THE HISTORY OF THE DISCOVERY OF THE VEGETATIVE (AUTONOMIC) NERVOUS SYSTEM

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PREHISTORY†

THE STRUCTURES which are known today as the peripheral vegetative nervous system were morphologically rather well known to Galen (A.D. 130–200), the greatest anatomist and physiologist of antiquity.[1] His descriptions suggest that he gained his knowledge mostly from dissecting pigs. His so-called 'sixth cranial nerve' comprises what we call today the ninth (glossopharyngeal), tenth (vagus), eleventh (accessory) nerves and the sympathetic chain. He described the superior cervical ganglion, the inferior cervical ganglion, the semilunar ganglion and the rami communicantes. These anatomical notions are still to be found in the basic *Traité des nerfs* of Tissot in 1778.[2]

Unfortunately Galen's physiological ideas are marred by his teleological zeal. He feels that these nerves are 'soft', because they come from the brain. Being soft they have to be purely sensory. He 'proves' then that they are there for this purpose anyhow. If by accident one of the nerves shows motor functions, it has in Galen's opinion dried up, and has become hard, and therefore motor. These nerves are hollow and make the so-called animal spirits go from one organ to the other, producing thus the phenomenon of 'sympathy'. Sympathy is an old and vague notion. In this case it accounts for the co-operation or co-ordination of organs, like irritation of the stomach producing syncope or convulsions by being transmitted via brain and nerves to the heart. Galen knew also a humoral kind of sympathy via bloodvessels, like for instance the relations of the pregnant uterus with the mammary glands.[2a]

As is well known, medical science remained stationary at best from Galen to the Renaissance. Even Vesalius, who in many points improved Galen's anatomical notions, left them unchanged as far as the so-called 'sixth nerve' was concerned. It is only his younger contemporary, the great Eustachius (1524–74), who in 1563 regarded the vagus and sympathetic as two different nerves. He described the sympathetic as the continuation of the abducens, our sixth cranial nerve.[3] An important event in the

history of the autonomic nervous system is the experimental cutting of the vagus by Piccolomini in 1586, which in this case was followed by the death of the animal.[4]

FROM WILLIS TO BICHAT

Great progress in our knowledge and understanding of the autonomic nervous system was achieved by Thomas Willis (1621–75) especially through his *De cerebri anatome* (1664) with the remarkable illustrations of the rebuilder of London (Christopher Wren). Willis's anatomical knowledge of the vagus and of the sympathetic, which he calls 'intercostalis', and therewith follows Eustachius in separating the two structures, was much better than that of his predecessors. But above all he made the momentous differentiation between voluntary motion, governed supposedly by the cerebrum, and involuntary motion, governed by the cerebellum, from which vagus and intercostalis descend. Sympathy is carried between the two systems through the rami communicantes. Nerves surrounding vessels are able to constrict them in a mechanical way. His experiences in cutting the vagus, undertaken partly with Richard Lower, are inconclusive.[5]

In 1727 François Pourfour du Petit of Paris (1664–1741), whose contribution to our knowledge of nervous function is vastly underrated, reported on an experiment of cutting through the superior sympathetic of a dog. He produced something which we call today, after the nineteenth-century Zürich ophthalmologist J. F. Horner, Horner's triad—that is myosis, ptosis, and enophthalmos. This convinced him of the important fact that the sympathetic does not simply descend from the brain, because impulses travel in a caudal cranial direction.[6]

Jacobus Benignus Winslow (1669–1760), the Danish-born Paris professor, decisively enlarged our anatomical knowledge and our physiological notions of the autonomic nervous system in 1732. He knew three 'sympathetic nerves': the 'small sympathetic nerve', our present-day facial; the 'middle sympathetic nerve', our vagus; and the 'large sympathetic nerve', the intercostalis of Willis and our present-day sympathetic ganglionic chain. He gives a far better and more extensive description of the anatomy of these structures than any of his predecessors. Like Pourfour du Petit, he considers that the sympathetic nerve does not descend from the cranium. He sees the possibility of a spinal origin for the sympathetic trunk, but essentially it is to him a product of the ganglia, and therefore an independent structure. The ganglia are 'small brains'. Winslow was essentially a morphologist. The 'little brains' were his one and only physiological speculation, but one that was extremely consequential. He differentiated also the white and grey rami communicantes.[7]

Through Winslow the notion of sympathy remained for ever associated with the nervous system. Otherwise it survives only as a notion of psychology. Sympathy had set out scientifically on a far more comprehensive career. With Theophrastus and the Stoic philosophers it was a cosmological principle and continued to play this role in the Renaissance with Pico, Paracelsus, Agrippa, Van Helmont, and above all Fracastoro. With Fracastoro sympathology reaches its climax. For him the modern notion of contagion, which he more or less created, was only a by-product of sympathy. To it he devoted a special treatise.[8] Thereafter 'sympathy' became more and more limited to living bodies. And in the animal body the nervous system now becomes

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more and more the sole vehicle for sympathy. Attempts to associate it with connective tissue or blood vessels failed. Haller still knew six kinds of sympathy. Piorry even eight. The effect of medicaments (for example, quinine) was still explained by 'sympathy' at the beginning of the nineteenth century.[9]

Robert Whytt of Edinburgh (1714–66) explained many results of his experiments, which to us would be today seen as either reflexes, or endocrine phenomena, as 'sympathies', which travel through brain and cord. A fertile notion, which he introduced, was the assumption that the involuntary movements of organs could be the result of local stimuli.[10]

J. F. Meckel, of Meckel's ganglion, professor of anatomy in Berlin (1714–74) saw in the ganglia primarily constructions facilitating a wider distribution of fibres, an idea which was appreciated only much later.[11]

With F. X. Bichat (1771–1802) a turning-point in the history of the autonomic nervous system was reached in 1800. He merged his own experimental results with the orientations of Willis and Winslow into an imposing anatomico-physiological system, which long governed medical thought and which is still rather influential even today, although it has been officially to a large extent abandoned.

Bichat assumed a physiological and anatomical separation of life in the animal body into two different forms of life: so-called organic life and so-called animal life, consequently also two nervous systems. Organic life is the life of the heart, intestines, lungs, etc. This inner life is in structure asymmetrical and disharmonious, but in function it is continuous. It is independent of habit and education and it is connected with the 'passions'. (Bichat's teacher Pinel located mental disease not accidentally in the abdominal ganglia.) It has several centres: the ganglia. It ends with the death of the heart. Animal life, the externally directed activity of the body, is on the contrary symmetrical, harmonious, discontinuous, formed by habit and education, governed by intellect, and has one centre, the brain. This life dies before many organs die, and its death is determined by the death of the brain.

The sympathetic trunk is not a nerve, but a chain of little brains. New fibres come out of the ganglia. Bichat therefore called the 'ganglionic nervous system' what we have become accustomed through his follower Reil to call 'vegetative nervous system'. After Langley the equally problematic term 'autonomic nervous system' has become prevalent in English-speaking countries. Bichat's theory of the independence of the organic life was widely accepted.[12] One of his German colleagues, Frederick Arnold, drew attention to the fact that the vegetative system has no conscience.[13]

FROM REMAK TO LANGLEY

Thought about the vegetative system was strongly influenced around the middle of the nineteenth century by the now expanding microscopic anatomy. Ehrenberg (1833) and Valentin (1836) discovered isolated cells in the ganglia. Robert Remak (1815–65), the greatest of the microscopical investigators of the nervous system, published no less than three basic discoveries in his doctoral thesis of 1838. He discovered the unmyelinated fibres in the sympathetic system. This explained the existence of gray and white rami. He furthermore discovered that nerve fibres always arise from ganglion cells. He also described the axis cylinder. He eventually found

accumulations of ganglionic cells in the heart, which are still called Remak's ganglia. He drew functional conclusions from this discovery and his discovery of similar accumulations in the bladder in 1840. The lasting refusal to acknowledge Remak's discoveries in this, as in other fields, by Henle, Valentin, Kölliker, etc., is one of the most shameful chapters in the history of nineteenth-century science. Remak, who through his Jewish origin was barred from an academic career, had to become a clinician, and as a practising neurologist he continued his interest in the vegetative system.[14] The microscopical results of Remak, Valentin and others constituted strong support for the assumptions of Bichat concerning the particular character of the vegetative nervous system.

This is quite obvious from the writings of two influential researchers in this field, F. H. Bidder (1810–94), and A. W. Volkmann (1800–77). They wrote the article on nerve physiology in R. Wagner's famous handbook, and published in 1842 a book under the provocative title *The Autonomy of the Sympathetic Nervous System*. They differentiated between 'thick' and 'thin' fibres in the nervous system, but took great care to affirm that this had nothing to do with Remak's special fibres. They also denied that fibres originated in the cells of ganglia. By laboriously counting post-ganglionic and pre-ganglionic fibres through the microscope they came to the important conclusion that the former were more numerous than the latter. (Johnstone had assumed the same in 1764 without microscopical inspection.) Their refusal to adopt Remak's discovery of the origin of fibres from ganglionic cells deprived them of the chance to understand their own observations. They saw in the vagus nothing but a subdivision of the sympathetic. Bidder discovered some more ganglia in the heart. His best work is probably that with curare in 1865 and 1868, whereby he found that curare did not prevent control of heart or intestine by way of the vegetative system. Bidder and Volkmann were eminent men, who made numerous contributions. They illustrate on the other hand the fact that insight often originates together with a great many errors.[15]

Henle had stated in 1840 that the nerve fibres going to the muscle fibres in the wall of vessels, control the latter. Benedict Stilling (1810–79) of Kassel, another forgotten pioneer of neurological research and surgery, was a friend of Magendie and Claude Bernard, received the Prix Monthyon 1860,[16] and in 1840 coined the expression 'vasomotor system' for this apparatus, of which he is at least the co-discoverer. The vasomotor system became more widely known through the experiments of Claude Bernard (1813–78) in 1851 and of Ch. E. Brown-Séquard (1817–94) in 1852. Claude Bernard obtained dilatation of vessels by sectioning the sympathetic, Brown-Séquard obtained contraction through stimulating the cut end. Thus the sympathetic was identified as vasoconstrictor. M. Schiff (1823–96) demonstrated in 1856 vasodilating nervous elements and Bernard in 1858 showed a vasodilating effect through excitation of the chorda tympani.[17]

Another important detail concerning the vegetative system was brought to light through the experiments of the brothers Ernst Heinrich Weber (1795–1878) and Eduard Weber (1806–71) of Leipzig. Thus they were able to arrest the heart by stimulation of the vagus in 1845. They discovered therefore not only an important phenomenon, but a whole new notion in neuro-physiology, that of inhibition. Their explanation was violently opposed by Schiff, Moleschott and Budge, but victoriously

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defended by von Bezold.[18] On the other hand Le Gallois, Valentin, von Humboldt, Arnold and Budge had already succeeded in accelerating heart action by irritation of different nervous structures. Bezold repeated these experiments successfully in 1862 and demonstrated a motor heart centre in the medulla oblongata.[19] Pflüger, Bidder, and the Webers showed the influence of the vagus on the intestine.[20]

While these microscopic findings and experiments did little to undermine the influence of Bichat's theory of the absolute autonomy of the extracranial vegetative system, a turn of the tide started with Claude Bernard's famous experiment of 1850. He produced glycosuria through puncturing the fourth ventricle, an effect which was not obtained when the splenic nerves were cut. Further evidence that the vegetative system had higher centres in the medulla and even in the basal ganglia, accumulated in the following decades (e.g. polyuria produced by K. Eckhard in 1860; embryological research on the genesis of the sympathetic trunk by Balfour in 1881, etc).[21]

A very important role in this evolution was undoubtedly played by the experiments of L. J. Budge (1811–84) and A. V. Waller (1816–70). Budge claimed throughout his life priority over the Webers on the question of inhibition, which he undoubtedly does not deserve.[22] He also tended to play down the role of the great Waller in their common work. But he has still enough remarkable work to his own credit. Budge and Waller rediscovered the results of Pourfour du Petit in 1851, showed that the cervical sympathetic comes partly out of the cord, and described a cilio-spinal centre in the medulla. For this discovery they obtained the famous Prix Monthyon in 1852. · Budge discovered in 1858 a similar genito-spinal centre, thus definitely bringing into the picture the vegetative elements of the cord. Waller clarified the composition of the vagus in 1856 by his new degeneration method and obtained in the same year a second Prix Monthyon.[23]

All modern work on the vegetative system is based on the research of W. H. Gaskell (1847–1914) and John Newport Langley (1852–1925) of Cambridge. With their work England again became prominent in this part of physiological research. Gaskell devoted himself primarily to heart physiology. Still he made the following important discoveries in our field: he demonstrated in 1885 that the sympathetic communicates with the cord exclusively through the white rami communicantes; in 1886 he postulated that the sympathetic outflow from the cord came from a column of cells in the lateral horn; in the same year he adumbrated the existence of two antagonistic systems within the involuntary system.[24]

All these points were elaborated through the monumental work of Langley. Langley called the vegetative system the 'autonomic nervous system'. He developed the notion of antagonism between sympathetic and parasympathetic systems. First through experiments with the heart and the stomach, later with blood vessels, he demonstrated the pre-ganglionic and post-ganglionic neurones in the sympathetic. His usual technique after 1889 was interruption of the synapses in the sympathetic ganglia by the application of nicotine. Hirschmann had demonstrated in 1863 that nicotine paralyses the cervical sympathetic. With this method Langley could show amongst other things that sensory fibres traverse the ganglia without interruption.[25] In 1901 Langley's disciple T. R. Elliott (1877–1961) showed that epinephrine has the same general effect as stimulation of the sympathetic.

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The twentieth century has been primarily occupied with the intracranial parts of the vegetative nervous system and its relations with the endocrine glands. J. L. Karplus (1866–1938) and A. Kreidl had shown as early as 1909 that the hypothalamus controls the cervical sympathetic and that the hypothalamus remains effective in curare intoxication. In 1926 they were able to produce hypertension by way of the hypothalamus after excision of the adrenals and the hypophysis.[26]

Walter B. Cannon (1871–1945) of Boston[27] engaged during the 1920s in intensive studies on the ways the sympathetic system and the adrenal medulla produce visceral adjustments to stress. Harvey Cushing had shown in 1913 connexions between the hypothalamus and the pituitary gland. Regulation of organ function seemed to be a combined effect of stimulation of certain brain structures and of hormones. S. Ranson (1880–1942) and his school elucidated the hypothalamic innervation of the pituitary. Walter R. Hess of Zürich (1881–1973)[28] demonstrated brilliantly the influence of the hypothalamus on the vegetative system, beginning these experiments in the 1920s. He obtained the Nobel Prize in 1949. He differentiated between so-called trophotropic impulses carried through the parasympathetic and ergotrophic impulses carried through the sympathetic. As prototype he demonstrated in his famous electrode experiments for the former the function of the sleep centre in the lower brain, for the latter that of defence centres. These experiments and further experiments, e.g. by J. F. Fulton, showed that parts of the brain controlled hypothalamic centres and that on the other hand these vegetative centres influenced the cortex. The involvement of the cortex in vegetative processes had already been demonstrated in the work of I. P. Pavlov (1849–1936) and his school on conditioned reflexes.

The other great line of discoveries in the vegetative nervous system during the twentieth century has been so far the elucidation of chemical transmission of nervous impulses in the vegetative system. Dixon had observed in 1907 the vagus-like effects of muscarine. Lehmann had described in the same year cholin. In 1921 O. Loewi (1873–1961) discovered the transmission of impulses in the vagus by means of acetyl-cholin. Chemical transmission in the sympathetic had been assumed by T. R. Elliott. H. H. Dale (1875–1968) had shown in 1905 sympathetic-like effects of ergot; Cannon had isolated an adrenalin-like substance, sympathin, in 1931. But it was von Euler, who discovered in 1946 the true agent of transmission in the sympathicus, noradrenaline.[29] We now differentiate adrenergic and cholinergic neurones and synapses.

After the establishment of the theory of an independent vegetative nervous system, it was but logical to make this new system the basis of a large number of unexplained clinical phenomena. The first rather extensive attempt in this direction, which is known to me, is that by J. G. Lobstein (1777–1835) in 1823.[30] Lobstein discussed as diseases of the vegetative system the following: hypochondria, mania and melancholia, lead colic, asthma, angina pectoris, miliary disease, latent arthritis, malaria(!), sudden death (Ruysch already had claimed sudden death through hitting the solar plexus), migraine, insomnia, toothache and ophthalmological diseases.

When A. Eulenburg (1840–1917) published in 1863 another authoritative discussion

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of diseases of the vegetative system[31] he presented the following syndromes: mechanical damage, migraine, Graves' disease, unilateral hyperhidrosis, glaucoma, optic nerve paralyses, progressive muscle atrophy, angina pectoris, hyperesthesia, colic, anaesthesias, sympathetic paralyses of voluntary muscles, epilepsy, locomotor ataxia, Addison's disease, and diabetes. Later discoveries made this list look so poor that in 1910 H. Eppinger (1879–1946) and Leo Hess tried again to tackle the problem with their notion of sympathicotonic and vagotonic individuals and diseases.[32] Eppinger listed as vagotonic diseases the following: asthma, spastic constipation, colitis, urticaria, hay fever, serum sickness. This list did not fare much better than its predecessors. Neither did Feer's 'vegetative neurosis' of 1923 which turned out to be simple calomel poisoning. It is not likely that the now fashionable diagnosis of neurovegetative dystonia will do much better. As extremely helpful as our knowledge of the vegetative system has been in the understanding and treatment of many diseases, it has not been a useful foundation for a pathophysiological system.

Pharmacotherapy of the system grew out of the above-described physiological discoveries. Attempts to influence the vegetative system, especially the sympathetic, by surgical means start probably with W. Alexander of Liverpool ligating the vertebral arteries in epileptics in 1889. Yet successful sympathetic surgery dates only from René Leriche (1879–1955) who introduced periarterial sympathectomy in 1916 and A. W. Adson and G. E. Brown who did cervical sympathectomy for Raynaud's disease in 1925.[33] Even in this field and that of the vagotomies quite a number of indications have since been abandoned.

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