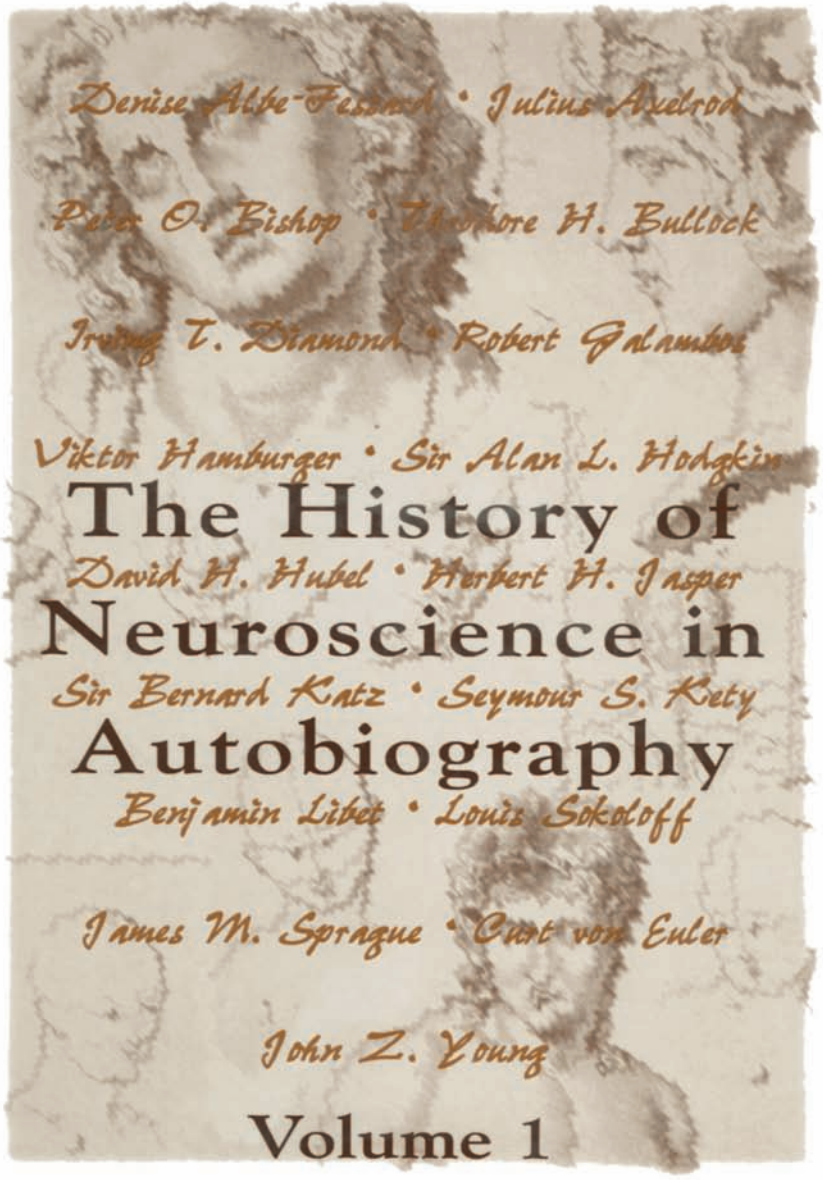

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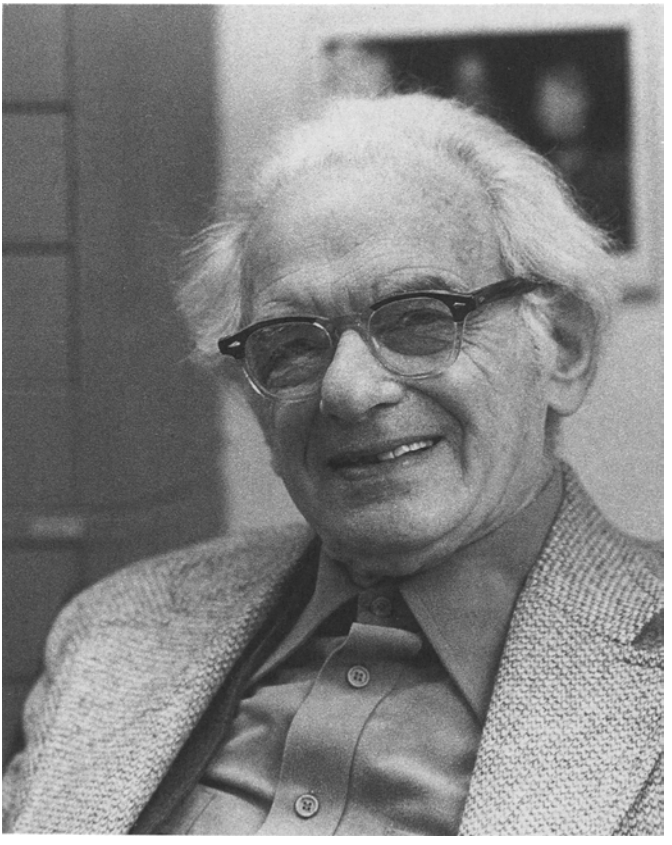

Viktor Hamburger

BORN:

Landeshut Silesia, Germany (now Poland)
July 9, 1900

EDUCATION:

University of Heidelberg, 1919
University of Freiburg, Ph.D., 1920 (Zoology with H. Spemann, 1925)

APPOINTMENTS:

University of Göttingen (1925)
Kaiser-Wilhelm Institute for Biology, Berlin-Dahlem, Germany (1926)
University of Freiburg (1928)
University of Chicago (1932)
Washington University, St. Louis (1935)
Mallinkrodt Distinguished Professor Emeritus, Washington University (1969)

HONORS AND AWARDS (SELECTED):

Society for Developmental Biology (President, 1950, 1951)
National Academy of Sciences USA (1953)
American Society of Biologists (President, 1955)
Ralph W. Gerard Prize, Society for Neuroscience (1985)
National Medal of Science (1989)
Karl Lashley Award, American Philosophical Society (1990)

Viktor Hamburger is best known for his pioneering work in experimental neuroembryology, including the effects of peripheral tissue on the development of the central nervous system, and the emergence of behavior in the embryo.

Viktor Hamburger

Childhood and Youth

I grew up in a small town, Landeshut, Germany, in the remote southeastern corner of the Prussian province of Silesia, which is now Polish. Landeshut had about 12,000 inhabitants, half of whom were textile factory workers. My father was the owner of one of several textile plants. I was born in 1900 in the comfortable house of my parents, and was the eldest of three boys. My parents had grown up in Breslau, the capital of Silesia, about two hours by train from Landeshut. They had moved to Landeshut in the late 1890s when my father, Max Hamburger, took over the family business. He was married to Else Gradenwitz, the daughter of a banker. The family ties to both grandparents were tight, and mutual visits were frequent. As a teenager, I spent many vacations in Breslau and I became acquainted with city life, visited the art museum, and attended concerts and theater performances.

Our two-story house was a block away from the textile factory. The house had a large veranda in the back, overlooking a flower garden. Near the factory was a large vegetable garden with cherry and pear trees, and a tennis court. Next to our house was a large office building that included storage rooms used for shipping merchandise to all parts of the country. The building housed the offices of my father, the co-director, and the bookkeepers. The textile business flourished in the early part of the 19th century, the number of looms grew from 150 to about 600, and auxiliary facilities were built.

Father was a leader in the business community and for many years the chairman of the local chamber of commerce. He was also active in politics, in the liberal Democratic Party, a stronghold of the Weimar Republic that otherwise had few friends in the upper middle class. My parents were sociable; business friends, artists, writers, and politicians were frequent house guests. The house was decorated with original paintings by contemporary artists. A few miles from Landeshut, in the countryside, was a Benedictine monastery and a large Baroque church next to it. The church's facade was praised as one of the most beautiful in Germany. My memories of its grandiose interior and the frescoes of angels on the ceiling are still vivid. Thus, early on, art became part of my life. We were frequent visitors of the church and my parents befriended the abbot and Pater Luterotti, the art historian of the monastery.

My mother was the gentle, warm-hearted, and circumspect mistress of a large household. She cared particularly for the women working in our factory; she provided a kindergarten for their children. I grew up with two younger brothers: Rudi became an architect and Otto entered our father's business. Early on, I took a strong interest in nature: plants, animals, and rocks. Landeshut and its environs were ideally suited to nourish this disposition. Beyond the villages and meadows were forested hillsides, rock formations, and brooks at the foothills of the Riesengebirge (Giant Mountains). The highest peak, rising above timberline, is visible from the outskirts of the town. Mother took us many times in the horse-drawn carriage to see this beautiful scenery.

Before I was 10 years old, I started collecting plants and preserving them in an herbarium. In a freshwater pond, I found mussels and water beetles, and in the spring the eggs of frogs and salamanders. I took the eggs home to watch them develop in large aquaria. At age 13, I exhibited native amphibians and reptiles, including a poisonous viper, at the annual show of the local Aquarium and Terrarium Society. In a nearby quarry, I collected carboniferous fossils. I had the good fortune to have two excellent biology teachers in the Gymnasium. I befriended the younger one, with whom I explored the subalpine flora of the Giant Mountains. Another friend, Walther Arndt, somewhat older than I, introduced me to some rare animal species in our county. He later became a distinguished taxonomist at the Berlin Museum of Natural History. All this happened before and during World War I.

In the spring of 1918, I passed the Abitur, the graduation from the Gymnasium, with honors. A few months later, I was drafted into the army and sent to Breslau, but I was discharged in November when the war ended.

Much later, when I spent the years 1926 to 1928 in Berlin-Dahlem at the Kaiser Wilhelm Institute for Biology, Walther and I embarked on an ambitious enterprise: we planned and edited a two-volume book about our homeland, the county of Landeshut (*Heimatbuch des Kreises Landeshut*). It was a comprehensive account of nature, history, art, local dialect, folk lore, industry, and agriculture, including vignettes of small towns and villages, with many illustrations. Walther wrote the chapter on zoology and I the one on geology. The book was published in 1929. We were deeply rooted in our homeland (Heimat). Four years later, I was exiled by the Nazis. In 1944, Walther Arndt made some disparaging remarks about Hitler to a trusted friend who betrayed him; at his trial Walther refused to recant, and he was executed. In 1946, Silesia was annexed by Poland, and all its inhabitants were forced to emigrate.

University Life

There had never been any doubt in my mind about having an academic career in the natural sciences. For the winter semester of 1918 to 1919, I enrolled at the University of Breslau to study zoology, botany, geology, and

mathematics. The only memory I have of those days is that of getting acquainted with the Mendelian laws in a botany course, which fascinated me. But now it was time to reach out. Apart from a few summer vacations at the shore of the Baltic Sea and perhaps a visit to Berlin, I had never crossed the border of Silesia. My parents suggested I attend the University of Heidelberg, where my aunt, Dr. Clara Hamburger, was a senior assistant at the Zoological Institute and the right hand of the then well-known Professor Otto Bütschli. My parents thought that my aunt would take care of me, which she did. I spent two semesters there, from 1919 to 1920. When Bütschli died, the experimental embryologist, Curt Herbst, became his successor.

Besides zoology, I studied botany and geology. Professor Salomon, the geologist, was an excellent teacher. During a field trip to the Swabian Alb, a mountainous region in South Germany in the summer of 1920, I became acquainted with a variety of colorful stratified rocks containing a wealth of fossils. That experience almost converted me to a career in geology. But when I discussed this prospect with my mother, she said: "Do you really want to spend your life with rocks?" With that comment, she laid my doubts to rest.

Shortly thereafter, Professor Herbst admitted me, a beginner, to an advanced seminar on experimental embryology. We read and discussed some of the works of Wilhelm Roux, the founder of experimental embryology, which Roux called "developmental mechanics." Although Roux's writings are dense, opaque, and long-winded, I became intrigued by the causal-analytical, experimental approach to the study of development, and I envisioned a future of doing experiments on embryos; however, I was not interested in the experimental work that Herbst and his students did at that time.

In the spring of 1920, a friend and I spent a vacation in Freiburg and the Black Forest, which reminded me of the Giant Mountains where I had grown up. I was enchanted by the medieval spirit of Freiburg, which the center of the city had preserved. The city's narrow, winding streets were lined by small brooklets. In the center, the large cathedral square (Münsterplatz) was flanked by Renaissance, Baroque, and modern buildings. The large gothic cathedral (Münster) is one of the most beautiful in Germany, decorated with sculptures, altar paintings, and stained glass windows by famous artists. The environs of Freiburg are unique. To the west extends the Rhine Valley, populated by prosperous villages surrounded by vineyards. To the east rises the Black Forest. We climbed the highest peak, the Feldberg. Clearly this region appeared much better to me for hiking and skiing than the hills near Heidelberg. When I found out that Professor Hans Spemann, who already had a sound reputation as an experimental embryologist, had become the chairman of the zoology department of the University of Freiburg, I made up my mind to transfer

to that university. I arrived there in the spring of 1920. The salamander breeding season was approaching, and preparations for the experiments were in full swing.

The department was dominated by experimental embryology. Spemann soon became the leader in that field in Germany and all of Europe. Dr. Otto Mangold was Spemann's oldest and favorite student. He was a skillful experimentalist, and he did some original work. The only other prominent figure was Professor Fritz Baltzer, a geneticist and, like Spemann, a student of the famous cytogeneticist, Theodor Boveri. Through Baltzer's lecture courses and some private instruction, he instilled in me a deep interest in developmental genetics, a field to which I later devoted several years of experimental work. Baltzer left in 1922 to become the chairman of zoology at the university of his hometown, Bern, in Switzerland; he was not replaced by another geneticist. Spemann had recruited Dr. Bruno Geinitz, an entomologist, for experimental embryological work, but Geinitz soon returned to his specialty. The remaining faculty consisted of an undistinguished ornithologist and another lecturer, whose courses I did not take. In 1924, Dr. Fritz Süffert, an excellent scientist with original ideas, joined the department. His field was the study of adaptive coloration in butterflies and moths. We became friends, particularly after my return to Freiburg in 1928.

We students attended lecture courses in the sciences, philosophy, and literature, and laboratory courses in our minor fields (mine were botany and geology). 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.

Hilde Proescholdt and Johannes Holtfreter had also joined the department in 1920. We were assigned adjacent tables, and I befriended both of them. Hilde was somewhat older and more advanced than Hannes and I, and had already started her Ph.D. project in the spring of 1921. She transplanted the upper lip of the blastopore of salamander embryos to the belly region. The experiment became famous later as the "organizer experiment." I still remember the excitement of Spemann and all of us, one morning in May 1921, when Hilde showed us the first induced secondary embryo. She married Otto Mangold later that year, and they moved to Berlin-Dahlem, where Mangold became Spemann's successor at the Kaiser-Wilhelm Institute for Biology. Hilde was not destined to enjoy her success. She died of severe burns after an accident at her home in 1924, the year in which her article with Spemann on the organizer was published. Holtfreter and I remained lifelong friends. He became the most imaginative and most productive experimental embryologist of his generation.

The atmosphere in the department was relaxed. Spemann was not the stern Herr Geheimrat (Privy Councillor) as he is sometimes portrayed. He had a subtle sense of humor. In seminars he could be very critical, but his criticism was usually softened by a touch of humor. We came closest to knowing him when the staff and students working on their Ph.D. dissertations, the Doktoranden, met in the afternoon for tea in the reprint room. There were lively discussions of ongoing research, discoveries in our field, evolution, and philosophical themes, but rarely of politics. Life in the department was animated by many guests from abroad. Fritz Lehmann and Oscar Schotté from Switzerland worked there for several years. Ross Harrison from Yale, who was close to Spemann, visited frequently during the summer. Sam Detwiler, Elmer Butler, and Charles Parmenter came from the United States; John Runnstroem came from Sweden; Martin Woerdeman from Holland; Tadao Sato from Japan; and Georg Schmidt from Russia.

In all those years, Spemann had instilled in all of us an understanding of the intricacies of embryonic development as a sequence of inductive interactions and morphogenetic movements—and a great respect for the living embryo that integrates all these interactions. On the other hand, he gave us confidence that our minds could unravel this complex interplay of forces by the well-thought-out analytical experiment. I think we were not then fully aware of our limitations. We had at our disposal only two methods: extirpation and transplantation. The scope of the latter had been broadened by Spemann's introduction of hetero- and xenoplastic transplantation. In retrospect, it seems remarkable how much information was obtained by these modest methods.

In the spring of 1923, I asked Spemann to assign a topic for my Ph.D. dissertation. He suggested a topic that was remote from his own major interests. I think his idea was to create for me a field of research independent of his own, which would later facilitate my academic career. I was to settle a dubious claim by Bernhard Dürken that the normal development of frog larvae depends on a normal supply of innervation. Dürken had extirpated the right eye of young larvae and found more or less severe abnormalities of the hind limbs in a high percentage of cases. He had assumed that the defects were neurogenic in nature. He had observed, as expected, a hypoplasia of the left midbrain and hypothesized a cascade of neural deficiencies all the way down to the lumbar spinal cord and the leg innervation. I did many hundreds of eye extirpations, with several variants, such as the stage of development at which the operation was done, and obtained a small percentage of defects limited to the toes. These defects were minimal compared to those in Dürken's experiments; the leg abnormalities were probably due to nutritional deficiencies. Although my results had been equivocal, my dissertation had two notable consequences: it launched my lifelong career in neuroembryology, and it led to

the design of my first original experiment, the production of nerveless legs, which I discuss below. I also derived a valuable personal benefit from my first exercise: self-sufficiency. There was nobody around with whom I could discuss my project. Experimental neuroembryology was then a modest side branch of experimental embryology and was practiced almost exclusively by Professor Harrison and his students at Yale.

I received the Ph.D. degree (summa cum laude) in June of 1925. The months of January to April 1925 I spent at the Zoological Station in Naples. In preparation for an academic career in zoology, I was supposed to become familiar with the marine fauna. The Mediterranean fauna was rich and beautiful. Every morning I awaited the return of the fishing boats. Most of the catch was destined for the international group of researchers, but enough was left for us beginners. My particular favorites were the transparent coelenterates and mollusks. I filled several notebooks with sketches. And in the company of my friend, Hannes Holtfreter, I explored the beautiful environs of Naples. This was my first trip abroad, and I made the acquaintance of a number of distinguished European and American biologists.

Göttingen, Winter 1925–1926

To broaden my proficiency in biology further, Spemann provided me the opportunity to work in the laboratory of his friend, Professor Alfred Kühn, in Göttingen. Kühn was a polymath, equally at home in genetics, comparative physiology, embryology, and systematics. His textbook of zoology had practically a monopoly. He worked at that time on the development of pigment patterns, such as eye spots, in the scales of butterflies and moths, in collaboration with his senior assistant, Karl Henke. Kühn suggested that I work on a topic that he and several of his students had dealt with: color vision in fish. He had refined these studies by the use of spectroscopy. I was to test whether superimposed complementary colors would be seen as white, as in higher vertebrates. I trained minnows to jump for food presented in front of a white strip at the wall of the aquarium. Indeed, they responded when superimposed complementary colors were presented. Their performance improved when ultraviolet light was added; hence, their visual color spectrum was shown to extend further than that of higher vertebrates.

I profited greatly from discussions with Kühn and Henke, and I befriended Henke and his family. At their house, I became reacquainted with my future wife, Martha Fricke, whom I had met when she visited a friend in Freiburg. At that time, she was studying for a state examination that would qualify her to teach biology at a Gymnasium. We married in 1928. We had two daughters: Doris, born in 1930, who became a geologist and environmentalist at Berkeley; and Carola, born in 1937, who became a professor of ancient languages and literature at Wesleyan University in

Connecticut and then switched to medicine. Carola practiced at several clinics in New York and is now connected with Yale Medical School; her major concern is AIDS in women.

Berlin-Dahlem, 1926–1928

In the spring of 1926, Otto Mangold offered me an assistantship in his department of experimental embryology at the Kaiser Wilhelm (later called the Max Planck) Institute for Biology in Berlin-Dahlem. This was an ideal position; I could devote all my time to research. Mangold was supportive; we respected each other but did not get very close. I completed the experiment of producing nerveless legs in frog larvae. The unilateral and bilateral extirpations of the lumbar segments of the spinal cord were done at the neurula stage. I had to do hundreds of experiments because I had to cope with two predicaments: after unilateral extirpation, the neural tube frequently regenerated to different degrees; and the bilateral extirpation incapacitated the mobility of the tail, and swimming. Fortunately, the few specimens that went through metamorphosis provided an unequivocal conclusion: the morphology, skeleton, and musculature of the nerveless legs were completely normal, except that the muscles had atrophied. Thus Dürken's hypothesis that the normal development of legs depends on the normal supply of innervation was disproved. My results were published in *Roux's Archiv* in 1928. The specimens with partially regenerated spinal cords showed various degrees of incomplete nerve patterns in the leg. I had no help, so I did all the sectioning and staining myself.

My interest in genetics was fostered by a group of young geneticists in the genetics department, the director of which was Professor Richard Goldschmidt. I participated in their seminars and befriended Curt Stern, his assistant. One summer, I spent several weeks in Stern's laboratory. I learned how to cross *Drosophila* mutants, and I actually identified a new mutant. Stern later became one of the leaders in the field. Our friendship continued after we emigrated to the United States.

Berlin was then the vibrant cultural center of the Weimar Republic; theater, music, dance, and expressionist painting flourished. I was too busy to participate actively, but I remember Max Reinhardt, who dominated the theater, the dancer Mary Wigman, the plays of Bert Brecht, and outstanding cabarets. The Depression and inflation were behind us, the country was fairly prosperous, and the political scene was still rather peaceful.

Instructor in Freiburg

In 1927, Spemann offered me an instructorship, and later that year I returned to my alma mater. My duties were to supervise the elementary and advanced laboratory courses. In my spare time, I continued a project

in developmental genetics that I had started in Dahlem. I shall deal with it only briefly because it was discontinued, unfinished when I moved to the United States. Although most experimental embryologists showed no interest in the role of genes in development, I considered the analysis of gene action as important as the analysis of induction or regulation. My view was reinforced by my contact with the Goldschmidt group in Dahlem. I had in mind to combine the methods of experimental embryology and genetics. This plan meant that I would stay with amphibians and cope with a serious drawback: no mutants were known so I was confined to species hybridization. The obvious choices were the two common salamander species, *Triturus cristatus* and *Triturus taeniatus*. These species differ significantly in the growth rate of the forelimbs and particularly of the four digits. I spent several breeding seasons constructing growth curves for the parent species and the reciprocal hybrids. These data were supposed to be the basis for planned transplantation experiments, but I never got to the point of doing these experiments and I terminated the project.

Chicago, 1932–1935

In the fall of 1932, I received a one-year Rockefeller Fellowship to work in the laboratory of Dr. Frank R. Lillie, a friend of Spemann's, at the zoology department of the University of Chicago. Lillie's classic book, *The Development of the Chick*, had introduced the use of the chick embryo in research and teaching; but at that time, experimentation had been limited to chorioallantoic grafts and hormone injections. Spemann suggested that I try his microsurgical technique on chick embryos. I arrived in Chicago late in October 1932. Lillie was then the dean of biological and medical sciences, and Dr. Benjamin Willier had taken his position as professor of embryology in the zoology department. At my first meeting with Lillie, he reminded me that 25 years earlier his student, Dr. M.C. Shorey, had removed leg buds by electrocautery, which resulted in severe deficiencies of the lumbar spinal ganglia and lateral motor columns. Sam Detwiler, a student of Ross G. Harrison, had repeated the experiment on salamander embryos; the spinal ganglia were reduced in size, but the motor centers seemed to be unaffected. Lillie thought that this experiment would be a good starter for a beginner, that it met with my interest in neuroembryology, and that I might resolve the discrepancy between the observations of Shorey and Detwiler.

Willier and his research associate, Dr. Mary Rawles, taught me how to handle chick embryos, how to saw a window in a shell, and how to remove the membranes. Within a few months, I had mastered the craft of extirpation and transplantation of limb buds to the flank. My mentors and the graduate students were much impressed by the sight of perfectly normal supernumerary wings and legs between the normal ones. The transplants were even motile, if they were connected with the brachial or lumbar plexus.

The wing bud extirpation experiment was done with glass needles on 3-day embryos; the embryos were fixed five to six days later. Both brachial spinal ganglia and lateral motor columns were greatly reduced, compared with those on the contralateral side, confirming Shorey's findings. I was intrigued by the idea that I was now facing the problem of nerve influence on limb development in reverse: how do the structures of the limb regulate the nerve centers which innervate them? The first step of the analysis would be to find out whether there was a quantitative relationship between the loss of target structures and the hypoplasia of the nerve centers which innervate them. I counted the number of motor neurons and measured the volume of spinal ganglia on both sides. At this point, the inaccuracy of my operations, as a beginner, turned out to be a blessing in disguise. In addition to removing the wing musculature, I had removed a varying degree of pectoral muscles, ranging from 90 to 30 percent. The loss of the number of motor neurons corresponded exactly to the muscle loss in every case. On the other hand, the loss of sense organs in the skin and the reduced volume of spinal ganglia showed little variation. The loss amounted to about 50 percent in both. This finding suggested "the idea that each peripheral field controls the quantitative development of its own nerve center," and, furthermore, that "the stimuli going from the peripheral fields to their nerve centers are probably transmitted centripetally by the nerve fibers" (Hamburger, 1934, p. 491).

Thus, the foundation was laid for a deeper understanding of the relationship between the target structures and their nerve centers. I stated this in a three-point paradigm:

> 1) The targets, that is, the musculature and the sense organs, generate two specific agents, one controlling the spinal ganglia and the other controlling the lateral motor columns.
> 2) The agents travel retrogradely in the nerves to their respective nerve centers, the lateral motor columns and the spinal ganglia.
> 3) The agents regulate the development of the nerve centers in a quantitative way.

The paradigm has stood the test of time well; two decades later, the discovery of nerve growth factor (NGF) identified one of the two agents postulated in the first point.

The third point, the mode of action of the agents, was not obvious. I suggested a hypothesis based on my familiarity with the notion of embryonic induction. I assumed that in early stages the nerve centers would contain a reservoir of undifferentiated neuroblasts; that early differentiating neurons would send out pioneer fibers that would explore the size of the targets; and that the neurons from which the pioneer fibers had emerged would induce

an appropriate number of neuroblasts to differentiate into neurons and join them. This recruitment hypothesis would explain the hypoplasia of nerve centers in the absence of limbs and their hyperplasia in the presence of transplanted supernumerary limbs. The hypothesis turned out to be erroneous, but, as we shall see, my error was a blessing in disguise. This, my first publication in English, appeared in 1934. My first venture with the chick embryo proved its superiority over amphibian embryos in neuroembryology: the motor units are more clearly defined, and one gets results in days rather than weeks or months, and all year round.

My transition from amphibian to chick embryos coincided with my move from the Old World to the New World. Before, I had spent most of my life in idyllic small towns. On first arriving in the New World in October 1932, the skyscrapers of New York called for a readiness to forget the past for a while, and to adjust to a powerful, impressive, but somewhat scary new scenery. In the company of several other Rockefeller Fellows who had crossed the ocean with me, I called on the headquarters of the Rockefeller Foundation and then did several days of sightseeing, visited museums, and climbed the Woolworth Tower, then the tallest building in the world.

Then I traveled by train to Chicago and stayed for a while in the International House, a donation of the Rockefeller Foundation to the University of Chicago. The university is located on the South Side of Chicago, which was then a quiet neighborhood. I went downtown infrequently, to purchase materials for my experiments, or for movies and occasional dinners in a German restaurant in the company of some other German inhabitants of the International House. From the beginning, I was most impressed by the friendliness of everybody and the informality of all human relationships, reflecting an easy-going acceptance of others that one did not find in Germany. I was soon on a first-name basis with the graduate students around me, and before long Dr. Willier was "Benjie" and Dr. Rawles was "Mary."

The most striking difference between the zoological institutes in Freiburg and Chicago was the narrow specialization in the former and the wide range of special fields represented in the latter. Of course, the University of Chicago was many times the size of the University of Freiburg; but, as I have mentioned, specialization was typical of German university departments. In Chicago, Willier represented embryology; Sewall Wright was already a famous geneticist; and Charles M. Child, the originator of the gradient theory, was also prominent. Also present were Warden C. Allee, one of the founders of modern ecology; Carl Moore, a distinguished endocrinologist; Ralph Emerson, an entomologist; and several others. Now, for the first time, I could "talk shop" with prominent neurobiologists and behaviorists. I became acquainted with Dr. C. Judson Herrick, with Dr. Karl Lashley, whose seminar on comparative psychology I attended, and with his colleague, Heinrich Klüver. They all took an interest in my experiments.

The tranquillity of life in Chicago was disrupted when the Nazis came to power in January 1933. In April, I received a letter from the dean in Freiburg, telling me that I was discharged from my assistantship. Naturally, I was shaken by this sudden uprooting, the separation from family and friends, and an uncertain future in a foreign country. But I was lucky in that the Rockefeller Foundation immediately created an emergency fund for displaced German scholars, which supported me for another two years. I became an assistant and participated in the teaching and laboratory work in the comparative anatomy and embryology courses that were then a requirement for premedical students in the United States.

In Chicago, I became acquainted with the routine of the college curriculum of American universities. Thus, I was well prepared when I received an offer of an assistant professorship in the zoology department of Washington University in St. Louis in 1934 which, of course, I accepted. In the meantime, I had returned to Germany for a short visit early in 1934. My wife had already dissolved our household in Freiburg. Back in Chicago we lived in a small apartment. Our four-year-old daughter was enrolled in the university kindergarten, and she soon surpassed her parents in spoken English.

St. Louis

We moved to St. Louis in September 1935. The zoology department occupied a large building on the Hill Campus together with botany. The campus overlooks the large Forest Park; the medical school and hospitals are just visible at the other end of the park. While the medical school already had a reputation as one of the best in the country, the college and graduate school were just average; they were populated mostly by local students. Their quality improved markedly when, many years later, dormitories were built, and the physicist Arthur Compton, a Nobel Laureate, became chancellor after World War II. He brought with him and recruited faculty of very high standards. The chairman of the zoology department, Dr. Caswell Grave, was an elderly gentleman, kind and unpretentious, a benevolent administrator.

The greatest asset of the department was a young biophysicist, Frank Schmitt, one of the best minds on the campus and one of the pioneers in the study of cell structure with the polarization microscope and by x-ray diffraction. His vitality and enthusiasm were contagious. My encounter with him broadened my scientific outlook profoundly. For the first time, I came in contact with a strictly reductionist, physico-chemical approach to biology. We were both open-minded and profited from our exchange of ideas. Frank had probably never seen an embryo before, but he soon realized that the processes with which I dealt might provide the biophysicist with intriguing opportunities. Our discussions led to a joint project on tissue density in amphibian gastrulae and neurulae, which was executed by a competent research assistant, Dr. Morden Brown. We organized a weekly seminar for advanced students in which theo-

retical and philosophical books by Julian Huxley, J.B.S. Haldane, Erwin Schroedinger, and others were read and discussed. Frank had also organized the *Schmitty Verein*, which included all prominent scientists of the Hill Campus and the medical school and met once a month to report on their latest discoveries and other events. One evening, Carl Cori gave the first demonstration of the enzyme that earned him and his wife Gerty the Nobel Prize.

I was promoted to associate professor with tenure in 1939. In the meantime, Dr. Grave had retired, and Frank Schmitt became the chairman, but not for long. In 1941, he moved to the Massachusetts Institute of Technology as the chairman of a newly established biology department. I became his successor and a full professor. Around the same time, two younger staff members had left, and I had the challenging opportunity to rebuild the department practically from the ground up. Through friends and colleagues, I recruited three recent Ph.D.s: the geneticist Harry Stalker, the cytologist Hampton Carson, and the biochemist Florence Moog. We were joined later by a more seasoned physiologist, Burr Steinbach. I was lucky in that all of them became prominent in their fields and highly regarded teachers. We all were exceptionally compatible and became friends. Carson and Stalker soon formed a successful research team. We all had lunch together in the conference room, and much of the department business, the curriculum, and new appointments were discussed there.

In 1945, another stroke of good luck came my way. I received a letter from Dr. Tom Hall inquiring about an opening in the department. He taught at Purdue and wished to return to his family in St. Louis. He had excellent credentials and turned out to be a brilliant educator with original ideas. He took over the elementary zoology course and redesigned it completely. He made the students think! Tom shared my interest in wildlife, in the arts, and in literature, and we became close friends. We spent weeks together in the Colorado and California mountains. Soon the administration discovered his propensity for general education ideas; he became the dean of the Faculty of Arts and Sciences and stayed in the administration for 13 years. In 1955, Owen Sexton joined the zoology department as an ecologist. He complemented the strongly experimental, laboratory-oriented faculty by his teaching, his field trips, and his research in a forested wildlife reserve owned by the university. Five of us—Stalker, Moog, Sexton, Hall, and I—stayed at Washington University until our retirement; Carson stayed for three decades. This tenacity is testimony to an unusual compatibility and also the favorable academic and living conditions in St. Louis.

The Marine Biological Laboratory in Woods Hole, Massachusetts

I think the MBL needs no introduction. Dr. Grave spent all his summers there. He owned a house in Woods Hole, did his research on ascidians, and

was a member of the Board of Trustees. He did me a great favor by providing me with an instructorship in the embryology course. I started it in 1936 and carried on for 10 years. When its director, Dr. Hubert Goodrich, retired in 1941, I became his successor. Until then, the course had dealt with the description of the development of fishes and marine invertebrates. I initiated a radical change and placed experimentation on eggs and embryos at the core of the course work, and I found competent and enthusiastic colleagues to help me.

For me, the fairly isolated newcomer from the midwest, the contact with colleagues from other parts of the country, who met regularly every summer, was of incalculable value. The daily conversations, shop talk, and exchange of ideas created strong bonds. We visited each other in the laboratories and had meals together in the Mess Hall. Many of us brought our families along. Our spouses and children enjoyed the two beaches, and there was a Nature Study School for older children. Lasting friendships were formed. Dr. Lillie was at that time one of the most respected figures. He had been director of the MBL for many years; during his tenure, the laboratory had attained its great national reputation. I got together with him much more frequently there than in Chicago.

The atmosphere of the MBL was conducive to all kinds of gatherings of people who shared interests in special fields. A group of about a dozen experimental embryologists met every few weeks in the dunes of Truro Beach in Barnstable, northwest of Woods Hole. We brought our lunch and talked for hours; each time, the discussions focused on a different topic. We became known as the "sandpipers," after the birds that shared the dunes with us. These meetings generated a tangible product: three of us—Benjie Willier, Paul Weiss, and I—got the idea of producing a comprehensive survey of the state-of-the-art of experimental embryology. We recruited over 20 colleagues, who contributed chapters on special topics. The book, *Analysis of Development*, under the editorship of the three of us, appeared in 1955. For quite a while, it was the standard book in the field. My contribution was a chapter, jointly with Holtfreter, on amphibians which, at that time, still played the key role in the field. The collaboration with Hannes, who was then at the University of Rochester, was not easy because our styles of thinking and writing were very different. We exchanged many drafts and letters, criticizing each other; but in the end, Hannes conceded that our chapter had considerable merit.

Back in St. Louis

Now back to St. Louis and chick embryos. I turned my attention to limb bud transplantations. First, I asked whether nerve centers would show a hyperplasia when their target area was enlarged. Because limb buds transplanted to the flank received little innervation, I used wing buds transplanted

immediately behind the normal wing buds, and leg buds transplanted in front of the normal leg buds. The transplants were innervated predominantly by brachial and lumbar plexuses, respectively. The hyperplasia in the lateral motor columns was only slight, and that in the spinal ganglia somewhat greater. The most significant observation was that only motor segments and ganglia that actually sent nerves to the transplants were affected, whereas neighboring segments that did not contribute to their innervation showed no hyperplasia. This finding proved beyond a doubt that the hypothetical agents produced by the targets were transported to their nerve centers by retrograde transport in the nerves, as postulated in my paradigm, and not by diffusion (Hamburger, 1939).

Harrison had shown by transplantation of the left limb anlage to the right side, and by rotation, that in tail bud stages of salamander embryos the anterior-posterior axis is determined earlier than the dorso-ventral axis. I repeated these experiments on 2- to 2.5-day chick embryos in which the limb anlagen were either not yet elevated or recognizable as narrow ridges. In all 50 cases that were raised to advanced stages, both wings and legs developed according to their original axial orientation; that is, both axes were programmed at the earliest stages used for my experiments (Hamburger, 1938).

Inadvertently, I obtained nerveless limbs; in some cases, the limb primordia had not healed where placed but had slipped into the coelomic cavity where they differentiated in complete isolation. Later, I produced nerveless wings and legs on a large scale and showed that all structures had differentiated normally, thus confirming my earlier observations on the nerveless legs of frog larvae.

A chance observation directed my attention to the mitotic activity in the spinal cord. It was known that all dividing cells are assembled at the inner lining of the central canal. One day, in the laboratory course of embryology, I looked through the microscope of a student who studied sections of a 10 mm pig embryo. I was struck by the observation that all mitotic figures were concentrated in the (dorsal) alar plate, whereas there were very few in the (ventral) basal plate. I turned to my collection of chick embryos and found that there was indeed a remarkable temporal shift of mitotic activity from ventral to dorsal. Mitotic activity in the ventral plate that produces motor neurons, among other types, peaks at three days of incubation, whereas the peak in the alar plate that produces internuncial neurons occurs three days later. All proliferation is near its end on the eighth day. As a result, the motor neurons mature three days earlier than the interneurons, which then connect with the spinal ganglia. This pattern applies also to mammals, and probably to all vertebrates. I was surprised to find that it had never been described before. The observations were published in 1948. Fifteen years later, when I began to study motility in chick embryos, one of my first findings was that motility starts three days before the first reflexes can be elicited. That was exactly what I might have predicted in 1948—if I had been smart enough.

My interest in developmental genetics was still alive; I taught an advanced course on this topic. In the early 1940s, I returned to this field, motivated by the fact that mutants were available in chicks—a great advantage over amphibians. Moreover, I had access to these mutants through Walter Landauer, whom I had befriended during our student years in Heidelberg in the laboratory of Professor Herbst. Landauer had emigrated to the United States long before I did and was then in charge of poultry science at the Agricultural Experiment Station located on the campus of the University of Connecticut in Storrs, then a small village in the countryside, with a few buildings for agricultural sciences. One of the mutants that he had studied in detail was the Creeper fowl. It attracted my attention because the legs of the heterozygotes showed severe abnormalities, and the eyes of homozygotes showed an abnormality called coloboma. Transplants of Creeper leg and eye primordia to the flank of normal embryos gave rise to the expected abnormalities. But the transplantation of a potentially colobomatous eye primordium to the site of an eye primordium of a normal embryo brought a surprise: a perfectly normal eye was formed. This meant that we were dealing with an indirect gene effect. The gene was probably responsible for a deficiency in the vascular layer surrounding the eye. The outcome of the experiment showed that experimental embryology can contribute in a modest way to the analysis of gene action. But I realized the limitation of this approach, and I returned to neuroembyrology. A general account on the work with the Creeper fowl was published in 1942.

The Discovery of Nerve Growth Factor

I had sent a reprint of my article on wing bud extirpation (1934) to Professor Guiseppe Levi, director of the anatomy department of the medical school of the University of Turin, Italy, who was well known for his studies of nerve cells in tissue culture. He had given the reprint to his research associate, Dr. Rita Levi-Montalcini, who had also done experiments on chick embryos. The idea that the target structures influence the development of the nerve centers which innervate them, and my paradigm, intrigued her. But intuitively, she felt that my recruitment hypothesis, which tried to explain this influence, was improbable. In her previous work, she had become familiar with spinal ganglia. She did hind limb bud extirpations and then counted the numbers of undifferentiated and differentiated neurons in a lumbar ganglion. Up to the sixth day of incubation, the cell numbers were the same in the left and right ganglion. In the following two days, the number of differentiated neurons decreased substantially on the operated side, and only a few neurons remained toward the end of incubation. She concluded that neurons differentiate normally up to a certain point, but then they perish if their axons fail to

establish contact with their target structures. Thus my recruitment hypothesis was replaced by one which had a solid foundation in facts; and my paradigm, on which her study was based, was strengthened. The results were published by Levi-Montalcini during World War II.

I became acquainted with her papers after the war. Of course, I accepted her version, but I felt that the analysis of the effect of limb extirpation could be carried further and that a collaboration with Levi-Montalcini might lead to the clarification of still unresolved issues, such as the nature of the target-produced agents that had been postulated in my paradigm. I wrote to Dr. Levi and asked whether Dr. Levi-Montalcini would be interested in working in my laboratory for a year. She consented and arrived in St. Louis in the fall of 1947. We agreed to repeat the limb bud extirpation experiment once more and, as the first step, to pay special attention to the finest details in the response of the spinal ganglia. Fortunately, we chose her preference; if my preference of the motor columns, which are more homogeneous than the ganglia, had prevailed, NGF would not have been discovered in my laboratory. The experiments and observations on the slides were done by Dr. Levi-Montalcini. I followed her work and discoveries with intense interest, and we were in close communication all the time. The one year originally planned was extended, and eventually she stayed in the department for 25 years; in due time, she was promoted to a full professorship.

Within a short time, Rita had made an important observation: beginning at 4.5 days of incubation, pyknotic neurons appeared in the brachial ganglia on the side of the operation. Degeneration reached its peak at days 5 and 6, and declined thereafter. The peak period coincided with the arrival of the axons at the target area. Few healthy neurons were left in pre-hatching stages. This finding was a welcome confirmation of the conclusions she had reached on the basis of her earlier work. But a much more exciting surprise was in the offing: when she surveyed other regions, she found the same pattern of neuronal degeneration in cervical and thoracic spinal ganglia that had not been affected by the operation. This was the momentous discovery of naturally occurring neuronal death. In our joint publication (Hamburger and Levi-Montalcini, 1949), we stated: "Substances necessary for neuroblast growth and maintenance would not be provided in adequate quantities, when the limb bud is removed" (p. 493), and "in early stages, cervical and thoracic neurons send out more neurites than the periphery can support. They are highly susceptible to environmental conditions" (p. 495). We mentioned in passing that cell death was found also in the normal brachial lateral motor column.

The obvious next project was to identify the maintenance factor for spinal ganglia, presumably a chemical agent. We looked for tissues that were more homogeneous than limb tissue and implanted skin, muscle, brain, and liver fragments in the place of limb buds. The results were not

conclusive. At this critical moment, I received a reprint from my former student, Elmer Bueker, who was then at the anatomy department of Georgetown University. In his Ph.D. dissertation, he had learned to implant limb buds with and without the adjacent spinal cord into the coelomic cavity. In his publication, he described the implantation of mouse sarcomas 180 and 37 into the coelomic cavity. The tumors had been invaded by axons from adjacent spinal ganglia (which were hyperplastic), but bypassed by motor nerves. We could not have asked for a more favorable answer to our plight. The tumors were homogeneous and available in large quantities, and they shared our interest in spinal ganglia.

We obtained mice with these sarcomas from the Jackson Laboratory in Maine and, with the consent of Dr. Bueker, Rita repeated his experiment on a large scale. Beginning at day seven, the tumors were invaded by massive bundles of sensory and sympathetic nerve fibers, but motor axons bypassed the tumors. In several cases, volume measurements of paravertebral sympathetic ganglia of 13- to 15-day embryos involved in tumor neurotization, showed a 5- to 6-fold enlargement. Area measurements of spinal ganglia that sent axon bundles to the tumors in 9- to 13-day embryos showed a 2- to 3-fold increase. Again, motor fibers did not enter the tumors. "All available data indicate that the sarcomas 180 and 37 produce specific growth promoting agents which stimulate selectively the growth of some types of nerve fibers but not of others" (Levi-Montalcini and Hamburger, 1951, p. 349). In a subsequent publication (Levi-Montalcini and Hamburger, 1953), we reported that tumors implanted in the chick chorioallantoic membrane (a vascularized membrane underneath the shell) likewise induced great enlargements of sympathetic ganglia, although they were far removed from nerve centers. Hence, the hypothetical agent can be transported by diffusion, though in normal development it is transported retrogradely in axons, as shown in the earlier experiment.

At this point, identifying the chemical agent produced by the tumor became our highest priority. We realized that we needed the collaboration of a biochemist. In 1953 we were joined by a young postdoc, Stanley Cohen, who was recommended to us by a friend in the medical school, Martin Kamen. We could not have wished for a more brilliant or more congenial collaborator. He isolated NGF protein in the late 1950s. As is well known, it became the progenitor of a large family of growth factors. The Nobel Prize was awarded to Dr. Levi-Montalcini in 1986. Stanley Cohen shared it for the discovery of the epidermal growth factor, which had its roots in observations he had made on newborn mice treated with a tumor fraction. In the mid-1950s, I withdrew from the project. I could no longer contribute to it because of its biochemical nature; but of course, I followed its progress with keen interest. I think that the collaboration of an experimental embryologist, a neurologist, and a biochemist contributed a great deal to the success of this project in which NGF was discovered and characterized.

Spontaneous Motility

Early on, I had been interested in problems of animal behavior. In fact, I had planned experiments on birds before I left Freiburg for Chicago. In the many years of experimentation on chick embryos, I had noticed that their motility showed strange features. In the 1960s, I decided to make a systematic study of this phenomenon, which had not received much attention so far. A lively interest in embryonic behavior had existed in the 1920s to 1940s, but it had faded. According to the behaviorists, who dominated psychology at that time, behavior begins, by definition, with the first responses of the embryo to stimulation, and the stimulus-response mode is maintained throughout development. A lone outsider, Dr. George Coghill, who at that time studied the behavior of salamander larvae, maintained that behavior is integrated from the first movements of the head eventually to swimming and feeding, and that local reflexes originate secondarily by what he called "individuation." His findings were supported by detailed parallel studies of the development of neural structures and synapse formation. I had met Dr. Coghill in Woods Hole in the 1930s and had long discussions with him and admired him, but at that time I was deeply involved in other scientific questions.

A glance at undisturbed chick embryos shows that they do not conform to either one of the two models. A closer inspection reveals two characteristic features. The first characteristic is that the movements of the different parts—head, body, wings, legs, beak, and eyelids—are uncoordinated until late in the incubation period. Any part can move simultaneously with any other part. The wings do not move simultaneously, nor do the legs alternate. The other characteristic is periodicity; activity periods alternate with inactivity periods. When motility begins at 3.5 days of incubation, the activity periods are brief, followed by long periods of quiescence. Gradually, the activity phases lengthen, and after day 13, motility is interrupted only by short inactivity periods. This pattern suggests that stimulation plays no role in the motility. It seems that we are dealing with nonreflexogenic, *spontaneous motility*.

Together with a group of capable and enthusiastic doctoral and postdoctoral fellows, I spent the 1960s analyzing spontaneous motility. This concept received strong support from the observation that motility begins at 3.5 days of incubation with the bending of the head, but the first response to stimulation cannot be elicited until 7.5 days of incubation. This finding agrees with the observation on mitotic activity. I found that we had not been the first to discover prereflexogenic motility in the chick embryo. The distinguished German psychologist, William Preyer, had reported in his book *Spezielle Physiologie des Embryo* (1885) exactly the same finding, that chick embryos become responsive to stimulation four days after the onset of motility. He had called the prereflexogenic movements "impulsive."

The obvious next step was to design a deafferentation experiment. We chose the right leg for this purpose. In 2- to 2.5-day embryos, the dorsal half of the lumbar spinal cord, which includes the precursors of the spinal ganglia, was extirpated. To exclude sensory input from the brain and rostral spinal cord, a segment of the posterior thoracic spinal cord was also removed. The motility of the deafferented legs was tested in 8.5- to 17-day embryos; of course, they were not responsive to stimulation. The controls were embryos in which only the posterior thoracic segments had been excised. The activity phases of the embryos were about 40 percent shorter than those of normal embryos. The completely deafferented embryos showed a pattern of activity exactly identical to that of the controls. Thus, spontaneous motility extends throughout most of the incubation period. We concluded: "The experiment proves that the overt cyclic motility of the leg is the result of discharges generated in the ventral part of the spinal cord, and that sensory input neither initiates nor sustains the motility" (Hamburger et al., 1966, p. 148). The experiments were done in collaboration with Eleanor Wenger and Ron Oppenheim.

We did follow up the idea that spontaneous motility is the result of electrical discharges of spinal cord motor neurons. This experiment required electrophysiological equipment that was not available in my laboratory. I enlisted the help of Dr. Tom Sandel, chairman of the psychology department. Drs. Ron Oppenheim, Robert Provine, and Sansar Sharma did the experiments, which were done again on the legs. An electrode was placed on the dorsal surface of the lumbar spinal cord and then lowered in incremental steps. Polyneuronal burst activity was highest in the ventral region. The bursts were exactly synchronous with the activity phases of the leg all the way from four to 21 days of incubation. To ascertain that the electrical discharges caused the motility, and not vice versa, Provine curarized the embryos and recorded from the sciatic nerve; the periodic bursts persisted. Thus, our paradigm was confirmed beyond doubt. Finally, in collaboration with C.H. Narayanan and Michael Fox, I did a thorough study of motility in rat fetuses. We found the same pattern of periodic random movements as in chick embryos. The main differences are that the rat fetus is more advanced; it has legs with toes when motility begins, and it has no prereflexogenic period (see general review in Hamburger, 1973). Spontaneous motility had been observed occasionally in earlier times, but it was ignored because it was in conflict with the basic tenet of the behaviorists. I assume that the paradigm of uncoordinated, periodic spontaneous motility has now been adopted for all embryos and fetuses of warm-blooded vertebrates.

It is obvious that the uncoordinated movements of the chick embryo are not suitable for its escape from the shell. Hatching requires a coordinated, goal-directed activity. A search of the literature revealed, to our astonishment, that bits and pieces of the hatching process had been

described, but no coherent picture of it had ever been presented. The best description so far dated back to de Réaumur in the 1750s! Why had no poultry scientist found it worthwhile to study this critical event? Ron Oppenheim and I spent several months of intense concentration on what turned out to be a very complex sequence of integrated movements that begins at incubation day 17 and ends with hatching on day 21. Our observations were published in 1967.

Return to Trophic Interactions

Strangely enough, the discovery of neuronal death in normal spinal ganglia by Dr. Levi-Montalcini in the late 1940s remained almost unnoticed for several decades. Levi-Montalcini herself never returned to this topic. I decided to set the record straight for the lateral motor columns. I studied first the effects of leg bud extirpation (Hamburger, 1958) and then the loss of neurons in normal embryos (Hamburger, 1975). I made counts of neurons and of degenerating cells on both sides of the lumbar motor columns. The pattern was strikingly similar in both instances: the maximum number of mature motor neurons was present on the fifth day of incubation. Shortly thereafter, degeneration began, reached its peak on the sixth to eighth day, and was nearly completed on the ninth day. The neuron loss amounted to about 40 percent in normal embryos and to more than 90 percent in embryos in which the leg bud had been removed. Thus the conclusions derived from the corresponding analysis of spinal ganglia were confirmed for another neural unit. In the meantime, it has been established that most units in the central and peripheral nervous system lose 40 to 50 percent of differentiated neurons in the course of normal development. As a rule, this happens when their axons reach their target structures. This finding means that my paradigm of 1934 has universal validity. While one of the two agents postulated in the paradigm, the one regulating the size of the spinal ganglia has been identified as the NGF protein, the ongoing search for the trophic agent sustaining motor neurons is also close to a solution.

The last phase of my activity in the laboratory, between 1976 and 1981, was devoted to an extension of the analysis of trophic interactions. I shall give a brief account of the results. In an experiment with Margaret Hollyday (1976), leg buds were transplanted in front of the normal leg buds. The transplants were sparsely innervated by thoracic and anterior lumbar nerves. Cell counts of the lateral motor column showed that from 11 to 17 percent of the motor neurons that would have died, were rescued. In an experiment with Judy Brunso-Bechtold (1979), gel pellets impregnated with labeled NGF were implanted subcutaneously in the leg of 10-day embryos. The embryos were processed for autoradiography eight hours later. All lumbar dorsal root ganglia on the side of injection were labeled selectively, showing once more that

growth factors travel retrogradely in axons to their perikarya. Finally, we subjected the capacity of NGF to sustain the survival of sensory neurons to a particularly stringent test; in collaboration with Joe Yip, wing buds were extirpated in two-day embryos and small doses of NGF were injected into the coelomic cavity. The dosage was increased with advancing age of the embryos. Again, the majority of sensory neurons were kept alive (Hamburger and Yip, 1984). All these findings, together with similar results obtained in mammals, prove convincingly that NGF is the naturally occurring trophic maintenance factor for dorsal root ganglia.

The Stage Series of Chick Embryos

The Hamburger-Hamilton stage series of the chick embryo, published in 1951 and republished in 1992, has been adopted by most developmental biologists who work on chick embryos. It was conceived at a meeting of the Society of Zoologists in Chapel Hill, N.C., when Howard Hamilton told me that he was preparing a new edition of F.R. Lillie's widely used *Development of the Chick*. I already knew Hamilton well; he had been a student of my friend, Benjie Willier, and was then a professor of zoology at Iowa State College in Ames, Iowa. I pointed out to him that the description of stages in Lillie's book was entirely inadequate—it was based on chronology, that is, days and hours of incubation. The pitfalls of this method are discussed in the introduction to the stage series. We agreed to prepare a description that would be based on readily recognizable morphological criteria. I quote from my afterword to the 1992 edition: "Development is a continuum and all stage series are frames taken from a film, as Dr. Harrison once put it. The major issue is to decide which frames to designate as stages. The two ground rules are: that the stages can be identified unequivocally by one or more morphological features, and that successive stages are spaced as closely as possible. . . .In the first week, the changes are so rapid that the stages are only hours apart. During the second half of incubation, the stages are a day apart" (Hamburger, 1992, p. 275). I identified the stages of 2- to 9-day embryos and Howard identified the others. A good deal of the success can be ascribed to the excellent photographs, done by our students and collaborators.

The idea of a stage series was not new to me. Since my student days, I had been made aware of one of the basic tenets in experimental embryology: to be precise in identifying the stage of development at which a particular event or interaction occurs. And we were familiar with the prototype: Harrison's stage series of the salamander, *Ambystoma*.

The Hamburger-Hamilton stage series is still one of the most frequently quoted publications in developmental biology. It owes this record to two facts: it is a tool, and not a report of a new discovery; and the number of investigators using chick embryos is still rising. For me, the greatest reward is the fact that in all these years, nobody has suggested to me a change or improvement.

Teaching

Teaching has been an essential part of my academic life. I tried to convey to students the satisfaction one gets from the mastery of a broad field and from the elucidation of the complex interplay of forces in evolution and development. And I enjoyed the contact with young people. I prepared my lectures carefully. For advanced courses, I read the pertinent literature before each lecture. I had complete notes, but usually I spoke freely. I think students liked my style of lecturing because it was lucid and, at the same time, exacting.

I regularly taught the course in comparative anatomy and embryology which was then obligatory for premedical students. In this, I was joined by my colleague, Florence Moog. At first we taught it in the traditional way: one semester comparative anatomy and one semester embryology. Then Florence had the idea to integrate the two fields and to deal with each organ system, such as the skeleton, first from the developmental and then from the evolutionary point of view. At my suggestion, she wrote a manual for the course which was adopted widely. Florence was a congenial partner for several decades.

An innovation of far greater impact was my design of a laboratory course in experimental embryology shortly after my arrival in St. Louis. It was taught to a small group of 10 to 12 advanced undergraduate and graduate students every other year. I knew that doing experiments on living amphibian embryos and watching the outcome was one of the most exciting experiences imaginable. I realized also that the course required a high degree of manual skills and perseverance, and much extra time, because water had to be changed, drawings and protocols had to be made at short intervals, the larvae had to be fed, and the high mortality, for which we then had no remedy, made it necessary to do many experiments. I was careful in the selection of students and, despite all the difficulties, the course became a great success.

The semester began a few weeks before the amphibian breeding season, and all instruments were prepared when, early in March, we made field trips to ponds at the outskirts of St. Louis to collect salamander and frog eggs, the mainstay of the course. In addition, we used planarians for regeneration experiments. After a few years, I decided to share my innovation with my colleagues; I wrote *A Manual of Experimental Embryology* that was published in 1942, and a revised edition appeared in 1960 (Hamburger, 1942, 1960). The detailed description of each experiment was preceded by the theoretical and conceptual premises of that experiment. Apparently many institutions introduced a similar course; when the manual went out of print in the 1980s, it had sold more than 10,000 copies.

Administration

The central administration of Washington University has always been liberal and broadminded. Throughout my tenure as chairman of the zoology

department, from 1941 to 1966, I was on good terms with a succession of chancellors and deans. As I have mentioned, my friend Tom Hall was dean of the Faculty of Arts and Sciences during half of that period. He was unique in that he involved the entire faculty in lively discussions of fundamental issues in teaching and general education; he created several committees for this purpose, which met regularly for a year or two. I served on this and numerous other committees and attended endless faculty meetings, most of them of little consequence.

One of the outstanding scholars whom Tom Hall, as dean, brought to Washington University was Tom Eliot, who became chairman of the department of political science. We happened to be neighbors in a suburb; our families became friends, and our children were playmates. Everybody recognized Eliot's superior administrative abilities, and he became chancellor when that position became vacant. He was instrumental in a substantial strengthening of the zoology department, by adding a large new building dedicated to research. He obtained half of the required funds from the Monsanto Chemical Company in St. Louis, after which the building is named. I obtained the other half from the National Institutes of Health (NIH). I introduced Tom Eliot to the NIH authorities in Washington, D.C. who were in charge of funding. They were familiar with my work and the discoveries that had been made in my laboratory, and we had no difficulty in getting what we needed. Thus, Monsanto Biological Laboratories were opened in 1964.

I do not remember details of my considerable administrative work; that means that all went smoothly, thanks primarily to my congenial colleagues. Mine was the first department in which two women, Florence Moog and Rita Levi-Montalcini, became full professors; and the first laboratory in which the work of two Nobel Laureates was initiated. Until the mid-1950s, all research was funded by the Rockefeller Foundation; thereafter NIH took over. In those golden days, the majority of grant applications were funded; I never had a rejection. I was the last chairman of zoology. After my retirement, the zoology and botany departments were combined to form the biology department.

Historical Writings

When my experimental work came to an end in the early 1980s, I turned to the history of my special fields of interest, experimental embryology and neuroembryology. I do not know when and how I acquired my historical perspective. But early on, I was aware of the fact that significant changes and innovations in the continuum of the history of biology are brought about by creative minds who combine intuition with profound thought, keen powers of observation, and mastery of a particular methodology. Names like Carl Ernst von Baer, Santiago Ramón y Cajal, Wilhelm Roux, and in my own orbit, Hans Spemann, Ross Harrison, Rita Levi-Montalcini, and Johannes Holtfreter come to mind.

My most ambitious project was the book *The Heritage of Experimental Embryology* (Hamburger, 1988). Several considerations attracted me to this enterprise. First and foremost, I saw the German contributions to experimental embryology during the first half of this century as an exciting story with a modest beginning, several highlights, and an ending that was actually a transformation of Spemann's organismic approach to a reductionist, cellular, and eventually a molecular approach. I was an eyewitness to some of the most important discoveries in Spemann's laboratory, but not an active participant because my Ph.D. dissertation was not in the mainstream of the Spemann school; hence I could be objective and critical. I knew all and befriended some of the main participants and developed a close personal relationship with Spemann and Holtfreter, the key players in this saga. Another motive was the consideration that the literature I dealt with was written in German and that my book would make the prevailing ideas and experiments accessible to a readership not conversant with the German language.

Of my contributions to the history of neuroembryology, I mention only one essay, which I think contains an original idea: a lecture given at the annual meeting of the Society for Neuroscience in 1987 and published in *The Journal of Neuroscience* (Hamburger, 1988), titled "Ontogeny of Neuroembryology". I suggested that modern developmental neurology represents the confluence of two originally very different currents of inquiry that were based on different frames of reference and different methodologies. The histogenetic approach was founded by the German histologist, Wilhelm His, and the Spanish histologist, Santiago Ramón y Cajal, in the late 1880s and the 1890s. They established the neuron and axonal outgrowth theories and thus refuted the then prevailing reticular theory of axon formation. In doing so they created modern neuroanatomy and an understanding of the wiring of the central nervous system. The mastery of the silver impregnation method by Ramón y Cajal was crucial in this enterprise.

The causal-analytical, experimental approach was introduced by Ross Harrison of Yale University in the early 1900s, using amphibian embryos. He made two crucial contributions: the invention of the tissue culture method, by which he confirmed the axon outgrowth theory; and the introduction of the limb transplantation experiment, which became the model for the analysis of nerve pattern formation and of the interactions between nerve centers and their target structures. He provided his many students and followers, including myself, with challenges for a lifetime. I was fortunate, indeed, to have two men of this stature, Spemann and Harrison, as my guides.

Travels

A short trip to Berlin in 1937 turned out to be my last crossing of the Atlantic Ocean for two decades. My family spent the summers of 1936 to 1945 in Woods Hole, where I taught in the embryology course. This left no time to

travel elsewhere. In the summer of 1947, I taught a course in the zoology department of the University of Chicago. At last in 1948, we got a chance to spend a carefree vacation in the Colorado Rockies and to visit Mesa Verde. In 1950, I taught summer school in Berkeley, and we had an opportunity to get acquainted with the attractions of the West Coast—the redwoods and the Sierra Nevada—truly a New World to the European immigrants.

In the spring of 1951, my family suffered a severe setback. My wife was struck with schizophrenia and was hospitalized for a decade. I visited her regularly and avoided long absences. But in the summer of 1954 I accepted an invitation to attend a meeting of embryologists in Oxford, where I reported on the spectacular effects of mouse tumors on spinal and sympathetic ganglia. I used the opportunity to visit the continent, and after two decades was reunited with colleagues and friends in Germany and Switzerland. In 1958, an international group of biologists gathered in London to celebrate the centennial of Darwin's *Origin of Species*. I gave a talk and had the unpleasant experience of having my briefcase, including notes and slides, stolen shortly before my lecture. I managed to improvise and to make my point with the aid of a blackboard. Then I spent several weeks in Germany, Austria, and Switzerland, in the company of my younger daughter, in a newly acquired Volkswagen. I finally saw Freiburg again, and I hiked in the Alps with my brother and his wife.

In 1960, I spent six weeks in Japan. I think that the first contact of Westerners with Japanese culture makes them aware of its much more formal style. But, of course, I found myself immediately at home in the laboratories of my fellow embryologists. In Tokyo, I spent several weeks with Dr. T. Fujii and his many students, among them the son of the emperor. The large museum introduced me to Japanese art which made an enduring impression on me. My hosts in Nagoya were two friends from my German past, Drs. Tuneo Yamada and Tadao Sato. Of several other places I saw, Kyoto was by far the most impressive; its temples and shrines, and the oldest temples in nearby Nara, are unsurpassed. A unique event was an audience with Emperor Hirohito at his biological laboratory on the palace grounds; he was an ardent marine zoologist. I was introduced to him by Dr. Sato, who had been his assistant years ago. For almost an hour, the emperor was an interested listener to my report on my research, and he inquired about my visits to the Japanese laboratories. He was anything but imperious; he was cordial and professional in the conversation translated by Sato. I later published an account of this visit (Hamburger, 1962).

In 1961, my wife was discharged from the hospital and moved to be near our daughter in California. Now I was free to travel, and I took full advantage of the opportunity. In the 1960s and 1970s I spent most summers in Europe. The most vivid memories are visits with my friend Fritz Baltzer in Bern and with Professor Karl von Frisch, well known for his studies on honey bees and their language, at his Austrian summer residence in Brunnwinkel.

My second trip to Japan, in 1965, was to a joint meeting of American and Japanese embryologists that I had helped to organize. About 20 Americans and 40 Japanese met in Tokyo for several days. I do not want to go into detail, but mention only that Howard Schneiderman gave the welcoming address in Japanese. Afterward, we Americans visited the laboratory in Fukuoka on the island of Kiu-shu, and the active volcano of Mount Aso, with red lava—a rare sight.

My friend Ernst Hadorn in Zürich arranged two trips to Africa for about 20 of his academic colleagues and me in 1972 and 1974. We traveled in two buses across the wildlife preserves of Kenya and Tanzania. The encounters with herds of elephants, zebras and giraffes, baboons, packs of lions, and thousands of flamingos populating the lakes are unforgettable.

Concluding Remarks

In retrospect, I realize the extent to which my scientific perspective has been shaped by my mentor, Hans Spemann. I do not share his vitalistic world view (Weltanschauung), but I do share his organismic creed, which implies that everything developmental biologists explore occurs in the context of the living, developing organism. This creed is entirely compatible with a rigorous reductionist analysis of development, all the way down to the molecular level.

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