

Historical Aspects of the Autonomic Nervous System

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THERE was little possibility for any systematic or scientific investigation of the anatomy, physiology or pharmacology of the autonomic nervous system until those disciplines had begun their tortuous developments, following the European Renaissance. There had been glimmerings, however, that some functions of the body, such as heart action, vomiting, purgation, and sweating, might not be subject to voluntary control, and might indeed have something to do with special nerves, which were supposed to carry "animal spirits" to all parts of the body for movement and glandular action.

Calen (130–200 A.D.), the greatest of the Greco-Roman medical writers, had actually demonstrated the function of the recurrent laryngeal nerve in animals, but this seems to have been a chance observation. Descartes (1596–1650) had shown in his study of human physiology, *De Homini* (Leyden, 1662), that there are reflex actions which do not involve the brain. Indeed, much earlier, Aristotle (384–322 B.C.) had supposed that the heart might be the location of consciousness as a result of its marked fluctuations under emotional conditions.

The first significant anatomical appreciation of the autonomic nervous system came with Thomas Willis (1621–1675). In his *Practice of Physick* (London, 1684) he showed the connections between intercostal and spinal nerves. But earlier in his great *Cerebri anatome* (London, 1664), with illustrations by the great architect, Sir Christopher Wren (1632–1723), he had clearly recognized the sympathetic nervous system. Bartolommeo Eustacchio (1520–1574) had depicted the sympathetic nervous system earlier, but his work was not published until much later (Rome, 1714).

It was François Pourfour du Petit (1664–1741) who showed that ligation of certain nerves in the neck produce disturbances in the eyes and face on the same side. Jacob Wins-

low (1669–1760) in his *Exposition Anatomique* (Paris, 1732), designated the ganglion chain in the chest the "grand sympathetic nerve," and its branches the "lesser sympathetics." Marie François Bichat (1771–1802) introduced the term "vegetative nervous system" for what we now call the autonomic nervous system. H. Friedrich Bidder (1810–1894) and Alfred W. Volkmann (1800–1877) showed the sympathetic nervous system to consist of small medullated fibers originating from the sympathetic and spinal ganglia.

The great French physiologist, Claude Bernard (1813–1878), brilliantly demonstrated the physiologic significance of the autonomic nervous system with his discovery of vasomotor responses to stimulation of sympathetic nerve trunks and slowing of the heart by stimulation of the vagus nerve. His pupil, Charles E. Brown-Séquard (1817–1894), further extended the knowledge of the vasomotor effects of the sympathetic nerves. The first indication of an association between the sympathetic nervous system and secretory activity of glands was in the work of Henry Fraser Campbell (1824–1891). Claude Bernard's description of the sympathetic control of pupillary, sudomotor, and pilomotor functions as well as vasomotor function was confirmed clinically by Johann F. Horner (1831–1886). Horner showed that ptosis, "Horner's syndrome," is due to a lesion of the cervical sympathetic.

Walter Holbrook Gaskell (1847–1914) laid the histological foundation of our modern study of the autonomic nervous system. John Newport Langley (1852–1925), in defining the autonomic nervous system as an essentially efferent system, divided it into the orthosympathetic system on the one hand, and the parasympathetic system on the other, demonstrating their complementary and often antagonistic physiologic and pharmacologic reactions. He showed that the two systems are distinctive, embryologically, anatomically, physiologically and pharmacologically. Using nicotine to paralyze ganglionic synapses, he was able to locate the short postganglionic fibers in the parasympathetic system as well as the long

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postganglionic fibers characterizing the sympathetic system. It was his work which definitively established our understanding of the autonomic nervous system and its complementary division. Langley's use of nicotine as an anatomical tool was a brilliant exposition of the results to be obtained by co-ordinating anatomical, physiologic and pharmacologic experimentation. The summary account of his work (*The Autonomic Nervous System*, Cambridge, 1921) is a great classic in physiology.

One of the most important aspects of the autonomic nervous system is its dependence on chemical mediation of nerve impulse. Thomas R. Elliott (1877-1957) first suggested (*J. Physiol.* 31: XX, 1904) that a sympathetic nerve impulse liberates adrenin when it arrives at a smooth-muscle cell, with the adrenin acting as a chemical stimulator to the cell. John J. Abel (1857-1938) had discovered and characterized epinephrine in 1897 as the active pressor agent of the adrenal medulla. Reid Hunt (1870-1948) first discovered the remarkable blood-pressure-lowering effects of acetylcholine, and the greatest of modern pharmacologists, Henry Hallett Dale, who is still with us at 92, demonstrated the inhibitory effect of this compound on the heart. Reid Hunt also showed that tissues are more sensitive to acetylcholine after treatment with physostigmine. Most important were the reports of Otto Loewi (1873-1961), who demonstrated (*Arch. Ges. Physiol.* 189: 239, 1921) that vagal stimulation releases acetylcholine in the heart, and he further, in 1924, established the existence of cholinesterase, the enzyme that splits acetylcholine and another enzyme that may also aid in its synthesis. At the same time he showed that the action of physostigmine is to inhibit this enzyme.

Walter Bradford Cannon (1871-1945) gradually developed the evidence to support the notion that stimulation of sympathetic nerves results in the release of a chemical agent related to adrenalin. It was U. S. von Euler who showed that this was noradrenaline. Cannon and his pupil, Arturo Rosenbleuth, summarized the evidence for the chemical mediation of autonomic nervous action in a work (*Autonomic Neuro-Effector Systems*, New York, 1937), which stimulated Norbert Wiener (1894-1964) to develop the important feedback regulatory neurochemical mechanism which he called cybernetics (1948). This principle is paramount not only in autonomic

nervous system functioning, but also in computer technology.

Cannon and his followers also showed the partial dependence of the functioning of the autonomic nervous system on central nervous system activity. The autonomic nervous system seems to be particularly responsive to chemical events in the cells of the brain stem, including the reticular alerting system, as described by H. W. Magoun and his associates. It is in connection with the brain-stem factors involved in autonomic nervous system activity that anesthesia plays a significant role. It is remarkable that disturbances in autonomic nervous activity in relation to general anesthesia occur chiefly during induction and during recovery. During general anesthesia itself autonomic nervous system activity usually corresponds to the normal situation.

Autonomic neuroeffector transmission is thoroughly discussed from the standpoint of recent developments by U. S. von Euler (*Handbook of Physiology: Neurophysiology*, Vol. 1, 215-237, 1959). The wide functional activity controlled in large part by the autonomic nervous system invites an understanding of its physiology and pharmacology. The balanced neurochemical regulation of the autonomic nervous system includes many aspects of respiratory activity, cardiovascular function, gastroenteric activity, renal conditions, as well as secretory activity of skin, salivary glands, stomach and pancreas. Even muscular tension may be regulated in part by autonomic neurochemical factors. Much detailed information is now being accumulated on the chemical factors of importance in relation to the autonomic nervous system, with particular reference to catecholamines, together with the enzymes and chemical agents which may increase or inhibit their activity.

The extraordinary balanced mechanisms of the autonomic nervous system in regulating the overall general functional activity of mammals, including humans, led to Walter Cannon's development of the idea of "homeostasis." This was beautifully outlined in his remarkable book, *The Wisdom of the Body* (New York, 1932). The idea is an extension of the notion first advanced by Claude Bernard, under the concept of "the internal steady state." It is the internal steady state in the body, or the homeostasis of the body, that the wise anesthesiologist seeks to preserve.