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BERTA V. SCHARRER

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A Biographical Memoir by

DOMINICK P. PURPURA

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Berta Scharrer

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BERTA SCHARRER, CO-FOUNDER of the discipline that has come to be known as neuroendocrinology, was an exemplar of science and conscience. Her long and prolific life, bracketed by but a few years on either side of the twentieth century, is an inspiring record of scientific achievement. It is also an historical record of the triumphs and horrors and the social and political progress and perversions of this most extraordinary period.

Throughout Scharrer's sixty-five-year scientific career, she faced resistance to her unconventional ideas, prejudice against women, and personal tragedy, along with a few jackbooted thugs posing as politicians. Yet, she persevered in her boundless quest for knowledge, advancing the bold new concept of neurosecretion and reinventing her career many times along the way. Berta's strength, dedication, and enthusiasm touched many during her peripatetic journey through life and lives on in the colleagues, students, and other friends she has left behind.

EARLY LIFE

Berta Vogel Scharrer was born on December 1, 1906, in Munich, Germany, to Johanna Weiss Vogel and Karl Phillip Vogel, a prosperous judge who served as vice-president of

the federal court of Bavaria. Her childhood with her three siblings was happy—filled with music, art, and all the cultural charms of Munich. Berta received an excellent early education at gymnasium, where she developed an interest in biology that would guide her life's work. As a young girl she set her sights on becoming a research scientist, although she knew the chances for an academic career in biology were slim then for a person who happened to be born with two X chromosomes.

In pursuit of her goal Berta attended the University of Munich, where she became interested in the work of the bee behavioral biologist Professor Karl von Frisch, whose own long life was punctuated with the 1973 Nobel Prize for physiology or medicine. She joined his laboratory for her doctoral work, a comparison of the taste and nutritional quality of various sugars for the honeybee. Berta Vogel received her Ph.D. in 1930 and published her thesis and associated research papers in 1931.

Berta's choice of dissertation laboratory was fortunate, and not simply because Professor von Frisch made a good advisor; it was here that the seeds for her future career in the field of neurosecretion were sown, in the form of her acquaintance with another of von Frisch's students, Ernst Scharrer. These two young scientists soon began a partnership, both professional and personal. From the time of Berta's graduation until Ernst's death in 1965, they would be a team, in research as well as life.

Berta and Ernst's first move together was to the Research Institute of Psychiatry in Munich, headed by Walter Spielmeyer. There Berta took up bacteriology briefly, studying spirochetes and brain infections in birds and amphibians, while Ernst completed an additional degree in medicine. Berta hedged her bets against the prevailing prejudices toward women in research and studied for a certificate to

teach at gymnasium during this period, but her heart remained set on a life in science.

BIRTH OF THE NEUROSECRETION HYPOTHESIS

The year 1934 should have been the beginning of halcyon days for Berta. She and Ernst moved to the University of Frankfurt, where Ernst had been appointed director of the Edinger Institute for Brain Research. With this job and a small stipend from Berta's uncle to support them, Berta and Ernst wed. Berta herself worked without pay. Rules against nepotism were strongly enforced at this time, and Ernst took them quite seriously. While Berta did obtain research space at the university, she was given neither academic title nor salary.

This move foreshadowed many years of research and teaching without formal recognition or recompense, but Berta was philosophical about the decision: "An academic career at that time did not look promising at all for a woman. I must say that I could not have done what I have if I had not been married to a biologist who gave me a chance to do my work."[1] Unfortunately, that work would slowly fall into the shadows of the rising influence of Adolf Hitler and the Nazi party.

In 1928, during his thesis studies in von Frisch's lab, Ernst Scharrer had discovered secretory droplets in certain hypothalamic neurons of the European minnow *Phoxinus*. He termed these neurons "nerve-gland cells," and he proposed that they were capable of secreting substances in the same manner that endocrine cells secrete hormones. In Frankfurt, both Scharrers took up further investigation of this controversial hypothesis.

At that time, conventional wisdom held that nerve function was purely an electrical phenomenon. Few scientists were willing to accept that nerve cells secreted any sub-

stance, much less hormones. "Remember, synaptic chemical transmission wasn't even known at the time of our first neurosecretion publications. The idea that neurons may be capable of dispatching neurohormonal, or blood-borne signals, an activity previously associated only with endocrine cells, met with powerful resistance."

To bolster Ernst's initial observation in fish, the Scharrers began seeking nerve-gland cells in other organisms. They decided from the start on a comparative approach; Berta would explore the invertebrate animals, while Ernst focused on vertebrates. This strategy proved prescient. Not only did the invertebrate world offer rich diversity, but it revealed parallels with vertebrate biology that would cement and extend the concept of neurosecretion and many years later would inform Berta's novel ideas on the evolution of the neuroendocrine system.

Berta rapidly established the wide distribution of nerve-gland cells in invertebrates. Her classic first papers on the topic, in which she described neurosecretory cells in the Opisthobranch snail *Aplysia* and in the Polychaete worm *Nereis,* appeared in 1935 and 1936. This comparative evidence was essential, as it proved that Ernst Scharrer's initial observation of secretory neurons in fish was not simply an artifact. Still, the theory of neurosecretion remained tenuous; it was based solely on cytological evidence of secretory granules.

During these earliest years of their collaboration, Berta and Ernst Scharrer worked in isolation, outside the mainstream scientific community. "I think it was vital that my husband and I had each other to talk to. We could reassure each other that what we were doing had a future. I don't know how long a single mind could have stuck with the same topic hoping for success." The resistance of their scientific colleagues was to become the least of their problems.

Initially, the Scharrers' time at the Edinger Institute had been a happy and exciting one. They had made lasting friends of individuals like Wolfgang Bargmann and Albrecht Bethe. They summered at the renowned Zoological Station in Naples, collecting scientific samples from the Mediterranean and enjoying the company of the many biologists who flocked there each year. Their research was productive, and political concerns seemed distant. "Because it was a privately endowed research facility not closely connected with university affairs, we thought we would have a chance to work for a few years in a somewhat sheltered situation. But this outlook . . . did not last very long."

On April 1, 1933, the *Reichstag*—Hermann Göring presiding—passed the infamous "Law for the Restoration of the German Civil Service," which mandated the dismissal of all civil servants, including university professors who were defined as Jews under the law. Some saw the resulting vacancies as opportunities; Berta and her husband soon found them intolerable. By 1937 the academic environment had been reduced to parody. "Some professors went into the classroom . . . in full uniform. There were obligatory programs to attend, indoctrination meetings. . . ." The Scharrers experienced increasing pressure to join Nazi organizations and to shun Jewish colleagues. "What the two of us were particularly opposed to was this senseless and immoral philosophy of the Nazis, the idea of racial superiority, anti-Semitism, genocide. . . . We decided that it was impossible for us to be part of this system any longer."

The Scylla of remaining, however, was no less dangerous than was the Charybdis of leaving. They would have to adopt a certain cloak-and-dagger approach to yet another strategic bit of teamwork. As a physician, Ernst was a valuable commodity in a country preparing for war. The springboard for exodus was a one-year Rockefeller fellowship for Ernst

at the University of Chicago for which the Scharrers duped the authorities, pretending that they would be returning to Germany. In 1937 Berta and Ernst Scharrer left their full life, their friends, and all of their research materials. They came to the United States with nothing but two suitcases, the four dollars each they were permitted to carry out of Germany, and a united clear conscience.

STARTING OVER

Berta Scharrer thus once again started her research from scratch. Even while fleeing, however, the Scharrers began to rebuild their work on neurosecretion—their eastward passage allowed for stops in Africa, the Philippines, and Japan to collect animals for study. At Chicago, Berta managed to obtain a small laboratory space, and although she was again unsalaried, she was able to resume her studies of neurosecretory cells. With little space and no money to buy supplies, her options for experimental animals were limited. She initially worked with *Drosophila,* but soon, with the help of a friendly custodian, she discovered cockroaches in the basement of her building. She trapped these and studied them, setting the precedent for the extensive work with roaches that lasted into her eighties.

The year at Chicago was difficult. She knew very little English, and visa nuisances required time-consuming travel to Cuba and Switzerland. Yet she managed to publish two papers her first year in the United States, both in English, with help from a retired professor who edited her manuscripts.

In 1938 Ernst took a position as a visiting investigator in the laboratory of Herbert Gasser at the Rockefeller Institute for Medical Research (now Rockefeller University) in New York City. Again, Berta acquired limited lab space and the unpaid position of research associate. During the next

few years, Berta described neurosecretory cells in her cockroaches and other arthropods, adding to the ever-expanding menagerie of animals that supported the Scharrers' ideas. And during this time, as the world was plunged into the winter of Hitler's discontent, the sun of reason slowly began to thaw resistance to neurosecretion. At Rockefeller, the Scharrers prepared a landmark paper that they presented in 1940 at a meeting of the Association for Research in Nervous and Mental Diseases. This was the U.S. scientific community's first introduction to the new field of neurosecretion, and the paper was respectfully received.

PHYSIOLOGICAL RELEVANCE OF NEUROSECRETION

Near the end of her stay at Rockefeller, Berta discovered the animal that would eventually help her demonstrate the function and importance of insect nerve-gland cells: the woodroach. Soon after her arrival in New York, she had inquired as to the availability of cockroaches to replenish her stock. For the first time in recorded history, the city had none to offer—at least not in the basement of her building. But in 1940 Berta happened upon some unusual specimens in a shipment of monkeys from South America. These were *Leucophaea maderae*, or woodroaches, and they were particularly well suited to Berta's research. They were larger than American roaches, being about two inches long, and obligingly slower. Furthermore, their brains and nervous systems were amenable to the microsurgery that Berta would soon undertake to demonstrate the importance of neurosecretory bodies.

Berta took these roaches along to her next destination: Western Reserve University (now Case Western Reserve University) in Cleveland, Ohio. Normand Hoerr, an old friend from Chicago and the new chair of the Department of Anatomy, had offered Ernst a position as assistant profes-

sor. From 1940 to 1946, Berta served as instructor and fellow, teaching in the histology laboratory and conducting research—again with no salary.

The Scharrers' life in Ohio was modest. They lived in a small apartment near the school and often worked late into the night alongside their students. Their wanderlust, however, continued to reveal itself. They continued to spend summers on the east coast, at the Marine Biological Laboratory at Woods Hole; they also enjoyed trips to Lake Erie for collection of fish samples, and to Colorado, where they rode horseback and studied English. In 1945 both Berta and Ernst Scharrer became U.S. citizens.

During this time the Scharrers established their lifelong friendship with the anatomist Sanford Palay, then just starting his medical education. Palay has described the prejudices that Berta still faced as a woman scientist, even fifteen years into her career. Initially, she was not even allowed to attend department seminars; this decision was not reversed until she agreed to prepare tea for the faculty. Certain members of the faculty, illustrating the depths of irrationality to which even men of science can fall, blamed Berta for every cockroach they encountered in the hallway, despite the fact that these were roaches of the native variety and clearly not the giant South American species that Berta used in her research.

Berta had established a breeding colony of these woodroaches in her office at Western Reserve and soon set out to elucidate the function of several neuroglandular bodies of the head, including especially the corpus allatum and the corpus cardiacum. Using the microsurgical techniques of cell ablation and nerve section, Berta steadily built up a picture of neurosecretory function in roaches. She found that removal of the corpus allatum had severe effects on the development of the roach due to a resulting hormonal

imbalance, nymphs underwent metamorphosis prematurely. Removal of the corpus allatum and the hormones it produced also affected egg development in females. She then went on to show that removal of an associated brain gland, the corpus cardiacum, had no observable effect, for reasons that were quite germane to the neurosecretory hypothesis.

Although the corpus cardiacum did indeed contain important hormones, it served only as a storage depot and transfer station. The hormones were shipped to this body by neurosecretory cells. These neurons continued pumping out hormones even in the absence of the storage point; the sustained flow ensured proper development of eggs and nymphs in animals in which the corpus cardiacum had been removed. Berta was able to demonstrate further that neurosecretory cells conveyed their output of secretory granules to the corpus cardiacum by transport down the nerve axon. These studies provided definitive evidence of the production, transport, and secretion of essential hormones by cells of the nervous system of insects.

Another interesting discovery from this time was the induction of distant tumors by the removal of the corpus allatum and corpus cardiacum. This effect was due not to hormone deficiency, but rather to the unavoidable severing of a nerve during the surgeries. Berta showed that section of the recurrent nerve in roaches led to tumor growth in the stomach and other organs controlled by this nerve, providing a novel insight into potential mechanisms of cancer.

As hoped, Berta's work on invertebrates was complementing Ernst's work marvelously. There were numerous interesting parallels between the corpus allatum-corpus cardiacum system of the insect and the hypothalamic-hypophyseal system of the vertebrates. Indeed, there was growing evidence that the neurosecretory cells of the hypothalamus delivered hor-

mones along nerves to storage points near the brain; Ernst and Berta rightly suspected that one such storage point was the posterior lobe of the pituitary gland. This insight might not have been reached so quickly had it not been for the comparative approach undertaken by the Scharrers.

During the time of their important studies establishing the physiological importance of neurosecretion, Berta and Ernst moved yet again. In 1946 Ernst became associate professor in the University of Colorado Medical School in Denver. Still an unsalaried instructor, Berta had to look beyond her school to finally receive some financial support and some recognition of her accomplishments and international reputation. She first won a prestigious Guggenheim fellowship for the 1947-48 year and then a special fellowship from the U.S. Public Health Service.

Berta finally received her first academic title (but still no salary) in 1950, twenty years after she received her doctoral degree. This acknowledgment came in a roundabout way; she was asked to organize an international meeting in Paris, and had nothing to offer when asked her academic rank. "I felt a little embarrassed for our school and went to the dean. He said he would grant me the listing in the bulletin as assistant professor (research)unsalaried. It seems unusual, but it was what happened at the time."

This was an especially happy and active time for the Scharrers. They loved horseback riding and skiing in Colorado's mountains. They bought a van and learned to drive so they could make expeditions together. As in their research, they divided the labor. "We had an arrangement. I drove up to the mountains, and he drove down."

This was also a productive time. Berta completed the groundbreaking work she had begun in Ohio demonstrating the physiology of the neurosecretory system in insects. Others began advancing the field of neurosecretion as well.

The Scharrer's friend Wolfgang Bargmann and his colleagues learned to stain secretory granules in mammals, enabling new views of the structure of the neurosecretory cell. These studies revealed the architecture of the hypothalamus and the hypophysis, their relationship with one another, and the path taken by secreted granules.

Suddenly, secretion by neurons gained wide acceptance, endorsing the foundation erected by the Scharrers. By the early 1950s the concept of chemical transmission of nerve impulse at the synapse was also widely accepted; neurosecretion became one of the central tenets of nervous system function and the founding principle of the new field of neuroendocrinology.

In 1953 Berta and Ernst visited the site of some of their earliest work, the Zoological Station in Naples. The occasion was the First International Symposium on Neurosecretion, a meeting that put the final stamp of approval on the once-controversial field founded by the Scharrers.

ON TO EINSTEIN

The Scharrers' peregrinations brought them to their final, most important academic destination in 1955. At the newly founded Albert Einstein College of Medicine of Yeshiva University, Berta Scharrer at last came into her own. Ernst had been offered the founding chairmanship of the Department of Anatomy by the dean of the school, Marcus Kogel. "Dean Kogel invited us for an interview. And, to my surprise, without anything being requested on my part, he offered me a full professorship. I finally caught up. By that time I had acquired . . . a certain reputation of my own. He said, 'I know about the nepotism rule, but we are an entirely new school. We can do something a little progressive.'"

And so the Scharrers set off across the United States on a train, bringing crates of noisy woodroaches to their new

home in the Bronx. Berta joined her husband's new department as a founding member of the faculty. "[Ernst and I] worked very well together. I worked for half my salary throughout the lifetime of my husband. It was a young school and it needed money, and we felt we were happy with our new appointments. . . . There was only enthusiasm and satisfaction that first year." Berta left aside her own research for several years to develop a course in histology, of which she was course leader. She also advised the medical school's first classes of students, who found her to be a thoughtful and approachable mentor.

The next decade passed with quiet accomplishment. The college, the anatomy department, and the field of neuroendocrinology all matured and flourished. The Scharrers built a small house an easy walk from Einstein and settled in. Together in 1960 they delivered a series of Jesup lectures at Columbia, summarizing the state of neurosecretion research and their comparative studies in vertebrates and invertebrates. These lectures served as the basis for their classic 1963 book *Neuroendocrinology,* which became one of the premier texts in the rapidly expanding field.

In April 1965 the Scharrers went to Miami for the annual anatomy meetings. When Berta returned a few days later, she was alone. During a short and fateful vacation after the meeting, she and Ernst had gone swimming in the Atlantic. A strong undertow swept away Berta's husband and scientific partner of thirty years, and nearly claimed her own life.

Once again Berta was forced to reinvent her career, this time as a solo researcher. "There was a very important turning point after my husband's death. I had to show that I could go it on my own." In fact, shortly before Ernst's death, she had already embarked on a rich new course of study, taking advantage of the new technology of electron microscopy. Berta would pursue microscopic investigation for fif-

teen years, focusing on secretory vesicles and the structure of neurosecretory cells. She was among the first to detail the fine structure of the insect nervous system.

Berta's work revealed the ultrastructure of the classic neurosecretory cell—these are often constructed much like any other nerve cell, with an extended axon, dendrites, and synapses. She showed that secretory vesicles are elaborated from the endoplasmic reticulum and Golgi bodies of neurosecretory cells, just as they are in other types of secretory cells. These membrane-bound granules are transported down the axon of the cell and released at the axon terminals.

Perhaps Berta's most important contribution in this area was the elucidation of the various targets of these secretory granules. Often the granules are released into blood vessels and reach their targets over a distance through the circulation, just as conventional hormones do. But Berta also showed that other pathways are possible, including secretory granule release from terminals in close contact with target cells, including other neurons, a concept similar to our understanding of chemical transmission at the synapse.

In addition to publishing more than a dozen papers on the fine structure of the insect nervous system, Berta took on new administrative responsibilities following Ernst's death. Although she did not want to be appointed permanent chair of the anatomy department in his place, she did agree to serve as acting chair. She guided the department for the next two years, until my appointment. And, for the first time, she received full salary for her work. She would serve again as acting chair in 1976, when she was influential in the recruitment of the department's present chair, Peter Satir.

She also lent her administrative talents to the world beyond Einstein, serving as president of the American Association of Anatomists in 1978-79, only the second woman to hold this position, and as associate editor of the journals

Cell and Tissue Research and *Advances in Neuroimmunology*. Her humanitarian impulses also informed her activities with the National Academy of Sciences committee on human rights.

Fate's twistings dictated that Berta Scharrer began to receive formal public recognition of her work in neurosecretion just years after her close partner in that work was lost. Ernst Scharrer was not present to share in the validation of the couple's work when Berta was elected to the National Academy of Sciences in 1967, one of only a handful of women members. That same year Berta was elected to the American Academy of Arts and Sciences; in 1972 she became a member of the venerable Deutsche Akademie der Naturforscher Leopoldina.

Berta held honorary degrees from eleven institutions, and received numerous awards, including the Kraepelin Gold Medal (1978), the Fred C. Koch Award of the Endocrine Society (1980), the Henry Gray Award of the American Association of Anatomists (1982), and the Schleiden Medal of the Leopoldina (1983). In 1983 she traveled to the White House to accept the nation's highest scientific honor, the National Medal of Science. And in 1994 she received the Order of Merit from her original home state of Bavaria. A final tribute saw a species of cockroach dubbed *scharrerae*.

LATER CAREER

As these awards and tributes began to flow in, Berta Scharrer scaled back her research to focus on an intellectual synthesis of a lifetime of observations. She became distinguished university professor emerita in 1978, but this standing by no means curtailed her work. During the period from 1975 to 1981 she penned nearly a dozen reviews of the field of neurosecretion and neuroendocrinology, emphasizing the fruits of comparative research in verte-

brates and invertebrates. This comparison led her to new theories of the evolution of the nervous and endocrine systems.

As the Scharrers' work made clear, neurosecretory cells are conserved across a wide range of vertebrate and invertebrate animals, as are their varied modes of granule transport and release. In addition, the nature of the neuropeptides that comprise those granules are similar across phylogenetic lines. And while neurosecretory cells are often quite similar structurally to conventional neurons, so they are often similar functionally to glandular secretory cells. Finally, the neuropeptides released by neurosecretory cells are often quite similar to conventional hormones.

These observations led Berta to formulate a comprehensive theory of the evolutionary origins of neurosecretory cells. She proposed that secretory neurons were not a late product of evolution, but were in fact the initial means of intracellular communication of primitive organisms, from which the highly specialized endocrine and synaptic nervous systems evolved. These novel theories are expounded in several of her publications from the late 1970s, showing that even in her seventh decade, Berta Scharrer could still stir up the scientific status quo. And she was not yet finished doing so.

In the early 1980s, at an age when most people would happily retire, Berta leapt back into research. In these "early" years of her new career she studied the nature, action, and evolutionary conservation of neuropeptides, in collaboration with George Stefano and Georg and Bente Hansen. In the late 1980s her attention turned to an entirely new field, that of comparative neuroimmunology. Berta and her colleagues showed that invertebrate neurosecretory cells and neuropeptides participate in regulation of the immune system and vice versa; these interactions bear striking similarities to the behavior of analogous vertebrate systems. Berta

Scharrer continued this work until her death on July 23, 1995. She was eighty-eight years old.

Berta's legacy of influence continues through the numerous scientists she taught and mentored, through her publications and lectures at international symposia, and her worldwide network of friends and colleagues. Her work, and that of Ernst, launched exciting new intellectual enterprises in the face of vigorous opposition. "One couldn't have foreseen the spectacular developments. . . . It has been shown that the early observations were not artifacts or a figment of the imagination. However, we had made bold claims and it is understandable that it took about twenty years of work for most people to accept these concepts." Only a scientist of Berta Scharrer's insight, tenacity, and sheer joy in learning was capable of carrying these ideas through to fruition—ideas from which we benefit today whenever we consider the transformed discipline of neuroscience.

DURING THE PREPARATION of this memoir, I made use of an interview with Berta Scharrer conducted in the preparation of the article "On Journeys Well Traveled."[1] I also found much useful information in a biography of Berta Scharrer by Birgit and Peter Satir in *Women in the Biological Sciences: A Biobibliographic Sourcebook* (eds. L. S. Grinstein, C. A. Bierman, and R. K. Rose. Greenwood Publishing Group, 1997) and in a speech given in 1982 by Sanford Palay in presentation of the Henry Gray Award to Berta Scharrer at the ninety-fifth meeting of the American Association of Anatomists.

NOTE

1. All unattributed quotes are from an interview with Berta Scharrer that appeared in the article "On Journeys Well Traveled" in *Einstein*, ed. S. K. Millen, Spring/Summer 1989, pp. 3-6, Bronx, N.Y.: Albert Einstein College of Medicine.

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