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NOBEL LAUREATES IN NEUROSCIENCE: 1904–1981

Herbert H. Jasper

Centre de recherche en sciences neurologiques de l'Université de Montréal and The Montreal Neurological Institute of McGill University, Montreal, Canada H3C 3J7

Theodore L. Sourkes

Departments of Psychiatry and Biochemistry, Faculty of Medicine, McGill University, Montreal, Canada H3A 1A1

Introduction

Prompted by the award of the Nobel Prize in Physiology or Medicine to three of our most distinguished neuroscientists in 1981, David Hubel, Torsten Wiesel, and Roger Sperry, it would seem an appropriate time to present a brief review of Nobel Laureates in Neuroscience over the years. This provides an interesting thumbnail sketch of some of the highlights in the historical development of neuroscience since the turn of the century.[1]

The field of neuroscience has become so broad during recent years as to involve aspects of most biological and many medical sciences, as well as many discoveries in physics and chemistry. We confine our selection to the Prizes in Physiology or Medicine for discoveries directly related to the nervous system. This account is further condensed by the format of this Prefatory Chapter, but we try to overcome this limitation to some extent by giving references to some of the principal publications of each of the Prize winners in the bibliography. We present our own evaluations and

[1]Our principal source of information for this brief review has been the four-volume publication of the Nobel Foundation in 1972 of *Nobel Lectures, Physiology or Medicine 1901–1970.* This publication contains the citations and evaluations of the Nobel Committee, in addition to biographies and lectures of the Prize winners themselves. Information for the period of 1970–1981 was obtained from accounts published in *Science* and elsewhere, in addition to our personal acquaintance with the neuroscientists themselves and with their work.

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comments on the significance of the work of each Laureate for neuroscience, in addition to those of the Nobel Committee.

Out of the total of 74 Nobel Awards in Physiology or Medicine, we select 22 that we consider direct contributions to neuroscience. There were 129 individual laureates in Physiology or Medicine, some sharing an award with one or two others. Of these we have chosen 41 for this review of Nobel Laureates in neuroscience.

1904 Ivan Petrovich Pavlov

In recognition of his work on the physiology of digestion, through which knowledge of vital aspects of the subject has been transformed and enlarged.

Ivan Pavlov was born in Ryazan, a small city just south of Moscow, in 1849. He studied at St. Petersburg University, where he graduated from its Medico-Chirurgical Academy in 1879 and where he began his research in physiology. After two years of training in Germany with Ludwig and Heidenhain, he returned to become professor of pharmacology at the Military Medical Academy. He later held the chair of physiology. In 1891 he was appointed Director of the Department of Physiology of the Institute of Experimental Medicine in St. Petersburg, where for over 30 years he devoted himself to studies of conditioned reflexes. He continued his work and lectures there and abroad until his death in 1936 at the age of 87.

Pavlov's Nobel Lecture was entitled "Physiology of Digestion," although he is better known to neuroscience for his work on conditioned reflexes. This research developed from his observations on the "psychic" control of salivary and gastric secretion, which he was able to demonstrate by the use of indwelling salivary and gastric fistulae in the chronic, alert dog preparation. The sight or smell of food caused profuse secretion, which was arrested by section of the vagus nerves, and could be reproduced by electrical stimulation of these nerves in chronic preparations. A bell, the conditioned stimulus (CS) was then sounded. Eventually, the sound of the bell alone could provoke secretion.

Pavlov was greatly influenced by Sechenov's theory of the reflex mechanisms of psychic activity. His initial work, however, appeared to be concerned mainly with the psychic influences upon reflex activity, the central or "psychic" control of functions of the autonomic nervous system. With his colleagues he elaborated a series of complex forms of conditioned reflex (CR) (delayed, trace, cyclic, etc), together with second- and third-order CR, which he considered to be the mechanism for the acquisition of language and symbolic thought, or "higher nervous activity." For example, he delivered an address to the International Medical Congress in Madrid (1903) on "The Experimental Psychology and Psychopathology of Animals."

The work of Pavlov[2] and his school has had a long-lasting influence upon concepts of learning and of the brain mechanisms underlying behavior and mental function, both normal and abnormal. The precise measurements made possible by the various forms of CR paradigm still form the methods of choice for most studies on physiological mechanisms of learning.

1906 Camillo Golgi and Santiago Ramón y Cajal

In recognition of their work on the structure of the nervous system.

Camillo Golgi (1843–1926) was born in Córteno (Brescia), Italy. He obtained his medical training at the University of Padua, the second oldest university in Italy, from which he graduated in 1865. He was first attracted to psychiatry by Lombroso, and then to cellular pathology by Virchow. He began working in the histology laboratories at the University of Pavia in northern Italy, where he studied neuroglia. In 1872, unfortunate circumstances forced him to take a position in a small hospital for incurables at Abbiategrasso, where, in spite of the lack of laboratory facilities, in 1873 he developed his famous silver impregnation method for the selective staining of nerve cells. He later used gold as well. He was appointed professor of anatomy at the University of Siena in 1879, but returned to Pavia the following year to become Extraordinary Professor of Histology and to take the chair of general pathology. For his work in neurohistology and neuropathology and his studies of malaria he received many awards and honorary degrees, becoming one of the best known Italian medical scientists of his time. He became Rector of the University of Pavia before his death.

Golgi's Nobel Lecture was entitled "The Neuron Doctrine, Theory and Facts." The neuron doctrine was then a controversial subject. In spite of the elegance of his "black staining" of individual nerve cells, with all their axonal and dendritic appendages, Golgi was never convinced of the structural discreteness of nerve cells. In his Nobel Lecture he stated, "In my opinion, we cannot draw any conclusion, one way or the other, from all that has been said on the importance which different structures identified in ganglion cells have, in being for or against the neurone doctrine. . . . Anatomical arguments . . . do not offer any basis firm enough to uphold this doctrine." He believed that nerve cells were interconnected by a neurofibrillary continuity, a viewpoint strongly opposed by Cajal.

Golgi is best known for his silver staining techniques and for identifying several types of nerve cells that bear his name: The Golgi cells of the

[2]An English translation of Pavlov's *The Work of the Digestive Glands* was provided by W. H. Thompson in 1902. His work on *Conditioned Reflexes* was translated by Anrep and published in 1927. His colleague, Boris P. Babkin, wrote his biography in 1949, *Pavlov: A Biography.*

cerebellum; Golgi II interneurons with axons that remain within the local gray matter; Golgi tendon organs; and the "Golgi apparatus." His work was summarized in four large volumes, *Opera Omnia,* published in 1903.

Cajal (1852–1934) was born in Petilla, a small village in the Spanish Pyrenees. He studied medicine in Zaragoza, where he graduated in 1873, and obtained his MD at Madrid, before returning to Zaragoza where he became professor of anatomy in 1877. He later held the chairs of anatomy at Valencia and Barcelona. It was in those universities that he began his work with the Golgi silver stain, which culminated in his incomparable two volume work on the histology of the nervous sytem. In 1892 he was appointed Professor of Normal Histology and Pathological Anatomy at the University of Madrid. He remained there until his death at the age of 82.

Cajal's Nobel Lecture was entitled "The Structure and Connections of Neurons." With his own reduced silver method and his refinements of the Golgi technique, Cajal studied all kinds of cells and their interconnections throughout the nervous system, including the sense organs. His microscopic preparations, and especially his drawings, are works of precision and art that have never been surpassed. Contrary to the opinion of Golgi, Cajal gave strong support to the "neuron doctrine" that synaptic relationships between neurons are by contiguity rather than by continuity, and that each nerve cell is a separate independent biological unit. He described the dynamic polarization of the neuron and speculated on the significance of the integrative capacity of the large receptor surface of dendrites. Equally outstanding were his pioneering studies of embryonic development and degeneration and regeneration in the nervous system (Cajal 1928).

Cajal is truly one of the giants of neuroscience. His studies continue to provide a firm foundation for our knowledge of the cellular morphology of the nervous system, in spite of the modern revolution in neuroanatomy made possible with the new techniques of electron microscopy, radioautography, and cytochemistry.

Much of Cajal's work was published in a two-volume edition in French in 1909 entitled *Histologie du Système Nerveux de l'Homme et des Vertébrés* (republished in 1952–1955 as *Histologie du Système Nerveux* by L. Azoulay, Instituto Ramón y Cajal). Most of his original slides and elegant pen-and-ink drawings can still be seen at the Cajal Museum in Madrid.

Cajal has been honored and commemorated in many ways: among them were an international symposium held in his honor by the Karolinska Institute in Sweden in 1952 (*Acta Physiol. Scand.* Vol. 29, Suppl. 106) and the formation of the Cajal Club of the American Anatomical Society. A fascinating autobiography in two volumes, translated by Craigie & Cano, *Recollections of My Life,* was published by the American Philosophical Society in 1937.

1911 Allvar Gullstrand

For his work on the dioptrics of the eye.

Allvar Gullstrand was a Swedish ophthalmologist, born in Landskrona in 1862. He studied at the Universities of Uppsala, Vienna, and Stockholm. He defended his doctorate thesis at Stockholm University in 1890, was named Docent in Ophthalmology in 1891, and was called later to the new chair of ophthalmology at Uppsala. He was self-taught in geometrics and physiological optics. His thesis in 1890, "A Contribution to the Theory of Astigmatism," contained the foundation of his most notable later work on the "intracapsular mechanism of accommodation."

Gullstrand was able to determine from his mathematical analysis and the dioptric investigation of the lens during accommodation that only about two-thirds of accommodation is extracapsular, and one third is due to rearrangement of the internal structure of the lens, i.e. "intracapsular." His sophisticated studies of physiological optics enabled him also to explain astigmatism and monochromatic aberrations, and contributed to our knowledge of the structure and function of the cornea. His Nobel Lecture was entitled, "How I Found the Mechanisms of Intracapsular Accommodation."

Gullstrand designed and improved many ophthalmological instruments, including glasses for use after removal of cataracts and a reflex-free ophthalmoscope. His most important invention was the slit-lamp, which, when combined with a binocular microscope, became an indispensable part of every ophthalmological examination. An account of Gullstrand's work was published as an appendix to Helmholtz's *Physiological Optics* (1924).

1914 Robert Bárány

For his work on the physiology and pathology of the vestibular apparatus.

Bárány (1876–1936), born in Vienna, studied medicine at the University there, graduated in 1900, and took up otology as his specialty. During the First World War, he was a surgeon in the Austrian army, and was a prisoner in a Russian prisoner-of-war camp when the announcement of his Nobel Prize came in 1914. Through the intervention of the King of Sweden and the Red Cross he was released and received his Prize in 1915. While in prison he wrote a treatise on consciousness and the mind-body problem. After the war he left Vienna because of a controversy with his Austrian colleagues. He emigrated to Uppsala, Sweden, and established the Otological Institute at the Uppsala University.

Bárány's interest in the vestibular system began when he observed the effect of temperature on the nystagmus produced by irrigation of the ears,

the "caloric reaction." He then developed the Bárány rotating chair test and other tests of vestibular and cerebellar function, in order to establish relationships between the vestibular system and cerebellum in the control of muscle tone and posture. He was among the first to use local cooling as a means of producing reversible paralysis of a specific small area of the brain.

1922 Archibald Vivian Hill

For his discovery relating to the production of heat in muscles (Hill).

Archibald Vivian Hill (b. 1886), was one of the most distinguished British biophysicists. He studied mathematics at Trinity College, Cambridge, but then joined F. G. Hopkins in the Department of Biochemistry, where he investigated the formation of lactic acid in muscle. He then studied with Bürker in Germany (1910–1911). After the First World War he was appointed to the chair of physiology at Manchester, and later moved to London as the Jodrell Professor of Physiology at University College. In 1926 he became Foulerton Professor of the Royal Society. He was Secretary (and Foreign Secretary) of the Society (1935–1946) and served as Secretary-General of the International Council of Scientific Unions (1952–1956).

Hill's Nobel Lecture was entitled "The Mechanism of Muscular Contraction." With the help of his very able technician, Peter Downing, he was able to construct an ultrasensitive miniature thermopile and galvanometers capable of rapid measurement of the heat produced by the contraction of muscle, of the order of 0.003°C, in a few hundredths of a second. He found that the initial heat was anaerobic, only the later, or "recovery," heat requiring oxygen. The actual contraction did not need oxygen, so the heat produced during that phase could not have come from the oxidation of lactic acid. This raised doubts about the role of lactate in the mechanism of muscular contraction. Hill found that the oxygen debt was paid off and the lactic acid removed only during the phase of recovery from contraction. His discovery of glycolysis during muscular contraction had far-reaching consequences for our understanding of metabolic events in muscle as well as other tissues of the body, including the nervous system. His studies of muscle were published by the Royal Society, London (1938), and summarized in an article in the *British Medical Bulletin* (1956).

After this work Hill turned his attention to studies of the excitability, conduction, and metabolism of nerve fibers. He developed a mathematical theory of electrical excitability of nerve that accounted for the rising and falling phase of the spike, the strength-duration curve of excitability, the mechanisms of "accommodation" to slowly rising currents, and the shorter time constant of large diameter fibers.

He then proceeded, in collaboration with Peter Downing, Ralph Gerard, and Y. Zotterman, to measure the heat produced by various nerves. With Downing's ultrasensitive thermopile and galvanometer, they were able to measure heat production even in the resting nerve (about 6×10^{-5} cal/g/-sec). It was approximately doubled during maximum excitation. As in muscle, there were an initial evolution of heat and two phases of delayed or recovery heat that followed excitation. This first phase lasted 20–30 sec. This was followed by the much longer and larger phase of recovery heat, which reached 15 to 50 times the initial heat, a far greater increase than that observed in muscle. Both initial and delayed heat in nerve occurred undiminished in the absence of oxygen, though nerve became inexcitable more quickly than did muscle. Oxygen consumption was increased during excitation and recovery when present, but increased much more if the nerve had been excited in the absence of oxygen. It showed an oxygen debt as did muscle. These important studies of nerve excitability and metabolism were described by Hill in his Liversidge Lecture at Cambridge in 1932.

1927 Julius Wagner-Jauregg

For his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica.

Wagner-Jauregg (1857–1940) was born in Wels, Austria. He completed his medical education at the University of Vienna in 1880. Following studies in experimental pathology and internal medicine, he took up psychiatry. Except for a short period at the University of Graz (1889–1892) where he was Professor of Psychiatry, he spent his career at the University of Vienna. He became Professor of Neurology and Psychiatry there in 1902 (following Krafft-Ebing), and held that position until his retirement in 1928.

Wagner-Jauregg had noticed as early as 1887 that some patients with general paralysis of the insane (GPI) underwent remission when suffering from an infection accompanied by fever. At that time it occurred to him that the induction of an infectious disease to duplicate these "natural experiments" might be useful in the treatment of GPI, and he thought malaria, which could be interrupted with quinine, and erysipelas might be suitable diseases. In 1917 he carried out that study when a wounded soldier with malaria was admitted to his ward. He inoculated nine patients suffering from GPI with malaria: six patients had extensive remission, three of them lasting at least ten years. Fever therapy in a variety of forms came to be used in GPI, but was supplanted when it was found in the 1940s that the disease responds to large doses of penicillin.

Wagner-Jauregg's discovery of treatment of GPI by means of a heroic measure provided a new therapy for an important mental disease. In the

area of medical theory it provided a convincing measure of support for the organic nature of mental disease. In this connection it should also be noted that he was a very early proponent of fortification of table salt with iodine, for use in areas of endemic goiter, as a means of prevention against cretinism.

1929 Christiaan Eijkman

For his discovery of the antineuritic vitamin.

Christiaan Eijkman (1858–1930) was born in Nijkerk, The Netherlands. He studied physiology at the University of Amsterdam starting in 1875 and, having received his medical degree there, he joined the Dutch army for service in the East Indies. He spent two periods in Batavia (1883–1885 and 1886–1896), and received training in bacteriology in Holland during the interval. In 1886 he became Director of the Laboratory of Bacteriology and Pathology, where he carried out his investigations on beri-beri, an endemic disorder with neurological, cardiac, and other manifestations. From 1896 to 1928 he was Professor of Hygiene at the University of Utrecht. He shared the Nobel Prize in 1929 with (Sir) Frederick Gowland Hopkins.

In 1889 Eijkman observed an outbreak of avian disease in the chicken-run of his Batavian laboratory, and was struck by its resemblance to human beri-beri: unsteady gait, muscular weakness causing falls, progressive paralysis, cyanosis, hypothermia, stupor, and finally death. Pathological examination showed it to be a polyneuritis. When the disease suddenly cleared up he learned that the attendant had changed the birds' diet from polished rice to rice containing the pericarp (hull) and much of the germ. A deliberate feeding experiment with the two types of rice confirmed the nutritional etiology of the disorder (Eijkman 1930). Initially Eijkman thought that a nutrient in the hull neutralized the damage caused by a starch-rich diet, but he later gave up that idea. Colleagues related to him their experience with the various rice diets in the prisons and among the native population generally, and its relation to the incidence of beri-beri. Conclusive experiments were finally carried out by Eijkman's successor, C. Grijns, with prisoners. Grijns defined beri-beri as a deficiency disease and showed that protection was endowed by a factor in an extract of beans. He was the first to provide the correct interpretation of the connection between consumption of the polished rice diet and the etiology of beri-beri. Subsequently, the prophylactic effect of extracts of rice hulls and of beans was demonstrated, and ultimately shown to be due to the content of thiamine, then known as vitamin B_1. In the 1930s, R. A. Peters showed that in thiamine deficiency the tissues metabolize pyruvate defectively; K. Lohmann and P. Schuster proved that the vitamin is the organic portion of cocarboxylase. In 1939,

I. Banga, S. Ochoa, and R. A. Peters showed that the thiamine coenzyme is active in correcting pyruvate metabolism in vitro.

Beri-beri is now recognized as resulting from the chronic deficiency of thiamine in the diet. The acute deficiency gives rise to Wernicke's encephalopathy. Eijkman's investigations, which led to the description of the nutritional origin of certain neurological disorders, eliminated the mass of conflicting theories about the etiology of beri-beri, such as the involvement of toxic, microbiological, climatic, and other factors. The possible nervous system functions of a large number of vitamins (and mineral cofactors) continue to interest many biochemists as a fruitful area of research.

1932 Sir Charles Scott Sherrington and Edgar Douglas (Lord) Adrian

For their discoveries regarding the function of neurons.

Sherrington was born in Islington, London, in 1857. He obtained his scientific and medical education at Cambridge and at St. Thomas's Hospital Medical School in London. His interest in the physiology and pathology of the nervous system developed during his medical studies, as well as through contacts with the work of Goltz in Strasbourg and David Ferrier on the localization of function in the brain, and by his association with Virchow in neuropathology. His own researches began while he was a lecturer at St. Thomas's and a fellow at Cambridge. He was responsible for inviting Cajal to deliver the Croonian Lecture (1894) of the Royal Society in London. He was appointed in 1895 to the chair of physiology at University College, Liverpool, where he did much of the work for which the Nobel Prize was awarded. He remained in Liverpool until 1913 when he became Waynflete Professor of Physiology at Oxford, a post that he held until his retirement in 1936. He died in 1952, at the age of 95 years.

Sherrington's Nobel Lecture of 1932 was entitled "Inhibition as a Coordinative Factor." He described the form and plasticity of spinal reflexes, including reflex stepping movements, as based upon a balance of central inhibitory and excitatory states and emphasized the importance of inhibition in the sculpturing of posture and in the control of the reciprocal action of antagonistic muscles in movement and locomotion.

Sherrington traveled to Canada and the United States in 1903, and the next year delivered the Silliman Memorial Lectures at Yale University. His book, *The Integrative Action of the Nervous System,* which was based upon those lectures, has remained a classic of neuroscience ever since. After many publications and lectures on the reflex organization of the spinal cord, he was invited to present the Rede Lecture at Cambridge in 1933. He delivered the Gifford Lectures in Edinburgh in 1937–1938; this

resulted in the publication of still another classic, *Man on His Nature* (1940). In this book he elaborated on his dualistic view of man's nature: body and mind.

Adrian (1889–1977), who shared the prize with Sherrington, though at a younger age, was born in London. He studied medicine in London and Cambridge, receiving his MD degree from Trinity College in 1915. He began his work in neurophysiology with Keith Lucas at Cambridge, where he was Research Professor of the Royal Society from 1929–1937. He became professor, succeeding Barcroft as director of the Department of Physiology, in 1937. He retired in 1951 to become Master of Trinity. He also served as President of the Royal Society, the Royal Society of Medicine, and the British Association for the Advancement of Science. He retired as Master of Trinity in 1965 to become Vice-Chancellor, and then Chancellor, of Cambridge, 1968–1976.

Adrian's Nobel Lecture was entitled simply, "The Activity of Nerve Fibres." He was the first to record action potentials from single sensory and motor nerve fibers by a delicate dissection technique, and by the use of vacuum tube amplification and a more rapidly moving oscillograph, the capillary electrometer and later the Matthews mirror oscillograph.

In 1925 Adrian and Y. Zotterman were the first to record the impulse traffic in a single sensory fiber stimulated by the adequate—physiological—stimulation of its nerve ending. From their records they could state that the transmission in sensory nerve fibers occurs according to what today would be called "impulse frequency modulation," which 20 years later was introduced in radio technique (FM) as the safest way of communication. Strength of contraction in muscle was also related to frequency of firing in motor nerve fibers (with D. Bronk). He proposed that there were long duration potentials in nerve centers and in sense organs causing repetitive firing of nerve fibers (now known as "generator potentials").

Adrian explored all forms of sensation, including auditory, olfactory, and visual, as well as somatic sensations from skin and muscle. He then became interested in sensory representation in the cerebral cortex and cerebellum, which he recorded with the technique of evoked potentials. He discovered an additional somatic sensory area, II, and topographically organized connections between the sensory cortex and cerebellum. He also studied the spontaneous electrical activity in the water beetle and gold fish. He was one of the first to confirm, with B. H. C. Matthews, the work of Hans Berger on the human electroencephalogram.

Some of Adrian's principal publications were *The Basis of Sensation, The Action of Sense Organs* (1927), *The Mechanism of Nervous Action* (1932), and *The Physical Background of Perception* (1947).

1935 Hans Spemann

For his discovery of the organizer effect in embryonic development.

Hans Spemann (1869–1941) was born in Stuttgart, Germany and studied medicine at the Universities of Heidelberg, Munich, and Wurzburg. He worked at the Zoological Institute at Wurzburg until 1908, when he accepted the chair of zoology and comparative anatomy at Rostock. In 1914 he became Director of the Kaiser Wilhelm Institute for Biology in Berlin-Dahlem. He then went to the University of Freiburg-im-Breisgau as professor until his retirement in 1935.

Spemann's experiments were carried out on young amphibian embryos. By the transposition of tissue from one part of the developing embryo to another, he was able to show that groups of cells, originally destined for one part of the body, changed their direction of development when transplanted to a different region. For example, he was able to show that the optic cup is able to bring about the formation of a lens from epidermis transplanted from a distant part of the body that is not normally involved in lens production. Similarly, the covering epidermis clears, as in the formation of a transparent cornea, despite its "foreign" noncorneal origin. Division of the embryo or transplantation of pieces of the medullary plate showed that rearranged cells develop according to their new local environment. In 1918 Spemann presented his concept of the "organizers" to explain his observation that the morphogenesis of the embryo is the result of interactions between different regions of tissue. He became the leader of a school of experimental embryologists who provided many examples of embryonic induction in development.

Spemann's findings were confirmed in other species and led to studies of the chemistry of embryonic development by Joseph Needham and Jean Brachet, with particular regard to the chemical nature of the organizer.

1936 Sir Henry Hallett Dale and Otto Loewi

For their discoveries relating to chemical transmission of the nerve impulse.

Born in London in 1875, Sir Henry Dale trained as a pharmacologist at Trinity College, Cambridge. In 1906 he became Director of the Wellcome Physiological Research Laboratories, where he spent many years. He became Director of the National Institute for Medical Research in London in 1928. During his career he also served as President of the Royal Society and of the Royal Society of Medicine.

Dale's Nobel Lecture was entitled "Some Recent Extensions of the Chemical Transmission of the Effects of Nerve Impulses." The extensions

he referred to were the demonstration, with his colleagues Feldberg, Gaddum, Brown, and Vogt, of evidence that neuromuscular transmission in striate muscle, as well as synaptic transmission in the superior cervical ganglion, is mediated by the liberation of acetylcholine at the prejunctional axonal terminals. Dale summarized this work further in his *Harvey Lectures* (1937) and in his autobiography (1953).

Loewi had shown, with the help of Dale's work on acetylcholine, that this substance is liberated from the vagus nerve to cause slowing of the isolated frog heart. It was assumed that adrenaline mediated the action of sympathetic nerves to the heart, although this was questioned by Walter B. Cannon. Cannon proposed instead that two substances, sympathin E and sympathin I, are involved as transmitters of the peripheral sympathetic system, and that these are not identical with adrenaline.

Otto Loewi (1873–1961) was born in Frankfurt-am-Main. He met Dale while working in Starling's laboratory in London. He worked also with Elliott in Cambridge. He then was appointed Professor of Pharmacology at the University of Graz, Austria, but was forced to leave his post when the country was invaded by the Germans in 1938. He went first to Brussels, then to Oxford, and finally settled in New York City, where he was appointed Professor in the College of Medicine of New York University in 1940, and adopted American citizenship. His Nobel Lecture was entitled, "The Chemical Transmission of Nerve Action."

Chemical transmission had long been suspected to occur in the peripheral autonomic neuromuscular system. In 1904, T. R. Elliott proposed that adrenaline might be involved in the sympathetic system. A few years later, W. E. Dixon suggested that an unknown chemical mediator might be involved in the action of the vagus nerve on the heart. There was no definitive proof for these hypotheses, until Loewi performed his elegantly simple experiments. Utilizing the frog heart preparation he was able to show that stimulation of the vagus nerve liberated a substance into the Ringer's solution bathing the heart, and that this substance was able to slow a second isolated "test" heart beating in the same solution. This action was blocked by atropine, prolonged by eserine, and duplicated by acetylcholine, in accordance with the muscarinic action of acetylcholine previously described by Dale.

The extension of the principle of chemical transmission to the neuromuscular junction in striate muscle, and to synapses in the cervical ganglion, was a much greater surprise, since it was generally believed in the 1930s that transmission in these, as in central synapses, was electrical in nature. One of the strongest proponents of the electrical theory was J. C. Eccles, then working in Sherrington's laboratory at Oxford. For several years the meet-

ings of the Physiological Society were enlivened by the heated debates between Dale and Eccles, but Eccles subsequently became convinced of the inadequacy of the electrical theory, and proceeded to provide elegant evidence for chemical transmission at synapses on the anterior horn cells of the spinal cord. This is discussed below in relation to Eccles' own Nobel Prize award. (See also Eccles' chapter in Volume 5 of the *Annual Review of Neuroscience.*)

The establishment of chemical transmission throughout the central nervous system, as well as for ganglionic and junctional synapses in the peripheral autonomic system and at striate neuromuscular junctions, represented a revolutionary advance in neuroscience, the importance of which has become more fully appreciated in recent years with the discovery of many new transmitter substances in the central and peripheral nervous systems.

1938 Corneille Jean François Heymans

For the discovery of the role played by sinus and aortic mechanisms in the regulation of respiration.

Heymans (1892–1968) was born in Ghent, Belgium. He was the son of Dr. J. F. Heymans, Professor of Pharmacology and Rector of the University of Ghent, as well as founder of the Heymans Institute of Pharmacology, Pharmacodynamics and Toxicology. Heyman's father was his first and principal teacher and it was with him that the original experiments, that led to the award of the Nobel Prize, were begun. Corneille Heymans also studied with E. Gley in Paris, N. M. Arthus in Lausanne, H. H. Meyer in Vienna, and E. H. Starling in London. He spent one year (1927–1928) in the United States. He succeeded his father as Director of the Heymans Institute of Pharmacology and also became Rector of the University.

Heyman's Nobel Lecture was entitled "The Part Played by Presso- and Chemoreceptors in Respiratory Control." By use of a crossed perfusion from one dog to the isolated head of another he was able to show that there were chemo- and pressoreceptors in the carotid sinus and aortic arch capable of controlling respiration and blood pressure, as well as cerebral circulation. In 1937 the sensory nature of this control was demonstrated independently by Rijlant, Stella, and Zotterman, who recorded action potentials from carotid sinus nerves in response to controlled pressor and chemical stimuli administered to the carotid body. These studies represented a major advance in our knowledge of the reflex mechanisms that control respiration and blood pressure and are of critical importance for the regulation of the cerebral circulation (Heymans & Neil 1958).

1944 Joseph Erlanger and Herbert Spencer Gasser

For their discoveries regarding the highly differentiated functions of single nerve fibers.

Joseph Erlanger (1874–1965) was born in San Francisco. He received his BS degree in chemistry from the University of California and in 1899 his MD degree from Johns Hopkins University. He was appointed assistant in the Department of Physiology and soon became Associate Professor at Johns Hopkins University Medical School. He then joined the faculty of the newly founded University of Wisconsin as their first professor of physiology. Herbert Gasser was one of his pupils there. In 1910, Erlanger was appointed Professor and Head of the Department of Physiology at Washington University in St. Louis, where Gasser joined him in the joint research that earned them the Nobel Prize. Erlanger became Professor Emeritus in 1944. His Nobel Lecture was entitled, "Some Observations on the Response of Single Nerve Fibers."

Herbert Gasser (1888–1963) was born in Platteville, a small town in Wisconsin. He studied at the State Normal School and at the State University, where he was introduced to physiology by Erlanger. He graduated in medicine from Johns Hopkins in 1915. He returned to Wisconsin for a year in pharmacology, and then joined Erlanger in St. Louis, where he became Professor of Pharmacology in 1921. With the help of the Rockefeller Foundation, he spent two years studying in Europe and then returned to St. Louis. In 1931 he was appointed Professor of Physiology at Cornell Medical School in New York City. In 1935 he became Director of the Rockefeller Institute for Medical Research until his retirement from that post in 1953. He continued to carry out electrophysiological research into the properties of ultrafine nerve fibers until his death. His Nobel Lecture was entitled, "Mammalian Nerve Fibers."

Before the work of Erlanger & Gasser in the early 1920s, the true form of the nerve action potential was unknown, owing to the lack of sufficiently rapid and sensitive recording instruments. Erlanger & Gasser, with the help of George Bishop, solved this problem by the combination of high gain vacuum tube amplification with the relatively inertialess cathode-ray oscilloscope, which is an adaptation of the Braun tube long known to physics. With their new instrumentation they could discern various groups of fibers in a mixed nerve by their different thresholds and velocities of conduction. The fibers differed also in their refractory periods and after-potentials. A near-linear relationship was found between fiber diameter and velocity, the most rapid A fibers conducting at over 100 m/sec, whereas the velocity of the unmyelinated C fibers was only about 1 m/sec. The large fibers had a much greater spike height as well as the lowest threshold and shortest time constant (chronaxie) for electrical stimulation. The widely different delays

in the transmission of sensory information to the CNS were very important to our understanding of central processing of sensory information. Muscle afferents were most rapid, while pain was found to be conducted by two groups of fibers, the A delta and C fibers, having very different velocities, which accounted for "rapid" and "slow" pain perception.

Erlanger concluded his Nobel Lecture with the statement that he had pursued his studies because, "In the investigation of this comparatively simple structure, the nerve fiber, lies the hope of finding clues to an understanding of the much more complicated mechanisms that determine the activities of peripheral and central nervous mechanisms." Erlanger & Gasser did not realize, at the time, how "much more complicated" these mechanisms of the central nervous system would become after the discovery of chemical transmission at central synapses and the highly specialized properties of cells and dendrites as compared to their axons. Their work was summarized in their Johnson Foundation Lectures (1937) and in Gasser's Harvey Lecture (1937).

1949 Walter Rudolf Hess and Antonio Egas Moniz

For his discovery of the functional organization of the interbrain as a coordinator of the activities of the internal organs (Hess).

For his discovery of the therapeutic value of prefrontal leucotomy in certain psychoses (Moniz).

Born in Frauenfeld in eastern Switzerland, Walter Hess (1881–1973) studied medicine in Lausanne, Berne, Berlin, Kiel, and Zurich, where he obtained his MD in 1906. He practiced ophthalmology for a few years, but then decided to devote himself to the study of physiology. He was appointed Director of the Physiological Institute in Zurich in 1917. After the First World War he studied with Langley in England, where he became particularly interested in the autonomic nervous system. He also worked in the laboratories of Sherrington, Starling, Hopkins, and Dale before returning to his position at the Physiological Institute in Zurich. After becoming Professor Emeritus in 1951, Hess continued to pursue his major interest in the central autonomic system in relation to behavior and mental functions, attempting to bridge the gap between physiology and psychiatry. His Nobel Lecture was entitled, "The Central Control of the Activity of the Internal Organs."

Hess developed a chronic implanted electrode technique in order to study cinematographically the responses of unanesthetized, freely moving cats to electrical stimulation of local points in the diencephalon. The exposed tips (0.2 mm) of the fine insulated steel needle electrodes were then located by histological studies to establish anatomical relationships to behavioral and

physiological responses. A very large series of such experiments formed the basis for his functional atlas of the diencephalon. This made it possible for the first time to observe not only specific autonomic responses in unanesthetized animals, but also to observe their interrelationships with each other and their integration with the behavior of the animal in a relatively normal environmental situation.

Hess mapped out diencephalic regions controlling blood pressure, respiration, pupillary dilatation, defecation and micturition, vomiting, and bulimia, as well as coordinated "extrapyramidal" motor responses such as head and eye turning, licking and chewing movements, and coordinated emotional behavior such as fear or rage. Sleep was produced by stimulation of the medial thalamus. Hypothalamic responses were classified as either ergotropic (dynamogenic) or trophotropic, corresponding roughly to their mediation by the sympathetic or parasympathetic systems, respectively. The integration of autonomic responses with appropriate somatomotor and emotional behavior made these pioneering studies of far-reaching importance to neuroscience in general and particularly to clinical neuropsychiatry. A summary of Hess' work was published in English in 1954 entitled *Diencephalon: Autonomic and Extrapyramidal Functions.*

Egas Moniz (1874–1955), who shared the prize with Walter Hess, was a leading Portugese neurologist and politician, born in Avança. He studied in the medical faculty of Coimbra, where he was appointed professor in 1902. In 1911, he became the first occupant of the chair of neurology in Lisbon. In addition to his important contributions to neurology and to medical literature, Moniz was active in the political life of Portugal, serving as Minister of Foreign Affairs and as President of the Portugese delegation to the Paris Peace Conference in 1918.

Moniz made two important contributions to neurology in collaboration with Almeida Lima: (*a*) they developed the x-ray technique of cerebral angiography; (*b*) they introduced the practice of prefontal leucotomy (for which Moniz was cited in the Nobel Prize). Moniz published a large monograph on the diagnosis of cerebral tumors by angiography in 1931; his first memoir on prefrontal leucotomy appeared in 1936.

Moniz was seeking some way to treat patients with intractable mental diseases, which he believed "are deeply rooted in the synaptic complex which regulates matters of knowledge in the consciousness. . . . It is necessary to alter the synaptic arrangements . . . thereby the corresponding thoughts are altered and forced into other channels." His interest in the frontal lobes was derived from animal experiments of Bechterew & Luzaro in Russia, and especially the experiments of Fulton & Jacobsen in the U.S. on the effects of bifrontal lesions in the chimpanzee. He was also influenced by the effects of neurosurgical removal of the frontal lobes in man, as reported by Brickner & Dandy, and by Penfield.

Moniz & Lima performed their first prefrontal leucotomy in 1935, thus inaugurating psychosurgery. The operation consisted of lesions restricted to the white matter of both frontal lobes, usually performed by the use of a leucotome. During the following years thousands of severely disturbed psychiatric patients were "treated" by this method with some beneficial results in the most severe cases, but with many serious and sometimes disastrous side effects. Fortunately, the use of this method has been almost entirely discontinued with the advent of effective psychopharmacology.

1957 Daniel Bovet

For his discoveries relating to synthetic compounds that inhibit the action of certain body substances, and especially their action on the vascular system and the skeletal muscles.

Daniel Bovet was born in Neuchâtel, Switzerland in 1907. He attended the University of Geneva, from which he received the DSc degree in 1929. He at once joined the laboratory of Ernest Fourneau, an eminent chemist at the Pasteur Institute in Paris, and remained there until 1947, when he moved to the Istituto Superiore di Sanità in Rome to open a new laboratory of chemotherapeutics. He was aided in this venture by his wife, Philomena Nitti, also a chemist, with whom he wrote an extensive monograph on drug structure in relation to pharmacodynamic activity on the autonomic nervous system (1958). Bovet's Nobel Lecture was entitled, "The Relationships Between Isosterism and Competitive Phenomena in the Field of Drug Therapy of the Autonomic Nervous System and that of the Neuromuscular Transmission."

Bovet's experience in Fourneau's laboratory introduced him to the modern practice of medicinal chemistry: the synthesis of large numbers of new molecules expected to exert biological activity, along with extensive screening in biological tests for such activities. Fourneau was seeking agonists and antagonists of the biogenic amines, particularly epinephrine and histamine; Bovet's work with him led to the discovery of some of the early antihistaminic drugs.

By the early 1940s, experience with antivitamins, especially with the then dramatic new substance sulfanilamide as an antagonist of the bacterial vitamin *p*-aminobenzoic acid, lent great credence to the "antimetabolite hypothesis." The hypothesis quickly became the justification for research programs in medicinal chemistry in hundreds of centers.

Bovet was a pioneer in the study of synthetic compounds affecting the metabolism and the postsynaptic action of biogenic amines and neurotransmitters such as adrenaline, noradrenaline, 5-hydroxytryptamine, acetylcholine, and histamine. He was particularly interested in noradrenergic blocking agents, antihistamines, and curariform anticholinergic compounds such as decamethonium and succinylcholine, synthetic atropine-like sub-

stances, and derivatives of lysergic acid. With his colleague, Longo, he made important observations on the pharmacology of the reticular system in relation to the electroencephalogram. This type of research produced a great increase in the size and efficacy of the physician's armamentarium, and freed therapeutics from dependence upon the handful of natural drugs that are useful in human disease.

1961 George von Békésy

For his discoveries concerning the physical mechanisms of stimulation within the cochlea.

Von Békésy was a Hungarian physicist, born in Budapest in 1899. After obtaining his primary education in many countries (his father was a diplomat), he obtained his PhD degree in physics at the University of Budapest. He worked in the Hungarian Telephone Research Laboratory, where he developed an ingenious and rapid method for discovering defects in the network of telephone lines by their resonant responses to click stimuli, a principle he later used to analyze the properties of the cochlea of the inner ear.

Von Békésy became Professor of Experimental Physics at the University of Budapest in 1939, and held that post until 1946, when he emigrated to Stockholm to work at the Royal Caroline Medical Institute and at the Royal Institute of Technology. He moved again, in 1947, to the Psycho-Acoustic Laboratories of Harvard University in Cambridge, where he pursued much of the work for which he received the Nobel award. He retired to the University of Hawaii in Honolulu, where he died in 1972.

Von Békésy was the first physicist to receive the Nobel Prize in Physiology or Medicine, for his ingenious applications of physical principles to sensory physiology, especially to our knowledge of the middle and internal ear in audition. His Nobel Lecture was entitled, "Concerning the Pleasures of Observing, and the Mechanics of the Inner Ear."

Von Békésy measured the physical properties of the inner ear and cochlear membrane with a highly sensitive microelectrode technique. This enabled him to apply mechanical stimuli to local regions of the basilar membrane while recording the electrical potentials in the hair cells that give rise to action potentials in different fibers of the auditory nerve. He was able to measure how sound waves are transmitted by the ossicles of the middle ear to the ear drum and then by traveling waves in the endolymph to excite frequency-selective portions of the basilar membrane. With these data he was able to construct a physical model of the auditory apparatus that explained the function of the inner ear. He then found that some of the principles could be applied to skin sensation, which also involved the phenomenon of "surround inhibition," i.e. increased contrast between the site

stimulated and the surrounding area of skin. This principle was found to apply to the retina as well. Von Békésy's ingenious application of the principles of physics to sensory physiology, his direct measurements by the use of high gain amplifiers and microscopic stroboscopy, and the testing of his theories of psychophysical techniques did much to solve many problems in acoustics, as well as to improve our understanding of other modalities of sensation (tactile, visual, and olfactory). He invented several diagnostic instruments, such as the audiometer that bears his name, which enables the otologist to distinguish between cochlear and nerve deafness. A translation of von Békésy's work on the inner ear was published in the *Journal of the Acoustical Society of America* in 1949 and summarized in his book, *Experiments in Hearing,* in 1960. An account of the more general applications to other sensory modalities was published in 1967.

1963 John Carew Eccles, Alan Lloyd Hodgkin, and Andrew Fielding Huxley

For their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane.

John Eccles (Sir John), born in Melbourne, Australia in 1903, received his degree in medicine at Melbourne University in 1925 and continued his studies in Sherrington's Department of Physiology at Oxford, where he obtained his PhD in 1929. He studied excitation and inhibition at Oxford until 1937 when he was appointed director of a medical research laboratory in Sydney. In 1944 he went to the University of Otago in New Zealand, but then returned to Australia to become Professor of Physiology at the newly-founded National University in Canberra. Upon retiring from Canberra, he came to the Institute for Biomedical Research in Chicago (1966–1968). He was subsequently appointed Professor of Physiology at the State University of Buffalo in New York (1968–1975), where he continued his neurophysiological studies of the cerebellum. He has continued his writing and lecturing from his retirement retreat in Ticino, Switzerland.

John Eccles has been one of the most productive and prolific contributors to neuroscience in our century. His Nobel Lecture was entitled, "The Ionic Mechanisms of Postsynaptic Inhibition." Although while at Oxford, Eccles was a strong defender of the electrical theory of transmission in central synapses, he convinced himself of the inadequacy of this theory by his elegant intracellular microelectrode studies of spinal neurones. [See Eccles (1982) for his own account.] He then provided convincing evidence for the chemical nature of central synaptic transmission, by the use of ultrafine

glass micropipettes, first devised by Ling & Gerard in Chicago. He used them both for intracellular recording of membrane and synaptic potentials as well as for the iontophoretic ejection of chemical substances. He was able to determine the ionic mechanisms involved in the response of nerve cell membranes to neurotransmitter substances as measured by excitatory (Na^+ and K^+) and inhibitory (Cl^- and K^+) postsynaptic potentials (EPSP and IPSP). He was able to demonstrate the importance of inhibitory interneurons, such as the Renshaw cells in the spinal cord, and to describe the mechanisms and properties of presynaptic inhibition.

Eccles then turned his attention to suprasegmental portions of the nervous system, where he applied his microphysiological techniques to a comprehensive study of synaptic mechanisms of the cerebellum (Eccles, Ito & Szentágothai 1967). The thalamus, cerebral cortex, and hippocampus were also explored in research directed toward an understanding of what Eccles termed "the neurophysiological basis of the mind," which was the title of his Waynflete Lectures at Oxford in 1952. Among many other important publications of Eccles are his Herter Lectures delivered at Johns Hopkins 1955, published under the title of *The Physiology of Nerve Cells,* The Ferrier Lecture of the Royal Society in 1960, and his most comprehensive review of central synaptic mechanisms published in 1964 under the title, *The Physiology of Synapses.* He delivered the Gifford Lectures in Edinburgh (1977–1979).

Alan Hodgkin was born in Banbury, Oxfordshire, in 1914. He began his scientific studies at Cambridge in 1932. His work on the physiology of nerve fibers led to an invitation by Gasser to work at the Rockefeller Institute in New York (1937–1938). While in the United States he worked at the Woods Hole Marine Biological Laboratory with K. S. Cole, who, with H. J. Curtis and J. Z. Young, introduced him to the use of the squid giant axon, a preparation that became of critical importance to his Nobel Prize research. During the Second World War he was a scientific officer in the Air Ministry. He returned to the Department of Physiology at Cambridge in 1945, where A. F. Huxley was among his students. Hodgkin became a Fellow and Foulerton Research Professor of the Royal Society, winning its Royal Medal in 1958.

Andrew Huxley was born in London in 1917. He entered Cambridge in 1935 and specialized at first in the physical sciences. Becoming interested in physiology in 1939, he joined Hodgkin at the Plymouth Marine Biological Laboratory, where he carried out his first research in 1939. After the war he returned to Cambridge, where he worked until 1960, when he was appointed Professor of Physiology and Head of the Department at University College in London. He was elected to the Royal Society in 1955.

The classical work of Hodgkin & Huxley on the ionic basis of excitation and conduction in nerve fibers was carried out in close collaboration. Hodgkin's Nobel Lecture was entitled, "The Ionic Basis of Nervous Conduction," while that of Huxley was entitled "The Quantitative Analysis of Excitation and Conduction in Nerve."

Hodgkin & Huxley set out to test Bernstein's theory of the ionic basis for the resting and action potentials in the "semipermeable" nerve membrane. By the use of a glass micropipette inserted into the axoplasm, and with the voltage clamp technique developed by Cole, Hodgkin & Huxley were able to measure separately the inward Na^+ current responsible for the overshoot of the action potential well above the level of the resting potential. The outward K^+ current was measured directly by the use of radioactive K^+ ions. Ionic concentrations could be manipulated both inside and outside the axon, and measured in the extruded axoplasm.

A mathematical model was then developed, with the aid of electronic computers, which would predict the form of the action potential at various ionic concentrations inside and outside the axon. The predictions corresponded closely with their experimental results. Huxley concluded his Nobel Lecture with the statement,

> I would not like to leave you with the impression that the particular equations we produced in 1952 are definitive. . . . Both Hodgkin and I feel that these equations should be regarded as a first approximation which needs to be refined and extended in many ways in the search for the actual mechanisms of permeability changes on the molecular scale.

Their theory has stood the test of time as applied to many nerves, and we are approaching an understanding of nerve membrane on the "molecular scale." [See Hodgkin (1964) for a summary of the work of Hodgkin & Huxley.]

1967 Ragnar Granit, Haldane Keffer Hartline, and George Wald

> For their discoveries concerning the primary physiological and chemical visual processes in the eye.

In his evaluation of the work of Granit, Hartline & Wald, Professor Bernhard of the Nobel Committee stated that this work provided "a deepened insight into the subtle processes in the eye which form the basis for our ability to perceive light and to distinguish brightness, color, form and movement, . . . of paramount importance to understanding sensory processes in general."

Ragnar Granit was born in Finland in 1900, and graduated from Helsingfors University in 1919. While in school he took part in Finland's War of Liberation and was decorated with the Cross of Freedom IV Class "with

sword" in 1918. Granit first became interested in psychology while studying at the Ålbo Academy. He graduated Mag. Phil. in 1923 from the University of Helsingfors. He proceeded to take his MD (1927) there in order to pursue his research on vision, which had interested him from the beginning. In 1929, he became Docent in Tigerstedt's Physiological Institute.

Granit was a Fellow in Medical Physics at the Johnson Foundation (1929–1931) with Detlev Bronk, where he became associated with Keffer Hartline. He studied in Sherrington's laboratories in Oxford as a Fellow of the Rockefeller Foundation, and then returned to Helsinki as Professor of Physiology. In 1940 he accepted an appointment at the Royal Caroline Institute in Stockholm. His laboratories became a part of the Nobel Medical Institute, where he received a personal research chair and was Director of the Institute of Neurophysiology (1945–1967). He was member of the Swedish Medical Research Council and president of the Royal Swedish Academy of Sciences.

Granit retired as Professor Emeritus in 1967, but has remained active in writing and lecturing and is still a roving ambassador of neuroscience. He was visiting professor at the Rockefeller University in New York and at Oxford, and Fogarty Scholar at the National Institutes of Health in Bethesda. He was visiting professor at Düsseldorf in 1974 and at the Max Planck Institute in 1976. He has been consultant to Moruzzi's Institute in Pisa for several years.

Granit's Nobel Lecture was entitled, "The Development of Retinal Neurophysiology." This was his first research interest, begun in the 1920s, but only one of many important contributions he has made over the years to our more general understanding of sensory perception and to mechanisms of sensorimotor control.

Granit's early studies were concerned with an analysis of the significance of the various components of the electroretinogram (ERG) in relation to excitatory and inhibitory processes of the retina. He found that flicker fusion was not only related to light intensity but also to the area of the visual field illuminated; this he attributed to surround inhibition.

Influenced by Adrian's work on sensory messages in individual nerve fibers, he began a long series of studies on the response of individual ganglion cells in the mammalian retina to controlled light and color stimuli. He discovered "on" and "off" as well as "on/off" cells. In his analysis of unit retinal responses to color he discovered "modulator bands" of interaction between absorption spectra, sharpening contrast, "crispening of information by interaction, largely inhibitory in nature." He also found that some cells in the vertebrate retina are hyperpolarized rather than depolarized by light, and that inhibitory interactions between retinal elements play an important role, as shown by Kuffler and Hartline, accounting for the

"off" discharge as well as for visual contrast. He made extensive studies of the retinal mechanisms of light and dark adaptation and the spectral properties of retinal elements in a variety of animals (frog, cat, guinea pig, etc). These studies were summarized by Granit in 1947 and in his Silliman Memorial Lectures at Yale published in 1955.

By the time Grant received his Nobel award he had abandoned the visual system and launched his "second career" in studies of muscle afferents and mechanisms of alpha and gamma motor control in spinal cord, cerebellum, and motor cortex. This work was partially reviewed in his Silliman Lectures, which described also his thoughts about sensory discrimination and integration in general.

Granit received many honors and delivered many honorary lectures, including the Sherrington Memorial Lectures of the Royal Society of Medicine in London in 1967 and in Liverpool in 1970. He initiated an important series of Nobel Symposia on *Muscular Afferents and Motor Control* (1966). He also published two books on this subject: *Basis of Motor Control* (1970) and *Mechanisms Regulating the Discharge of Motoneurons* (1972). His more philosophical thoughts were expressed in his recent book (1977), entitled *The Purposive Brain.*

Keffer Hartline was born in Bloomsburg, Pennsylvania, in 1903. He received his MD at Johns Hopkins and then studied physics on an NRC fellowship there and abroad. Upon his return to the United States, he worked at the Johnson Foundation for Medical Physics at the University of Pennsylvania. For a time, he was Associate Professor of Physiology at Cornell Medical College in New York City, but returned to the Johnson Foundation until 1949 when he became Professor of Biophysics at Johns Hopkins University. Here he was joined by his colleague Floyd Ratliff in 1954. He then moved his laboratories in 1963 to the Rockefeller University in New York City where he remained as Professor until retirement.

Hartline's Nobel Lecture was entitled, "Visual Receptors and Retinal Interaction." He began his studies by single fiber analysis of the optic nerve of the frog, but most of his research was carried out on the eye and optic nerve of the horseshoe crab (*Limulus*). In this relatively simple eye, the electrical activity of individual nerve fibers and photoreceptors (ommatidia) could be recorded by dissection and by intracellular microelectrodes. The photoreceptors could also be stimulated individually so that the generator potentials and action potentials to local light stimulation could be recorded, as well as the interaction between adjacent receptors. Surround inhibition was thus subjected to quantitative study, which provided direct evidence for retinal mechanisms underlying the phenomena of visual contrast and Mach's bands in human vision. [See Hartline (1941–1942) on "The Neural Mechanisms of Vision".]

George Wald was born in New York City in 1906. He studied at New York University and pursued graduate studies in zoology at Columbia with Selig Hecht (PhD 1932). He then worked with Otto Warburg in Berlin-Dahlem on an NRC Fellowship, at which time he first identified vitamin A in the retina. After further studies in Heidelberg, Zurich, and Chicago, Wald returned to Harvard (1935) as a tutor in biochemistry, then became Professor in the Department of Biology (1944–1948) and later University Professor (1948–1977) until 1977, when he became Professor Emeritus. In 1953 he received the Lasker Award.

Wald's principal research was on the photochemistry and biochemistry of visual pigments in the retina. His Nobel Lecture was entitled, "The Molecular Basis of Visual Excitation."

Wald determined the chemical composition of photopigments of the retina: the retinals, 1 and 2, which, in vertebrates, combine with the rod opsin to form rhodopsin and porphyropsin, and with cone opsin to form iodopsin and cyanopsin. The retinals are aldehydes derived from vitamins A_1 and A_2 by dehydrogenation of the alcoholic group, and they act as visual pigments when the side chain is in the 11-*cis* configuration, one that facilitates union with the opsins. On exposure to light the pigments are converted to a steady-state mixture of carotenoids, with various proportions of the geometrical isomers of the retinals. The pigments must be reisomerized to the 11-*cis* configuration before they can combine again with the opsins to regenerate visual pigment. The manner in which these reactions are transduced into electrical potentials and action potentials in ganglion cells must still be clarified. Wald's original work was summarized in the *Annual Review of Biochemistry* in 1953 (Vol. 22).

1970 Julius Axelrod, Ulf Svante von Euler, and Bernard Katz

For their discoveries concerning the humoral transmitters in the nerve terminals and the mechanisms for their storage, release, and inactivation.

Axelrod was born in New York City in 1912. He obtained the BS degree from the College of the City of New York in 1933, and then worked at various jobs during the depression. He returned to graduate studies, receiving the MS degree from New York University in 1941. One of his jobs brought him under the leadership of B. B. Brodie, whom he followed to Bethesda, when Brodie established a research laboratory at the National Heart Institute in the early 1950s. While working there, Axelrod earned the PhD degree from George Washington University (1955). The work for which he was recognized by the Nobel Committee was performed at the Heart Institute and is described in his Nobel Prize Lecture, "Noradrenaline:

Fate and Control of its Biosynthesis." He continues his research at the National Institute of Mental Health, where he is Chief of the Section on Pharmacology at the Laboratory of Clinical Science.

Axelrod's work mentioned in the citation stemmed from his studies of the metabolism of catecholamines containing tritium in high specific activity. It was thought that noradrenaline labeled in this way would be eminently useful in detecting its pathways of intermediary metabolism. The experiments yielded an unexpected result: the tracer amine was rapidly taken up by organs with a sympathetic innervation, and specifically into the postganglionic nerve endings, where it was then stored just like endogenously synthesized amine and was released under the influence of nerve impulses. With his colleagues, Axelrod demonstrated the factors determining the "uptake," storage, and release of catecholamines and the role of many important drugs in affecting these processes. His investigations of the metabolism of catecholamines led to extensive study of transmethylation processes in their inactivation, and carried over to the methylation of a derivative of serotonin in the course of biosynthesis of melatonin in the pineal gland. Axelrod has also studied the neural and endocrine regulation of catecholamine biosynthesis in the adrenal medulla, and has demonstrated the transsynaptic induction of tyrosine hydroxylase and dopamine beta-hydroxylase. Most recently, he has investigated the role of methylation of phospholipids in membrane transformations.

Ulf Svante von Euler was born in Stockholm in 1905. Both his parents were scientists: his father had shared the Nobel Prize in Chemistry with A. Harden in 1929. Ulf von Euler received his medical degree from the Karolinska Institute in 1930, and later studied with Sir Henry Dale, Sir John Gaddum, and I. de Burgh Daly in England, and with Corneille Heymans in Belgium. In 1939 he became Professor of Physiology at the Karolinska, where he has remained for his entire professional life. At one time he was chairman of the Nobel Committee for the Prize in Physiology or Medicine, and from 1965–1975 was President of the Nobel Foundation.

Von Euler's outstanding contribution for which he received the Nobel citation was his discovery in 1946 that the transmitter at sympathetic postganglionic nerve endings is noradrenaline (not adrenaline, as had been suggested by others), and that it is released upon stimulation and partly excreted in the urine. The results of his studies of catecholamine release from the adrenal gland in a wide variety of experimental and clinical states, including stress, have long been incorporated into standard textbooks. Much of his earlier research was summarized in a monograph entitled simply, *Noradrenaline* (1956), and in his Nobel Prize Lecture, "Adrenergic Neurotransmitter Functions" (1971). In 1951 he demonstrated (with A. Engel) the increased output of urinary catecholamines in pheo-

chromocytoma, and the value of that measurement in diagnosing the presence of chromaffin tumours. In 1956 he showed with A. Hillarp that noradrenaline is stored in the nerves in subcellular particles from which it is released on stimulation.

Von Euler has made other important contributions to physiology. While at the National Institute for Medical Research in London during the early 1930s, he and Gaddum discovered Substance P. A few years later he discovered prostaglandin. These contributions laid the basis for the current intensive investigations of polypeptides as hormones and pharmacological agents and of the prostaglandins and thromboxanes.

Von Euler is a member of the Royal Society of London and the National Academy of Science in Washington. He has received many honorary degrees from universities in Europe and North and South America. A symposium, edited by Wolstenholme & O'Connor, was held in his honor by the Ciba Foundation in 1968, entitled "Adrenergic Neurotransmission." Von Euler also organized and edited with B. Pernow a Nobel Symposium on Substance P in Stockholm (1976) and published a book on prostaglandins (with R. Eliasson) in 1967.

Bernard Katz was born in Leipzig, Germany, in 1911. He obtained his MD from the University of Leipzig in 1935 and then studied with A. V. Hill at University College, London, where he received the PhD in 1938. He worked with Eccles and Kuffler on neuromuscular physiology on a Carnegie Research Fellowship in Sydney, Australia and returned to University College for his DSc in 1942. He was appointed the first professor of biophysics at University College in 1952. He is a Fellow of the Royal Society and of the Royal Society of Medicine. He was knighted in 1967.

The title of Katz's Nobel Lecture was, "On the Quantal Mechanism of Neural Transmitter Release." His classical microphysiological studies of the release of acetylcholine at the neuromuscular junction were carried out in collaboration with Paul Fatt, J. del Castillo, and R. Miledi. They discovered miniature end-plate potentials, which they proved to be due to the spontaneous quantal release of packets of acetylcholine molecules presumably stored in synaptic vesicles in the axonal terminals at the end-plate. They showed that this release was Ca^{2+}-dependent. Depolarization of the axonal terminals by the action potential caused an influx of Ca^{2+} that caused the release by exocytosis of many vesicles. The acetylcholine then acted upon receptors in the post-junctional membrane to allow a sudden influx of Na^+ and K^+ to set up a large end-plate potential sufficient to excite adjacent muscle fibers. The award winning experiments were described in the *Proceedings of the Royal Society* by Katz & Miledi in 1965 (Katz & Miledi 1965a–c).

Katz showed that there was considerable plasticity in the ACh transmitter mechanism as shown by "desensitization and potentiation," making it an important model synapse, as described by Katz in his books *Nerve, Muscle, and Synapse* (1966) and *The Release of Neural Transmitter Substances* (1969).

1973 Karl von Frisch, Konrad Lorenz, and Nikolaas Tinbergen

For their discoveries concerning organization and elicitation of individual and social behavior patterns.

This was the first Nobel Prize to recognize the importance of the naturalistic approach to an understanding of animal behavior. The systematic observation and recording of the development of characteristic patterns of behavior in animals raised in their natural habitat, or with systematic alterations in their environment during early development, has given much insight into the interaction of social and environmental factors upon the development of inborn patterns of behavior.

Karl von Frisch was a German zoologist born in Vienna in 1886. His zoological studies were carried out in the universities of Vienna and Munich. He became Professor and Director of the Zoological Institute at Rostock University in 1921, but later moved to Breslau, Munich and to Graz before settling at the University of Munich (1950–1958). He received international renown for his studies of the language of bees, published in his remarkable book *The Dancing Bees* (1961) and in *The Dance Language and Orientation of Bees* (1967). He has received many honors, including membership in the Academies of Sciences in Washington, Uppsala, Munich, Vienna, and Stockholm. He was able to show that the pattern of the flying "dance" of the bees could inform the swarm of the direction, distance, location, and even the quality of food to be sought there. He has made detailed studies of the sensory capacity of fish and insects.

Konrad Lorenz, an Austrian anatomist and animal psychologist, was born in Vienna in 1903. He studied at the University of Vienna, where he was an Assistant in the Institute of Anatomy (1928–1935) and Lecturer in Comparative Anatomy and Animal Psychology (1937–1940). He then became head of the Department of Psychology at Königsberg (1940–1945) and Director of the Max Planck Institute for Physiology and Behavior (1961–1973) at Seewiesen in Bavaria. He became Director of the Department of Animal Sociology at the Institute of Comparative Ethology of the Austrian Academy of Sciences in 1973. Among his many honors were

membership in the Royal Society, London, and the Kalinga Prize from UNESCO. Lorenz is the acknowledged founder of the science of ethology.

Lorenz studied animal behavior in natural habitats and the modification of instinctive behavior patterns by the environment and by social contacts, especially with man. His favorite animal of study was the greylag goose, in which he discovered the phenomenon of "imprinting." This rapid form of learning is possible only at a critical period of the gosling's life, when the bird may become attached to man as a parental object and remain so. He also discovered "innate release mechanisms," which conditioned an animal's reaction to environmental and social stimuli. His many other observations of animal behavior had important consequences for our understanding of developmental and social aspects of human behavior as well. His publications include *King Solomon's Ring* (1952), *Evolution and Modification of Behavior* (1965), and *Studies in Animal and Human Behavior* (1970).

Tinbergen began naturalistic studies of animal behavior in The Netherlands, where he was born in 1907. He studied Zoology at the Universities of Leiden, Vienna, and Yale, returning to join the Faculty of Zoology at Leiden in 1936. It was at Leiden that he did much to develop the new science of ethology, and where he became Professor Emeritus of Experimental Zoology in 1949. He then moved to Oxford, became a British citizen in 1955, and was appointed Professor of Animal Behavior (1966–1974).

Tinbergen studied the behavior of insects, fish, and birds in their natural habitat. He analyzed the innate or instinctive factors as well as the sensory and social influences controlling their behavior. His principal publications include *Study of Instinct* (1951), *Animal Behavior* (1965), and *Social Behavior in Animals* (1953).

1976 Baruch S. Blumberg[3] and D. Carleton Gajdusek

For their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases.

Daniel Carleton Gajdusek was born in Yonkers, New York in 1923. He took his undergraduate degree at the University of Rochester in 1943 and his medical degree at Harvard in 1946. His specialty training was initially in pediatrics, but he ultimately turned to virology. During an extended visit to the Walter and Eliza Hall Institute, headed by Sir MacFarlane Burnet (Nobel Prize, 1960), in Melbourne, Australia, Gajdusek learned about kuru, which led to his extensive studies in New Guinea. He has had experience with infectious disease in the field also in the United States and Iran. Since 1958 he has been at the National Institute of Neurological and Communicative Disorders and Stroke where, as Chief of the Laboratory of Central

[3]Blumberg is omitted from this review of neuroscience.

Nervous System Studies, he has developed knowledge of latent viruses and the diseases they cause.

Gajdusek's visit to New Guinea followed by only two years the discovery of a new neurological disorder, kuru, among members of a tribe of the Fore people living in the interior of the island, north of Port Moresby. In his Nobel Lecture he describes this disease as being "characterized by cerebellar ataxia and a shivering-like tremor that progresses to complete motor incapacity and death in less than one year from onset" (1977). The circumstances of the disease challenged Gajdusek's anthropological propensities, as well as his medical interest, and he spent the better part of a year living with the tribe. He was able to obtain tissue specimens for later analysis. The clinical and laboratory results were published when Gajdusek returned to the United States (1957), but the cause of kuru was still unknown. Soon after this, W. Hadlow drew attention to the similarities between kuru and a disease of sheep, scrapie, that belongs to a group of diseases known as "slow viral infections," i.e. infections that require prolonged incubation periods before generating pathology. Gajdusek, by this time established at the National Institute of Neurological and Communicative Disorders and Stroke, then succeeded in transmitting kuru to a subhuman primate in 1963. This was the first chronic degenerative disease of man demonstrated to be due to a slow virus. Transmission of the virus among the tribal people was attributed to the consumption of the infected brain of the deceased by the mourners. This success prompted Gajdusek to postulate that other degenerative diseases of man, or diseases occurring in a familial pattern, might also be due to slow viruses. Acting on this hypothesis he was able to transmit Creutzfeldt-Jakob disease to chimpanzees (1968). His efforts to transmit other human degenerative dementias (Alzheimer's disease, Pick's disease, Huntington's chorea, and Parkinsonism-dementia) to laboratory animals have not yet been successful.

1977 Roger C. L. Guillemin, Andrew V. Schally, and Rosalyn S. Yalow

For discoveries concerning the peptide hormones of the brain (Guillemin and Schally).

For the development of radioimmunoassays of peptide hormones (Yalow).

Roger Guillemin was born in Dijon, France in 1924. He received his undergraduate education there. After completing medical studies in Lyons (1949), he went to the Université de Montréal where he carried out research under the direction of Hans Selye, and received the PhD in 1952. He moved to Baylor University College of Medicine in 1953 and remained there for the next 17 years, except for a few years' interlude at the Collège de France in Paris. In 1970 he became a Fellow and Director of the Neuroendo-

crinology Laboratories at the Salk Institute for Biological Studies, where he still carries on his research.

Andrew Victor Schally was born in Wilno, Poland in 1926. He worked at the National Institute of Medical Research in London for some time, but emigrated to Canada where he completed his undergraduate studies at McGill University in 1955. While still an undergraduate, he had begun research under the direction of Murray Saffran at the Allan Memorial Institute of Psychiatry—work that led to the description of the first releasing hormone, CRF—and received the PhD degree in 1957. He then took a position with Guillemin at Baylor University College of Medicine, but in 1962 was appointed Chief of the Endocrine and Polypeptide Laboratories of the Veterans Administration Hospital in New Orleans. He is currently a Professor of Medicine at the Tulane University School of Medicine.

When the late Geoffrey Harris, a British endocrinologist and anatomist, proposed (1955) that the activities of the anterior pituitary gland are controlled by the brain, he was laying the foundation for the present-day recognition of the brain as an endocrine organ. Nervous control of endocrine secretion had been recognized many years earlier in respect to secretion of adrenal catecholamines, but the concept of nervous regulation of the secretion of the trophic hormones of the pituitary gland was entirely novel. The description by the Scharrers of hypothalamic neurons with an apparently secretory function (1963) made Harris's suggestion much more readily acceptable, as did Harris's demonstration of the hypothalamo-hypophyseal portal system and the deleterious consequences for pituitary function of its interruption. In 1955 Saffran & Schally described the first hypothalamic activity that could be attributed to a hormone, corticotropin-releasing factor (CRF). Five years later, Harris in Great Britain and S. M. McCann in the United States reported on the luteinizing hormone-releasing factor (LRF). These findings were the actual starting-point for the investigations that eventually brought the Nobel Prize to Guillemin and Schally.

Following his research at McGill University, Schally worked with Guillemin in Houston. Their initial research dealt with CRF, but the task was a forbidding one because of the great difficulty in purification and characterization of the molecule. Indeed, it was not until the end of 1981 that this task was accomplished (Vale et al 1981). In 1962, Schally established his own laboratory in New Orleans. Both he and Guillemin, now working independently, turned the efforts of their respective teams to the thyrotropin-releasing factor (TRF). Schally chose to work with pig hypothalamus, Guillemin continued with ovine tissue. After seven years' work, they provided the structure of TRF, an unusual tripeptide. They then took up the investigation of LRF: the two teams succeeded in isolating sheep and pig

LRF in 1971 and demonstrated that they are identical. Schally's group defined the structure of LRF at that time.

The factor causing release of growth hormones (GH) was the next in line of attack, but before much headway could be made, Guillemin discovered a substance in the hypothalamus that prevents the release of GH from the anterior pituitary gland, now known as somatostatin, and successfully identified its structure. The efforts to unravel the structures of these hypothalamic hormones are described in detail in their respective Nobel Lectures (1978).

In the succeeding years Guillemin has investigated endorphins. In 1976, his laboratory reported on the primary structure of α-endorphin, a hexadecapeptide, and γ-endorphin, a peptide with one more amino acid residue. These two endorphins contain metenkephalin as the amino-terminal sequence.

Rosalyn Sussman Yalow was born in New York in 1921. She studied at Hunter College (AB 1941), and then moved to the University of Illinois for graduate studies in physics (MS 1942, PhD 1945). She returned to Hunter College as Assistant Professor of Physics, but in 1950 took a position at the Veterans Administration Hospital of the Bronx, New York where she has been ever since. She is now Chief of the Radioimmunoassay Reference Laboratory there and the Nuclear Medicine Service.

In the mid-1950s, Yalow and the late S. Berson were testing a hypothesis proposed earlier by I. A. Mirsky about the biochemical defect in diabetes. Their experiments required the determination of the rate of metabolism of insulin, and they did this by administering ^{131}I-labeled insulin to diabetic and nondiabetic subjects, as well as to others who had received large amounts of insulin for the treatment of schizophrenia. Subjects receiving insulin therapeutically metabolized the labeled material more slowly, as judged by the rate of disappearance of the ^{131}I from the plasma. They postulated that the labeled insulin was being bound to antibodies, raised by the introduction of the exogenous insulin. Because of the low titer of such antibodies and their failure to precipitate, Yalow & Berson devised isotopic methods that would detect a soluble antigen-antibody complex. By electrophoresis of labeled insulin from plasma of their subjects, they were able to detect such antibodies, and this was reported in 1956. In her Nobel Prize address (1978), "Radioimmunoassay: A Probe for the Fine Structure of Biologic Systems," Yalow defined the new technique (RIA) as follows:

> The concentration of the unknown labeled antigen is obtained by comparing its inhibitory effect on the binding of radioactively labeled antigen to specific antibody with the inhibitory effect of known standards. . . . The RIA principle . . . can be extended to other systems in which in place of the specific antibody there is a specific reaction or binding substance.

These extensions took place slowly over the next decade, in relation to the binding of ^{60}Co-labeled vitamin B_{12} to intrinsic factor, as developed by V. Herbert, S. P. Rothenberg, and R. P. Ekins; with ^{131}I-labeled thyroxine through its binding by a specific serum globulin, through the studies of Ekins and B. E. P. Murphy; and the binding of plasma corticoids to transcortin, the serum corticosteroid-binding globulin, also by Murphy. These hormone studies verified the great sensitivity of what now became known as competitive protein-binding radioassays. These radioassays are receiving increasing attention by neuroscientists for mapping and detection of brain hormones. In fact, Yalow pointed out in her Nobel Lecture that the joint recognition of work in brain peptides and RIA signalized these new applications of the principle she had elaborated to the study of brain and nerve.

1979 Allan MacLeod Cormack and Godfrey Newbold Hounsfield

For the development of a revolutionary X-ray technique, computer axial tomography (CAT) scan.

Allen MacLeod Cormack was born in South Africa in 1924. After studying nuclear physics at Cambridge University, he returned to Capetown, where he became a member of the University faculty. In 1956 he was asked to serve as a part-time medical physicist at the Groote Schuur Hospital there. This gave him the opportunity to observe how the dose of radiation that patients were to receive in therapy was selected. Because of the variable attentuation of the x-ray beam by the skull and the soft tissues lying in its path, the radiologist was compelled to make an estimate of the dose that would ultimately reach the target, rather than a precise calculation. This was the genesis of his thinking about the problem that later came to be known as computerized tomography. After a sabbatical leave at the Harvard Cyclotron Laboratory, he began to work on the theory of image reconstruction and proceeded to test his ideas on models. In 1957, Cormack returned to the United States, taking a post in the Physics Department at Tufts University, where he has served as departmental chairman.

Godfrey Newbold Hounsfield was born in England in 1919. He is an electronics engineer at the Central Research Laboratories of EMI, (Electronic Musical Industries), a firm that he joined in the early 1950s. He directed the group that designed the first large solid state computer in the United Kingdom. He became interested in problems of pattern recognition in 1967, and soon undertook to extend the work to use of radiation, starting with γ-rays. Hounsfield is now the Head of the Medical Systems Department at the EMI Laboratories.

When a penetrating beam (e.g. X-rays or γ-rays) passes through an object, the coefficient of attentuation is the logarithm of the ratio of incident energy to transmitted energy. For homogeneous objects, this coefficient g is readily measurable as an exponential function, but for a nonhomogeneous body it is a composite of differential attentuations along the line of the beam. Cormack reasoned that if one could determine the attentuation coefficients of tissues by measurements made external to the body, the dose adjustments in radiation therapy would be much simpler to make. Such information would have a further dramatic consequence. If one thinks of the tissue to be imaged as composed of numerous thin slices layered one on top of the other, with the x-ray beam passed through the sections edgewise, the resulting data could be synthesized into a two-dimensional reconstruction of the internal structure of the organ. But in order to do so one would have to solve the problem of how to sort out the fluctuations in attenuation mathematically. Cormack showed that if g were determined for all lines intersecting the body, this could be achieved in two dimensions. His mathematical solution was published in two papers in the *Journal of Applied Physics* in 1963 and 1964; they met with little interest at the time. Yet his solution lies at the basis of the imaging technique used in computed tomography (CT), or computerized axial tomography (CAT scanning).

Hounsfield was intent upon improving the conventional x-ray technique to make it serviceable for imaging of hidden (internal) structures. Like Cormack, he constructed models for testing, but used a somewhat different mathematical solution. The successes with phantoms showed the way to clinical application. Hounsfield successfully devised a clinical tomograph, completed in 1971. Its computer made use of Cormack's algorithm. In effect, this was a method for resolving the more than 28,000 measurements, each the dependent variable of an integral equation. Hounsfield's earlier experience with γ-rays convinced him to turn to the more powerful X-rays for scanning of the brain. He later adapted the instrument for examining other parts of the body.

Cormack and Hounsfield were not alone in conceiving of tomographic principles. In 1961, W. H. Oldendorf, a California neurologist, concerned with improving the imaging of the brain without employing invasive procedures such as angiography and pneumoencephalography, suggested that the variable absorbances of the brain could be used to obtain an image of its internal structure. He actually constructed a model, but without computer reconstruction, and obtained a patent for its use with γ-rays. Oldendorf's paper (1961) on the utilization of these "radiodensity discontinuities" was the first to deal with radiographic tomography. For this work he received the Lasker Award for 1975 with Hounsfield.

Sometime after 1970, Cormack learned that his mathematical solution had been determined in 1917 by J. H. Radon. As it turned out the imaging problem was not the only one that needed the answer Cormack had provided: it was also important for problems of statistics, radio astronomy, electron microscopy, and optics (Cormack 1980).

With the introduction of CAT scanning, the need for pneumoencephalography and cerebral angiography has been sharply reduced. The technique serves in the diagnosis of brain tumors, brain hemorrhages, lesions of various types, and hydrocephalus, and is being used in studies of aging, dementia, and degenerative disorders. The principles of computed tomography can be applied to the use of nuclear magnetic resonance instead of X-rays, and this should provide information about the chemical composition of tissues. Hounsfield (1980) sees the two methods as becoming complementary to one another.

The 1979 citation recalls the award of the first Nobel Prize (in Physics) to Röntgen, a physicist, for his discovery of X-rays.

1981 David Hunter Hubel, Torsten Nils Wiesel, and Roger Wolcott Sperry

For discovering how sight stimulation in infancy is tied to future vision and how the brain interprets signals from the eye (Hubel & Wiesel).

For his research into the specialized functions of each side of the brain (Sperry).

David Hubel was born in Windsor, Ontario, Canada in 1926. He obtained his BSc in Physics at McGill University in Montreal in 1947 and his MD in 1951. He was a fellow at the Montreal Neurological Institute 1952–1954, where he studied with H. Jasper and W. Penfield. He was a resident in neurology at Johns Hopkins in 1954 and, as a US citizen, he was drafted to the Walter Reed Army Medical Research Institute in Washington (1955–1958), where he developed his tungsten microelectrode technique for recording from single cells in the cerebral cortex. He returned to Johns Hopkins where he became Associate Professor of Neurophysiology and Neuropharmacology, and later Professor of Neurophysiology. It was here that he became associated with Vernon Mountcastle, Stephen Kuffler, and Torsten Wiesel. He moved to Harvard Medical School with Kuffler in 1959, became Professor of Physiology in 1965, and was appointed George Packer Berry Professor of Neurobiology at the Harvard Medical School in 1968.

Torsten Wiesel was born in Uppsala, Sweden in 1924 and obtained his MD at the Karolinska Institute in 1954. He became Instructor in Physiology at the Royal Caroline Medical-Surgical Institute and Assistant in the Department of Child Psychiatry. He was then appointed Assistant Professor of Ophthalmology and Physiology at Johns Hopkins University, 1958–

1959. He moved with Kuffler to Harvard Medical School in 1959, where he later became Robert Winthrop Professor of Neurobiology. He succeeded Kuffler as Head of the Department of Neurobiology.

Most of the work done by Hubel and Wiesel was in such close collaboration that it can be described jointly. Their work was based upon extracellular microelectrode records of the firing of single cells in the visual cortex and lateral geniculate body in response to different points, patterns, movement, and color of photic stimulation. Electrophysiological studies were supplemented by anatomical studies using modern techniques of autoradiography, intracellular injection of fluorescent dyes, and Sokoloff's deoxyglucose method for determining the uptake of glucose in local areas of the visual cortex. This combination of precise microphysiological and histological study of the visual system in cats and monkeys, together with their studies of factors affecting the normal and abnormal development of this system in young animals, has provided a remarkably clear picture of the modular and hierarchical organization of the visual system from the retina, through the lateral geniculate bodies, to the primary and secondary areas of the visual cortex. Hubel & Wiesel demonstrated how this synaptic organization can be disturbed or permanently deformed by lack of appropriate visual experience early in life. As described by the Nobel Prize Committee, Hubel & Wiesel's work "represents a breakthrough in research into the ability of the brain to interpret the message from the eyes." (See Hubel 1982 for a brief historical account of the development of cortical neurobiology.)

Radially oriented columns of cells were found in the visual cortex that responded selectively to the orientation and direction of movement of lines and patterns in the visual field. These cells were described as "simple," "complex," or "hypercomplex" depending upon the complexity of visual pattern to which they were attuned. The more complex cells were found in the upper layers of the primary visual cortex, and especially in the parastriate cortex (areas 18 and 19).

Alternating columns of cells were also found for ocular dominance and confirmed by anatomical studies making use of the transynaptic axonal transport of radioactive amino acids injected into one eye. These results were confirmed by the use of Sokoloff's ^{3}H-deoxyglucose technique to study the effect of illumination of one eye upon glucose uptake in the striate cortex.

Suturing of one eye during the first few weeks of life in the cat or monkey caused a marked decrease in the ocular dominance columns for that eye, from which the animals might not recover. The synaptic organization of the various "feature detectors" in the visual system was found to be dependent upon visual experience during an early critical period of development in infancy.

Vernon Mountcastle, who first demonstrated the columnar organization of the cortex in the somatosensory system, has shown the general importance of this discovery for the specialized "modular" organization of all cortical areas. At the same time, he has pointed out that cortical areas cannot function as isolated units, but require "distributed systems" of integration for the organization of perception and motor behavior in the intact organism (Mountcastle 1978).

David Hubel delivered the Ferrier Lecture of the Royal Society in 1971 and has received several additional prizes and honors, including membership in the National Academy of Sciences and the Karl Lashley Prize of the American Philosophical Society in 1977. Torsten Wiesel is also a member of the National Academy of Sciences, and (with Hubel) was the recipient of the Lewis Rosenstiel Prize of Brandeis University and the Louisa Horwitz Prize of Columbia University.

Roger Sperry was born in Hartford, Connecticut, in 1913. He began his secondary education at Oberlin College in the early 1930s, majoring in English literature. He took his Master's degree at Oberlin in psychology and then went on to earn his PhD in zoology at the University of Chicago in 1941. He did postdoctoral work in psychobiology at Harvard University and later at the Yerkes Laboratories of Primate Biology in Georgia. He was Assistant Professor of Anatomy and Associate Professor of Psychology at the University of Chicago from 1946 to 1952. He was Section Chief of Developmental Neurology at the NIH in 1952–1953, but was then appointed Hixon Professor of Psychobiology at the California Institute of Technology in Pasadena in 1954, where he carried out his Nobel Prize research. He might well have received another Nobel award for equally distinguished work in the developmental biology of the nervous system, which he carried out chiefly at the University of Chicago, beginning with his work as a graduate student in Paul Weiss' laboratories there in 1940.

Sperry's (1945) previous work in developmental neurobiology was summarized in an important paper in the *Proceedings of the National Academy of Sciences* in 1963 (Vol. 50) in a paper entitled, "Chemoaffinity in the Orderly Growth of Nerve Fiber Patterns of Connections." His Nobel Prize research started about 20 years later. The functional significance of the great mass of nerve fibers connecting the right and left hemispheres, known as the corpus callosum, in man was unknown except for its ability to conduct epileptic discharge from one hemisphere to the other. Roger Sperry and his student, Ronald Myers, had already shown in animals that section of the corpus callosum prevented the transfer of training from one hemisphere to the other. An opportunity to study the effects of callosal section in man was provided for Sperry by the epileptic patients operated upon by the neurosurgeon Joseph Bogen for the control of intractable seizures.

Following what is now known as the "split brain" operation, Sperry and his students were able to demonstrate also a splitting of conscious awareness: objects presented to the right hemisphere alone were not recognized verbally by the language-dominant left hemisphere, even though they produced appropriate responses of the left hand. Verbal expression of conscious awareness was possible only for objects presented to the left hemisphere, which also seemed to excel in certain thought processes. However, the right hemisphere was found superior to the left in nonverbal processes such as spatial orientation, and probably some other abilities.

In spite of this lack of communication between the two hemispheres, patients with section of corpus callosum appeared quite normal and only occasionally had difficulty in coordinating the behavior of the hands. Sperry described these observations in his Harvey Lectures (1968), "Mental Unity Following Surgical Disconnection of the Cerebral Hemispheres."

Sperry was always concerned with the problems of the mechanisms of conscious awareness, though opposed to the dualist views expressed by some neuroscientists. The Nobel Award Committee cited Sperry for succeeding "brilliantly in extracting the secrets from both hemispheres of the brain and demonstrating that they are highly specialized and also that many higher functions are centered in the right hemisphere." Sperry wrote the Prefatory Chapter to Volume 4 of the *Annual Review of Neuroscience.*

Commentary

This brief review of Nobel Laureates in Neuroscience has highlighted many of the most important discoveries and developments in this area of scientific inquiry. The range of topics is wide, but they are all concerned with knowledge and understanding of the structure and function of the nervous system that have been gained since the turn of the century. Neuroscience has become such a wide-ranging conglomerate of biological, physical, mathematical, and medical sciences during the past 15–20 years that we are no longer surprised to find significant new discoveries and concepts coming from unexpected quarters. For example, the Neuroscience Research Program, pioneered by Frank Schmitt some 20 years ago, has brought dozens of different disciplines to bear on particular problems of neuroscience. In fact, before that time there was no formally organized discipline of neuroscience, except perhaps through the activities of the interdisciplinary International Brain Research Organization (IBRO), established in 1960.

In view of the responsibilities of the Nobel Committee for Physiology or Medicine to select only one prize each year in the whole field of biological and medical sciences, the fact that 22 out of the 74 awards made have been for discoveries considered of importance to neuroscience is a remarkable record. Even more significant is the number of individual scientists cited,

since frequently an annual prize has been shared by two or three investigators for different, though often related, contributions or discoveries. Of the 129 individual Laureates in Physiology or Medicine, the work of 47 has had direct relevance to basic or clinical neuroscience. It is apparent, with the passage of time and evolution of new experience, that the contributions of some of those selected have been minor, although the contributions of most have been outstanding and lasting. Revolutionary discoveries, such as have been made recently in molecular biology, are rare, and when they do occur in neuroscience they are often the result of a team effort by several investigators. This has made selection of the prize-winners even more difficult. Despite these difficulties, it is remarkable how many of the most important discoveries in neuroscience have been recognized and honored by the Nobel Committee over the years, and how many of the leading neuroscientists involved have become Nobel Laureates.

Appreciation of the work of these Laureates must be viewed in its historical perspective. The work of Pavlov and his school of conditioned reflex physiology, for example, represented at the turn of the century a true breakthrough in our understanding of the nervous control of the autonomic system. Furthermore, it provided objective measurements and a conceptual framework for the learning process, and for the analytic and integrative functions of the cerebral cortex, although Pavlov's oversimplified notions of brain mechanisms may not now be acceptable in the light of present knowledge. Even the original and brilliant work of Cajal, which provided the foundation for our knowledge of the cellular morphology of the nervous system, has been surpassed during recent years by revolutionary advances in ultramicroscopic, autoradiographic, and histochemical techniques of neuroanatomy and neuropathology.

The development of techniques by Erlanger & Gasser in the 1920s for the accurate visualization of the action potential from individual nerve fibers with wide-ranging conduction velocities, coupled with Adrian's recordings from individual sensory and motor nerve fibers, represented a true breakthrough in neuroscience at the time. Sherrington, who shared the prize with Adrian, did not make any revolutionary discoveries but had a profound influence upon the development of neuroscience by his thoughtful analysis of the balance of excitatory and inhibitory states in the organization of the reflex and integrative functions of the nervous system. This brings us to another major advance in the early 1930s, with the discovery by Otto Loewi and by Sir Henry Dale and co-workers of the chemical transmission of the nerve impulse at neuromuscular and synaptic junctions.

It was not until after the second world war, about 30 years after Loewi and Dale's discovery, that the classical work of Eccles and of Hodgkin & Huxley was honored by the Nobel Committee for their discoveries of the

ionic mechanisms involved in the generation and conduction of the action potential in peripheral axons as well as in the chemical transmission of excitatory and inhibitory postsynaptic potentials in spinal motoneurons. A clear picture of ionic mechanisms involved in electrical conduction of nerve impulses and in chemically mediated synaptic transmission in the peripheral and central nervous systems and at neuromuscular junctions was becoming firmly established. The identification of many new chemical transmitter substances had just begun.

Major advances in our understanding of sensory mechanisms during the post war period were recognized by the awards to von Békésy and to Granit, Hartline, and Wald. These were followed shortly by acknowledgment of major discoveries in our understanding of the metabolism and mechanisms of storage and release of humoral transmitters achieved through the work of Axelrod, von Euler, and Katz. The broadening view of neuroscience, from the cellular and molecular to the behavioral, was marked by the award to von Frisch, Lorenz, and Tinbergen for their careful naturalistic studies of animal behavior, and in the recent recognition of the work of Roger Sperry on the biological basis of conscious awareness and voluntary movement in man as revealed by carefully controlled studies of functions of the left and right hemisphere in patients with section of the corpus callosum.

Discoveries of major clinical significance have been recognized in the work of Gullstrand, Bárány, Wagner-Jauregg, Eijkman, Heymans, Moniz, Bovet, Gajdusek, and the most recent award to Cormack and Hounsfield for their development of computerized axial tomography.

Two of the most important recent developments in neuroscience are (*a*) the proliferation of many new transmitter or modulator substances, especially the neuropeptides, and (*b*) the cellular physiology of the brain in relation to complex perceptual and motor behavior. The "peptide revolution" was started by von Euler by his discovery of Substance P; more recent developments have been partially recognized by awards to Guillemin, Schally, and Yalow. Advances in our understanding of the cellular organization of the brain have been made possible by the perfection of microelectrode techniques introduced over 20 years ago, techniques that make it possible to record from anatomically identified single cells throughout the brain in relation to simple and complex perceptual and motor behavior. These studies have been well exemplified in the work of Hubel & Wiesel, who not only demonstrated the columnar, or modular, organization of assemblies of cortical cells for the detection of specific features of visual environment, but have shown how this organization can be modified by early visual experience. Their microphysiological studies were confirmed and complemented by the use of recently developed anatomical techniques.

ACKNOWLEDGMENTS

In the course of this review we have been impressed once again with the great contribution the Nobel Foundation has made to Neuroscience over the years. Not only have their most prestigious and generous prizes served to stimulate and to gain world wide recognition for many of the most outstanding discoveries and developments in experimental techniques and concepts, but the Foundation has fostered and supported research laboratories and the exchange of information in the neurosciences through their Symposia and workshops. The wisdom of the Committee on Prizes in Physiology or Medicine has been vindicated, with few exceptions, by the far-reaching and lasting importance of the contributions made by Nobel Laureates in neuroscience to its increasingly rapid growth during recent years.

Finally we would like to express our appreciation to Professor Ulf von Euler and Professor Yngve Zotterman and to the Editor, Dr. Max Cowan, for their critical reviews of this manuscript.

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