamma, and delta. The best fit between the actual compound action potential and the reconstructed plot was obtained when the action potential in the individual axon was given a duration of 1 millisecond, the amplitude of the externally recorded action potential in each axon was made proportional to axonal size, and conduction velocity was related directly to axonal diameter.

Other important questions were pursued. For example, was conduction in the various fibers independent? As the strength of a stimulus was increased, first the largest and then the smaller axons were excited. If a weak shock that excited only the largest (A alpha) axons was given and then, while they were refractory, a second stronger shock was delivered, the latter evoked no alpha wave but only later deflections. This indicated that action potentials in the larger and smaller fibers were conducted independently. Subsequently, it was possible to record the action potential in an

individual axon and to measure directly its time course. Studies were also made on the absolute and relative refractory periods following impulse activity.

The first observation of the C fiber action potential was made by Peter Heinbecker, a research fellow with George Bishop. Applying exceedingly strong shocks to the cervical sympathetic nerve of the turtle, he saw small, very late potential elevations that conducted very slowly. These were the responses of unmyelinated or C fibers. Erlanger and Gasser explored the details of the C fiber potentials, publishing a detailed paper in 1930. Decades later Gasser was to return to this problem. The threshold of C fibers to electrical stimulation was nearly 100 times that of A fibers. C fiber action potentials were longer in duration than those in A fibers; the proportionality between conduction velocity and diameter was also different, although the relationship appeared to be linear.

Myelinated preganglionic sympathetic fibers were designated B fibers. Their properties differed from A fibers in duration of action potential, relation between fiber diameter and conduction velocity, and in after-potentials.

The order in which nerve fibers were blocked by cocaine was found to be from smallest to largest. Conversely, pressure blocked the largest fibers first, the smaller fibers later. This was useful in relating function to the various fiber groups, a topic of lasting interest to both Gasser and to Bishop.

Toward the end of his St. Louis tenure, Gasser, together with Erlanger, became interested in the potential changes that follow the brief nerve impulse, the after-potentials, and their effect on excitability. After the nerve impulse or "spike," the potential only gradually returned to the baseline level; the potential during this period being negative to the baseline, it was called the negative after-potential. During the nega-

tive after-potential, a smaller than normal stimulus was needed to excite the nerve; it was a period of supernormal excitability. There then followed a much slower change in which the potential became positive to the baseline, a positive after-potential. During this period the nerve was subnormal in its excitability. The after-potentials showed characteristic differences in A, B, and C fibers. Also, the size of the after-potentials depended on the amount of preceding activity. The excitability changes produced by the relatively long lasting positive after-potentials in peripheral nerve fibers and their augmentation by preceding repetitive activity were of interest because they might help explain certain long-lasting excitability changes in the central nervous system.

With the widespread interest in studies of electrical conduction, group discussions took place at the time of the annual meetings of the American Physiological Society. In 1930 Ralph Gerard invited a group of ten, representing seven different institutions, to meet the day before the scheduled program. They adopted the name "axonologists," a term proposed by Alexander Forbes of Harvard. Three members were from St. Louis: Erlanger, Gasser, and F. O. Schmitt. The size of the group expanded over successive annual meetings until the council of the Physiological Society protested that its regular program was being diminished; the axonologists disbanded.

In 1926 Gasser made an interesting appointment to the Department of Pharmacology, that of Helen Tredway Graham. The wife of Evarts Graham, then head of surgery at Washington University, she had been an outstanding student at Bryn Mawr and later received a doctorate from the University of Chicago. At this time, prejudice against women in science was strong. Even a woman as gifted and privileged as Graham had difficulty finding a suitable position. Though Graham was a neurophysiologist, it was Gasser, rather

than Erlanger (then head of physiology), who gave her a position. In subsequent publications Gasser referred to her simply as H. T. Graham. They collaborated on five articles, two dealing with pharmacology. Graham later did important independent studies on nerve function and went on to very original work on histamine. Her description of Gasser as she remembered him during their collaboration reveals his enjoyment of lively interchange:

> To Dr. Gasser an integral aspect of research is discussion and, in those days when he had the right partner, discussion seemed never to weary him. Many were the hours spent over endless cups of coffee in the physiology seminar room, in the cafeteria (then run on a leisurely schedule in the medical school without a closing hour for lunch), in friends' houses or in neighboring or downtown restaurants; and many were the diagrams drawn on odd envelopes, on cafeteria checks, on paper napkins, or even on restaurant tablecloths. His indifference to time and his ability to make his colleagues ignore it not infrequently prolonged the Monday afternoon physiological seminars to an hour that tried the patience of the colleagues' families waiting at home for dinner. But there was a limit even to Gasser's zeal for discussion: during an era when lactic acid was regarded as the key to muscular contraction he announced privately, if not publicly, that he was too fed up with lactic acid to attend one more session of a certain group in the school given to a discussion of its metabolism.

Helen Graham and Gasser remained in contact for many years thereafter, and she continued to seek his advice even after he became Director of the Rockefeller Institute. Clearly, she regarded him as her mentor, and their friendship was enduring.

CORNELL UNIVERSITY MEDICAL COLLEGE (1931-35)

In 1932 new structures going up on East 68th Street in Manhattan united the previously separate Cornell Medical College and the New York Hospital. In that same year the professor of physiology was to retire and Gasser was approached to replace him. He accepted the position in 1931

with one free year to formulate his plans. During this time, he prepared the first student manual for experiments using the oscillograph, to eliminate the old spring-wound kymographs, and ran through the experiments to check them out.

In 1934, the year of his election to the National Academy of Sciences, the final meeting of the axonologists occurred in New York City under Gasser's leadership. At that meeting, much speculation was given to the topic of synaptic transmission—whether it was chemical or electrical.

When Gasser moved to Cornell, the direction of his work changed slightly. With Grundfest he investigated mammalian peripheral nerve fibers and found important quantitative differences between amphibian and mammalian nerve. With Hughes he studied potentials within the spinal cord, work that he had initiated with Helen Graham in St. Louis.

In 1937 Gasser gave a Harvey Lecture on "The Control of Excitation in the Nervous System." In this talk he considered possible mechanisms of excitation and inhibition that operate within the central nervous system and the possible relevance to this of information gained by the study of peripheral nerve. At that time, little was known about the underlying processes of activity in the central nervous system. His insights seem remarkably clear and imaginative. Some of these ideas found expression in the later studies of Lorente de Nó, Renshaw, and Lloyd at the Rockefeller Institute.

Gasser attempted to relate the phenomenon of inhibition in the central nervous system to some properties of peripheral nerve—namely, the subnormality that followed activity. He devised a scheme to explain reciprocal inhibition on this basis, although it was later found that inhibition has a quite different mechanism. Lloyd's studies (1941)

showed clearly that inhibition could occur without prior excitation.

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

After only three years at Cornell, the Rockefeller Institute for Medical Research invited Gasser to become its new Director. Charles Stockard, professor of anatomy at Cornell, and a member of the Board of Scientific Directors of the Rockefeller Institute, had suggested his name. The offer surprised Gasser, and he doubted his administrative abilities. But he was attracted ". . . by the argument that the most important function of a director of a research institute was maintenance of assurance of complete freedom to the investigators."

In 1935 Gasser did accept the Directorship, although with some reluctance. It would offer him funds for developing superior recording equipment and freedom from teaching. He was assured that experienced and competent support staff would make his administrative duties light. Clearly, the Rockefellers, concerned about the effect of the continued economic depression on the institute's endowment, needed a director who would be a wise steward of funds. The institute did provide Gasser, a bachelor, with an apartment in the east 60s sufficiently large for entertainment.

Before taking his position, Gasser went to Russia where he gave a paper at the Georgian Academy of Sciences. During this trip, he located a master instrument designer, J. F. Toennies, who had lost his position through the political upheavals in Germany. Toennies came to Gasser's staff in the physiology division for a three-year term.

Gasser at once designed his laboratories for neurophysiological studies on the unoccupied first floor of the "new North" building, then only five years old. Since its opening, the Institute had utilized d.c. current generated in its own

power plant. Gasser had alternating current, necessary for more modern equipment, brought to this area. By 1936 the new laboratories and an instrument shop with heavy equipment were in operation, with experienced toolmakers from European apprenticeships. Neurophysiological equipment then had to be constructed locally from purchased parts, to be installed in freestanding upright racks. Toennies' new design for amplifiers, with better frequency response and rejection of common mode noise, greatly improved the accuracy of recording.

The assurances that Flexner's established system for running the Institute would give Gasser free time for his own laboratory work were fulfilled fairly well for six years. There was an array of very competent people in charge of support services. During his first six years there, Gasser published eleven papers, six under his name alone.

In 1935 Erlanger and Gasser were invited to give a series of lectures at the Johnson Foundation in Philadelphia. These were published in a volume titled *Electrical Signs of Nervous Activity* in 1936. By this time their views had diverged, as they openly acknowledged in their joint preface:

> Two summers ago, as we sat on a ledge high up in the Rocky Mountains, resting from our walk and viewing the panorama of lofty peaks spread out before us, our conversation turned to problems of nerve physiology. We were on holiday together, one of us had just arrived and much had gone on in our widely separated laboratories which we had not had an opportunity to discuss. After a while during a pause in the conversation one of us said, "Shall we ever be able to collaborate in a set of lectures when there are so many points which we interpret differently?"

The problem was resolved by their each giving an independent series of lectures.

Gasser soon established the Institute as a major center for research in neurophysiology. He brought a group of investigators there, including Harry Grundfest, Raphael

Lorente de Nó, Birdsey Renshaw, and David P. C. Lloyd. A number of visitors also worked there for various periods of time, among them Alan Hodgkin (1937-38), who carried out his classical experiments on the role of local current circuits in the propagation of the nerve impulse.

Gasser's own laboratory work represented a continuation of his research at Cornell. In 1938 he published papers on recruitment of nerve fibers and on properties of mammalian nerve fibers of slowest conduction with Grundfest and Richards and in 1939 an article on axons as samples of nervous tissue.

Starting with the tense prewar days of 1941, Gasser's administrative responsibilities made it progressively more difficult for him to devote time to research. In the ensuing thirteen years, Gasser published six articles, his colleagues sixty-five. In 1942 the neurophysiological laboratories were closed, Lloyd moved to Yale University for two years, and Gasser devoted his energies toward the war effort. Under Gasser's direction, the Institute had a number of contracts from the Office of Scientific Research and Development, chiefly for work on nitrogen mustard agents in which Gasser himself was involved.

In October 1944 a cablegram from Stockholm announced that Erlanger and Gasser had won the Nobel Prize for their work on nerve function. Gasser learned of this when he was in the office of one of the Institute's trustees. He wrote of himself: "Dismay rather than elation was his immediate reaction. So estranged from his thinking had become the physiology of nerve fibers, that at the end of the conference he went into retreat in order to regain touch with the state of the subject through reading his own reprints." This comment reflects his exceptional honesty and lack of pretense. The award was presented in New York because of the

war; the Stockholm formalities took place on December 10, 1945, when peace had returned.

GASSER AS DIRECTOR OF THE ROCKEFELLER INSTITUTE

In taking up the reins from Simon Flexner, Gasser devoted much time to studying the staff and the ongoing research, visiting each laboratory in turn. So effective did he find this method that he arranged for staff to visit laboratories in place of certain Friday staff meetings. Gasser served on both the Board of Scientific Advisors and the Board of Trustees (known collectively as the "Corporation"), which determined policies.

Each laboratory submitted an annual report for the Corporation, which was carefully reviewed by Gasser. He was also concerned with many other details of the Institute's operation, dealing with appointments and promotions as well as the retirement of a number of members who approached their sixty-fifth year. Some of them chose to remain as working scientists with small staffs (Michaelis, Osterhout, and Landsteiner), Avery keeping an office, while Rufus Cole, Florence Sabin, and Alexis Carrel left.

Under Gasser there was a change from Simon Flexner's policy of abolishing a laboratory and disbanding its staff when a member left or died. In contrast, when a member departed, Gasser judged everyone in that laboratory individually and retained those whom he judged would offer productive years in research.

Expenditures were held down from 1935 through the period of the Second World War. By then the aging laboratories were in need of refurbishing. Gasser designed standardized laboratory furniture, beautiful oak cabinetry of modular dimensions. He made a thorough upgrading of the facilities, again relying on the Institute's "shops" to re-

build, rewire, and replumb those laboratories. Also, a southern extension of the Rockefeller Hospital was built.

Through pressure from the Trustees, the Princeton branch of the Institute, which had contained the Department of Animal Pathology since 1913 and the Department of Plant Pathology since 1931, was to be discontinued; the task fell to Gasser. New quarters were made for those who wished to transfer their activities to New York, and a number of greenhouses were built.

Central to Gasser's Directorship was the maintenance of the individual investigator's independence to study the problems of his or her choice. This had been a key factor in attracting Gasser himself to the Institute. Some of his remarks indicate how strongly he was committed to this policy:

> The product of the Rockefeller Institute is new knowledge. . . . It cannot be forecast and it can not be achieved through administrative direction. All that can be done is to create optimal conditions for its production.
>
> The opportunity which the Institute has above all else is to concentrate on the production of scientific capital. . . . The production cannot be planned. No one knows how. But the conditions for it can be maintained, as they are now and always have been. That means fostering individuals and allowing them freedom.
>
> . . . grants are made in the interest of defined projects and for a limited period. . . . In order to receive aid an individual must outline a project. At the onset, he is in effect being asked to make a prediction. . . . Projects, by definition, are not consonant with free inquiry.

While he was Director, Gasser refused to accept federal funds to compensate the institute for laboratory expenses of postdoctoral students. He feared this might compromise the Institute's independence. This policy was abandoned at once after he retired.

RETIREMENT

The war's hiatus and the weight of administrative obligations kept Gasser from active laboratory work until his re-

tirement as Director. On returning to the bench, he took up the same problems he had left earlier because he felt that this was the area where he could best contribute. Concerned that his research might not be optimal for training a young scientist, Gasser decided to work without a collaborator.

The major aim of his research after retirement was to continue exploring the structure and function of unmyelinated axons in peripheral nerve. When he studied this matter earlier, accurate measurement of axon diameters in unmyelinated axons had not been possible because they were so small; silver staining of such axons allowed them to be visualized but rendered measurement of their diameters inaccurate. Fortunately, new techniques of electron microscopy were being developed at the Institute as Gasser was approaching retirement.

The Princeton branch saw the usefulness of the electron microscope when Wendell Stanley went to the RCA laboratories in Camden, New Jersey, and shortly one was acquired by the Princeton branch for examining viruses. In 1947 the International Health Division of the Rockefeller Foundation, located in the Institute, purchased an electron microscope, and it became available to Porter.

Keith Porter and George Palade were working on problems of fixation, embedding and sectioning of tissues for study under the electron microscope. If this could be done satisfactorily, accurate measurements of axon diameters would be possible. Thomas Rivers's opinion that electron microscopy would not be useful for examining tissues may have made Gasser hesitant, but he came to believe otherwise. With his delayed decision, the Institute itself purchased an electron microscope in 1948. Palade and Porter were able to obtain sufficiently thin sections of tissues embedded in methacrylate, using a microtome that Porter and Blum de-

veloped. These early electron microscopic studies of cellular fine structure at the Institute, of great importance to the development of cell biology, provided a way for Gasser to study the morphology of the small unmyelinated axons.

The electron microscopic studies of nerve, initiated by Gasser with the help of Porter and Palade, permitted the size of unmyelinated axons to be measured accurately and also showed their relationship to the Schwann cells in which they are embedded. The outer membrane of the Schwann cell is infolded to enclose an unmyelinated axon, an arrangement Gasser called a mesaxon by analogy with the mesentery. The unmyelinated axon was thus surrounded by a thin layer of extracellular space, although lying within the Schwann cell. Since a number of axons could be contained within one Schwann cell, Gasser was interested in finding whether interactions might occur between such axons. He made three-dimensional reconstructions to determine over what length one axon might lie close to another. This turned out to be quite limited, suggesting that interactions from this cause were not likely to be important.

Unmyelinated axons in peripheral nerve may be sensory, their cell bodies lying in the dorsal root ganglion, or efferent, postganglionic sympathetic fibers en route to the periphery. Gasser found that these two types of C fibers showed differences in their physiological properties. In comparing the unmyelinated axons of dorsal root ganglion cells central to and distal to the ganglion, Gasser found that their diameters diminished by about an order of magnitude central to their cell bodies as compared to the periphery.

Reconstruction of the compound action potential of unmyelinated (C) axons from the diameter distribution of the axons was impressively successful, based on a linear relationship between axon diameter and conduction velocity

and on appropriate contributions of after-potentials to the recorded action potentials.

With the higher resolution of the electron microscope, Gasser examined olfactory nerve fibers in mammals and in the pike. The unmyelinated fibers were found to be extremely small. The length of the olfactory nerve in the pike permitted recording from these nerve fibers. Although afferent, they showed action potentials that differed from those of mammalian dorsal root C axons, showing a simple form consonant with all of the axons having nearly the same diameter.

Gasser also sought an answer to a problem in the recording of the compound action potential, which had long bothered him. The problem arose from the fact that the potential was recorded by two electrodes, one at the end of the nerve and the other some distance centrally. Even if the nerve end was crushed and treated with a local anesthetic, impulses in some fibers propagated into the stretch between the recording electrodes, creating an artifact. The solution was to integrate the response recorded by a pair of electrodes located quite close together on the nerve, a procedure that he called a tangent lead. The results showed that some of the previously described elevations were artifactual; in the compound action potential produced by myelinated fibers of mammalian cutaneous nerves there were only two peaks, the alpha and delta. This finding was consonant with the size distribution of myelinated axons in these nerves. The paper describing these studies was his last.

Working alone or with one or two collaborators, Gasser was a very focused investigator, intensely concentrated on his subject. Most of his research was, in fact, within a circumscribed although important area. An approach he utilized throughout his career was reconstruction of the com-

pound action potential from the calculated sum of the activities of the unitary axons. He returned to this approach, first used in St. Louis, after his retirement as Director. As Lloyd later wrote of Gasser's style of selecting problems: ". . . Gasser espoused the principle that there are two times for working on a problem—before anyone has thought of it and after everyone else has left it. As a result, Gasser was always the innovator or the finalist."

GASSER IN PERSON

As Director of the Rockefeller Institute, Gasser was a striking figure. Tall, elegant, and graced for many years with an extraordinarily youthful appearance, his formidable intellect made him impatient with trivial conversation. While he was clearly a fastidious man of great integrity, those privileged to know him realized that he was also a warm, engaging person who treated friends with much kindness, loyalty, and concern. He had a keen sense of humor, enjoyed puns, and could be very good company. Fine art, classical music, and good food were among his pleasures. He read widely and his knowledge on many topics was profound. His high-pitched voice reflected a hormonal deficiency, but a strong personality and rigorous intellect made this unimportant. Not a facile speaker, Gasser wrote beautifully, with clarity and grace.

An example of Gasser's uncompromising standards can be seen in his response to a letter from Erlanger in 1938, requesting information to be transmitted to the Nobel committee. Their colleague, Dr. Evarts Graham, had nominated them. Gasser wrote Erlanger:

> It must be well known in Stockholm that nominations for the Nobel Prize coming to hand with full information must be made with the cooperation of the nominee. One is thus forced into the position of appearing, at least in some measure, to nominate oneself. . . . I am greatly pleased that Evarts

should value our work highly enough to place it in nomination, and I am grateful to him for the proposal, but my considered opinion about the effect of our becoming a party to the proposal impels me into not consenting to do so.

While such an attitude may seem quaint today, it reflected Gasser's deeply rooted antipathy to any kind of self-promotion.

Gasser's laboratory days ended when he suffered a cerebral accident on April 17, 1961, at the age of seventy-three, eight years after resigning as Director. Thereafter he resided in the New York Hospital. He made a partial recovery from his stroke but died from a respiratory infection in the hospital on May 11, 1963.

The fact that this memoir is written almost thirty years after his death permits some perspective on Gasser's view that independence of scientific inquiry was essential. By the time he retired in 1953, grant support had expanded considerably, and Gasser's reservations seemed old-fashioned to many. There was then an abundance of governmental money, and research of quality found support with proposals that were liberally and flexibly reviewed. Gasser had admitted that under a grant system "there is no gain-saying that accomplishments of the highest type can come out of it in spite of its shortcomings." Now, with the stringency of funding, an applicant for federal grant support must not only predict the results to be obtained but must also demonstrate that the proposed experiments will yield the anticipated results. Thus, the investigator's independence is even more compromised than Gasser once feared. From the vantage point of the 1990s, his concerns now appear prescient.

VALUED SOURCES ARE GASSER'S autobiography, published posthumously with an introduction by Joseph C. Hinsey in *Experimental*

Neurology, 10 (Suppl. 1, 1964):1-38 (our quotations from Gasser come from this), also David P. C. Lloyd's obituary of Dr. Gasser in volume 5 of the *Dictionary of Scientific Biography,* pp. 290, 291 (New York: Charles Scribner's Sons, 1972) and Lord Adrian's article in the *Biographical Memoir of Fellows of the Royal Society,* 10(1964):75-82. The history of the axonologists comes from F. O. Schmitt to MWC and is recounted in volume 2 of *Advances in American Medicine: Essays at the Bicentennial* in the article "The Neurosciences" by Robert J. Frank, Louise H. Marshall, and H. J. Magoun, pp. 552-616 (New York: Josiah Macy, Jr., Foundation, 1976). The reference to the status of women in science, as related to H. T. Graham, comes from M. W. Rossiter's *Women Scientists in America* (Baltimore: Johns Hopkins University Press, 1984). The homemade cathode ray tube and its trundling to the XIII International Congress of Physiology in Boston, 1929, is described in Hallowell Davis' memoir of Joseph Erlanger in *Biographical Memoirs*, vol. 41, pp. 111-39 (Washington, D.C.: National Academy of Sciences, 1976). It is to be noted that the 1936 book by Erlanger and Gasser was reprinted thirty-one years later by the trustees of the University of Pennsylvania, along with Gasser's bibliography and a foreword by David P. C. Lloyd. Gasser's picture was taken at age forty-seven, shortly after he became Director of the Rockefeller Institute for Medical Research.

HONORS AND DISTINCTIONS

AWARDS AND MEMBERSHIPS

1924	Physiological Society (British), Ordinary Member
1934	National Academy of Sciences
1935-53	Director, The Rockefeller Institute for Medical Research
1936	Sociedad Argentina de Biologia, Corresponding Member
1937	American Philosophical Society
1942	Asociacion Medica Argentina, Honorary Member
1943	Asociacion Medica Argentina de Buenos Aires, Honorary Member
	Royal Society of Edinburgh, Honorary Fellow
1944-45	Nobel Prize in Physiology and Medicine (with J. Erlanger)
1946	Royal Society of London, Foreign Member
	Royal Swedish Academy of Sciences, Foreign Member
1947	Finnish Academy of Sciences, Foreign Member
	Académie Royale de Médicine de Belgique, Corresponding Member
	American Society of Electroencephalography, Honorary Member
1948	American Academy of Arts and Sciences
	Accademia della Scienze dell' Istituto di Bologna, Corresponding Member
1949	Physiological Society (British), Honorary Member
1953	Société Philomathique de Paris, Corresponding Member
1954	Kober Medal, Association of American Physicians
1958	Société de Biologie, Collège de France, Associate Member

HONORARY DEGREES

1936	Sc.D., University of Pennsylvania
1940	Sc.D., University of Rochester
	LL.D., Washington University
1941	Sc.D., University of Wisconsin
1945	Sc.D., Columbia University
1947	LL.D., Johns Hopkins University

	Sc.D., Oxford University
1948	Sc.D., Harvard University
1949	Doctor honoris causa, Université Libre de Bruxelles
	Doctor of Medicine, Honorary, Université Catholique de Louvain
1953	Honorique de docteur, Université de Paris
1959	Sc.D., The Rockefeller University

PROFESSIONAL ORGANIZATIONS

American Physiological Society
American Association for the Advancement of Science, Fellow
Society for Experimental Biology and Medicine, President, 1937-39
Harvey Society, President 1940-42
Association for Research in Nervous and Mental Diseases
American Society of Pharmacology and Experimental Therapeutics
Association of American Physicians
History of Science Society
New York State Society for Medical Research
American Neurological Association (Associate Member)

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1917

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1918

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1919

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1921

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1922

With J. Erlanger. A study of the action currents of nerve with the cathode ray oscillograph. *Am. J. Physiol.* 62:496-524.

1924

With J. Erlanger and the collaboration in some of the experiments of G. H. Bishop. The compound nature of the action current in nerve as disclosed by the cathode ray oscillograph. *Am. J. Physiol.* 70:624-66.

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1926

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With G. H. Bishop and J. Erlanger. Distortion of action potentials as recorded from the nerve surface. *Am. J. Physiol.* 78:592-609.

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