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A Biographical Memoir by
JANE OVERTON

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PAUL ALFRED WEISS was a gifted biologist who worked in the fields of growth, differentiation, and neurobiology over a period of five decades. The precision and breadth of his thought and elegance of his experimental design had a major influence on the development of these fields and on aspects of medicine as well. Some of his early views, which seemed innovative at the time, have become commonplace today. In addition, he took an active role in the affairs of scientific societies, where he promoted interaction between diverse disciplines.

Paul Weiss was born on March 21, 1898, in Vienna, Austria, the son of Carl S. Weiss, a successful businessman, and Rosalie Kohn Weiss. The major cultural interests of the family lay not in science but in music, poetry, and philosophy. An uncle stimulated young Paul's interest in Science. In 1916 Paul received his bachelor's degree and immediately entered the Austrian army, where he served for three years during World War I as an officer in the artillery.

At the end of the war Weiss began his university study at the Technische Hochschule in Vienna, having decided on a career in mechanical engineering. He soon shifted his interest to biology, where he was introduced to the newest results of Edmond B. Wilson, Edwin G. Concklin, and Theodor Bovari, which led to his continuing interest in dynamic causation in biology. He chose physics as his minor subject, and this, with his training in mathematics and engineering, had a strong effect on his later work in biology. Weiss's work was carried out under Hans Prizbram, director of the Biological Research Institute of the Academy of Sciences in Vienna. In his thesis, published in 1922, he studied responses of butterflies to light and gravity, arguing that the nervous system cannot be reduced to a rigid tropistic machine, but that the elementary steps in behavior are subordinated to the state of the whole, a view he extended later in studies of the vertebrate nervous system.

Weiss's nonscientific activities centered on music (he played the violin), sports, and travel. In 1926 he married Maria Helen Blaschka. After receiving his degree he worked in a number of European laboratories and traveled and lectured widely. Weiss later moved to the United States where career opportunities were greater. He became an American citizen in 1939. He taught first at the University of Chicago and later moved to Rockefeller University. In 1947 he was elected to the National Academy of Sciences.

During the period in which Weiss worked in Europe he initiated research in several areas that he was to return to later, most notably in cellular differentiation during regeneration, neural coordination of movement, and patterns of cell growth in tissue culture. In his studies of regeneration in newts he demonstrated that regeneration of the limb involved not merely the reformation of each tissue from the corresponding tissue of the stump, but differentiation of skeletal elements from non-skelatinous tissue, since a normal limb could form after removal of all skeletal components from the stump.

In subsequent work with the newt limb, Weiss was able to show that whole limbs could be transplanted and would become enervated and capable of movement. Movement of the grafted limb was fully coordinated and synchronized with the adjacent host limb, suggesting a relation between central and peripheral coordination. He tested this relation by muscle transplantation in mammals in the surgical clinic of Bier and, while at the Hungarian railway station there, obtained an adult frog found in nature with two supernumerary limbs in full functional condition, which moved in a manner that confirmed his experimental findings. The frog was featured in his European lectures and the idea of the "natural experiment" became a teaching device and later found its way into his text and teaching lectures.

Weiss's initial studies in tissue culture involved observation of the pattern of outgrowth of cells into the medium. He was able to modify the direction and intensity of outgrowth of chick heart fibroblasts by stretching the plasma clot in which cells were cultured over a small triangular frame. This produced three areas of preferential outgrowth with a marked orientation, indicating that fibroblasts responded to the orientation of the substrate.

In 1931 Weiss received a Sterling fellowship to work with Ross G. Harrison at Yale, where he continued his earlier tissue culture work, now applying it to the study of nerve growth. He obtained negative results in his study of effects of chemical attraction and electrical orientation, but was able to show that nerve fiber outgrowth, just like cell growth studied earlier, can be guided by the ultrastructure of the medium.

In 1933 he was offered a teaching position on the zoology faculty at the University of Chicago to replace Benjamin H. Willier, and in 1942 Weiss was promoted to professor of zoology. He remained at Chicago until 1954. During his twenty-one years of teaching and research at Chicago he was involved in investigation of many new areas in embryonic development and regeneration. However, the subject of neural organization and nerve outgrowth remained a central interest.

Weiss continued his studies of coordination of grafted limbs, comparing the movement of graft and control limbs using slow motion cinematography to identify the time of onset and duration of key muscles controlling each joint. Using a musical analogy, he recorded a “score” on a “staff” for each muscle; just as in orchestral music, the score records the onset and duration of each instrumental part. By this means he was able to show that activity of a grafted muscle corresponded exactly with that of the corresponding muscle of the host. Another important result of these studies was that, if movement of grafted limbs was unadaptive—for example, if reversed limbs caused an animal to approach rather than retreat from a noxious chemical—this behavior was never changed. These findings were consistent with the view that basic neural patterns of coordination were self-differentiating rather than learned.

Coordination of muscle activity was then studied in mammals. Tendons or nerves were crossed so that a flexor muscle, when activated, would have the effect of extending rather than flexing the joint. These studies confirmed the fixed patterns of reflexes, while demonstrating the much greater plasticity in higher vertebrates. Another natural experiment (in the form of a girl with three supernumerary fingers) was analyzed and confirmed earlier observations that homologous muscles have similar scores of activity. However, in this case, the pattern of simultaneous activity, which is fixed in lower vertebrates, could be modified by training, although the learned behavior failed when the girl’s attention was diverted. At this time a study was undertaken of twenty-two patients with poliomyelitis in which healthy muscles were transplanted to replace paralyzed ones. A new technique of electromyographic determination of muscle action was developed to analyze these cases. Weiss's interpretation of these carefully analyzed studies of muscular coordination in a variety of systems was based on the assumption that the path of nerve outgrowth in development and regeneration was determined by orientation of the substrate, since he had shown that substrate orientation could be a decisive factor in tissue culture. Contrary evidence was discovered later by his postdoctoral student Roger Sperry, who went on to receive a Nobel Prize.

In further studies of nerve outgrowth Weiss grafted segments of neural cord and limb some distance apart in the gelatinous matrix of the newt dorsal fin. This provided satisfactory material for observing formation of neural connections between the two grafts, but also revealed the unexpected observation that the limb, when enervated, underwent continuous spontaneous convulsions, indicating a new finding, namely that spontaneous rhythmic discharges were a characteristic property of nerve pools. This was in contrast to prevalent views at the time. Studies of this kind, as well as many observations under a variety of experimental conditions of nerve growth in tissue culture in the embryo and in regeneration, led to the concept that in nerve formation pioneering fibers first grew out followed by application of later fibers, termed "fasciculation," and finally, upon reaching the end organ, by towing.

At this time Weiss was also concerned with a number of other problems related to morphogenesis, among them growth control of homologous organs and the dependence of cell patterns in cartilage on mechanical factors. In addition, he wrote his textbook *Principles of Development,* which was regarded as the leading text in the field.

With the entry of the United States into World War II he served as a member of the Conference on Peripheral Nerve Injuries of the National Research Council and took part in the planning and development of work related to repair of injured nerves, a major problem of war surgery. Under a program of the Office of Scientific Research he undertook a study of nerve growth and regeneration that might apply to nerve surgery and be of potential clinical value. New techniques of nerve repair were devised, the most successful of which was a sutureless one in which the two free ends of the severed nerve were united by an arterial sleeve that became attached to the nerve ends by clotted blood and lymph. In such preparations the erythrocytes degenerated, but the fibrin network persisted and became separated from the arterial sleeve by proteolysis, leaving a cylindrical clot subject to mild tension by the nerve. Tension oriented the fibrin and formed a straight bridge that the outgrowing axons followed, just as had been demonstrated a decade earlier by subjecting a fibrin clot in tissue culture to tension. Frozen dried and rehydrated arterial sleeves were also used with the view of developing tissue storage. Later, tantalum foil was used to form the sleeve. If heated under specific conditions, this normally pliable foil became elastic and could be formed into a coil of appropriate diameter. A patent was granted for this process. Surgical techniques developed in animal models were later extended to clinical application in selected Army and Navy hospitals.

The fundamental research that came from his laboratory during this same period included many aspects of nerve outgrowth and neural connections, but a major finding at this time was the demonstration that the outgrowth of neurons and their maintenance depended on axonal flow from the nucleated cell bodies in nerve centers. A pressure block (by suture, by passage into a fibrotic zone such as a scar, or by other means) caused piling up of the material of an intact axon on the nuclear side and reduction in diameter on the distal side of the constriction. With release of the constriction the characteristic conformation was regained. The pile up of axonal material formed complex nodules and spirals, which, when analyzed and reproduced in a mechanical model, showed that the effect could be produced by translational movement of the axon as a whole. Application of a second block distal to the first had the same result, indicating that the growth process was continuous.

During World War II Weiss concentrated on neurological problems exclusively, but, when the war was over, he returned to following up his interests in morphogenesis. He focused on cell-cell and cell-substrate contacts and developed a concept of molecular interaction, applied to problems of growth and morphogenesis. This scheme was termed "molecular ecology" and was presented in very general terms with diagrams of complementary geometric shapes between adjacent cell surfaces and between cell and substrate. There was widespread interest in this paper at the time.

Weiss designed a number of experiments consistent with his molecular hypothesis illustrating the specificity of cell behavior. In amphibian larvae grafts of epithelial sheets fused readily with adjacent tissue if the tissues were adjacent to each other normally; otherwise, the grafts were expelled. Chick embryonic pigment cells injected into early chick embryos by a vascular route persisted and matured only in regions that normally formed pigment. Cartilage cells of embryonic chick sclera and limb formed very different conformations and, when dispersed and allowed to reaggregate, each cell type formed patterns characteristic of the tissue of origin. In this group of experiments perhaps the most dramatic was the finding that, when organs from chick embryos in advanced stages of morphogenesis were dispersed into single cell suspensions, pelleted, and allowed to reorganize on the chick chorioallantoic membrane, remarkably complete organ structure of the same type was reconstituted. He also initiated studies of cell substrate contacts using an early tabletop electron microscope.

In 1954 plans to change the Rockefeller Institute to Rockefeller University drew him to New York; he became one of the university's first professors and directed a new laboratory specializing in wound healing, cancer, and development and repair of the nervous system. A major interest during this time was the further analysis of axonal flow. Numerous experiments were carried out, and involved whole animal studies and tissue culture using currently available techniques, including electron microscopy, phase contrast with cinematography, and isotopic labeling. Distribution of neurofilaments and microtubules within the axon were recorded, as well as detailed behavior of neurons in tissue culture. A particularly innovative approach was the injection of leucine-H 3 into the posterior chamber of the eye where it was confined by the sclera surrounding the eyeball, yet could bathe the optic ganglion cells and permit a quantitative study of axon labeling. Although involved with detailed quantitative studies in much of his work, Weiss never lost sight of the larger picture, stating that "the realization of the intensive and incessant activity of the neuron has an immediate bearing on the problem of specific qualitative adaptability of neurons such as underlies functional plasticity of the central nervous system as manifested in learning, habituation, acquired hypersensitivities, idiosyncrasies, addictions, and so forth."[1]

He remained an active faculty member at Rockefeller for the next fifteen years, alternating his research there with occasional interruptions to teach elsewhere around the world. He served as visiting professor at ten major universities and as dean of a new graduate school of biomedical sciences at the University of Texas. He was elected a member of the American Philosophical Society (1953) and the American Academy of Arts and Sciences (1954), and received many other honors and awards. In 1979 President Carter awarded him the National Medal of Science.

Weiss's close association with European laboratories in the 1920s and early 1930s was maintained, and this brought postdoctoral students and many visitors from Europe to his laboratories at Chicago and Rockefeller. After World War II he served on a Marshall Plan commission set up to revive scientific activity in Europe.

In 1930 he came to the United States because negotiations for a job at the University of Frankfurt were terminated due to the general financial collapse in Germany. Realizing that conditions for scientific work on the continent were deteriorating, Weiss decided to devote his energy to a country where the scientific spirit was in the ascendancy—the United States. Jane Oppenheimer reports that in 1950 Weiss was asked at an informal gathering why he worked so hard and was overheard to reply that his reason for wishing to be a good embryologist was that by doing so he might help repay the United States for what it had done for him.[2]

Paul Weiss was a gifted investigator and a stimulating and supportive teacher. His interest and enthusiasm for the subject was contagious. He put a high value on spacial organization in biological systems and emphasized its importance to students and colleagues alike. He felt that, "The complex engineering performances of technology are a much more pertinent model of the nature of morphogenesis than are the more elementary phenomena dealt with in basic physics and chemistry."[3] At a time when respiratory intermediates were still being discovered he deplored the fact that some biologists seemed to consider the cell a bag of enzymes. When demonstrating tissue culture procedures for students in the days before commercially available media, he personally prepared plasma and embryo extract. While doing so he invariably held up two tubes, one with intact embryos and the other with embryos after homogenization, and pointed out with delight that both tubes contained the same molecular components. He took a serious interest in teaching and in programs that integrated the various specialties in biology. He also put great emphasis on terminology. In his general embryology course he devoted several lectures to topics such as how the meaning of a given embryological term had changed over time or how a given term used currently by different investigators might have somewhat different meanings. Bernice Grafstein points out that many of his terms have become part of our scientific discourse. "Axonal flow," for example, although neither strictly axonal nor strictly flow still crystalizes a complex set of related ideas and is used today in cataloging. Other terms such as "neurobiology" and "developmental biology" have this same characteristic.[4] In referring to Weiss, James Ebert has noted that "his life has been a life devoted to improving science and its language."[5]

Weiss gave considerable time to the biological community and served as a member and officer of the Society for Development and Growth (president, 1939-41). He was president of the American Association for the Advancement of Science (1952-53), the Harvey Society (1962), and the International Society for Cell Biology (1962). He emphasized to his colleagues and students the importance of interaction between various biological disciplines. He wrote, "While scientific workers are more and more constrained into narrower and narrower confines in which to pursue their specialties, science as a whole cannot develop into a healthy and proportionate organism unless specialists will leave their burrows on periodic occasions and meet on common ground."[6]

In the case of the Society for Development and Growth (now the Society for Developmental Biology), he was strongly instrumental in designating the society, and more important the discipline, as developmental biology and not plant and animal embryology. The study of bacteria, fungi, and viruses were promptly incorporated into the new discipline, which played an important role in promoting the later development of molecular genetics as an integral part of the study of development.[7]

I HAVE DRAWN ON background material provided by the National Academy of Sciences and on part of Weiss's extensive publications. He republished more than fifty of his review articles that he considered scattered in less accessible locations in book form, *Dynamics of Development* (1968) and *Biomedical Excursions (*1971). His text book *Analysis of Development* was reprinted in facsimile in 1969.

NOTES

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3. P. Weiss. *An Introduction to Genetic Neurology,* p.1. Chicago: University of Chicago Press, 1950.
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