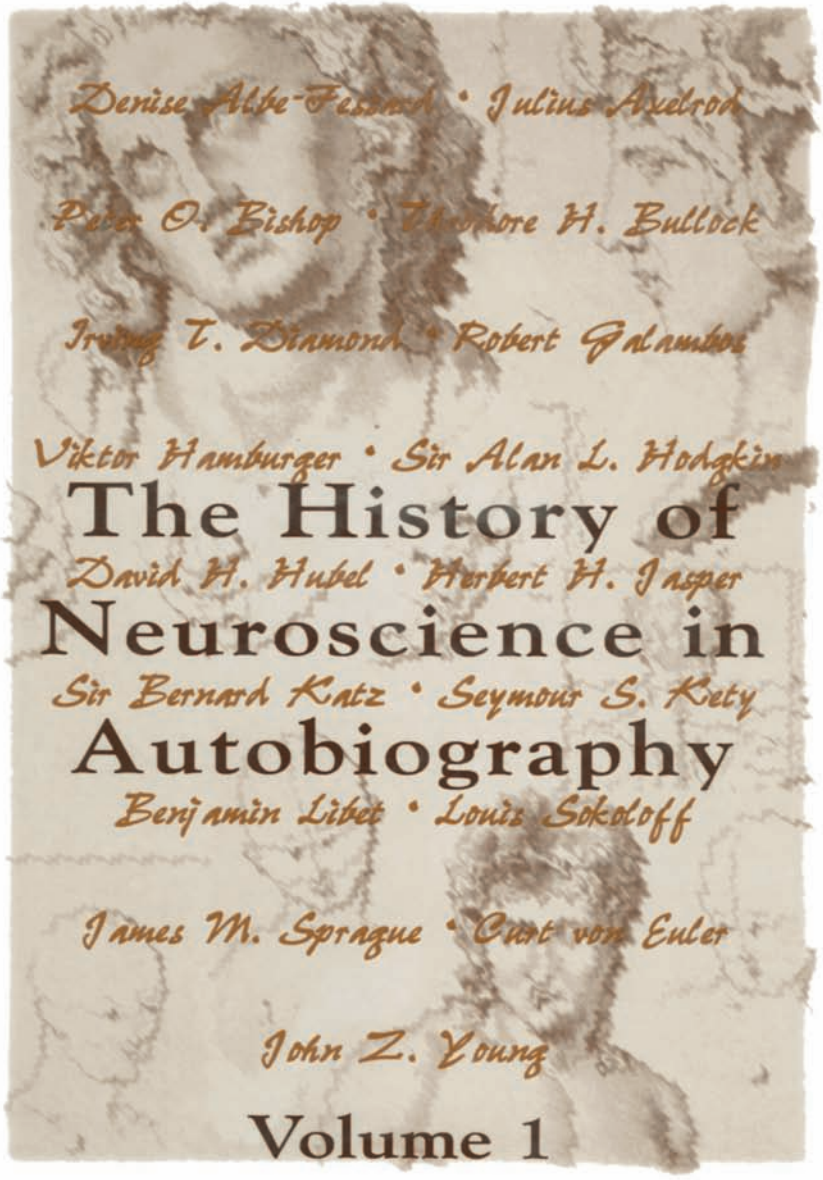

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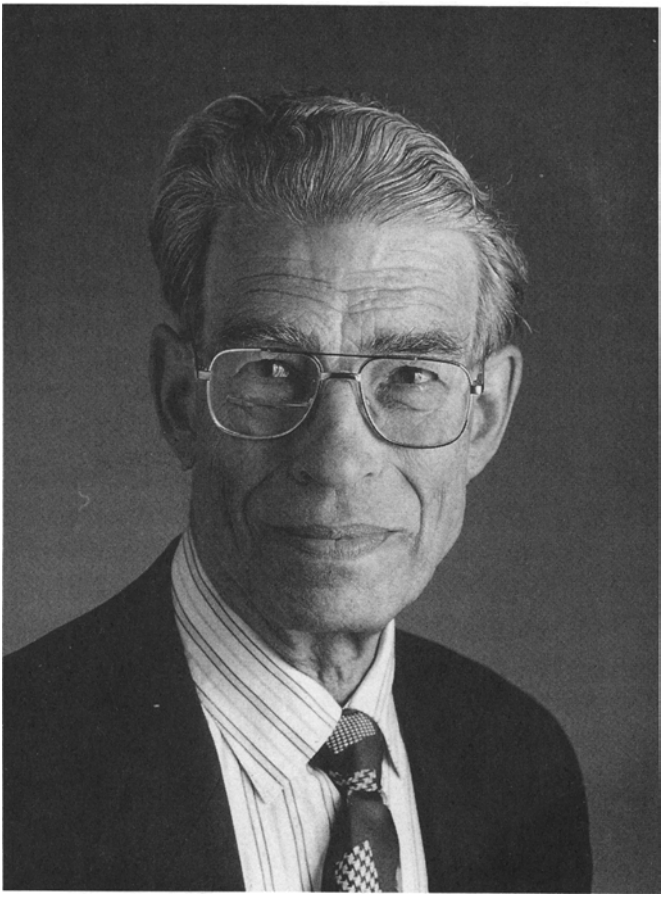

Curt von Euler

BORN:

Stockholm County, Sweden
October 22, 1918

EDUCATION:

Karolinska Institute, B.M., 1940
Karolinska Institute, M.D., 1945
Karolinska Institute, Ph.D., 1947

APPOINTMENTS:

Karolinska Institute (1948)
Professor Emeritus, Karolinska Institute (1985)

HONORS AND AWARDS (SELECTED):

Norwegian Academy of Sciences (foreign member)

Curt von Euler conducted pioneering work on the central control of motor systems, brain mechanisms of thermoregulation, and on neural systems that control respiration.

Curt von Euler

Background

How did I come to devote my life to neurophysiology rather than to a clinical discipline? Why, in the first place, did I choose to study medicine rather than another branch of biology or other subjects within the natural sciences? And what guided me to make the turns on the road and follow what appeared to be bypaths? There are no simple answers to such questions, but certainly a number of accidental circumstances have intervened in important ways.

In attempting to give a brief account of the development of my personality and my research, I will try to point to some of the essentials as I see them—how one thing led to another and the intellectual flow of ideas, concepts, and research activities.

I am well aware of my inability to give a just and comprehensive account of the strong conceptual influences that scientific advances exerted on me and of the large number of colleagues in my own and other fields with whom I have exchanged ideas and facts.

My Family

I was born just before the end of World War I, on October 22, 1918, and grew up in a suburb of Stockholm. I arrived into a family devoted to science. My father, Hans von Euler, was professor of biochemistry at the University of Stockholm (Stockholms Högskola at that time). My mother, Beth, was also a chemist.

My father, born in 1873 in Augsburg, Germany, grew up in Munich. After a brief period as a student of art and painting, he decided to turn to the natural sciences. In less than three years, he earned his Ph.D. degree in Berlin and was offered a postdoctoral position in Walther H. Nernst's laboratory in Göttingen. In 1897 my father received an offer from Svante Arrhenius to work with him for three years. However, before this period was finished, my father was offered a permanent position at Stockholms Högskola, first in physics, later in chemistry, and finally in biochemistry. In 1902 he married Astrid Cleve, herself a prominent scientist. She is the mother of my older half brothers and half sisters. Of these, Ulf S. von

Euler is well known to the scientific world as a professor of physiology at the Karolinska Institute, and he became a Nobel laureate in 1970.

My father and my mother, Beth Uggles, married in 1913. I am their third son. Their fourth child, my youngest brother, was born in 1929, the year my father won his Nobel Prize in chemistry. In autumn 1929, my father's new Institute for Biochemistry was inagurated, financed by generous donations from the Rockefeller and Wallenberg Foundations. The Institute, which was located in central Stockholm, also contained a private residence for my father and his family. Thus, from the age of 11, I grew up in the private apartment in the Institute for Biochemistry. The large number of prominent scientists whom I met as guests of my parents had a strong impact on me and my future. Among these I have strong memories and lasting impressions of Sir Henry Dale, Sven Hedin, Albert von Szent-Györgyi, Hans Spemann, Herman Staudinger, Adolf Butenandt, The Svedberg, Paul Karrer, and Ragnar Granit.

During my last years in high school, my interest in biology grew increasingly stronger, and I decided to devote my coming university studies to biology. I was advised by several people, including my older half brother Ulf (who was already an associate professor in physiology at the Karolinska Institute), that a medical school might provide a better biological education than a university faculty of natural science. I followed this advice and applied for entrance to the Karolinska Institute.

Immediately after finishing high school in 1937, and before beginning my studies in medicine at the Karolinska Institute, I spent four months at the University of Freiburg im Br. in Germany. There I attended lectures in chemistry by Herman Staudinger and in physical chemistry by Walter and Ida Noddack. I also had the opportunity to listen to some lectures and seminars on embryology given by Hans Spemann. I had met him the year before at home in Stockholm when he received his Nobel Prize "for his discovery of the organizer effect in embryonic development." In 1937 he had been forced to retire several years before the normal retirement age, because of his courageous opposition to the Nazi regime. He had, however, retained a laboratory in his old institute and was allowed to give some seminar lectures to the staff members. It was a great privilege for me to be able to meet him again and to attend his seminars.

My Time as a Student at the Karolinska Institute

I began my medical studies at the Karolinska Institute in the autumn of 1937. My teachers in medical chemistry were Professor Einar Hammarsten, a leading biochemist and a powerful figure on the faculty; Professor Hugo Theorell, who later became head of the Nobel Institute for Biochemistry; and Assistant Professor Torbjörn Casparsson, who later became the head of the Nobel Institute for Cytology. The chair in physiol-

ogy was vacant. This vacancy was filled by Associate Professor Yngve Zotterman, who later became professor of physiology at the Veterinary College of Stockholm, and by Ernst Barany, who later became professor of pharmacology at the University of Uppsala. In 1939 Ulf von Euler was given the chair in physiology. Pharmacology was taught by Professor Göran Liljestrand, a prominent physiologist and an influential member of the faculty and of the Nobel Committee.

My clinical studies began in the spring of 1940. In parallel with the courses and hospital duties, I devoted time to working on neurophysiological problems in my brother's department.

In 1940 Ragnar Granit, professor of physiology at the University of Helsinki, accepted an offer by the Karolinska Institute to become the head of a new department of neurophysiology established especially for him. He accepted this offer over a similar offer from Harvard Medical School for him to become director of the Howe Laboratory of Ophthalmology in the Massachusetts Eye and Ear Infirmary. I had already met Granit on a few occasions and was impressed by his work on the retinogram and his evidence for inhibitory mechanisms in the retina. I saw a great opportunity to work under him and to receive some guidance for my steps on the road toward Minerva.

During the later part of my medical studies, I became more and more interested in cognitive science and problems of mental disturbances in psychiatric disorders. I spent almost a year working in psychiatric clinics and hospitals, with the idea of devoting myself to experimental psychiatry. Granit gave me the good advice that if I wanted to accomplish something of scientific importance in experimental psychiatry, I should first acquire solid knowledge in the physiology of the nervous system. He offered me a place in his department doing full-time research with the aim of accomplishing a doctoral thesis.

The Nobel Institute for Neurophysiology

Ragnar Granit had devoted himself to research on vision since the beginning of the 1920s. When he arrived at the Karolinska Institute, his main research project was to determine the neurophysiological foundation of color discrimination and color vision. However, he was anxious to ensure that the research activity in his new department had a broader neurophysiological base than only his own area of interest and urged his younger collaborators, Carl Gustav Bernhard and Carl-Rudolf Skoglund, to develop research territories of their own. Skoglund performed important studies on the problems of accommodation. He also dealt with the "artificial synapse" at the cut end of a mixed peripheral nerve. The many problems pertaining to impulse propagation in the peripheral nerve have been an important part of the research at the Nobel Institute, a field which came to be pursued mainly by Bernhard Frankenhaeuser and his many collaborators.

Granit also wanted to promote clinical application of neurophysiology and develop neurophysiological research within clinical departments. Therefore, soon after his arrival in Stockholm, he asked his nearest clinical colleagues, the professors of neurology Nils Antoni, neurosurgery Herbert Olivecrona, and ophthalmology Wilhelm Nordensson, to recommend staff members who would do neurophysiological full-time research leading to a doctoral thesis. The idea was that these researchers would subsequently be in a good position to start new lines of clinical research in their own areas based on solid theoretical ground. The call was soon answered by Drs. Erik Kugelberg in neurology, Lars Leksell in neurosurgery, and Gösta Karpe in ophthalmology. All three later became professors in their fields and introduced neurophysiological research facilities in their clinics, an approach that also spread to the other medical schools in Sweden.

In 1948, the Nobel Institute of Neurophysiology moved to the new campus of the Karolinska Institute. The solemn inauguration took place in June 1948. Among the foreign guests were Professor E.D. (later Lord) Adrian of Cambridge and Professor Detlev Bronk, then president of the Johns Hopkins University, later president of the Rockefeller University.

The move to the new building and new campus meant a large expansion in space, facilities, equipment, and technical staff. In addition, the scientific staff was enlarged and its profile broadened. The neuroanatomist Bror Rexed was asked to join the staff; I had been promoted to associate professor; and Anders Lundberg and Bernhard Frankenhaeuser, both assistant professors, had been recruited. From then on, there have always been five to seven well-educated postgraduate guest scientists from different parts of the world working in the department for one or two years, contributing to the flourishing and multifaceted scientific and social atmosphere.

At the end of the 1940s Granit was about to leave his research in retinal physiology, to which he had devoted 25 years of his life. He had decided to take up motor control problems and analyses of those mechanisms at different levels of the central nervous system that guide our movements. Lars Leksell had just finished his fundamental work, under Ragnar Granit's supervision, on the gamma fibers and their efferent control of muscle spindles. This work opened up a new and virgin territory to be explored.

My Start and Early Development

I joined a productive department in October 1945 shortly after my marriage. My wife, Marianne, was a hospital nurse specializing in x-ray and surgery. Our lifelong companionship and our growing family have been of great importance during all stages in my career.

Granit had suggested that I start by studying problems of the peripheral nerve. He gave me a recent paper by Carl Gustav Bernhard and him-

self on peripheral nerve as a model sense organ. They had shown that rapid local temperature changes stimulate peripheral nerve fibers to discharge action potentials in the manner of a sensory organ. Granit suggested that I investigate the thermal sensitivities of nerve fibers of different diameters and different functional types. Thick myelinated fibers, I found, were selectively excited by local cooling, whereas thin fibers in the delta and C-range were excited by local warming but not by cooling. These differential excitabilities were associated with corresponding differences in membrane potential equilibrium. From these studies I turned toward investigating the temperature-sensitive structures in the hypothalamus and their role in control of body temperature.

I have had a preference for selecting my research projects across the borders of conventional disciplines. I have also tried to choose projects that, in addition to being of basic scientific importance, seem to have some clinical relevance. My inclination has had a mutually beneficial effect both on my own research and that of many guest scientists who had clinical backgrounds.

My investigations of the central thermosensitive mechanisms and temperature regulation set out from the fundamental work of Horace Magoun, Stephan W. Ranson, Harrison, and John Brobeck. They had demonstrated the presence of warm-sensitive structures in the anterior part of the hypothalamus and showed that warming these structures elicited panting. In my work I showed that these thermoceptive structures respond to temperature changes by eliciting local "generator potentials" or "receptor potentials." The sensitivity was high—10 mV per 0.1°C temperature change. The structures from which these temperature potentials could be recorded correspond closely to those from which thermoregulatory reactions could be elicited by focal warming, suggesting that these structures are causally involved in the elicitation of thermoregulatory reactions.

I found similar specific potential changes could be obtained in response to alterations in the osmolality of the blood from an area in the hypothalamus between the supraoptic and paraventricular nuclei. This area had been described by Ernest B. Verney in Cambridge and Bengt Andersson in Stockholm as being responsive to changes in osmolality of the blood and giving rise to changes in urine excretion.

The next step in my search for structures in the brain exhibiting sensory receptor properties took me into the area of chemical regulation of respiration. It had long been known that an increase in metabolic carbon dioxide production and a decrease in the oxygen level in the blood lead to compensatory changes in ventilation. With Ulf Söderberg, a graduate student, I investigated the mechanisms by which the carbon dioxide concentration in the blood is sensed and causes adaptive changes in ventilation.

At that time it had only recently been established that oxygen-sensitive structures are located in the carotid body, a discovery that had earned

Corneille Heymans the 1939 Nobel Prize in physiology or medicine. Yngve Zotterman with Ulf von Euler and Göran Liljestrand had been able to record the afferent impulse traffic in the nerve from the carotid body in response to changes in Po_2. However, the neural or receptive mechanisms underlying the ventilatory responsiveness to CO_2 or pH were still unknown. The common belief was that the excitability of respiratory neurons in the medulla oblongata was directly influenced by these humoral factors.

I was able to demonstrate, in work with Söderberg, that there is a genuine and specific receptor system sensitive to carbon dioxide in the medulla. This system responded with slow potential changes proportional to the stimulus in a manner similar to the receptor potentials in the hypothalamic temperature-sensitive and osmosensitive structures. Furthermore, we recorded tonic impulse discharges in proportion to the alterations in $P_{CO}{}^2$, resembling the characteristic behavior of a sensory organ.

These and other findings enabled us to conclude that the chemoreceptive structures in the medulla are involved in the chemical regulation of respiration and are sensory receptors in the general sense of the concept. These results were soon confirmed by my colleague in clinical physiology, Professor Hąkan Linderholm. He reported that certain groups of poliomyelitis patients showed a specific absence of ventilatory response to carbon dioxide, whereas their respiratory responses to a lack of oxygen and other respiratory stimuli were unimpaired.

Later, in the 1960s, Professor Hans Loeschcke in Bochum and his collaborator Marianne Schlaefke, reported in a long series of excellent papers on the localization and properties of these central chemoreceptor structures at the ventral surface of the medulla. Still later, in the 1970s, jointly with Professors Neil Cherniack, Fred Kao, and Dr. Ikuo Homma in my laboratory, I obtained strong evidence in support of this view, as will be mentioned in more detail.

My Sabbatical Year in Cambridge

In 1950 I attended my first international congress of physiology in Copenhagen. There I came to know, among many others, the Cambridge physiologists Alan Hodgkin, Andrew Huxley, and Richard Keynes, and the neuroendocrinologist Geoffrey Harris. By this time I had abandoned my plans for a career in experimental psychiatry. Instead, I wanted to expand my knowledge of central control functions and homeostasis mechanisms. I was fascinated by the work of Professor Harris on the hypothalamic control of the pituitary gland and the endocrine system. I talked with Ragnar Granit about venturing (for a while) into neuroendocrinology. Granit responded positively to this idea and encouraged me to discuss the matter with Harris. Harris generously offered me an opportunity to spend a year with him in the Physiological Laboratory in Cambridge.

Supported by a British Council Scholarship, I arrived in Cambridge in early September 1951. Only shortly before, Harris, with Dr. John D. Green, had established that the blood flow in the hypothalamo–hypophysial portal vessels was directed from the hypothalamus down to the anterior pituitary gland, contrary to the opinion held by many other researchers. Furthermore, Harris had demonstrated that the release of gonadotropic hormones was controlled by hypothalamic structures via this vascular route.

Harris invited me to join him in studies of the central nervous control of thyroid-stimulating hormone. We developed a method to follow the rate of release of thyroid hormone in intact, awake animals by the use of radioactive iodine. In a series of papers we reported on profound changes in the release of pituitary thyrotropic hormone in response to various central nervous stimuli and showed that these effects were mediated by the hypothalamo–hypophysial blood flow.

My collaboration with Harris gave me a solid insight into this new field. It also brought me into contact with important people in this area, including Wilhelm Feldberg, Marthe Vogt, Edith Bühlbring, and Herman Blaschko. It was Feldberg who had drawn Adrian's attention to the brilliancy of Geoffrey Harris and suggested that he deserved a staff position and facilities in the Physiological Laboratory.

The year in Cambridge also gave me the opportunity to follow closely the work of Alan Hodgkin, Andrew Huxley, and Bernard Katz, who frequently came up from London. William Rushton, whose friendship I had gained during his sabbatical year in Stockholm with Granit in 1948 to 1949, had invited me to stay with he and his wife Marjorie during my sojourn in Cambridge—hospitality which I greatly enjoyed and benefited from in many ways.

Shortly after my arrival in Cambridge, Adrian, whom I had met several times in Stockholm, was appointed Master of Trinity College and resigned from his position as head of the Physiological Laboratory. I had the great privilege of being present at the interesting and special installation ceremony, unique for Trinity College, that took place in the Great Court of Trinity.

Back home in Stockholm I continued the studies on the control of thyroid-stimulating hormone, in part with a Swedish-Chilean guest scientist, Björn Holmgren, on leave from the University of Santiago de Chile. Our aim was to determine where and by what mechanisms the thyroid hormone exerts a self-regulating feedback control of the pituitary secretion of thyroid-stimulating hormone. By employing a new microinjection technique it was possible to show that thyroxin exerts its thyrotropin-inhibiting action directly on the anterior lobe itself, without the mediation of central nervous structures. However, we also showed that intact vascular connections with the hypothalamus are necessary for this self-regulation to be "set" and adjusted to the levels of thyroxin production required by the highly variable metabolic and other kinds of demands.

These investigations concerning control of thyroxin secretion were followed up by Ulf Söderberg in his extensive doctoral thesis. In elegant experiments he was able to measure continuously the arterio-venous radioiodine difference, with a temporal accuracy of a few seconds. He further demonstrated that in the presence of thyrotropin, the rate of thyroxin secretion is controlled not only by thyroid-stimulating hormone but is also dependent on the rate of blood flow through the thyroid gland.

Return to Temperature Regulation

In parallel with my studies on the homeostasis mechanisms controlling thyroid hormone secretion, I returned to problems of temperature regulation. With Söderberg, I showed that the temperature-sensitive structures in the anterior hypothalamus exert a strong influence on the fusimotor system innervating the muscle spindles in the body's skeletal muscles. Warming these structures "silenced" the spindle discharges effectively, whereas cooling enhanced their rate of discharge. Thus, we demonstrated that the fusimotor mechanisms controlling muscle activity participate in the regulation of body temperature.

In light of this discovery we turned our attention to the reactions of cerebral cortical activity to small changes in body and hypothalamic temperature. A slight lowering of the temperature induced a low-voltage, fast-activity pattern in the electrical activity of the cortex characteristic of wakefulness, attention, and arousal. A modest increase in temperature, on the other hand, led to a slow-wave, high-voltage sleep-type pattern. Body temperature obviously exerts important influences on the general activating and inhibiting systems as described by H.W. Magoun, G. Moruzzi, and their schools.

Our studies further suggested that the concept of homeostasis had to be redefined. We found that the homeostatic mechanisms seem to strive for an optimization of the factors controlled—optimal with respect to the demands of the whole organism—rather than for maintenance of constancy, as originally suggested by Walter B. Cannon. Optimization is beginning to be regarded as an important mechanism providing the great adaptability characteristic of higher animals and especially prominent in humans. This view recently has been emphasized by several researchers, such as N.S. Cherniack, C.S. Poon, and M.C. Moore-Ede.

Our results also had bearing on the intricate interactions that arise because different homeostatic mechanisms employ, to a certain extent, the same effector mechanisms. For example, ventilation for gas exchange and polypnea for temperature regulation both involve the breathing apparatus, and regulation of water and salt balance is used both in the control of osmolality and as a mechanism involved in temperature regulation. In conditions of lowered oxygen availability, energy and thereby oxygen, can be saved, for example, by raising the temperature threshold for shivering.

Demands on one control mechanism cause considerable changes in the thresholds or "set points" of other controllers. The different systems influence one another like the different parts in a mobile sculpture.

Sabbatical Year at the University of California, Los Angeles

The bridge that our work had built between temperature regulation and the work by the Magoun school on the general action of the activating and inhibiting systems of the reticular formation made me keen to work for a year in Magoun's group. With my wife and two of our boys, I spent the academic year of 1955 to 1956 in south Long Beach and the department of anatomy at the University of California, Los Angeles (UCLA). There, however, I became engaged in studies on the electrical responses of cerebrocortical structures to direct and indirect afferent stimuli.

In collaboration with Professor John D. Green (whose earlier work with Geoffrey Harris is mentioned above) and Dr. Giovanni Ricci, I analyzed the potential responses which in the earlier literature had been attributed to activity in the dendrites of pyramidal cells. We demonstrated that certain previous conclusions did not hold up against critical analysis.

In other related projects, Green and I took advantage of the relatively simple design of the cortical networks in the hippocampus. Among the many results of this collaboration, which continued at the Nobel Institute in Stockholm during Green's sabbatical year with us, was the interesting finding that the hippocampal pyramidal cells frequently exhibit an "inactivation process." This process initially causes a brief excitation which, as the depolarization continues to deep depths, turns into inhibition by inactivation. In the hippocampus the inactivation process was often followed by another type of inhibition, hyperpolarization.

My collaboration with John Green in Los Angeles and Stockholm led to a warm friendship, which was broken by his sudden and tragic death in early November 1964. A heart attack while working in the laboratory ended his life in the middle of his career.

During my stay in Magoun's department and during meetings and extended travels on the American continent with visits to many laboratories, I made many important and inspiring contacts, and made some long-lasting bonds of friendship, a few of which will be mentioned later.

Motor Control of Breathing Behavior

I felt a growing desire to return to studying the control of respiration. Our rapidly increasing knowledge about motor control, gained to a great extent by Ragnar Granit and his group, offered valuable models for studies of the control of respiratory movements. Conversely, the respiratory system offered unique opportunities for analyses of physiologically

induced and naturally occurring movements in anesthetized or decerebrate animals, whereas experiments on the motor control of limb muscles depended largely on reflex activation and artificially induced movements. Studies of the breathing apparatus offered the additional advantage that the movements of this system are rhythmically recurrent and physiologically well controlled. The aims of the breathing movements are definable in terms of the quantitative relationship between the chemical drive and the magnitude and rate of respiratory movements. Thus, it seemed possible that respiratory control could serve as a model for the control of volitional movements.

My return to problems of respiratory control systems was directly attributable to Dr. Harry Fritts, who had come from Professor André Counand's laboratories at Columbia University and Bellvue Hospital in New York to work with Ragnar Granit. However, Harry Fritts wanted to work with me on respiratory problems. I saw this as a valuable opportunity to benefit from his knowledge and clinical experience in cardiovascular and respiratory physiology. This association led me into a long period of research on different aspects of respiratory control mechanisms and breathing behavior. Fritz and I performed an extensive quantitative analysis of the different proprioceptive and other afferent control systems involved in respiratory motor control. Among the different results of these studies I would like to mention only the findings that the vagal Hering-Breuer reflexes are not mediated by the fusimotor muscle spindle route, that inspiratory motor activity is facilitated proprioceptively, and that manifest stretch reflexes were demonstrated in the intercostal muscles.

The next step was to investigate the presence, properties, and functional roles of intercostal muscle spindles during spontaneous breathing, with and without intact gamma efferents, and to record impulse activity in the gamma fibers innervating the intercostal muscle spindles. In a long series of studies with Drs. Vaughn Critchlow from Baylor University in Texas, S. Rutkonski from Warsaw, Gösta Eklund from Uppsala, and Mario Corda from Florence, we showed that during inspiration the fusimotor activation of the inspiratory intercostal muscle spindles is strong enough to provide an additional excitatory drive on the inspiratory motoneurons. This was the first report on fusimotor contribution to the performance of physiologically induced movements. Later, such studies were performed by Karl-Erik Hagbarth and Ake Vallbo in humans and by Grigori Orlovski and Marc Shik in decorticate cats walking on a treadmill.

In the beginning and middle of the 1960s, Dr. T.A. Sears in Canberra and later in London, studied the activity of intercostal motoneurons and their reflex activation using intracellular recording techniques. The results, both from Sears' group and our own, have demonstrated that control of breathing is designed in much the same way as control of other skeletal motor systems. However, there is an important difference

between the control of intercostal muscles and of the diaphragm with respect to the role of muscle spindles. Whereas the intercostal muscles are well supplied with spindles, the diaphragm has only a scanty supply of these proprioceptors. With Mario Corda I performed a semiquantitative analysis of proprioceptive afferents from the diaphragm, which revealed a clear dominance of Golgi tendon organ afferents over the few muscle spindle afferents present.

This finding explains why a stretch reflex could not be demonstrated in the diaphragm. However, intercostal-to-phrenic reflexes act to control the diaphragm, as I demonstrated in collaboration with Dr. Emilio Decima from UCLA.

Dr. Moran E.J. Campbell of Middlesex Hospital, London, and his colleague Jack B.L. Howell of Manchester University had advanced the hypothesis that muscle spindles in the respiratory musculature might, under certain conditions, cause the pathological sensation of dyspnea, or breathlessness. We could now provide evidence that the intercostal muscles have a rich supply of fusimotor-controlled muscle spindles. Whether these, under certain circumstances, can be responsible for the sensation of breathlessness has been an interesting issue of discussion at many international symposia. It remains an open question.

Systems Analysis

My devotion to studying homeostasis and central error-correcting mechanisms had led me toward the science of "systems analysis," control theory, and cybernetics. The term cybernetics, originally coined by André Ampère to denote the science of "government," was revived by Norbert Wiener who used it to mean the "science of control and communication in animal and machine." Norbert Wiener's classical book on *Cybernetics*, which appeared in 1948, had a great impact.

However, information processing, regulation, and control mechanisms had been important issues for a long time in the physiological sciences. I have already mentioned the fundamental experimental and conceptual achievements of Claude Bernard and Walter Cannon. As early as 1868 Joseph Breuer and his teacher and mentor Ewald Hering had published their classical work on "self-steering of respiration through *nervus vagus*," in which they demonstrated the powerful feedback control of tidal volume and respiratory rate, although they did not use the term feedback.

The application of information theory and the mathematics of systems control and feedback regulation to problems of biological control functions, inspired by Norbert Wiener, opened new and quantitative approaches. In respiratory physiology, for instance, these new concepts provided possibilities for formalized quantitative analysis of the chemostatic control of ventilation and rhythmogenesis.

In 1956, during a visit with Professor Walter Rosenblith at the Massachusetts Institute of Technology, he introduced me to Norbert Wiener, a memorable event for me. I met Wiener briefly again in Stockholm in 1964 a couple of hours before his last lecture, which I also attended. In the intermission between the two lectures scheduled for him, he had a heart attack which tragically ended his life.

Could a systems analysis approach be fruitful in my work? To obtain guidance in this question, I contacted Professor Lazlo von Hàmos, head of the department of regulation and control sciences at the Royal College of Technology in Stockholm, and an eminent expert in the field. Von Hàmos was one of the many brilliant Hungarians who, for political reasons, left their country after World War II and enriched the cultural and scientific communities in many Western countries. This contact led to a long lasting and fruitful collaboration between our departments.

Among other beneficial effects this collaboration had an important impact on the work of my graduate student, Gunnar Lennerstrand, concerning quantitative analysis of static and dynamic properties of primary and secondary muscle spindle receptors in the intercostal muscles. Lennerstrand's extensive work also included mathematical model simulations, which led to new and more detailed quantitative understanding of the functional roles of fusimotor-muscle spindle control of movements. Lennerstrand's interests later shifted to problems of eye motor control. He is now a leading expert in that field and is professor of ophthalmology at the Karolinska Institute.

I had suggested to another of my graduate students, Jörgen Fex (now professor and head of the department of cochlear research at the National Institute on Deafness and Other Communication Disorders (NIDCD) in Bethesda, Maryland), that he extend the work of Robert Galambos on the crossed efferent fibers destined for the cochlea. Galambos had shown that stimulation of these fibers causes a reduction in the impulse potentials of the acoustic nerve. Jörgen Fex's work developed into an extensive and impressive study of the sensory feedback control system of auditory activity in centrifugal and centripetal cochlear fibers.

Control of Respiratory Pattern

I then turned to problems concerning the quantitative relationship between the ventilatory parameters tidal volume and respiratory rate in response to alterations in the demand for ventilation. Our aim was to elucidate the mechanisms involved in optimization of these parameters to ensure minimal respiratory work (Otis, Fenn, and Rahn, 1956) or minimal muscular effort (Mead, 1960). My starting point was the work by the Oxford group, led by Drs. D.J.C. Cunningham and B. Lloyd. They had shown that in humans there is a linear relationship between ventilation

and tidal volume as ventilation increases in response to increased chemical drive. The slope of this relationship was independent of the kind of chemical drive. In contrast, changes in body temperature caused selective changes in respiratory rate, altering the slope of this relationship.

With Drs. Fernando Herrero from Madrid (now professor of neurology in Seville) and Ira Wexler from the Downstate University in Brooklyn, New York, we confirmed and extended the results of the Oxford group. We showed in cats that after vagotomy there is hardly any change in respiratory rate in response to increments in chemical drive; only the tidal volume gets larger. Thus, the increase in respiratory rate and the shortening of inspiratory duration caused by chemical stimulation depend almost entirely on volume feedback from the pulmonary stretch receptors.

The next steps along these lines were taken with Drs. Francis (Frank) Clark from Purdue University and Charles Knox from the University of Minnesota. We analyzed the central reflex excitability curves of the Hering-Breuer vagal inspiration inhibiting reflex. The volume threshold for this reflex decreases steeply as a function of time from the beginning of the inspiratory phase. This volume threshold curve determines, we found, the vagal reflex control of the inspiratory duration. Because we also found that the expiratory time depends mainly on the preceding inspiration, the whole cycle time, and thus the respiratory rate, are largely determined by the volume threshold curve.

In humans we found that tidal volumes must be one and a half to two times greater than the resting tidal volume to reach the volume threshold and thus influence the duration of the inspiratory phase. Later, Dr. Ikuo Homma (now professor at Shiba University in Tokyo) demonstrated that in humans stimulation of intercostal muscle spindles by vibration causes a shift downward of this volume threshold, so that it becomes effective even at eupneic tidal volumes. This finding of Homma confirms in beautiful fashion the finding by Irja Marttila and John Remmers that the effects of secondary muscle spindle endings of intercostal muscles and pulmonary stretch receptors add together in inhibiting inspiration.

Next we studied the mechanisms by which inspiration is terminated in the absence of volume feedback. We found that the "off-switch" threshold increases with increasing chemical drive at the same time as the inspiratory activity increases. These two effects tend to affect the "off-switch" in opposite directions, and often they balance each other fairly well. Thus, in the absence of vagal feedback, inspiratory duration remains relatively constant. Only because of this increase in "off-switch" threshold can tidal volume increase in response to increased chemical drive. An increase in hypothalamic temperature also causes an increase in the rate of rise of inspiratory activity and volume. However, in sharp contrast to the effect of chemical stimulation, increased temperature causes practically no concomitant change in the "off-switch" threshold which, therefore, is reached earlier as

the rise time is quickened. The result is that inspiratory duration is shortened and respiratory rate is increased.

An "Off-Switch" Model

A realistic computer model of the neural construct of the inspiratory "off-switch" mechanism was gradually developed by stepwise alternations between animal experimentation and computer simulation trials incorporating the latest experimental results. These model studies proved to be a valuable aid in designing the most crucial and elucidating experiments. This work was done in collaboration with Bertil Roos from Professor von Hàmos' department at the Royal College of Technology and Graham Bradby from the University of Bristol, England. The scheme of the network derived from these efforts is still considered relevant in essential details.

Influence from Structures in the Dorsal Pons on Respiratory Pattern—The Phenomenon of Apneusis

The anatomical structures of Lumsden's "pneumotaxic center" were identified in 1971 by Morton Cohen at the Albert Einstein College, New York. Cohen found that this "center" of Lumsden's corresponds to the medial parabrachial and Kölliker-Fuse nuclei (NPBM-KF) in the rostral pons. Lesions of these nuclei, combined with bilateral vagotomy, usually result in apneusis; whereas electrical stimulation within these structures causes either inhibition or excitation of inspiratory activity, depending on the precise site of stimulation. Cohen further found that the characteristics of the inspiration-inhibiting action of such stimulation in this area closely correspond to those of stimulation of vagal stretch receptor afferents and to lung inflation.

I wanted to build on Cohen's results to explore further the inspiratory "off-switch" characteristics and to achieve better understanding of the functional role of the "pneumotaxic center" in the control of respiratory patterns. Projects with these aims were carried out with Dr. Theresa Trippenbach, a guest scientist from the Institute for Neurophysiology of the Polish Academy of Sciences in Warsaw (directed by Professor Witold Karczewski, with whom I have had a long-standing collaboration), Dr. John Remmers from Dartmouth College in Hanover, New Hampshire (now professor of physiology at the University of Calgary), and Dr. Irja Marttila from Helsinki, who had a background in neurosurgery. Trippenbach and I developed a technique for graded electrical stimulation of the inspiration-inhibiting loci in the NPBM-KF, which allowed us to map the entire excitability curve for the inspiratory "off-switch" functions under conditions of different chemical drives and temperatures. Using this technique we showed the existence of a close neural link between the neurons generating the inspiratory activity—the inspiratory ramp—and neurons involved in the "off-switch" mechanism.

We also studied the functional role of the NPBM-KF in the respiratory control system. Our results suggested that the main role of these structures in the control of respiration was to provide tonic excitatory input to the inspiratory "off-switch" mechanism, thereby lowering its threshold. We could detect no other influence on the generation of respiratory rhythm, and we could not confirm the hypothesis that these structures play a role in the mediation or integration of the chemical drive.

Our experiments led us to believe that the inspiratory "off-switch," when first activated, gives rise to complete inhibition in an "all-or-nothing" fashion. However, John Remmers, with Magdi Younes, showed in elegant experiments that when the "off-switch" threshold has just been reached, the inhibition is at first graded and reversible, and only thereafter develops into its final, irreversible second stage. Later, Diethelm Richter in Heidelberg (now in Göttingen) and his group identified the neural correlates of these two stages of the inspiratory "off-switch" using intracellular recording techniques. Current concepts of the design of the neural network and its synaptology originate largely from Richter and his collaborators.

In summarizing our findings concerning the excitability and the threshold of the "off-switch" function, we can conclude that these mechanisms are influenced by a corollary of the inspiratory ramp generator, chemical drive, input from the hypothalamic temperature regulating structures, vagal pulmonary stretch receptors, and intercostal muscle spindle afferents of the group II type, as well as by a tonic influence from the rostral pontine NPBM-KF.

Basic Rhythm Generation, Pattern Formation, and Drive Integration

Several researchers studying rhythmic motor activities such as locomotion and mastication, have advocated that it is advantageous to discuss the underlying mechanisms under two headings: mechanisms generating the basic pattern, and mechanisms for adaptive control and pattern formation. This, I have argued, is also useful when discussing control of breathing.

However, the generation and control of a behavior depends not only on the anatomical and functional connectivity of the pattern-generating neural networks but importantly also on the excitatory tonic drive inputs to those networks. This is certainly true for ventilation, the magnitude of which depends directly on the drive. The drive input to the respiratory pattern-generator originates both from the central and peripheral chemoreceptors, and from several other central and peripheral sources. Students of the chemical and neural control of respiration have paid little attention to the mechanisms that mediate and integrate these different drive factors. It can be assumed that there is a great deal of overlap and interaction among

these three sets of control mechanisms. My collaborators (in different constellations) and I have been interested in all three of these aspects.

Much of the work on the control of breathing had been concerned with the neural mechanisms underlying central pattern generation. Thus, we have learned that these mechanisms are capable of producing a stereotyped rhythmical activity even in the complete absence of all extrinsic reflexes and feedback loops, that is, when operating in an "open loop" mode. We, as well as several others, including Morton Cohen and Witold Karszervski, have studied the mechanisms involved in "fictive" breathing.

Chemoreceptors at the Ventral Surface of the Medulla

Once more, I wanted to study intracranial chemosensitive receptors responsible for the CO_2/pH-dependent drive for ventilation. Professor Hans H. Loescheke in the department of physiology at the University of Bochum and his collaborator, Professor Marianne E. Schlaefke, had already shown that these receptive structures were localized at or close to the ventral surface of the medulla. They had also succeeded in recording action potential discharges from these structures in response to changes in P_{CO_2}.

Despite our own results at the beginning of the 1950s and the impressive and extensive work of the Bochum school, some general uncertainty remained as to the functional significance of chemoceptive structures on the ventral surface of the medulla. I therefore decided to attack this problem with new experimental approaches using the technique of reversible, focal cold block.

Joining me as guest scientists in the 1960s and 1970s were Professor Neil S. Cherniack from the University of Pennsylvania at Philadelphia Medical School, Professor Fredrick F. Kao from the Downstate University at Brooklyn, and Dr. Ikuo Homma from Edi University of Tokyo. Neil Cherniack and I had first met in 1968 during my sabbatical term with Professor David Cugell at the medical school of Northwestern University. I met Neil again in 1974 at the International World Congress of Physiology in New Delhi and the satellite symposia in the Kashmir Valley arranged by my friend Professor Autar Paintal. There we agreed on a year of collaboration in Stockholm. I had known Fred Kao for a long time, an acquaintance mediated by Professor Chandler McC. Brooks, Dr. Ikuo Homma was with me for a second year. His father, Professor Saburo Homma, had spent a year with Ragnar Granit in 1958 and has since been a frequent guest in the laboratory; his son became a much appreciated member of our group.

Together, we explored the effects of transient focal cooling of areas on the ventral surface of the medulla. Cooling on certain small, restricted spots that had been described by the Bochum workers caused a temperature-dependent depression of ventilation, with complete apnea at temperatures around 20°C. This depression mimicked in great detail the effects of

decreases in P_{CO_2} and could be compensated by increments in P_{CO_2} corresponding to 3–5 mm Hg per degree centigrade.

Focal warming caused increases in ventilation with Q_{10} values between 4 and 5. Furthermore, we showed that focal cooling of the chemoceptive structures did not interfere with ventilatory responsiveness to changes in P_{O_2} or to other types of respiratory stimuli. Thus, the concept of central chemoceptors located on, or close to, the ventral surface of the medulla and responsible for the central ventilatory response to changes in P_{CO_2} had been strongly confirmed.

Using this technique of focal cooling together with other methods developed in my laboratory, we were also able to contribute to the understanding of the problems underlying instability in the pattern of breathing. These problems had interested Neil Cherniack and his collaborators for some time. By selective graded depression of the central chemoreceptors we could now confirm and firmly establish that instability, in the form of periodic breathing of the Chayne-Stoke's type, can be caused when the drive from the peripheral chemoreceptors is stronger than that from the central CO_2-sensitive receptors. Furthermore, we showed that instability is also induced when the feedback gain is increased to certain levels, as predicted from the laws of feedback regulation by Cherniack and his collaborators.

Integration of the Drive Factors

At this point I turned to problems concerning the structures and mechanisms responsible for the mediation and integration of the various drive factors. As already mentioned, the chemoreceptors at the ventral surface of the medulla did not have this function. They provided only the CO_2-related drive component. With Drs. Krystyna Budzinska from Warsaw, Tito Pantaleo from Florence, Professor Fred Kao (who had come back for another year with me), and Dr. Yuji Yamamoto (a Japanese graduate student), I set out to investigate these problems using a specially designed instrument furnished with two thin needle thermodes for transient focal cooling of small preselected spots in the brainstem.

These efforts demonstrated that a certain limited locus close to the lateral paragigantocellular nucleus about 2 mm above the ventral surface of the medulla is responsible for these integrative functions. Focal block of synaptic transmission by cooling the structures within this area to a temperature of about 20°C led to strong ventilatory depression or complete apnea, even when applied only unilaterally. This effect could not be compensated for by increased drive inputs from any other source, in sharp contrast to the depression caused by cooling the structures at the ventral surface of the medulla.

In agreement with Professor H. Arita and his group in Tokyo, we found that the neurons of this "apnea region" are characterized by tonic discharge patterns without significant respiratory modulation. Furthermore, we

found that these neurons receive convergent afferent inflow from peripheral and central chemoreceptors, muscle receptors and skin receptors, as well as from the "defense and alarm" areas in the posterior hypothalamus.

Forebrain Influences

The old problem concerning the mechanism behind the almost immediate increase in ventilation on onset of physical exercise was addressed with Drs. Richard Romaniuk from Warsaw and Antony DiMarco from Case Western Reserve University in Cleveland. A long time ago, in 1895, Jöns E. Johansson, professor of physiology at the Karolinska Institute, and later, in 1913, August Krogh and J. Lindhard of the University of Copenhagen, had advanced the hypothesis that the immediate increase in ventilation and heart rate might be mediated by corollary neural pathways from the executive motor areas in the forebrain to the respiratory and cardiac controllers in the medulla. However, experimental evidence for this kind of activation had never been reported. We decided to employ the technique of Grigori Orlovski and Marc Shik for studying the induced locomotion of decorticate cats walking on a treadmill. As a guest of the USSR Academy of Sciences, I paid profitable visits to Orlovski and Shik and their colleagues in Moscow. With the aid of their technique we showed that the respiratory controller receives direct corollary activation from suprabulbar motor control areas as soon as locomotion is initiated. Thus, we had obtained evidence suggesting that feedforward mechanisms are also at play in adapting the systems to expected changes in metabolic rate. Similar results were obtained at the same time and independently of our studies by Fred Eldridge and David Milhorn at the University of North Carolina.

My interest in systems analysis approaches to the control of breathing continued along several lines and led to the initiation of several projects jointly with Drs. Eugene W. Bruce from Case Western Reserve University and Sidney M. Yamashiro from the department of biophysics at the University of Southern California. Together, we performed dynamic studies, for example, of the neural mechanisms responsible for the control of the inspiratory ramp generation, with the aid of correlation, coherence spectral, and power spectral analyses. We found, among other things, that the trajectory of the inspiratory activity is subject to powerful feedback control. Later, the neural correlate to this mechanism was identified by Diethelm Richter and his group in Heidelberg.

Developmental Aspects of Breathing Control

For some time I had wanted to include developmental aspects in my research on respiratory control mechanisms. When Dr. Hugo Lagercrantz joined my group an expansion in this direction was assured. Hugo Lagercrantz was the

last graduate student of my half brother, Ulf, and is now professor of pediatrics and neonatology at the Karolinska Institute. Lagercrantz' doctoral thesis was an extensive and highly valued study of mechanisms underlying noradrenergic neurotransmission, with special reference to the structure and the release and uptake functions of the storage vesicles. As a postgraduate fellow he decided to shift his interest toward clinical research in pediatrics and neonatalogy. He developed a special interest in the respiratory problems of the neonatal period and the "sudden infant death syndrome," as well as in developmental changes in the roles of neurotransmitters and neuromodulators in respiratory neural networks. When Lagercrantz joined my group, he provided important new ideas and perspectives.

Several projects on the development of respiratory control functions were then being launched focusing on, among other things, the effects of various neuroactive substances and changes in these effects during development. Dr. Nanduri Prabhakar, who had spent several years working with Professor Hans Loeschecke, made valuable contributions to several of these projects as a guest scientist in my laboratory.

Hugo Lagercrantz, Nanduri Prabhakar, and I demonstrated that substance P exerts stimulatory effects both on the central respiratory mechanisms and on the peripheral chemoreceptors of the carotid body, suggesting that substance P may act as a neurotransmitter in the oxygen-controlling mechanisms. We found both of these effects to be abolished by a specific substance P antagonist.

Another focus of interest introduced by Hugo Lagercrantz concerned the effects of adenosine on respiratory control mechanisms. Adenosine, which is liberated from neuronal structures during hypoxia, was shown to exert depressant effects on respiratory functions. This finding has strong implications for an understanding of the increasing depression of fetal breathing during the latter part of pregnancy.

Nanduri Prabhakar moved on to Neil Cherniack's department at Case Western Reserve University where, among other research activities, he has continued his fundamental work on the role of substance P as a neurotransmitter in the chemoreception of the carotid body.

Psychophysics and Conscious Control of Breathing

Breathing, although highly automatic, is subject to willful intervention at any time. Even the automatically controlled breathing pattern can be altered by training. These facts raise several questions concerning the human's ability to control breathing behavior consciously. A graduate student with a background in experimental psychology, Miriam Katz-Salamon, was interested in studying these problems. That humans have the ability to judge the magnitude of their breaths had been reported by Marsh Tenney of Dartmouth College. Katz-Salamon confirmed these

results and performed an extensive and detailed psychophysical study on the ability of human subjects to estimate quantitatively different ventilatory parameters during normal and enhanced drive conditions and under different mechanical loads. All the parameters could be estimated with considerable accuracy by the subjects. She was able to show that their judgments follow Stevens' law of psychophysics which says that the objectively and the subjectively estimated magnitudes of tested parameters can be described by power functions with exponents close to or above 1.0.

Another aspect of the control of breathing in human subjects that interested me had to do with the specific demands placed on the breathing apparatus when it is used for vocalization, speech, and singing. A series of investigations was performed in collaboration with Professor Johan Sundberg from the department of speech transmission and music acoustics at the Royal College of Technology in Stockholm and with Professor Rolf Leandersson of the department of phoniatrics and speech therapy of the Karolinska Institute and Hospital. These studies were performed on both professional singers and untrained volunteers. Many new results of theoretical and practical importance on motor strategies for the precise control of subglottal pressure came out of these studies.

On July 1, 1985 I retired from my post as head of the Nobel Institute for Neurophysiology and became professor emeritus. I was able, however, to retain laboratory space, research facilities, and project grants. Professor Sten Grillner was appointed as the new head of the department. The investigations concerning neuronal design of motor control mechanisms have continued and developed in new directions, combining systems neurophysiology with the molecular biology of membrane mechanisms and neurotransmitter and neuromodulator actions as well as sophisticated neurohistological studies of the elements involved in neural networks.

Developmental Dyslexia

Since the early 1940s I have had a steadily increasing interest in the cognitive sciences, information processing, and the development of the brain. Because of these interests, in the late 1970s I was asked if I would be willing to participate in organizing an international symposium on developmental dyslexia. Although my knowledge about this complex problem was almost nonexistent at that time, I promised to introduce myself to the vast literature on this subject and to help in designing the program. I thought that an international Wenner-Gren Symposium on this topic might strongly stimulate Swedish research on reading and reading disabilities. I knew Professor Ingvar Lundberg of the University of Umeą, who had a profound interest in the international dyslexia research community, and I knew that he felt rather lonely in his field in Sweden. With Ingvar Lundberg, Ragnar Granit, Yngve Zotterman, and Gunnar Lennerstrand,

we arranged the symposium, which took place in 1980. This work led me into a steadily increasing engagement in the problem of developmental dyslexia and the work of leading scientists in the fields of linguistics, neurology, cognitive sciences, and genetics, including Norman Geschwind, Patricia Goldman-Rakic and Pasko Rakic, Verne Caviness, Albert Galaburda, Antonio and Hanna Damasio, Rodolfo Llinas, Jack DeFries, Isabelle and Alvin Liberman, Bruce McEwen, Patricia Kuhl, Oliver Zangwill, Paula Tallal, Ursula Bellugi, and many others. As a result of this activity I became deeply involved in an extensive interdisciplinary, longitudinal study of dyslexia in a region of Sweden.

At the symposium in 1980 I renewed my acquaintance with Dr. Per Uddén, whose strong personal interest in developmental dyslexia gave birth to the idea of establishing an international academy for dyslexia research. The aim of this academy was to establish a forum for interdisciplinary exchange of facts and ideas and for the fostering of research collaboration on the complex problems of developmental dyslexia and dysphasia. Norman Geschwind immediately supported the idea, as did Ragnar Granit, David Ottoson (secretary general of the International Brain Research Organization), Oliver Zangwill, Albert Galaburda, Günter Baumgartner, and I. The outlines of such an academy, its aims and goals, were drawn up at a conference hosted by Per Uddén. In 1984 the *Academia Rodinensis Pro Remediatione* (The Rodin Remediation Academy) was formally founded at a large international conference in St. Andrews, Scotland. Granit became its first president, with David Ottoson and I as vice presidents. Princess Marianne Bernadotte was elected Honorary President. The name of the academy was chosen to honor Auguste Rodin's father for the excellent way in which he treated his gravely dyslectic, albeit superbly gifted son. The implication is that this handicap should not be allowed to be an obstacle to the full development of an individual's talents and intellectual capacities, which often are above normal and sometimes eminent. The activities of the academy, which now has 100 active scientific members (seven are Nobel laureates) and 160 corresponding members, have focused mainly on arranging international symposia and conferences on different aspects of developmental dyslexia and dysphasia. The academy had arranged 23 such conferences by December 1995.

When Ragnar Granit decided in 1988 to step down from his position as president of the academy, I was elected to be his successor, a position which I now hold.

Developmental dyslexia, too, greatly attracted me because of the intriguing muldisciplinary nature of the problems involved, and the great practical importance of increased knowledge about this handicap and its often severe individual and social consequences. During the last decades, dyslexia research has entered the midst of modern neurosciences, cognitive neuropsychology, linguistics, and genetics. The advancements in

these areas gained by international dyslexia research has opened new avenues for the development of new effective diagnostic and remedial methods and phonological training strategies. It is my sincere hope that the Rodin Remediation Academy will be able to continue and expand its important work to promote dyslexia research.

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