Viktor Hamburger

1900–2001

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Garland E. Allen

NATIONAL ACADEMY OF SCIENCES

VIKTOR **HAMBURGER**

July 09, 1900–June 12, 2001

Elected to the NAS, 1953

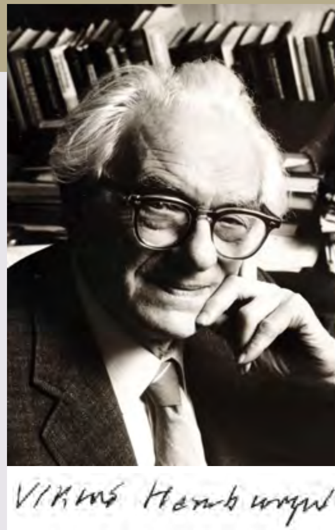

Photo courtesy of Washington University Department of Public Affairs.

By Garland E. Allen

Viktor Hamburger was one of the most influential neuro-embryologists of the twentieth century. A student of Hans Spemann at the University of Freiburg in the early 1920s, Hamburger was among the first to transfer the transplantation techniques worked out on amphibians in Spemann's lab, to the chick embryo as a model organism for studying vertebrate development. In the early part of his career, between 1925 and 1955, Hamburger studied the problem of how the vertebrate limb is innervated during embryonic development. This work, which he carried out from the late 1940s onward in partial collaboration with Rita Levi-Montalcini, led to discovery of nerve growth factor (NGF), a protein that maintains nerve cells as they grow from the central nervous system to a peripheral target, such as a limb bud. The work also led to appreciation of naturally occurring cell death as an important phenomenon in nervous system development (Oppenheim 2001). For isolating and characterizing NGF, Levi-Montalcini and the biochemist Stanley Cohen received the 1986 Nobel Prize in Medicine or Physiology, but their work was based upon work by Hamburger and carried out in his laboratory at Washington University in St. Louis.[1]

In the second half of Hamburger's career, between 1955 and 1985, he worked on the origin of endogenous behavior patterns in the chick embryo and its relationship to neuronal differentiation, as well as questions about the rates of cell proliferation and cell death during innervation from the lumbar spinal cord into excised or supernumerary limb bud tissue. Hamburger maintained a continuing interest in the history of his field over the course of fifty years, authoring a number of valuable historical studies, including one book, *The Heritage of Experimental Embryology* (1988), which is a detailed analysis of the work of the Spemann laboratory and its various students.

Hamburger attended the universities of Breslau, Heidelberg, Munich, and Freiburg, obtaining his PhD at the latter in 1925 under the direction of Hans Spemann. He served as a research associate at the University of Göttingen with Alfred Kühn from 1925 until 1926 and at the Kaiser-Wilhelm Institute for Biology in Berlin-Dahlem under Otto Mangold from 1926 until 1927. In 1927 he accepted a call by Spemann to return to Freiburg as privatdozent, a position he held for five years.

In 1932 he was awarded a Rockefeller Fellowship to work in the laboratory of Frank R. Lillie at the University of Chicago. While in Chicago, the National Socialist government came to power in Germany and Hamburger was informed by the provost, philosopher Martin Heidigger, that because of Jewish heritage he was dismissed from his post. With emergency funds from the Rockefeller Foundation, Hamburger remained in Chicago two more years, finally accepting a post as assistant professor of zoology at Washington University in St. Louis, where he remained for the rest of his life. He retired officially in 1966, but pursued his laboratory work for another twenty years and continued publishing reviews and historical papers until his ninety-ninth year. He died a few weeks short of his 101st birthday.

In his scientific and personal life, Hamburger was known for his quiet, almost self-effacing manner, his incisive views and dry wit. He worked intensively and with great concentration, always a hands-on experimentalist, with only minimum tolerance for the bureaucracy necessary to fund his research or administer the Zoology Department, of which he was chairman for twenty-five years (from 1941 until 1966). His lifestyle was relatively simple. Most of his travels were in conjunction with professional meetings, though he often made vacation sojourns near meeting locations and he took two extended photo safaris to Africa in the late 1960s. He bragged that he never used a typewriter or a computer, never played a sport (he liked to ski but did not consider that a "sport"), and though he loved sojourns into the mountains of both Europe and the American west, he claimed that he never camped or backpacked. One of his last such hiking trips was for a birthday outing to the Sierras in the mid-1970s with his daughters. Later hip replacements made such trips difficult.

In 1928, Hamburger married Martha Fricke, a young biologist whom he had met in Göttingen. They had two daughters, Doris (Sloan) and Carola (Marte), each with significant careers of their own: Doris as a geologist and Carola first as a classicist, and later as a medical doctor. Other than his family, science was Hamburger's first love.[2]

Hamburger was a member of many learned societies and institutions, including the American Society of Zoologists (of which he was president in 1955), the American Association for the Advancement of Science (of which he was vice-president and chairman of

Section F in 1960), the American Society of Naturalists, the Society for Developmental Biology (where he served as president from 1950 until 1951), the International Society for Cell Biology, and the International Society for Developmental Biology. He was elected to the National Academy of Sciences in 1953 and the American Academy of Arts and Sciences in 1959. He was an honorary member of Sigma Xi and Phi Beta Kappa.

In addition, Hamburger was awarded a number of prizes in recognition of his work in neuroembryology: the F. O. Schmitt Medal in Neuroscience (1976), The Ross G. Harrison Prize in Developmental Biology (1981), the Louisa Gross Horwitz Prize in Cell Biology and Developmental Neurobiology (1981), the Ralph Gerard Prize and Medal of the Society for Neuroscience (1985), the Fidia-Georgetown Award in Neuroscience (1987), the National Medal of Science (1989), the Karl Spencer Lashley Award of the American Philosophical Society (1990), and the first Lifetime Achievement Award from the Society of Developmental Biology (1999). He received honorary degrees from Washington University in 1976, from the University of Uppsala, Sweden, in 1984, and from the Rockefeller University in 1996.[3]

Family and cultural background

The career of Viktor Hamburger grew out of a confluence of social, intellectual, and personal factors that left their mark on both his research style and the way in which he conceptualized biological problems.[4] Born in 1900 in Landeshut, Silesia, a small town of approximately 12,000 located not far from the Bohemian border and just northeast of Prague (in what is now Poland), Hamburger grew up and matured intellectually in the shadow of World War I and its chaotic effects on German economic, social, and intellectual life. Just as his career was getting established in Germany, the National Socialists deprived him of his university position, so he found himself, like so many others, a refugee, forced to seek life and employment in another country. That he soon found a compatible home in the United States and was able to continue his research almost without interruption speaks to his intensity of purpose and personal adaptability.

It is impossible to understand Viktor Hamburger as a person and scientist, or to understand his importance to the field of developmental neurobiology, without knowing something of the context in which he was raised and the educational and cultural environment in which he matured. Hamburger's parents, Max and Else Hamburger, had moved from Breslau (now Wroclaw, Poland) to Landeshut when his father took over the family textile factory in the late nineteenth century. They were well off by middle-class standards of the time, but they were not wealthy. Max and Else Hamburger were liberal-minded and considered progressive for their day. In the late 1890s Else had a major hand in designing one of the first series of individual housing complexes, including a day care center, for workers in the family's textile plant. (This was not the same as the "company towns" associated with the U.S. industry in the same period.)

Both parents were well educated. Max was an avid art collector who knew a number of artists with both local and national reputations. In a letter to Hamburger later in his life, Max indicated that business was not his first love but was the means to an end, namely his cultural interests. Hamburger often said that while his mother introduced him to a love of nature, his father introduced him to a love of art (Hamburger, "My Parents:"1). Later in life, Hamburger became a modest collector of art himself, and one of his most favorite outings was always to visit the St. Louis Art Museum; the other was to go on field trips with his colleagues from the Zoology or Botany Departments at Washington University.

Seeing, and learning how to see, was something to which Hamburger returned again and again, both in his science and in leisure.

Hamburger's background played an important role in the course of his career and in his thinking about embryos and their processes of growth and differentiation. One major influence was his early love of nature and landscape ecology. For many in nineteenth and early twentieth-century central Europe, and especially those with German heritage, the landscape—the physiography, natural history, and geology of their homeland (the "Heimat," as Hamburger fondly called it)—and a close personal attachment to the land became an important inspiration and motivation for pursuit of a career in the life sciences.

The second influence was his appreciation of visual art (Hamburger 1992). Seeing, and learning how to see, was something to which Hamburger returned again and again, both in his science and in leisure. Seeing in an active, not a passive way, was an integral part of the way he experienced the world, whether through a great painting, the vistas from the Riesengebirge mountains, or the slowly developing embryo under a microscope. He frequently admitted he did not know how biologists pursued their science without a visual sense. One of his last papers, which was about the embryologist Wilhelm Roux (1850–1924), the founder of Entwicklungsmechanik, was titled "Visionary with a Blind Spot" (Hamburger 1997). The "blind spot" for Hamburger was that in 600+ pages of his collected writings, Roux included only six illustrations. He was astonished that anyone could write hundreds of pages about living organisms without any visual images of the structures or processes being discussed. Hamburger's own papers were always well illustrated, though the figures were germane to the topic at hand.

A hallmark of Hamburger's approach to biological problems was the incorporation of classical German philosophy, from the dualistic tension in the works of Kant and Hegel to the more holistic, albeit sometimes mystifying, writings of contemporaries such as Martin Heidegger (1889–1976) or embryologists Hans Driesch (1866–1945) and Ludwig von Bertalanffy (1901–1972). Like his mentor, Spemann, Hamburger saw the embryo as a whole, not merely a mosaic of separate organs, tissues, or traits. He was not opposed to reductionism as a strategy, but he recognized it only as a starting point in identifying the components of a biological process. He once said that he had made a "pact" with the embryo, that if it would yield to him some of its secrets he would never homogenize it in a Waring blender, and he remarked toward the end of his life, "I think we have both kept our promises" (Allen 2004).

"…I observed all this in the…jelly masses which I brought home and reared in aquaria. I remember that one day young salamanders had metamorphosed and escaped from the aquarium, and in the evening, when my parents had a party, crawled up the window curtains…"

A major stimulus for Hamburger's interest in nature, and biology in particular, grew out of his early life in the rural, largely agricultural region of Lower Silesia, with its rich animal and plant life, its unique geological and fossil deposits, and the flora and rare glacial relics of the nearby Riesengebirge mountains. The area provided ample natural haunts for Hamburger and his two brothers, Otto and Rudi, to explore. In his autobiographical notes, Hamburger wrote some years later about his early interest in exploring nature and collecting local organisms:

> *I remember that when I was 15 or 16 years old I explored the fauna of our native ponds in the environment of my hometown Landeshut…Freshwater clams and sponges were the rarities, but I was intrigued by the developing frog and salamander embryos and the hatching of larvae.*
> *I observed all this in the…jelly masses which I brought home and reared in aquaria. I remember that one day young salamanders had metamor-*

phosed and escaped from the aquarium, and in the evening, when my parents had a party, crawled up the window curtains—I don't remember whether my mother and the guests were bewildered or amused. At any rate, my interest in developing animals was alive early" (Hamburger Papers, n.d., 1).

So influential was the Landeshut region on his development that later, while he was working at the Kaiser-Wilhelm Institute for Biology in Berlin (in the suburb of Dahlem), he collaborated with his hometown friend, Walter Arndt (then a curator at the University of Berlin's Zoological Museum), on a heimatbuch (literally, homeland book) celebrating the uniqueness of the region. Published in 1929, it was a two-volume compendium describing the geology, history, economy, culture, and natural history of Landeshut. Hamburger wrote the introduction and section on geology, while other topics were covered by a variety of area residents, including Viktor's father, Max Hamburger. The whole publication was edited by a local teacher (Kunick 1929).

Education and early career, 1900–1932

After graduating from gymnasium in June of 1918, Hamburger was inducted into the German army and sent to basic training in Breslau. When the armistice was signed in early November, he was discharged but remained in Breslau, where he took several courses at the university— zoology, botany, geology, and mathematics—while trying to decide exactly what to do with his life. The turbulent social and economic conditions in Germany immediately after the war did not make such decisions easy.

He felt sure he wanted an academic career, so his parents suggested he should get some experience beyond the confines of Silesia. As it happened, his father's first cousin, Clara Hamburger, was an assistant to the distinguished protozoologist Otto Bütschli at the University of Heidelberg. So for the academic year of 1919–1920, Hamburger enrolled at Heidelberg as a full-time student. In addition to a philosophy seminar taught by Hans Driesch (the former embryologist and later a proponent of a new philosophical version of vitalism), the other course that made a considerable impression on Hamburger was a graduate seminar on developmental biology taught by Driesch's colleague and friend, Curt Herbst. Among the various works Hamburger read in Herbst's seminar, the writings of Wilhelm Roux, while "opaque and long-winded" (Hamburger's terms), stirred his imagination the most. Reporting on the seminar years later, Hamburger recalled:

Through this exposure, and discussions with Herbst and [his student] Walter Landauer (who worked on the role of the nucleus in species

> *hybrids of sea urchins)…my interests became pretty sharply focused on experimental embryology and developmental genetics."[5]*

However, the sort of experimental embryology that Herbst himself pursued—physiological studies of the effects of calcium, lithium, and other ions on patterns of development—did not seem to Hamburger to be very interesting. They were too chemical and reductionist. Hamburger never felt comfortable with chemistry, a viewpoint that was later reinforced by his mentor Hans Spemann who, he reported "discouraged me from studying chemistry" (Provine 2001). Hamburger looked for other possibilities.

In the spring of 1920 he and a friend visited the Black Forest area near Freiburg on a short holiday. The terrain reminded him of Landeshut, and he loved the medieval character of the city. More important, the hills and mountains nearby, especially the Feldberg, were distinctly more favorable to skiing than the "lowly Odenwald" around Heidelberg. When he reported his favorable impressions to Aunt Clara, she told him that a distinguished zoologist, Hans Spemann, had recently been hired to head the Zoological Institute there. So, it was decided: he would enroll at Freiburg. When he arrived later in the spring, Spemann accepted him as a graduate student at the institute, which was originally constructed in 1888 by August Weismann, Spemann's predecessor.

The atmosphere at Freiburg was open and relaxed. Students determined their own course of study, which was highly varied and almost wholly self-directed. As Hamburger described it:

> *We attended lecture and laboratory courses in our minor fields (mine were botany and geology) and philosophy, but most of our time was spent in the Grosse Praktikum, an all-day laboratory course, in which we each studied, at our own tempo, representatives of all phyla, from protozoa to mammals, using preserved specimens and microscope slides…There were no examinations in either lecture or laboratory courses. We were responsible for our own progress in scientific proficiency.*

It was in Spemann's institute that Hamburger met two other students who were to become among his closest friends: Johannes Holtfreter and Hilde Proescholdt, later Mangold, who was just then starting her ground-breaking work on transplantation of tissue from the dorsal "lip" of the blastopore (the area of invagination, or pushing inward of cells in the gastrula stage of embryonic development) that eventually led to the concept of the "Organizer" and Spemann's Nobel Prize in 1935.

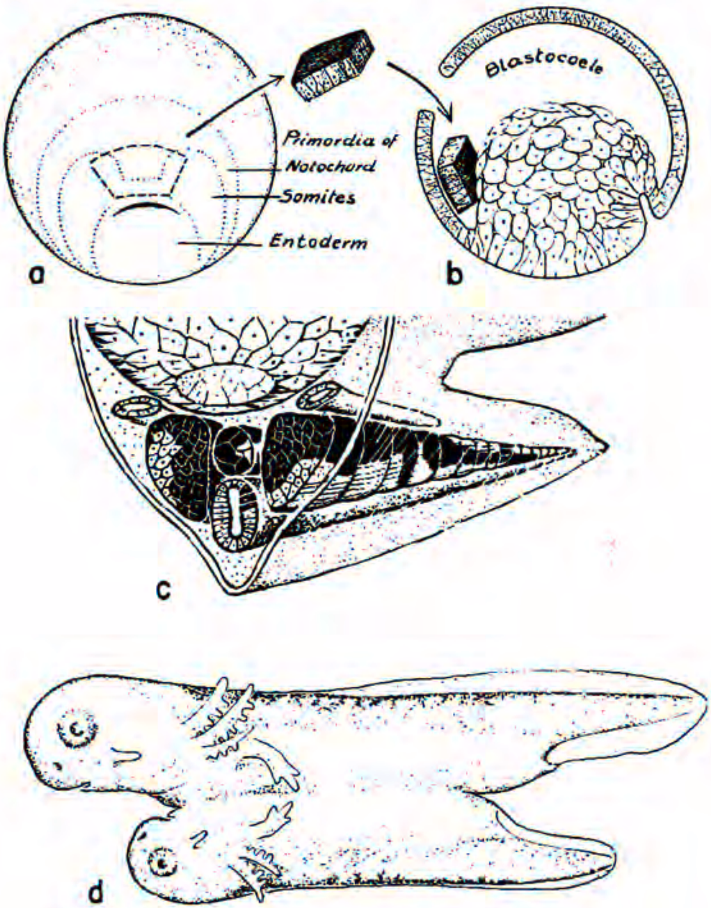

Figure 1. Hilde Mangold's experiment transplanting a section of the dorsal lip of the blastopore (a) from a gastrula into a late blastocoel, a slightly earlier stage, just before formation of the blastopore (b), which, after further development, forms a whole secondary embryo that includes both the host's and transplant's cells, shown in white and black, respectively. (From Holtfreter and Hamburger, "Amphibians," in Willier, Weiss, and Hamburger, eds, *Analysis of Development*, W.B. Saunders 1955, 244.)

The laboratory was an exciting and stimulating place. Discussions occurred daily among the students about their own work and every other conceivable subject. For example, Hamburger and Hilde shared interests in the philosophy of art, phenomenology, and aesthetics, and in the natural history of the Black Forest. As he wrote of her: "She was an unusually gifted, vivacious, and charming young woman. Her considerable scientific talents would undoubtedly have borne fruit, had her life not been cut short …" (Hamburger 1996).[6] One day in May 1923, Hamburger remembered vividly, Hilde

Figure 2. Satirical portrayal of the Spemann Lab by Johannes Holtfreter, 1925, suggesting the liveliness of the atmosphere at Freiburg. Spemann is driving the coach with the students as the horses, including Hilde Proscheldt (facing viewer), Holtfreter and Hamburger (wearing glasses), while the dog (at center) nipping at the heels of the students is Otto Mangold, Spemann's primary assistant (Reproduced with permission from the *International Journal of Developmental Biology* 1996, 40: 59-62.)

came in very excited with her first induced embryo, where dorsal lip tissue removed from a developing gastrula and implanted into the belly of an older, neurula-stage embryo had induced the formation of a secondary embryo (Figure 1) (Hamburger 1984). So, it was a lively and compatible group, which Holtfreter captured in one of his typical, satirical cartoons (Figure 2).

For his PhD thesis, Spemann assigned Hamburger a problem different from the recently discovered inductive powers of the dorsal lip: the role of the nervous system in the development of peripheral organs such as the limbs, using the frog, *Rana fusca*. Earlier work had suggested that ablation of developing eye tissue resulted in defective limb development. Repeating the earlier experiments, Hamburger found no clear relationship between eye and leg development. However, his experiments did suggest a novel finding: contrary to the then-current view, innervation was not necessary for normal limb bud development, although, of course, it would be necessary for later functioning of the limbs. He would establish this principle unambiguously later, while working at the Kaiser-Wilhelm Institute for Biology in Berlin-Dahlem. It was work on limb-bud innervation that constituted Hamburger's PhD dissertation, completed in the spring of 1925. In one context or another, he was to work on vertebrate limb and nervous system development for the rest of his scientific career.

After Freiburg, Hamburger spent several months working at the Stazione Zoologica in Naples (Naples Zoological Station) before taking up a post-doctoral position in Göttingen with Alfred Kühn, whom Hamburger described as a polymath and the "universal genius among German zoologists" (Hamburger 1988). Kühn turned over to Hamburger one of his many ongoing projects, studying color vision in fish. The project never got very far, but the stay in Göttingen did help Hamburger establish a number of contacts among leading German biologists who passed through Kühn's laboratory. Also, it was in Göttingen that Hamburger met his future wife, Marta Fricke.

Moving from Göttingen to the Mangold Laboratory at the Kaiser-Wilhelm Institute for Biology in 1926, Hamburger found himself in the center of new and exciting work, especially in the area of developmental genetics. The embryology department was on the first floor of the institute building, while Richard Goldschmidt's genetics department was on the floor above. Hamburger noted that his interest in genetics had begun in the winter semester of 1918 at Heidelberg University during a seminar with embryologist Curt Herbst, (Hamburger, "Contributions to developmental genetics," 1). So, while in Dahlem, Hamburger regularly attended the afternoon teas with the genetics group, where he became close friends with Curt Stern, who later became one of the twentieth century's leading geneticists.

Goldschmidt fostered a strong interest within his group in the relationship between genetics and development, a connection that had been largely ignored in Spemann's laboratory. Although an attempt in collaboration with Stern to carry out some breeding experiments with *Drosophila* did not yield any major results (he did localize a new mutant on one of the chromosomes), the relationship between genetics and embryology that this work inspired became a guiding principle for Hamburger's later studies on interspecific crosses among species of salamanders. Also, after arriving in the United States, it inspired his research on the developmental genetics of a mutation in chickens known as "creeper" for which the organisms have developmental defects in the limbs that produce creeping-like motion when they try to walk (Hamburger 1941, Hamburger 1942).

When Spemann recalled Hamburger to Freiburg in 1927 to become a privatdozent, his main teaching assignment was the "Grosse Prakticum." Hamburger succeeded in establishing an atmosphere of excitement among the students with his constant questioning and discussion of major developments in the field, especially experimental embryology and genetics. Hamburger's position and eventual ascendancy through the ranks at Freiburg seemed assured. It was at this time that he also took on his first graduate student, Salome Glücksohn (later Glücksohn-Waelsch, after her second marriage). In connection with experiments on developmental genetics that he was initiating during this period, Hamburger assigned her the task of preparing a detailed description of the stages of limb growth in the two main species of salamanders used in the Spemann lab: *Triton taeniatus* and *Triton cristatus*. He admitted it was not a very exciting topic, but it provided an extremely useful base comparison for growth rates in experimental hybrids between the species. Their relationship survived the thesis topic and remained especially strong after both came to reside in the United States.

In his developmental genetics experiments with salamanders, Hamburger made reciprocal crosses (*T. taeniatus* eggs with *T. cristatus* sperm, and *T. cristatus* eggs with *T. taeniatus* sperm). The former crosses all produced highly viable offspring, but the latter showed considerable developmental abnormalities, and only eight offspring ever survived to metamorphosis. Because the two species had several noticeable differences in phenotypic traits (limb structures and tadpole tail pigmentation in particular), Hamburger could measure developmental rates and determine, in the reciprocal crosses, when the maternal or paternal genomes came into play. In both types of crosses, the maternal genome determined almost all aspects of development up to the point where the young tadpole emerges from the egg. The changing developmental patterns in pigmentation also followed this course in both crosses. However, a difference showed up in the timing: in the hybrids, the *taeniatus* genes express themselves earlier than in the intraspecific t*aeniatus* x *taeniatus* crosses.

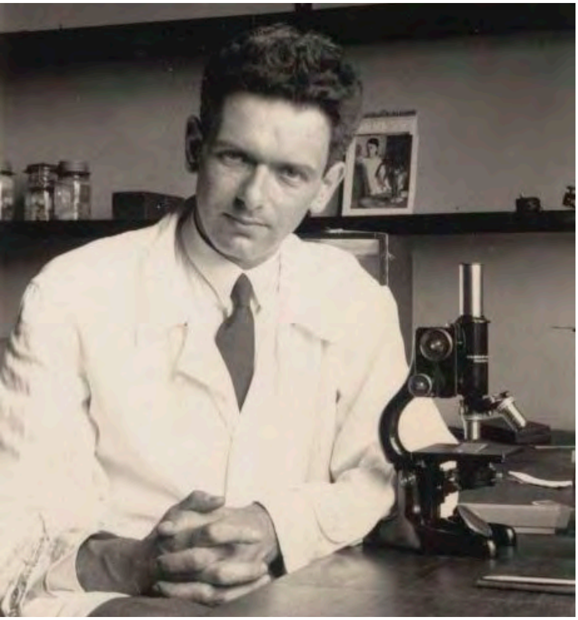

Figure 3. Viktor Hamburger after his arrival in the United States, in his laboratory at the Marine Biological Laboratory in Woods Hole, 1935. (From http://embryo.asu.edu/view/embryo:125918. Licensed under the Creative Commons Attribution-Share Alike 3.0 License.)

What these experiments showed was that the genomes of the two species affect development in specific ways, and that the compatibility of the genome and egg cytoplasm was very different in the reciprocal crosses. The system was cumbersome, however, and so little was known about the actual genetics of the two species that after publishing the results in one paper (Hamburger 1936), Hamburger abandoned the project.

In 1932, the Rockefeller Foundation invited Spemann to nominate a candidate for a one-year post-doctoral fellowship to the United States in the laboratory of F. R. Lillie at the University of Chicago. Spemann wanted to nominate Otto Mangold, but he was over the thirty-five year age limit stipulated by the foundation, so Spemann nominated Hamburger instead. Hamburger's main goal for this post-doctoral year was to adapt the methods and techniques of experimental transplantation developed for amphibians in the Freiburg lab to studies on chick embryos in Chicago. Leaving his family (including a three-year-old daughter) in Germany, Hamburger came to the Lillie lab in the fall of 1932 (Figure 3).

The initial problem on which Hamburger focused grew out of conflicting results obtained in 1909 by one of Lillie's former students, Elizabeth Shorey, who used the chick embryo, and a decade later (1919), those of one of Ross Harrison's graduate students, Sam Detwiler at Yale. The question related to the effects of damaging or removing developing chick limb buds on the further development of sensory and motor nerve tracts in the spinal cord. Using electrocautery, Shorey had destroyed developing limb buds and noticed hypoplasia (diminished development) of both the motor and sensory nerve columns that would have innervated that limb. By contrast, Detwiler found that extirpation of limb bud tissue caused hypoplasia only in sensory nerve columns, and that transplantation of limb buds to other areas of the embryo resulted in hyperplasia, primarily of sensory nerve ganglia. Lillie suggested that Hamburger re-investigate the problem, using the Spemann techniques of microsurgery on the chick to resolve the discrepancy.

Hamburger learned microsurgical methods for chick embryos from others in the lab, applying the glass needle and hair-loop techniques developed in Freiburg for limb bud extirpation to determine the effects on development of the adjacent nervous system. The results were clear: Shorey's observation that both sensory and motor neurons responded to extirpation with hypoplasia was confirmed. In addition to the results, Hamburger was immediately impressed with the use of the chick as a model for investigating vertebrate development. In contrast with amphibians, where motor neurons are not organized into the easily observed motor columns, in the chick embryo the motor columns are clearly visible and thus provide favorable material for analyzing changes in size and cell numbers. From this point onward the chick became Hamburger's primary model organism.

In February 1933, the middle of Hamburger's year in Chicago, the National Socialist government came to power in Germany and within months had promulgated the "Law for the Restoration of the Professional Civil Service," removing all civil servants (which included university employees) of Jewish descent from their jobs. Ironically, Hamburger's dismissal letter came from his former philosophy professor, Martin Heidegger, who by that time had joined the Nazi Party and had been promoted to rector of the university. Spemann wrote a sad letter to Hamburger indicating he was powerless to alter the decision. But, as Hamburger noted later, Spemann's letter "made no mention of Hitler's rise to power…he expressed his own personal regrets vividly and offered to help in finding a new job, but not a word of criticism of laws, nothing about his feelings about the momentous upheaval and the new Nazi regime" (Allen 2004).

With an emergency extension of the Rockefeller grant, Hamburger was able to remain in Chicago for another two years while he continued his research (after he had returned briefly to Germany to bring his family to the United States). After some searching for jobs both inside and outside the United States, a position opened up in 1935 at Washington University in St. Louis and he jumped at the opportunity. He had also considered a position at Swarthmore College in Pennsylvania, but it was a small, liberal arts college with a heavy teaching load, whereas Washington University was a research-based liberal arts college within a university that included a strong medical school, where he felt he

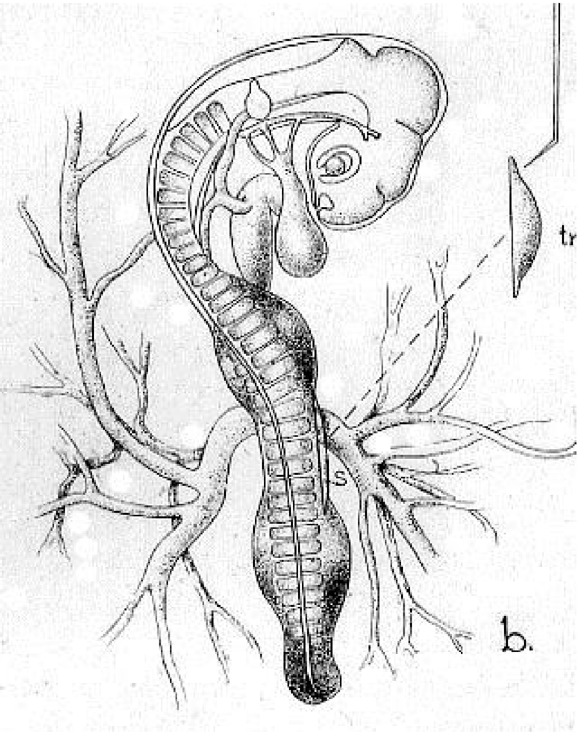

Figure 4. Hamburger's drawing showing the surgical technique for transplantation of a supernumerary limb bud (tr) removed from a three-day-old chick and inserted into a slit (s) in the flank of another embryo of the same age. Where the transplant limb bud is inserted, neuronal hyperplasia is observed. (From Hamburger's 1942 *Manual of Experimental Embryology*. Chicago: University of Chicago Press, 151.)

could pursue research more systematically. At Washington he advanced from assistant professor (1935–1939) to associate professor (1939–1941) and full professor (1941–1966). Then, after retirement from the teaching faculty in 1966, he was appointed Edward Malinckrodt Distinguished University Professor in 1968, taking emeritus status in 1969. He also served as department chairman for twenty-five years (1941–1966).

The vast majority of Hamburger's research work from the time of his arrival at Washington University through the 1980s focused on four major areas of chick development: 1) The effects of limb bud extirpation or transplantation on the development and outgrowth of motor columns in nearby regions of the spinal cord; 2) Developmental genetics of the creeper fowl; 3) The development of chick behavior, especially before hatching; and 4) Detailed cell counts for hypo- and hyperplasia in the lumbar motor columns of chick embryos in which limb buds were, respectively, extirpated or grafted onto the embryo, focusing on the role of neuronal cell death in these phenomena.

One of the outcomes of Hamburger's early extirpation work in Chicago was the accidental discovery (based upon his inadvertent removal of different amounts of limb bud tissue in different experiments) that there appeared to be a quantitative relationship between the amount of limb bud tissue removed and the degree of hypoplasia later observed in the lateral motor columns and related sensory neurons. He also noted that when he transplanted limb bud tissue to other regions of the embryo (the flank or belly), hyperplasia of the motor neurons was enhanced in those regions as well (Figure 4).

In a crucial 1934 paper, Hamburger interpreted this work, in the framework of Spemann's theory of induction, as what he called his "three-point paradigm": 1) The developing peripheral tissue (limb bud in this case) stimulates, by way of two inducer substances, the growth of motor and sensory axons toward the developing tissue; 2) The inducer substance is transported by retrograde movement from the growing neuron tip back to the cell body to stimulate further growth; and 3) The effect is quantitative: the greater the quantity of inducing tissue, the greater the rate of neuronal growth, and vice-versa, with removal of limb bud tissue. This work, and specifically the 1934 paper, laid the foundation for the studies on nerve growth factor and neuronal cell death that was to emerge in his collaboration with Levi-Montalcini beginning in 1947. Meanwhile, throughout the 1930s and during the war years, Hamburger carried out numerous limb-bud extirpation experiments, increasing the precision of his extirpation procedures and making numerous counts of cell numbers in the spinal cord as a way of quantifying the extent of neuronal hypoplasia. It was also at this time that he initiated another set of developmental genetic studies, this time on the creeper mutant in chickens.

Hamburger's work with the creeper mutation in chickens provided one model for how the problem of developmental genetics might be approached. The creeper mutant was of interest because in the heterozygous state, legs are greatly foreshortened due to retardation of growth during embryogenesis, while in the homozygous state the eye buds also develop a peculiar abnormality known as coloboma before the embryos die around the seventy-two-hour stage. (In the homozygous state the creeper mutation is lethal.) Since a single gene appeared to affect these two very different traits, Hamburger realized the creeper system and the transplantation techniques he had worked out in Chicago could be used to distinguish the ways in which genes might affect developmental pathways. When he transplanted limb- and eye-bud tissue from the heterozygous creeper strain to the flank of an embryo of a normal strain, the transplant developed the mutant phenotype, as expected (Hamburger 1942a). But, when he transplanted an eye primordium from a homozygous mutant to the eye region of a normal embryo, a perfectly normal eye developed. This meant that the genes in the eye primordium of a homozygous mutant were completely capable of normal development.

Hamburger's analysis suggested that the effect of the creeper mutation on limb and eye development must be quite different. The effect on limb growth appeared to be direct;

that is, the gene must control some process such as mitotic rate of cells that make up the limb tissue, thus retarding growth. On the other hand, the effect of the creeper mutation on eye development must be indirect, altering some secondary process external to the eye rather than the developmental potential of cells within the eye itself. The outcome of this work suggested that experimental embryology could contribute in at least a small way to an understanding of the ways in which genes function in development. For the future, he felt "the complete story of the mode of gene action must be written jointly by geneticists, embryologists and physiologists" (Hamburger 1942a).

But complex, multicellular organisms are difficult to manipulate for developmental genetics research, as others, such as Boris Ephrussi and George Beadle working with *Drosophila* in the 1930s and 1940s, had also discovered. Recognizing the limitations of the creeper fowl work at the time, Hamburger returned to neuroembryology.

The discovery of nerve growth factor

Figure 5. Viktor Hamburger and Rita Levi-Montalcini examining the Fidia-Georgetown Award, 1987. (From Hamburger Photo Collection, Biology Department, Washington University in St. Louis. Used with Permission)

Hamburger sent a copy of his 1934 paper on limb-bud extirpation to an eminent neuroanatomist, Giuseppe Levi, at the University of Turin Medical Faculty. Luckily, instead of simply reading it and filing it away, Levi passed it on to one of his young post-doctoral fellows, Rita Levi-Montalcini. Like Hamburger, her Jewish descent meant she lost her position in Turin after Mussolini and the Fascists came to power in 1940. By her own account, she got around to reading Hamburger's paper while sitting on the platform of a cattle car transporting her to a farm outside of Turin. Intrigued with Hamburger's results, Levi-Montalcini repeated the extirpation experiments during the war years in her small bedroom laboratory. Her observations differed from Hamburger's in two important details: 1) She focused on the sensory neurons rather than the motor

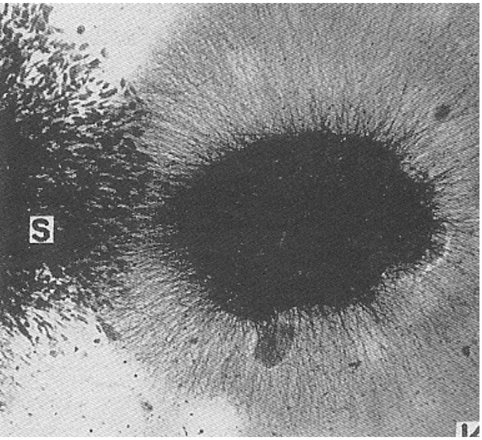

Figure 6. Mouse sarcoma 180 (labeled S, to left) causes extensive proliferation of sympathetic nerve ganglion after 24-hours exposure in a 13-day chick embryo. (Reprinted by permission from the American Association for Cancer Research: Levi-Montalcicni, Meyer and Hamburger, 1954, In vitro experiments on the effects of mouse sarcomas 180 and 37 on the spinal and sympathetic ganglia of the chick embryo. *Cancer Res.* 14:49–57. Fig. 8.)

columns; and 2) She began observing the developing neurons within the two or three days after extirpation of the limb bud, rather than waiting nine days or more as Hamburger had done.

Publishing her results after the war, Levi-Montalcini came up with a different interpretation from Hamburger's. She had noted that after an initial period of proliferation and growth in the non-extirpated side of the chick spinal cord, a certain percentage of the developing sensory neurons began to degenerate through a process known as neuronal death. This was apparently normal, though somehow Hamburger had missed it. The observation of neuronal death lead Levi-Montalcini to postulate that the limb bud does not have an inductive capacity—that is, the neurons do not need an agent from the developing limb bud to begin their development. What the limb bud does provide is a "maintenance factor" that prevents massive neuronal death. Hamburger had missed the normal tendency of early neuronal death because he started his observations later.

When Hamburger read Levi-Montalcini's papers after the war, he was impressed with her work and immediately invited her to St. Louis to work in his lab and try to resolve the discrepancies. With funds provided by the Rockefeller Foundation, Levi-Montalcini came to St. Louis in 1947 for what was intended to be a one-year period. As the work proceeded with exciting results, Hamburger arranged for an extension of the Rockefeller funds and eventually procured for Levi-Montalcini a faculty position at Washington University that she held for the next thirty years (Figure 5).

Repeating Hamburger's experiments in St. Louis, Levi-Montalcini confirmed in both of their minds that the limb bud must produce a maintenance factor rather than an inducing factor. The obvious next step was to isolate and identify the chemical agent responsible, but that would be difficult, perhaps impossible, because chick limb bud tissue exists in only very small quantities. Fortunately, in 1948 Hamburger received a paper from a former student, Elmer Bueker (then at Georgetown University Medical School), detailing an experiment in which he had transplanted a mouse sarcoma into a developing chick egg. Shortly afterward, he noted that the tumor had been thickly invaded by sensory neurons, suggesting that the tumor produced some sort of neuron-stimulating factor (Figure 6). With Bueker's permission, Hamburger and Levi-Montalcini repeated the experiment and observed a clear quantitative relationship between size of sarcoma implant and amount of neuronal growth. Levi-Montalcini also established that the sarcoma stimulated vigorous outgrowth of axons from a sympathetic ganglion when the two tissues were co-cultivated (Figure 6). This observation became the basis for a bioassay that was used thereafter to quantify the NGF activity of various tissues and/or tissue extracts in vitro.

Since neither Hamburger nor Levi-Montalcini were biochemists, Hamburger arranged to hire Stanley Cohen, a young post-doctoral fellow from the Washington University Medical School Biochemistry Department, to isolate and characterize active material from the tumor. Cohen quickly managed to isolate a nucleo-protein fraction that would stimulate neuronal growth significantly, but it was not clear whether the nucleic acid or protein component was the active agent. Using snake venom as a source of the nucleic-acid digesting enzyme phosphodiesterase, Cohen soon showed that it was the protein fraction that had the nerve-stimulating property. In another lucky turn, Cohen and Levi-Montalcini found that the snake venom itself had a thousand-fold greater potency for stimulating neuronal growth than the tumor protein. The system for isolating and characterizing the active fraction, which by now they called nerve growth factor, was enhanced further when Cohen realized that snake venom glands are modified salivary glands; he then tried male mouse salivary glands, which are far cheaper and easier to obtain than snake venom, as a source for NGF. This also turned out to be a lucky break since neither female mouse salivary glands, nor those of other male rodents, possess NGF activity. With this system, Cohen was eventually able to isolate and characterize the NGF protein (Cohen 1958). As the NGF work progressed, Hamburger began to step back from the day-to-day activity, leaving the project in the hands of Levi-Montalcini and Cohen.

When the Nobel Committee awarded the 1986 Nobel Prize in Physiology or Medicine to Levi-Montalcini and Cohen, Hamburger was not included, a point that disturbed him more than he often let on. The issue became public in March 1988 when an interview was published in the widely-circulated magazine *Omni*. In it, Levi-Montalcini publically marginalized Hamburger's role in the NGF work. The question of Hamburger's exclusion from the Nobel Prize has been discussed in several publications, including an article by Purves and Sanes in 1987, and it was discussed by Hamburger himself in several unpublished autobiographical accounts in the Hamburger Papers. In the long run, more than professional disappointment, he was personally disappointed by the developments arising from the Prize, as he felt a loss of the close friendship he had held with Levi-Montalcini in the earlier years. Admittedly, after the mid-1950s his own work began to move in other directions, though he did return to aspects of neuronal growth and survival and how these can influence limb buds, as discussed below. Nonetheless, he took solace from the realization that he had started the NGF work and promoted it intellectually and financially during the crucial early years, from 1934 to 1954. And although Levi-Montalcini had been the first to describe neuronal death and survival in the context of their control by peripheral targets, she subsequently abandoned this line of investigation in favor of the NGF story. (Cohen pursued the work in a new direction with the discovery of a whole family of epidermal growth factors that were involved in cell proliferation, survival, and differentiation).

Charting the stages of chick development: The Hamburger-Hamilton Series

One of Hamburger's most important contributions to the field of embryology was a standardized stage series for chick development, which he devised with Howard Hamilton (Hamburger and Hamilton 1951). It's important when studying the development of any organism to have a well-grounded reference system for the stages through which the embryo passes, so that comparisons between experiments can be made at comparable points in the developmental process. The only existing stage series for the chick was a rather loose one drawn up in F. R. Lillie's *Development of the Chick* (Lillie 1919). Lillie's series was based on chronology (hours of incubation), a criterion that can be misleading since incubators do not necessarily operate at the same temperature or maintain the same humidity, factors that influence growth rate.

Hamburger and Hamilton decided early on that what would be most useful would be a stage series based on visible anatomical characteristics. They agreed further that the stages should be chosen on the basis of clearly identifiable external features; successive stages should be spaced as closely together as possible; and wherever feasible, quantitative measurements, such a beak or toe length, should be used. Although not as intellectually exciting as some of his other work, this paper has been among the most frequently cited publications in all of biology, and according to many investigators in the field, the Hamburger-Hamilton stage series is likely to be one of Hamburger's most enduring legacies.

Follow-up investigation of motor column development in relation to the periphery

From the late 1950s through the late 1970s, several further contributions to the work on the relationship between the peripheral tissues and neuronal (particularly motor column) development came from Hamburger's laboratory, even after he had essentially left the work on NGF to Levi-Montalcini and Cohen. Between 1956 and 1958, Hamburger returned to the effects of limb-bud extirpation on the development of the lumbar lateral motor column (LMC). He showed that cell proliferation in the LMC was essentially complete by day 4 of incubation, and that the LMC was fully organized by day 5.5 (Hamburger 1958). He noted further that there was a considerable amount of cell death in the LMC between days 6 and 8, and that this process was accentuated by limb-bud extirpation. The significance of this work was that it showed clearly that motor neurons are also dependent on peripheral maintenance factors (though not necessarily the same NGF that functioned for the sensory system), thus bringing the motor system into line with the sensory system.

This work also marked the beginning of an emerging interest among neurobiologists in the phenomenon of programmed cell death during development (Hamburger and Oppenheim 1982). For example, in a landmark study in the mid-1970s, Hamburger initiated a quantitative examination of the death and survival of motor neurons in the LMC of a normal chick (Hamburger 1975), a process made feasible because of the temporal separation of cell proliferation and migration, and by the fact that the motor neurons were larger and more visible under a microscope. In this investigation, carried out on days 5.5, 6, 7, 8, 9, 12, and 18 of incubation, and on day 5 after hatching, Hamburger found that over the incubation period 5.5 to 12 days, the number of motor neurons decreased from 20,000 to 12,000 (a reduction of approximately 40 percent) and that most of this occurs in the first 3-4 days after the LMC is fully assembled (Cowan 2001, 588). An issue raised but not resolved by this study was whether the success of individual motor neurons in innervating the limb bud was a result of competition for available maintenance factor or for specific contact sites on the individual muscle fibers. As Hamburger noted, in 1975 there was no way to deduce the answer from these alternative hypotheses. However, subsequent research has shown that most, if not all, loss of motor neurons occurs following the initiation of limb innervation when the motor neuron axon terminals compete for limiting amounts of a muscle-derived maintenance (trophic) factor that they access at the nerve-muscle contact point. The losers undergo cell death. (Oppenheim, 1989).

Continuing along these same lines, in the 1970s, with a series of graduate students and post-doctoral fellows, Hamburger reinvestigated the issue of cell proliferation and natural cell death in the LMC. Although space does not permit examining all of this work, a few examples will illustrate the degree to which Hamburger and his collaborators amplified many of the earlier studies, beginning with those of Levi-Montalcini in the 1940s. One such set of experiments, carried out with post-doctoral fellow Margaret (Peggy) Hollyday, attempted to answer the question of whether the hyperplasia in the LMC observed after supernumerary limb transplants was due to an increase in cell proliferation, differentiation, or reduction in natural cell death. Building on Hamburger's 1975 cell count methods, Hollyday found that with additional limb transplants (made prior to 6 days of incubation and before the normal onset of cell death), there was a marked increase in cell survival (that is, a decrease in natural cell death) in agreement with the general conclusion that enlarging the "target field" for motor neurons, as with sensory neurons, increases their chances of survival (Hollyday and Hamburger 1976). Further experiments using tritiated thymidine [^{3}H] autoradiography confirmed that the vast majority (approximately 95 percent) of the motor neurons in the brachial region of the spinal cord are generated between 2.5 and 4 days of incubation, while those in the lumbar region are generated slightly later, at around 4 days (Hollyday and Hamburger 1977). This was a considerably more accurate method of estimation than earlier cytological studies that were based on counts of mitotic activity.

A final set of studies with Hollyday and Juanita Ferris focused on determining the origin of the motor neurons that innervate one specific muscle—in this case, the chick gastrocnemius—in transplanted and normal (control) limbs. To do this, they used as a marker the enzyme horseradish peroxidase injected into the muscle and then followed its retrograde transport back to the motor column. One of the unexpected findings from these experiments was that sets of motor neurons that innervate the muscles of limb transplants are different from those that supply their normal counterparts (Hollyday, Hamburger, and Ferris 1977). This finding paved the way for others to study what factors determine how neurons find their specific sites of innervation during development.

A follow-up on Hamburger's initial hypothesis, that the influential factor emanating from limb bud tissue was carried back to the developing cell body by "retrograde transport," was carried out with post-doctoral fellows Judy Brunso-Bechtold and Joe W. Yip in the late 1970s and early 1980s. In 1978, Brunso-Bechtold administered a radioactive tracer (125I-labeled NGF) to the developing leg limb-bud at day 10. Sections of the lumbar region, including the lumbar spinal cord and spinal (sensory) ganglia, were made 8 hours later and showed the intense presence of radioactive label (Brunso-Bechtold and Hamburger 1979). By contrast, other ganglia not associated with the injected limb bud (including sympathetic ganglia and motor columns) showed no increased uptake of labeled NGF. These experiments provided the first clear-cut demonstration of the uptake of NGF by developing sensory neurons, and thus confirmed Hamburger's initial 1934 hypothesis that some factor produced in the limb bud was transported back to the developing sensory ganglia, where it promoted neuronal growth (that is, as later framed, reduced programmed cell death). Further work by Brunso-Bechtold, Yip, and Hamburger showed that when limb buds were removed, administration of exogenous NGF rescued sensory neurons from both normal programmed cell death and programmed cell death after limb-bud extirpation (Hamburger et al. 1981; Hamburger and Yip 1984). These findings put the final pieces in place demonstrating that normal programmed cell death in sensory neurons was due to limiting amounts of NGF, as originally postulated by Hamburger and Levi-Montalcini in 1949. Typical of Hamburger's research style, he did not like to leave any aspect of a problem unconfirmed or left to purely speculative mechanisms. Collectively, this line of investigation, begun in the 1950s, established programmed neuronal cell death as an important factor in normal development and provided an actual mechanism (competition for target-derived trophic agents such as NGF) for its regulation (Oppenheim 2001).

Later work: the development of behavior

Inspired in part by the work of Austrian ethologist Konrad Lorenz, Hamburger had long been interested in the ontogeny of behavior in higher, vertebrate animals. In the late 1950s and 1960s, Hamburger took up a whole new line of experimental work on the neurobiological origin of behavior. Two assumptions guided this research: 1) Behavior has an internally guided ontogenesis, just as do physical organs and systems, and 2) The ontogeny of behavior and the structural development of the nervous system are inseparable processes.

When he entered this field, Hamburger was only dimly aware of the intense debate occurring among psychologists over the innate versus learned quality of even the simplest behavior. This was the period of the 1950s and 1960s, when American behaviorism (stimulated by the work of psychologist B. F. Skinner) was in its ascendancy, creating an atmosphere that left little room for ideas about innate factors in the origin of animal behavior. For example, one behaviorist-based theory argued that early bobbing movements of the chick head resulted from the embryonic heartbeat, which forced the head up and down repeatedly, "conditioning" the embryo for hatching and later adult pecking behavior. Recognizing that much of embryogenesis might be guided by internal factors, Hamburger decided to investigate the early origin of some simple chick behaviors. The behaviorist view would require, among other things, that the sensory and motor systems in the embryo would develop simultaneously, so that motor activity could occur in response to sensory input. Hamburger's approach was to test these alternative hypotheses by determining how neuronal development correlated with the development of observable behavior in the chick embryo in vivo.

After making initial observations, Hamburger encountered, or perhaps re-encountered, the late nineteenth-century work on chick behavior by Wilhelm Preyer, which showed that before sensory input from the peripheral musculature is established, the motor columns are assembled and have innervated the developing limb buds, thereby initiating motor behavior (Preyer 1885). Hamburger and a postdoctoral fellow, Martin Balaban, confirmed these observations by noting that the chick motor system began to develop before the sensory system, starting at the anterior and proceeding to the posterior region of the spinal cord (Hamburger 1963; Hamburger and Balaban 1963). With a series of graduate students, post-doctoral fellows, and faculty colleagues, Hamburger undertook an analysis of these movements, cataloguing their frequency, duration, and degree of complexity (Hamburger et al. 1966). The movements were found to be random and uncoordinated (one leg or wing would move, the other not) and the animals cycled through periods of activity and quiescence. As embryogenesis progressed, however, the frequency and complexity of the movements increased, while the periods of quiescence decreased (Hamburger et al. 1965; Hamburger et al. 1966; Oppenheim 1975). Motor neuron development also coincided with the appearance of numerous movements of the head and beak, starting at about 3.5 days, and progressing to the wings and hind limbs.

To determine if these movements were endogenously generated and not influenced by possible innervation from higher levels of the spinal cord and brain, Hamburger, with Eleanor Wenger and graduate student Ron Oppenheim, surgically removed the dorsal half of the 2.5-day-old chick spinal cord in the lower lumbar region (eliminating input from developing sensory nerves) and the neural crest tissue, from which the sensory ganglia are developed. The preliminary results showed that from the initiation of the experiment until around the tenth day, the spontaneous activity of the leg was similar between the experimental groups, in which all afferent nerves had been removed, and the control group, in which afferent nerves remained intact (Hamburger et al. 1965). And, as in previous observations, the movements of the two limbs were not coordinated with each other.

The next step was to determine if there was any form of coordination within the individual limb. After unsuccessful attempts to elicit a response by tactile stimulation of the right limb during various stages of development, Hamburger, with graduate student Anne Bekoff and a neurobiologist who had recently joined the department, Paul Stein, measured the motor output of the leg muscles with electromyographic techniques. These results showed that as early as day 7 of incubation, the extensor and flexor muscles were reciprocally linked; that is, when an extensor contracted its associated flexor relaxed, and vice versa. These observations suggested that even at this very early stage of development, the motor neuron and interneuron pools must form synapses in the developing spinal cord. To test this inference Hamburger made his one foray into electron microscopy with the aid of Robert Skoff, a postdoctoral fellow in his lab. Thin sections of the developing spinal cord did indeed show that as early as day 4 of incubation, some synapses were forming with interneurons in the developing chick spinal cord (Hamburger and Skoff 1974). It appeared that coordinated behavior within each limb structure began at a very early stage in embryonic development. Individual, intra-limb coordination thus precedes inter-limb coordination, which is organized from the spinal cord and higher brain centers.

To determine if these early movements originated in the spinal cord or the brain, graduate student Robert Provine, working with Hamburger, a post-doctoral fellow named Sansar Sharma, and Tom Sandel from the Washington University Psychology Department, initiated a lengthy series of investigations of the actual electrical events involved in limb movement. The technical problems were formidable: they included having to devise totally new methods for exposing the spinal cord and making electrical recordings in ovo from as early as 4 days of embryogenesis to 19-day chick embryos (Provine 2001). The results showed “massive bursts of synchronized neuronal firing within the ventral part of the spinal cord that swept through the cord’s rostral-caudal axis” (Provine 2001). These bursts of activity were synchronized with embryonic movements and similar bursts of activity in peripheral motor nerves (Provine et al. 1973), indicating the causal connection between electrical and motor events. As Hamburger had previously inferred, these bursts originated in the spinal cord and not the brain, a view confirmed by Provine and graduate student Lynn Rogers, who showed that embryos with spinal transections made at early stages of development continued to show the bursts of neuronal and muscular activity (Provine and Rogers 1977).

When all these various findings were put together, they showed clearly that motor activity precedes any sensory input. The motor activity must therefore be generated in the nervous system. This result refuted the orthodox behaviorist explanation that all behavior is a result of conditioned responses, that depend on sensory input beginning in the early embryo.

Hamburger's results were met with considerable opposition, especially within the psychological community. However, with his customary insight, Hamburger noted that spontaneous behavior and conditioned reflexes were not mutually exclusive processes in the ontogeny of behavior. But with a strong empirical basis, supported by numerous other experiments, including observations in rats in conjunction with post-doctoral fellow C. H. Naranyan, Hamburger was able to establish the generalized notion of spontaneous motor activity as the beginnings of behavior in vertebrates (Naranyan et al. 1971).

While the significance of these spontaneous movements remained unclear, Hamburger and several post-docs turned their attention to the chick's later hatching behavior, which is highly coordinated and culminates in the actual breaking of the shell between day 17 and day 21. In a now-classic paper, Hamburger and Ron Oppenheim provided detailed descriptions of these behaviors, which had been observed for generations, but had not been carefully analyzed (Hamburger and Oppenheim 1967). What was clear from this work was that "the entire structural framework for this [hatching] and possibly for every other behavior is laid down prior to the first appearance of the behavior and is only minimally influenced, if at all, by the behavior in question." (Cowan 1981).

Studies in the history of embryology

Even before he closed his laboratory in the mid 1980s, Hamburger had already demonstrated both his interest in the history of his field and his considerable skill as a historian of science. No doubt this came from his German educational background, where an appreciation for history and philosophy was particularly widespread. As both an undergraduate and graduate student, Hamburger was exposed to a variety of history and philosophy courses that taught him it was important to know where a field of research had come from to help shape where it should be going. In a more specific biological context, Hamburger grew up with the influence of Ernst Haeckel (1834–1919), whose popular book, *Die Welträtsel* (The Riddle of the Universe), he claimed was one of the most influential books he had read. Haeckel's insistence that the embryo's history—its ontogeny and its phylogeny—were crucial to understanding its development, provided a major conceptual framework within which to pursue both embryological and historical work. At any rate, it was clear that for Hamburger, history mattered, and he contributed significantly to our deeper understanding of that history. Unlike numerous elderly scientists who turn to writing history, Hamburger put himself seriously to the task of being a historian, not a scientist writing history. Like everything else he did, his work in the history of biology and embryology was carefully executed, with meticulous attention to detail, careful analysis, and yet peppered with his own personal experiences and insights.

His first major published work on the history of embryology was an article he wrote in the year of his own retirement on the legacy of the Spemann school (Hamburger 1969). In this article Hamburger provided background on Spemann's early work, including the induction of the lens in vertebrate eyes, but he focused mostly on the experimental and conceptual aspects of the famous 1924 organizer experiment and its interpretation. It is a clear and concise exposition of one of the most important, if controversial, theories in twentieth-century embryology. He followed this up with several articles: one tracing out "historical landmarks in neurogenesis," focusing on such figures as Santiago Ramon y Cajal, Wilhelm His, Ross Harrison, and Roger Sperry (Hamburger 1981a); a second on Hilde Mangold (1898-1924), Spemann's graduate student who actually performed the organizer experiments (Hamburger 1984); and another on the role of embryology in the evolutionary synthesis of the 1930s and 1940s (Hamburger 1980). Among other topics he treated during his career included several historical accounts of the discovery of nerve growth factor (Hamburger 1993, Hamburger 1997), and book reviews of historical works on Karl Ernst von Baer (Hamburger 1970) and Marcello Malpighi (Hamburger 1968). In 1981 he went as far afield as writing an insightful appreciation of Johann Wolfgang von Goethe's *Zur Farbenlehre* (*On the Theory of Color*), in connection with the acquisition of a first edition of this work by the Washington University Library (Hamburger 1981b).

The most masterful achievement of Hamburger's historical work came with the publication of his highly acclaimed book, *The Heritage of Experimental Embryology: Hans Spemann and the Organizer* (Hamburger 1988). This book provided a comprehensive history of Spemann's work and the lab group which he formed in Freiburg, including recollections of many of the participants, with special attention to Hamburger's close friend and colleague, Johannes Holtfreter (1901–1992) and his wife, Hiroko Holtfreter, a PhD and developmental biologist in her own right. In Hamburger's usual, succinct style, *The Heritage* treats the whole history of the organizer concept, including its complications and, according to some, its demise; but the book always relates the older work to insights on current issues in developmental biology. A special feature of the book is personal vignettes (set off in italic style) of various personalities and interactions from Hamburger's direct experience. *The Heritage of Experimental Embryology* received rave reviews in both scientific and historical journals (Witkowskki 1988; Hunt 1989; Allen 1993).

Hamburger continued contributing historical studies until the end of his life. The last, in his ninety-ninth year, was an introduction to and translation of a portion of Spemann's autobiography, focused on deconstructing his mentor's supposed vitalistic views to show that they were perfectly consistent with a materialist, though holistic anti-reductionist, philosophy, very much akin to Hamburger's own views (Hamburger 1999). His historical studies indicated that to Hamburger, the history of science, empirical research, and teaching were "a seamless enterprise…tales of real scientists struggling to gain insights about the biological world" (Provine 2001). This is a highly unusual, but welcome viewpoint among research scientists, and in this, as in the various areas of neuroembryology discussed above, Hamburger was a real pioneer. His interests in the interrelationships between science, its history, and teaching accounts for the fact that he promoted the scholarly pursuit of the history of science within his own department by creating two faculty positions, one in 1961 and another in 1966.[6] This was highly innovative at the time, but it started a trend that has slowly spread to other colleges and universities.

Teaching and administration

When it was clear that he was going to have to seek an academic job outside of Germany, Hamburger decided his best prospects lay in the United States. Among the opportunities that were available, Washington University in St. Louis looked the most promising. Like many other educational institutions at the time, Washington University was reeling from the effects of the Great Depression, and German émigrés were highly prized "not only for humanitarian, but also for economic reasons," as Hamburger put it, since "we refugees had no bargaining power." The chairman of the Zoology Department, Caswell Grave, was an invertebrate (ascidian) embryologist and a student of W. K. Brooks at Johns Hopkins University. Grave was, in Hamburger's words, "an elderly gentleman, kind and unpretentious, a benevolent administrator."[7] The opportunity looked promising and if St. Louis did not have the cosmopolitan air and attractions of Chicago, it was, as he said, "a city without distractions." He accepted a position as assistant professor for the fall of 1935.

Besides a highly prized art museum and a community of wealthy, private collectors, St. Louis did actually offer distractions of an intellectual sort that Hamburger found congenial. Within the biomedical community (including main-campus biologists and medical school faculty) there was a group equally as stimulating as what he had experienced in Chicago. Those with whom he found immediate intellectual and personal resonance included the young zoology instructor Francis O. Schmitt (1903–1995), who later established the Biophysical Research Program at the Massachusetts Institute of Technology (MIT); biochemists Carl Cori (1896–1984) and Gerti Cori (1896–1957), émigrés from Hungary and future Nobel laureates who pioneered early studies on phosphorylation of carbohydrates in glycolysis; art historian H.W. Janson (1913–1982); the Diderot scholar Herbert Dieckmann (1906–1986); neurophysiologists Joseph Erlanger (1874–1965) and Herbert Spencer Gasser (1888–1963), who were among the first to use the cathode ray oscilloscope to record voltage change during nerve conduction, and who were also future Nobel laureates; a young embryologist fresh from Columbia University, H. Burr Steinbach (1905–1981), later the director of the Marine Biological Laboratory in Woods Hole and president of the Woods Hole Oceanographic Institution; and Hampton L. Carson (1914–2004), an evolutionary biologist who used chromosomal patterns to trace migration and bottleneck effects in the Hawaiian *drosophilids*. This was a rich association that included monthly evening seminars and periodic weekend outings to natural areas in the Ozarks and their foothills. Hamburger was promoted to associate professor in 1939, and he became chair in 1941 when Schmitt, who had taken over as department chair when Grave retired, left for MIT.

Two aspects of the period after settling in St. Louis contributed significantly to Hamburger's further scientific development: his work as teacher and administrator in the Zoology Department, and his involvement with the embryology course at the Marine Biological Laboratory (MBL) in the summers from 1936 to 1947.

As both a teacher and administrator, Hamburger left an important legacy. Serving as Zoology Department chairman at Washington University for twenty-five years, he built up an outstanding group of faculty (including a number of women, whose work he championed). He taught at least one course every semester even while serving as department chairman. Two of those courses deserve special mention. One was a yearlong integrated course on comparative anatomy and development accompanied by two-hour lab sessions twice per week, that he originated and co-taught. The other was a laboratory course in experimental embryology, in which students repeated many classic experiments; for this course Hamburger prepared his widely used *Manual of Experimental Embryology*, which went through two editions (Hamburger 1942b; Hamburger 1960).

Figue 7. Viktor Hamburger on board one of the collecting vessels with students at the Marine Biological Laboratory Embryology course, 1945. (Photo courtesy Doris Sloan)

As a teacher, Hamburger was

> *an imposing presence who nicely fit the stereotype of Herr Professor—mild Germanic accent, tall, white-haired, crisp (but polite), and perfectionistic...[He] was also kind, considerate, sometimes humorous, but never suffered fools or sloppy work. Students in Viktor's courses knew they were getting something special—he routinely got standing ovations after the last lecture of the semester. The students appreciated that they were being taught by a pioneer and were participating in a tradition being passed down in direct line from Roux, Spemann and Harrison" (Provine 2001).*

Another of Hamburger's most important educational influences came through his association with the embryology course at the Marine Biological Laboratory in Woods Hole (Figure 7), first as instructor (1936–1941) and then as director of the course (1942–1947). As an instructor he was well received, but the course was based on a traditional, descriptive approach. When Hamburger took over as director, he converted it into an experimentally based course, engendering considerable excitement on the part of students. Through this association, Hamburger influenced a whole generation of developmental biologists to take up experimental work. The MBL experience was also salutary for Hamburger's research, as it brought him into contact for the whole summer with a wide variety of colleagues from all over the world.

It was through his association with other embryologists at Woods Hole that Hamburger and two other colleagues, Benjamin Willier (Johns Hopkins) and Paul Weiss (University of Chicago), developed the idea of a comprehensive review of the state of developmental biology in the mid-1950s, *The Analysis of Development* (Willier, Weiss, and Hamburger 1955). Articles were written by specialists on particular processes (gametogenesis, early cleavage, nuclear-cytoplasmic interactions) and on the development of particular animal groups. This book became the most influential compendium of experimental embryology of the mid-twentieth century. In preparing this work Hamburger served not only as editor, but also collaborated with his friend and colleague Johannes Holtfreter, on the chapter reviewing recent work on amphibian development.

Evaluation and legacy

This memoir would not be complete without a summary of Viktor Hamburger's legacy as a human being, as well as a scientist. The two aspects were inextricably connected in his life, and he never deviated from his chosen field of research any more than from his personal ethics and behavior. As a teacher and mentor he was rigorous and demanding, but in a quiet way, through which his concern for his students was always apparent. Johannes Holtfreter characterized him as

> *a gothic not a romantic type…There are no fancies or fads that attract him…Order and self-discipline have prevailed throughout his life. Self-critical and stern with himself, he is said to be demanding and critical to his students. But hidden behind this austere façade there dwells a compassionate heart. He is unselfish and unfailingly decent, and is as faithful to his aims as he is modest in his claims (Oppenheim 2001).*

His research philosophy, reflecting his early history in the Spemann laboratory, was non-reductionist, treating the embryo as an integrated whole, not a mosaic of parts. He was a conceptual but not a methodological innovator. Although he seemed to feel at times that his more traditional techniques paled by comparison to flashy molecular methods, new technologies, as such, never intrigued him unless he saw exactly how they could help answer an existing question (Provine 2001). Trendiness was never part of the Hamburger style.

As noted earlier, Hamburger once stated his overall research philosophy as what he called his "pact with the embryo:" "I promised the embryo that if it would reveal to me its secrets, I would never homogenize it in a Waring blender" (Allen 2004). In a similar vein, his graduate student, Anne Bekoff, recalled what Hamburger taught her about research:

"One of the most important lessons I learned from Viktor was to look at the embryo as my teacher. Instead of using technology to extract answers from unwilling embryos, the goal was to use technology to allow me to listen to what they had to tell me" (Bekoff 2001). To this she might have added that Hamburger frequently reminded his students "the embryo is the only teacher that is always right."

Although he was confined almost wholly to his home for the last year of his life, Hamburger remained intellectually active until a brief final illness that caused his death just four weeks short of his 101st birthday.

ACKNOWLEDGEMENTS

I would very much like to express my thanks to a number of people who have helped in reviewing this biographical sketch at various stages in its preparation. My colleagues Paul Stein, Professor of Biology and David Kirk, Professor of Biology, *Emeritus* in the Biology Department, Washington University in St. Louis have provided extremely valuable comments. Paul was especially helpful in directing my attention to the work of various graduate students studying the neurobiology of behavior in the later years. Several of these students/colleagues have helped fill in gaps in this work based on their direct experiences with Viktor in the laboratory: Ron Oppenheim, Professor *Emeritus*, The Neurobiology Program, Wake Forest University Medical School, Winston- Salem, NC, and Robert Provine, Research Professor/Professor *Emeritus*, Department of Psychology, University of Maryland, Baltimore County. Their incredible first-hand knowledge of the chick behavior research and the methodologies involved greatly enriched my understanding of Viktorís innovations. Jean Lauder, Professor *Emerita* at the University of North Carolina Medical School in Chapel Hill, provided a valuable overview of the whole manuscript. My long-time colleague and distinguished historian of embryology, Jane Maienschein, Regents' Professor in the College of Science and Society at Arizona State University, offered a valuable perspective on Viktor's work from the developmental biology side. Last, Viktor's daughters, Doris Sloan of Berkeley California and Carola Marte of Bethany, Connecticut read the whole manuscript and corrected some important factual errors in the discussion of Viktorís personal and family life. I am indebted to all of them, and consider this biographical sketch a truly collaborative effort from many different perspectives.

NOTES

1. Levi-Montalcini pursued work on NGF for the remainder of her career while Cohen went on to discover a whole series of epidermal growth factors that functioned as developmental regulators in peripheral and other regions of the developing and mature organism.
2. Starting in the 1950s, Hamburger's wife experienced period of depression that became increasingly more serious and required, ultimately, institutionalization. It was a matter of deep concern to him, but about which he rarely spoke.
3. Hamburger's personal and professional correspondence, his autobiographical notes, and a collection of his own reprints and the reprints he received form colleagues are all housed in the Special Collections section of the Marine Biological Laboratory/Woods Hole Oceanographic Institute Library (MBL/WHOI) in Woods Hole, Massachusetts. The letters and unpublished materials have been scanned but are not yet, as of this writing, accessible online. The actual documents are well organized with a finder's guide, and they can be used in the Special Collections area of the MBL/WHOI Library. Arrangements should be made ahead of time with the MBL/WHOI Librarian, who can be contacted at Marine Biological Laboratory, 1 Water Street, Woods Hole, MA 02543.
4. Hilde Mangold was tragically killed by the explosion of a kerosene stove in her kitchen in Dahlem, where her husband, Otto Mangold (1891–1962), had taken a position as Director of the Department of Embryology at the Kaiser-Wilhelm Institute for Biology.
5. In addition to a number of published biographical accounts by Hamburger himself and various colleagues (listed in the References), the Hamburger Papers include a number of unpublished autobiographical documents, some handwritten, others typed, relating to various aspects of his background. These go under rather loose titles, such as "My Parents," "Freiburg," "The Move to St. Louis," "Contributions to Experimental Neuroembryology," and the like. In addition, a sixty-page autobiographical account was submitted to the NAS, a copy of which is in the Academy's files and in the Hamburger Papers.
6. The first was occupied by Thomas S. Hall and the second by the present author.

REFERENCES

Allen, Garland E. (2004a). A pact with the embryo. *J. Hist. Biol.* 37: 421-475.

Allen, Garland E. (2004b). The Viktor Hamburger Papers and Reprint Collection in Woods Hole, Massachusetts. *The Mendel Newsletter, New Series #13* (March): 12–15.

Bueker, Elmer. (1948). Implantation of tumors in the hind limb field of the embryonic chick and the developmental response of the lumbo-sacral nervous system. *Anat. Record* 102:368–390.

Cohen, Stanley. (1958). A nerve growth promoting protein. In *Chemical Basis of Development*, edited by W.D. McElroy and Bentley Glass, pp. 665–676. Baltimore: Johns Hopkins University Press.

Cohen, Stanley and Rita Levi-Montalcini. (1956). A nerve growth stimulating factor, isolated from snake venom. *Proc. Nat. Acad. Sci. U.S.A.* 42:571–574.

Cowan, Maxwell W. (1981). Viktor Hamburger's contribution to developmental neurobiology: An appreciation. In Maxwell Cowan, ed., *Studies in Developmental Neurobiology*, pp. 3–21. New York: Oxford University Press.

Hamburger, Viktor. 1976–1989. Autobiographical Notes (unpublished typescripts), including: "The move to St. Louis, September, 1935 (1989); "Contributions to experimental embryology" (1976); "Contributions to developmental genetics" (n.d.); "Species hybrids in salamanders" (n.d.); "The stage series of the chick embryo" (n.d.); "Miscellaneous contributions" (n.d.). Hamburger Papers, MBL Archives.

Kirk, David L. and Garland E. Allen. (2001). "Viktor Hamburger: A prepared, persistent, and deserving mind favored by many fortuities. *Dev. Dynamics* 222:545–551.

Kunick, E. (1929). Heimatbuch des Kreises Landeshut. 2 vols. Landeshut. Privately published (no further details given).

Levi-Montalcini, Rita. (1997). *The Saga of the Nerve Growth Factor.* River Edge: New Jersey, World Scientific Publishing Company.

Levi-Montalcini, Rita and Viktor Hamburger (1951). Selective growth-stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. *J. Exp. Zool.* 116:321–361.

Levi-Montalcini, Rita and Giuseppe Levi. (1942). Les conséquences de la destruction d'un territoire d'innervation périphérique sur le développement des centres nerveus correspondants dans l'embryon de poulet. *Arch. de Bio*l. 53:537–545.

Levi-Montalcini, Rita, Herthe Meyer, and Viktor Hamburger. (1954). In vitro experiments on the effects of mouse sarcomas 180 and 37 on the spinal and sympathetic ganglia of the chick embryo. *Cancer Res.* 14:49–57.

Oppenheim, Ronald W. (1975). The role of supraspinal input in embryonic motility: a reexamination in the chick. *J. Comp. Neurol.* 160:37–50.

Oppenheim, Ronald W. (1989) The neurotophic theory and naturally occurring motoneuron death. *Trends in Neuoscience* 12:252-255.

Oppenheim, Ronald W. (2001). Viktor Hamburger (1900-2001): Journey of a neuroembryologist to the end of the millennium and beyond. *Neuron* 31:179–190.

Preyer, Wilhelm. (1885). *Spezialle Physiologie des Embryo*.

Provine, Robert R. (1972). Ontogeny of bioelectric activity in the spinal cord of the chick embryo and its behavioral implications. *Brain Res.* 41:365–378.

Provine, Robert R. (2001). In the trenches with Viktor Hamburger and Rita Levi-Montalcini (1965-1974): A student's perspective. Internatl. *J. Dev. Neurosci.* 19: 143–149.

Provine, Robert R. and Lynn Rogers. (1977). Development of spinal cord electrical activity in spinal chick embryos and its behavioral implications. *J. Neurobiol.* 8: 217–228.

Purves, Dale and Joshua Sanes. (1987). The 1986 Nobel Prize in Physiology or Medicine. *Trends Neurosci.* 10:231–235.

Ripley, K. L. and Provine, Robert R. (1972). Neuronal correlates of embryonic motility in the chick. *Brain Res.* 45:127–134.

Shorey, Elizabeth. (1909). The effect of the destruction of peripheral areas on the differentiation of the neuroblasts. *J. Exp. Zool.* 7:25–63.

Willier, Benjamin H., Paul Weiss, and Viktor Hamburger. (1955). *Analysis of Development.* Philadelphia: W. B. Saunders.

SELECTED BIBLIOGRAPHY

1925 Über den Einfluss des Nervensystems auf die Entwicklung der Extremitäten von Rana fusca. *Roux' Archiv.* 105: 149–201.

1927 Entwicklungsphysiologische Beziehhungen zwischen den Extremitäten der Amphibien und ihrer Innervation. *Naturwiss.* 15: 657–661; 677–681.

1928 Die Entwicklung experimentell erzeugter nervenloser und schwach innervierter Extremitäten von Anuren. *Roux' Archiv.* 114:272–362.

1934 The effects of wing bud extirpation on the development of the central nervous system in chick embryos. *J. Exp. Zool.* 68:449–494.

1936 The larval development of reciprocal species hybrids of Triton taeniatus, Leyd. (and Triton Palmatus, Duges) Í Triton cristatus, Laur. *J. Exp. Zool.* 73:319–373.

1938 Morphogenetic and axial self-differentiation of transplanted limb primordia of two-day chick embryos. *J. Exp. Zool.* 77:379–397.

1939 Motor and sensory hyperplasia following limb bud transplantations in chick embryos. *Physiol. Zool.* 12:268–284.

1940 With Dorothea Rudnick. On the identification of segregated phenotypes in progeny from creeper fowl matings. *Genetics* 25:215–224.

1941 Transplantation of limb primordia of homozygous and heterozygous chondrodystrophic ("creeper") chick embryos. *Physiol. Zool.* 14:355–364.

1942 (a) The developmental mechanics of hereditary abnormalities in the chick. *Biological Symposia* 6:311–334.

(b) *A Manual of Experimental Embryology.* Chicago: University of Chicago Press.

1947 Monsters in nature. *Ciba Symposium* 9:966–983.

1949 With Rita Levi-Montalcini. Proliferation, differentiation and degeneration in the spinal ganglia of the chick embryo under normal and experimental conditions. *J. Exp. Zool.* 111:457–502.

1951 With Rita Levi-Montalcini. Selective growth stimulating effects of mouse sarcoma, producing hyperplasia of sympathetic nervous system of the chick embryo. *J. Exp. Zool.* 116:321–362.

With Howard L. Hamilton. A series of normal stages in the development of the chick embryo. *J. Morph.* 88: 49-92. Reprinted in 1995 in *Developmental Dynamics* 195: 231–272.

1953 With Rita Levi-Montalcini. A diffusible agent of mouse sarcoma, producing hyperplasia of sympathetic ganglia and hyperneurotization of viscera in the chick embryo. *J. Exp. Zool.* 123:233–288.

1954 With Stanley Cohen and Rita Levi-Montalcini. A nerve-growth stimulating factor isolated from Sarcomas 37 and 180. *Proc. Natl. Acad. Sci. U.S.A.* 40:1014–1018.

1955 Trends in experimental neuroembryology. In *Biochemistry of the Developing Nervous System.* Proceedings of the First International Neurochemistry Symposium, edited by H. Waelsch, 52–73.

With Benjamin Willier and Paul Weiss, eds. *Analysis of Development.* Philadelphia: W.B. Saunders.

1957 The life history of a nerve cell. *Amer. Sci.* 45:263–277.

1959 Regression verses peripheral control of differentiation in motor hypoplasia. *Amer. J. Anat.* 102: 365–410.

1961 Experimental analysis of the dual origin of the trigeminal ganglion in the chick embryo. *J. Exp. Zool.* 148:91–123.

1963 Some aspects of the embryology of behavior. *Q. Rev. Biol.* 38:342–365.

With M. Balaban. Observations and experiments on spontaneous rhythmical behavior in the chick embryo. *Dev. Biol.* 7:533–545.

1964 Ontogeny of behavior and its structural basis. In *Comparative Neurochemistry: Proceedings of the Fifth International Neurochemistry Symposium*, edited by Derek Richter. New York: Macmillan, 21–34.

1965 With E. Wenger and Ron Oppenheim. Motility in the chick embryo in the absence of sensory input. *J. Exp. Zool.* 162:133–160.

1967 With Ron Oppenheim. Prehatching motility and hatching behavior in the chick. *J. Exp. Zool.* 166:171–20

1968 Emergence of nervous coordination. Origins of integrated behavior. 27th Symposium of the Society for Developmental Biology. *Dev. Biol. Supplement* 2:251–171.

1970 With R. R. Provine, S. C. Sharma and T. T. Sandel. Electrical activity of the isolated spinal cord of the chick embryo, in situ. *Proc. Natl. Acad. Sci. U.S.A.* 66:508–515.

1971 With C. H. Naranyan and M. W. Fox. Prenatal development of spontaneous and evoked activity in the rat (*Rattus norwegicus albinus*). *Behavior* 40:100–134.

1974 With R. Skoff. Fine structure of dendritic and axonal growth cones in embryonic chick spinal cord. *J. Comp. Neurology* 153:107–148.

1975 Cell death in the development of the lateral motor column of the chick embryo. *J. Comp. Neurology* 160:535–546.

With A. Bekoff and P. S. G. Stein. Coordinated motor output in the hindlimb of the 7-day chick embryo. *Proc. Natl. Acad. Sci. U.S.A.* 72:1245–1248.

1976 With Margaret Hollyday. Reduction of the normally occurring motor neuron loss by enlargement of the periphery. *J. Comp. Neurology* 170:311–320

1977 The developmental History of the Motor Neuron. The F.O. Schmitt Lecture. *Neurosci. Res. Prog. Bull.* (Supplement, April) 15:1–37.

With Margaret Hollyday. An autoradiographic study of the formation of the lateral motor column in the chick embryo. *Brain Res.* 132:197–208.

With Margaret Hollyday and Juanita Ferris. Localization of motor neuron pools supplying identified muscles in normal and supernumerary legs of chick embryos. *Proc. Natl. Acad. Sci. U.S.A.* 74:3582–3586.

With J. K. Brunso-Bechtold. Retrograde transport of nerve growth factor in chicken embryos. *Proc. Natl. Acad. Sci. U.S.A.* 76:1494–1496.

1980 S. Ramon y Cajal, R. G. Harrison and the beginnings of neuroembryology. *Persp. Biol and Med.* 23:600–616.

Prespecification and plasticity in neurogenesis. *Pontificiae Academiae Scientarum Scripta Vera* 45: 600-616. Reprinted in *Nerve Cells, Transmitters and Behaviour*, edited by R. Levi-Montalcini. Dordcrecht: Elsevier-North Holland Biomedical Press. 433–447.

Embryology and the modern synthesis in evolutionary theory. And, Evolutionary theory in Germany, a comment. Both in *The Evolutionary Symnthesis: Perspectives on the Unification of Biology*, edited by Ernst Mayr and William Provine Cambridge, MA: Harvard University Press. 97–112 and 303–308.

1984 With Joseph W. Yip. Reduction of experimentally induced neuronal death in spinal ganglia of the chick embryo by nerve growth factor. *J. Neurosci.* 4:767–774.

Hilde Mangold, Co-discoverer of the organizer. *J. Hit. Biol.* 17:1–11.

1985 Hans Spemann, Nobel Laureate 1935. *Trends in NeuroSciences* 8:385–387.

1988 *The Heritage of Experimental Embryology*.New York: Oxford University Press.

The ontogeny of neuroembryology. *J. Neurosci*. 8:3535–3540.

1990 Neuroembryology, the Selected Papers (Boston: Birkhäuser).

1992 History of the discovery of neuronal death in embryos. *Journal of Neurobiology* 23:1116–11123.

The history of the discovery of the nerve growth factor. J*ournal of Neurobiology* 24:893–897.

1997 Wilhelm Roux: Visionary with a Blind Spot. *Journal of the History of Biology* 30:229–238.