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REVIEW PAPER

A history of the autonomic nervous system: part II: from Reil to the modern era

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Abstract
Introduction The history of the study of the autonomic nervous system is rich. At the beginning of the nineteenth century, scientists were beginning to more firmly grasp the reality of this part of the human nervous system.
Conclusions The evolution of our understanding of the autonomic nervous system has a rich history. Our current understanding is based on centuries of research and trial and error.

Keywords History · Nerves · Vegetative system · Physiology · Anatomy

Introduction

As the nineteenth century opened, the recently published works of Bichat concerning his ganglionic system were on the rise [1]. By around 1830, most anatomists had accepted Bichat's conclusions [1]. Gross anatomy and embryology seemed to support his conclusions. For instance, observations of human fetuses with birth defects showed no record of complete absence of the ganglionic system. This led many to deduce that "a part never found wanting must be more fundamental to the organism than one often found missing or defective" [1]. And so, in embryology's early days, the evidence seemed to point to Bichat's conclusions. The prevailing belief at the century's beginning was that organ movement was caused by locally acting stimuli or autonomous ganglia. The brain's exact place in this system was unclear so far; however, some, such as Bichat, had observed how emotional disturbances could affect organ function, suggesting a potential bridge between the systems [1]. Despite its location and seemingly similar function, the vagus was still not included in the vegetative nervous system yet [1]. Once microscopic histogenesis had been established as a new field, however, new evidence began to contradict Bichat's claims.

Picking up the torch after Bichat's tragic death in 1802 was Reil [1]. He opened the century with a paper in 1807 that attempted to expand upon Bichat's system, and in which he introduced the term "vegetative nervous system" [2]. Reil focused on the problematic anatomical bridges between the cerebrospinal and ganglionic systems provided by the rami with which his predecessors Bichat and Johnstone had grappled. Reil's solution was comparing the rami to semiconductors he termed "Apparat der Halbleitung," representing in modern terms an electrical "make-and-break" key between the two systems [3]. Analogous to Johnstone's doctrine on ganglia, he believed physiologically that these structures prevented conduction of improper signals, but in a pathological state, it became a conductor of the signals, connecting the organic and animal lives [2]. Reil agreed with Winslow's belief that the ganglia were independent sources of nervous power and sought to confirm this belief by supplying new arguments and experiments in order to support this aspect of Bichat's doctrine further [2].

Despite the acceptance by many of Bichat's new doctrine, there were still dissenters in the community—one of whom was the British physiologist Wilson Philip. As a physiologist, Phillip contested the autonomy of the ganglionic system and claimed it ultimately to be under the control of the brain and spinal cord system. With this reasoning, he hearkened back to

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the beliefs of Willis, who classified the ganglia and their nerves as offshoots of the cerebrospinal axis. While Philip acknowledged that various organs functioned independently of the cerebrospinal system, he believed that through the ganglia, the central nervous system could exert an effect if need be [1]. Furthermore, he argued that these ganglia could not halt stimuli traveling through them such as Johnstone and Reil had proposed. So convincing was Philip's argument that when combined with experiments offering further evidence by physiologists Johannes Müller (in an experiment in 1835), E.H. Weber, Flourens, and Longet, the matter of ganglionic inhibition of signals was dismissed after approximately 50 years of acceptance [1].

A second physiologist contradicting Bichat in the early nineteenth century was Legallois. The new role and importance of physiology vis-à-vis anatomy had become manifest with his statement: "all the questions, I say, insoluble until now by means of anatomy are completely resolved by the experimental approach, and it is demonstrated at the same time that the ganglia can no longer be compared with little brains" [1]. Legallois maintained that the spinal cord actually was a component of both animal and vegetative life [2]. He opposed Bichat's notion of an independent ganglionic system, but he did not have a notable impact on beliefs at the time.

A third antagonist of the independence of the ganglionic system put forth by Bichat was J.G.C.F.M. Lobstein. He believed that so many independent centers of nervous power would have a disharmonious effect on the body. He also thought the organic and animal systems were separate but acted upon one another and did not operate in isolation. He believed these two systems "counterbalanced" one another [1]. He had three key conclusions from his work: (1) that the sympathetic nerve, despite its separateness from the cerebral nervous system, shared the same essential characteristics; (2) each system operated by the same "mode of action"; and (3) the autonomic nervous system and somatic nervous system exercise a constant influence on each other that becomes apparent during disease states [1].

Bichat's doctrine lived on despite the objections of these physiologists, in part due to the remarkable, if misguided, work of the microscopist Remak (Fig. 1). He has been described as the "most outstanding contributor to the earliest phase of achromatic microscopy applied to the nervous system" [1]. This statement is based upon several key findings attributed to him, including his discovery in 1838 of the non-myelinated or gray fiber, sometimes referred to as the "fiber of Remak" [2]. He described these fibers as "not tubular, that is, surrounded by a [myelin] sheath" but instead as "naked, being transparent as if gelatinous, and much finer than most of the primary tubes [myelinated fibers]" [1]. Remak believed that the larger, myelinated fibers were located solely in the central nervous system and bore motor or sensory functions [2]. He assigned the finer, non-myelinated fibers to the ganglionic system, which he believed served to control organ function. Remak's great progress in the field of neurohistology was misappropriated and used to uphold Bichat's doctrine [1]. In a nod to Bichat, he called the finer fibers "organic" and used his own term "gelatinous" occasionally. He believed these fibers to be responsible for the action of involuntary muscle and secretion organs, as well as other organs, blood vessels, and possibly even innervating skin. Furthermore, he claimed that these "organic fibers" influenced the quality and quantity of the secretions in various organs by acting on the actual blood vessels leading to the glands. Like Bichat, he believed organic fibers also traveled to muscle, giving tone to the structures [1]. Today, these organic fibers are known to be postganglionic visceral efferents and non-myelinated visceral afferents [3].

Fig. 1 Robert Remak https://en.wikipedia.org/wiki/Robert_Remak

Unfortunately for Remak, many were hesitant to accept his findings, and it was not until 1860 that they were widely accepted—a delay which some attribute to anti-Semitism in Germany at the time [2]. Nevertheless, Remak went on to formally propose a theory first mentioned by the underappreciated Whytt—that of the "nerve cell" or "neuron" in 1838: "The organic fibers originate from the very substance of the nucleated globules" [1]. While being one of the greatest leaps in neuroscience of the century, Remak's discovery found the scientific community unprepared for such a revolutionary speculation, and his claims were strongly opposed by many [2]. Remak remained convinced and pushed onward in an attempt to identify the function of the cells and fibers of the ganglia [1]. Declaring that since the organic fibers made up a good deal of the sympathetic nerves and spread outward from the nucleated globules making up the ganglia themselves, he declared that "sympathetic ganglia must be considered the true centers of the nervous system" [3]. After these descriptions of myelinated vs. demyelinated fibers, Remak went on to describe the posterior spinal root ganglia as belonging, in part, to the ganglionic system due to their homologous structure and his finding of organic fibers therein: "the spinal ganglia seem to relate to the organic nervous system […] I suspect that the spinal ganglia were specially constructed to receive the necessary organic fibers from the sympathetic ganglia by way of the posterior and mainly sensory spinal nerve roots" [1].

The findings of Remak encouraged Johannes Müller, his mentor [2]. He confirmed Remak's histological descriptions of white vs. gray rami communicantes. In a paper published in 1833, Müller held that there was a reciprocal relationship between the two systems [1]. He believed fibers belonging to the ganglionic system ran through the gray rami to the spinal nerves, by which they were distributed to the structures that they supplied [1]. By 1840, he concluded that there were three types of fibers in cerebrospinal nerves: sensitive and motor, both of which he believed to be myelinated and originating from the roots of the cerebrospinal nerves, and gray organic fibers, which originated in the ganglia or sympathetic nerve itself [2]. He asserted that the efferent fibers of the vegetative system, both preganglionic and postganglionic, were charged with relaying involuntary movement of muscles and (especially digestive) organs [1]. The motor and sensory somatic fibers, he believed, traveled to and from the cerebrospinal axis [2]. These conclusions were used along with Remak's to sustain Bichat's doctrine with new and convincing evidence [1]. Müller's other contribution to this history was proving by experiment on animals, along with several other physiologists, that irritation of the ganglia did in fact cause pain in the absence of a pathological state, and thus refuted the incorrect assumptions of Johnstone concerning the ganglia acting as "filters" [3].

One vehement opponent of Remak's and Müller's discoveries was G. G. Valentin (Fig. 2). After briefly being described by Ehrenberg first, Valentin provided greater detail of a nerve cell body under the microscope in a paper that documented his neurohistological research [1]. He termed the nerve cell body a "globule" [4]. Those within ganglia he named "ganglionic globules," or "ganglionic corpuscles," both of which became terms for the nerve cell body [1]. His most notable contribution to neurohistology, however, was to suggest that nervous tissue in both animal and organic systems was made exclusively of these previously described cell bodies and their nerve fibers, the latter of which he termed *Grundtypus*; however, he did not believe these to be connected [3]. He examined the rami communicantes and first described the white variety coming from the spinal roots and traveling to the ganglionic system and must have therefore been efferent in direction and function [1]. While some fibers were seen to enter a ganglion and end, others simply passed through without interruption

Fig. 2 John Newport Langley https://en.wikisource.org/wiki/Author:John_Newport_Langley#/media/File:John_Newport_Langley.jpg

[1]. In 1839, he argued that the ganglionic system directed and controlled the roles of metabolism, secretion, and circulation, among other functions, but he shared Willis' belief that the sympathetic nerve was dependent on the brain and the spinal cord, from which he believed the fibers all originated [2]. His basis for this belief was the assumption that the fibers entered the sympathetic trunk via the white rami communicantes and his finding that due to the fact that some fibers entered and left ganglia unchanged, the ganglia could not be independent [1]. However, he was incorrect in his rejection of the existence of the organic fibers described by Remak and Müller [3]. Instead, Valentin held the belief that ganglionic fibers were not unique in their structure or intercellular communications [1]. Instead, he argued they were merely extensions of the "cell body's capsule" and agreed with many of his contemporary German microscopists who believed them to be artifacts or unidentified connective tissue but certainly not a part of the nervous system [3]. He rationalized this rejection of connections between a ganglion's incoming fibers and its cells by citing Henle, who explained how fibers in the ganglia could influence one another without making direct contact in a sort of "crossover transmission" [2]. And so, Valentin was unique among physiologists in his time by rejecting Bichat's notion of an independent ganglionic system, but he did so based on a factually incorrect foundation [1]. His correct overarching conclusion was based on two errors, the first being his rejection of Remak's proposed "cell body-fiber union" and the second being his rejection of Remak's organic

fibers. Only in 1842 did he recant his views on the organic fibers described by Remak [1].

By the 1840s, enough opposition had mounted against Bichat's system that the independence of the autonomic nervous system was no longer held as an unassailable fact [1]. In 1842, two German scientists had undertaken anatomical studies to settle the issue once and for all: F. H. Bidder and A. W. Volkmann. They examined the microscopic components of the two nervous systems with great scrutiny. While, like Valentin, they rejected the organic fibers of Remak, they differed from Valentin in that they accepted the anatomical and therefore functional independence of the ganglionic system [1]. In lieu of Remak's fibers, they came up with a new system [2]. They believed that there were two types of fibers in the vegetative system: smaller fibers which made up the majority of the system and larger fibers that seemed to come from the cerebrospinal system [1]. They then turned their attention to the connections between the vegetative and cerebrospinal systems [1]. This was undertaken via comparative anatomy with a frog [3]. Microscopy of the frog's rami communicantes yielded the finding that white rami were largely efferent, confirming the opinion of Remak [1]. This allowed Bidder and Volkman to now argue that the majority of rami communicantes fibers were not autonomic but cerebrospinal, with less than a third originating from spinal root ganglia and being classified as ganglionic [3]. The results of Bidder and Volkman's study as a whole supported Bichat's doctrine; however, their findings were based on erroneous microscopic observations [2].

Opposing Bidder and Volkman's findings was the Swiss microscopist R.A. Von Koelliker. The turmoil of the 1840s persisted with his opposition of the two Germans who hoped to lay the matter to rest [1]. Koelliker occupied himself with the four parts believed to make up the vegetative ganglia of the vertebrate: connective tissue, Remak's organic fibers, other nerve fibers, and ganglia [2]. Like Bidder and Volkman, he denied the existence and importance of Remak's organic fibers as a functional unit of the nervous system [1]. He contended that the classification system of fibers based on size introduced by Bidder and Volkman was extraneous and misleading [4]. Furthermore, he did not believe that the small myelinated fibers were confined to the spinal and cranial nerves [1]. He refuted their findings in frogs that most rami fibers were somatic and were carried to the periphery in spinal nerves, with the rest originating from the spinal root ganglia, forming the sympathetic trunk and vegetative ganglia [1]. Koelliker's dissections with humans and rabbits led him to believe that the reverse was true, that is, he believed that the fibers of the rami ran, for the most part, medially, indicating a dependence upon the cerebrospinal axis [2]. It was also postulated that somatic fibers passed through rami and vegetative ganglia, further indicating that the system was partly dependent on the cerebrospinal cord [1]. However, Koelliker agreed with Bichat in his ultimate opinion that each ganglia had its own nervous power [3]. One other important finding of Koelliker concerning the ganglia was during the dissection of a cat: while teasing out the fourth sympathetic ganglion, he traced the non-myelinated process of a nerve cell through to a myelinated process, indicating that a nerve could be in possession of both components. As a result, he concluded that the process of a ganglion's neuron was the beginning of a nerve fiber [1].

Further opposition to the attempted conclusive studies of Bidder and Volkman was supplied by Thomas Snow Beck. The exact nature and function of the rami persisted as a mystery, but Beck in 1846 made some telling observations and conclusions that were not fully appreciated at the time [1]. In his dissection of humans, he found that cervical and sacral outflows of the sympathetic trunk only possessed gray rami, and so stood alone in his rebuttal of the then widely accepted view that ganglionic fibers were derived from the spinal nerves via the white rami [3]. He strove to support Remak's organic fibers as actual nervous structures rather than merely connective tissue or artifact [2]. He maintained that these fibers were key components of the ganglionic system and originated from the ganglia but were distinct in morphology and purpose from cerebrospinal fibers [1]. And so, Beck remained convinced that the two nervous systems had distinct morphological findings. In a later paper, Beck essayed to apply physiological sense to his anatomical findings [1]. He considered the two units to be independent but to have a considerable influence upon one another. As such, he belonged more in the Bichat camp than out of it and was seeking to provide evidence supporting his claims or modify them rather than refute them.

By the middle of the nineteenth century, there was still no conclusive evidence on either side of the debate over whether Bichat's doctrine was accurate or not [1]. Confusion also persisted in the area of the rami communicantes, with some believing the fibers arose solely from the spinal cord connected to the ganglia and others believing that the fibers originated in the ganglia and could travel either medially via the rami and spinal roots or peripherally on the nerves of the cerebrospinal axis [2]. In terms of overall evidence, it seemed that Bichat's conclusions from the very beginning of the century remained more sound than unsound, and thus still received considerable support [1]. Without any firm evidence as to the origins of the white rami fibers or gray, organic fibers, the matter could not truly be put to rest.

The second half of the nineteenth century was marked by discovery after discovery, which slowly closed the door on the notion of two independent nervous systems, as well as on the question of whether or not the ganglia were in possession of their own nervous power. This was mostly due to new evidence that the brain and spinal cord exerted control over certain structures traditionally considered under the tutelage of the ganglionic system [1]. Furthermore, the notion of independent vegetative reflexes was rejected once it was demonstrated that these occurred through the cerebrospinal nervous system, thereby refuting one of the then last bastions of belief left intact in Bichat's system [2]. By the 1880s, the last vestiges of Bichat's system were fading from greater acceptance; however, there was still no unifying explanation to take its place [1]. Gaskell and Langley (Fig. 3) of Cambridge then took it upon themselves to fill the void. Gaskell's area of expertise consisted of the anatomy of the vegetative nervous system, whereas Langley began a new kind of research: pharmacologic effects upon the autonomic nervous system [1].

Opening the investigations of the second half of the eighteenth century was Claude Bernard, who studied the nervous system's effects on the "regulation of chemical activity in the tissues" [3]. In March of 1852, he found that, following a sectioning of the cervical sympathetic trunk, the temperature of the ipsilateral side of the head increased due to subsequent vasodilation [2, 3]. His main concern, however, was with nervous regulation of blood vessels affecting tissue metabolism [3]. One of his main conclusions was that the human body functioned independently of its environment by developing a mechanism which he termed "*le milieu intérieur*" (a precursor of the modern notion of homeostasis) [3]. In 1878, Bernard postulated that this maintenance control of bodily fluids (which he had remarked remained strikingly constant) was under the control of the nervous system: "The nervous system is called upon to regulate the harmony which exists between all these conditions" [3]. His conclusions also included disproving one of Bichat's key claims: that the visceral reflexes were dependent solely on the ganglionic nervous system [3]. Bernard believed these functions to be controlled by the cerebrospinal system through reflex arcs that passed through the system, stating "the existence of centripetal sensory fibers must be admitted in the sympathetic as well as in the cerebrospinal system" [3]. One of Bernard's most important findings was from his *piqûre diabétique* of 1849 (possibly 1850), which gave incontrovertible evidence of an association between the medulla oblongata and carbohydrate metabolism [1, 2]. This function was believed to be absolutely governed by the ganglionic system (as were most if not all of the body's metabolic functions), but after puncture of the fourth ventricle produced glycosuria in the experiment, an effect not duplicated with the severing of splenic nerves, the evidence was now incontrovertible that the central nervous system held supremacy over the ganglia [2].

Fig. 3 Gabriel Valentin https://upload.wikimedia.org/wikipedia/commons/7/75/Gabriel_G._Valentin.jpg

Another advance in the middle of the eighteenth century was the elucidation of the function of the nerves that traveled with the blood vessels [2]. Willis had remarked upon nerves of the sympathetic system and their close association with blood vessels [1]. In 1840, Henle observed that some nerve endings actually entered the musculature of the vessels [2]. It was Ch. E. Brown-Séquard in 1852, however, who discovered the actual function of these nerves when he stimulated them: vasoconstriction [3]. Ernst Heinrich Weber and Eduard Weber also made a fascinating discovery concerning the nervous system's relationship with the circulatory system around this time as well [2]. In 1845, the German brothers stopped a beating heart by stimulating the vagus nerve to an extreme [2]. The importance of this finding went beyond a single observation, as now it had been demonstrated that the nervous system was capable of inhibition of function [2].

One half of the scientific team that "left few extensive gaps in the anatomical and physiological understanding of the autonomic nervous system" was Gaskell [1]. In 1886, Gaskell studied the peripheral autonomic plexuses and documented the three divisions of myelinated neurons sprouting from the spinal cord at its cranial, thoracolumbar, and sacral levels [1]. This research yielded the finding that "each nerve fibre [sic] leaves the central nervous system as a fine medullated [sic] nerve fibre [sic] which passes directly into its appropriate ganglion, and there in consequence of communication with one or more of the ganglion cells loses its medulla and passes out not as a single non-medullated [sic] fibre [sic] but as a group of non-medullated [sic] fibres [sic]" [2]. He believed that ganglionic cells helped to convert a single nerve fiber into a group of fibers, and in 1916, Gaskell went on to develop the term "involuntary nervous system" [3]. He defined it as a "system of motor nerve cells to involuntary structures" [1]. It was Gaskell, with Langley, who discovered each tissue was supplied by two sets of fibers with "opposite characters so that I look forward hopefully to the time when the whole nervous system shall be mapped out into two great districts of which the function of one is katabolic, of the other anabolic" [1]. With his work fine-tuning the anatomical details of the vegetative fibers complete, the conclusions of Bidder and Volkmann were refuted in turn [3].

The second half of the two-man team that so revolutionized how the autonomic nervous system was understood, and who derived the term in use today, was Langley [3]. Langley had established the division of two types of involuntary nerves in large part due to Hirchmann's discovery in 1863 that nicotine could inhibit pupillary dilation upon cervical sympathetic trunk stimulation [2]. This discovery led to work with Dickinson in 1889 which helped Langley discover that nicotine acts by paralyzing the synapses between preganglionic and postganglionic neurons in sympathetic ganglia [3]. Along with nerves that dilate the pupil, Langley discovered these synapses to be situated within the superior cervical ganglion [3]. He then went on to chart the exact location of the "cell stations," as well as the location of most preganglionic and postganglionic neurons, terms of his own devising [3]. In 1898, Langley introduced the term "autonomic" nervous system, and, like Gaskell, divided the system into cranial, thoracolumbar, and sacral outflows [2]. In 1901, Langley found a link between the effect of epinephrine and the stimulation of thoracolumbar fibers, a system of nerves which Langley collectively termed "sympathetic" [3]. In 1905, Langley discovered that pilocarpine acted in a similar manner on structures innervated by the finely myelinated fibers originating from the cranial and sacral levels of the spinal cord [3]. He decided to classify this nervous system as the "parasympathetic" division [3]. Langley then proved with experimentation that these two systems produced opposing effects in the heart, vasculature, and stomach [2].

In terms of overarching nomenclature, Langley objected to the term "visceral" popularized by Gaskell due to the fact that this term could not describe a system whose nerves were by no means confined to the viscera, citing the sympathetic present in skin among others [1]. And so, in 1898, Langley posited the term "autonomic": "The word implies a certain degree of independent action, but exercised under control of a higher power" [1]. He described his system as the nervous system governing the glands and involuntary muscles or, in other words, the organic functions of the body [2]. The term itself comes from the Greek *autos*, meaning self, and *nomos*, meaning law [1]. This term encompassed the vagus nerve as well and is now the equivalent of vegetative or visceral nervous systems [1]. Langley then proposed names for each division of the system, which is still in use today: the sympathetic and parasympathetic nervous systems [2].

Following the great advances of Langley and Gaskell, his mentors, was Sir Henry Hallett Dale (Fig. 4) and his revolutionary discovery regarding the synapses of these preganglionic and postganglionic fibers [4]. Many credit Dale with introducing the theory of chemical transmission signals at synapses [4]. The general belief that had been held for quite some time before his work was that currents "jumped" from the presynaptic to postsynaptic cell [4]. The roots of Dale's discovery lay with Bernard, who conducted several experiments with curare in 1854 which showed an inconsistency with the strictly electric theory of transmission [4]. Specifically, this experiment showed that curare acted only at the motor end plate of skeletal muscle, begging the question of why such a localized effect would be present [4]. Ironically, Bernard's successor at the Sorbonne, Louis Lapique, produced predictable mathematical models that produced an identical curve upon plotting nerve conduction behavior in various tissue types [4]. So convincing was this evidence for an electrical transmission across cells that it endured into the 1940s [4]. In 1904, Thomas Renton Elliott was the first to take Langley's observations and attempt to explain the findings in the frame of chemical transmission, indicating that Langley's discovery of certain chemicals generating a response similar to stimulation of the nerve was no coincidence [4]. He postulated that nerves transmit messages from endpoints to the target of innervation by this chemical transmission [4]. Dale was not unaware of Elliott's efforts before him, and in fact, dedicated his book *Adventures in Physiology* "To T. R. Elliott, who had so much to do with the beginning of these adventures" [4]. Walter Dixon produced a remarkable experiment through which he hoped to prove chemical transmission also occurred in the parasympathetic system [4]. After vagal stimulation of a heart, Dixon was able to isolate a compound that he then applied to a different heart and observed a slowing of the heart rate [3]. However, exact classification of the substance eluded Dixon [4].

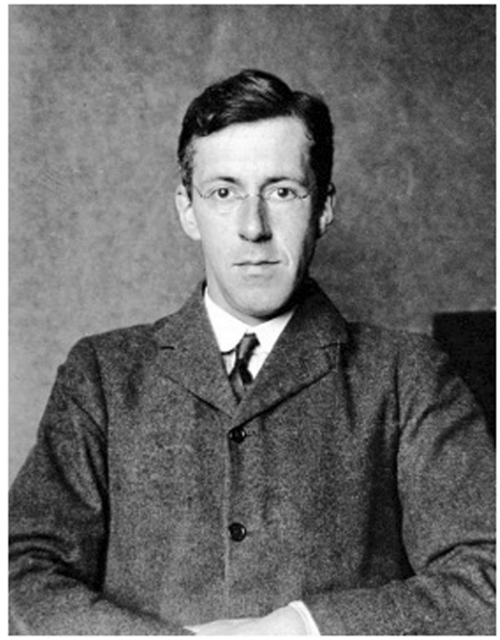

Fig. 4 Sir Henry Hallett Dale https://wellcomeimages.org/indexplus/image/M0013397EA.html

Dale's part in this story began unexpectedly and consisted of being assigned to examine some of the physical properties of a drug called ergot [4]. He discovered that ergot antagonized the effects of epinephrine [3]. Not long after, in 1906, Rene Taveau and Reid Hunt reported that acetylcholine had a remarkable ability to slow a beating heart [4]. Dale himself soon began experimenting with the newly discovered chemical [4]. Subsequent research allowed Dale to classify the effects of acetylcholine as either "muscarine-like" or "nicotine-like" [4]. The challenge Dale now faced was proving that acetylcholine indeed existed in living animals [3]. This Dale demonstrated in a horse spleen 1929 [4]. Dale believed he had gathered enough evidence to present the notion that acetylcholine was the chemical messenger released at the endpoints of the parasympathetic system [4]. While this was not a novel idea in its entirety, Dale was able to explain some inconsistencies and points of contention that were unanswerable to others who preceded him [3]. In light of Dale's discoveries concerning the specifics of chemical transmission, he proposed a new categorization: nerves that released acetylcholine were to be termed "cholinergic" whereas those using the adrenaline-like substance, yet to be discovered, would be termed "adrenergic" [4]. The discovery of noradrenaline was finally accomplished by Von Euler in 1946 [2].

Dale's research inspired some of his followers to expand upon his findings [4]. Two of Dale's pupils, Gaddum and Chang, were able to map out the locations of high concentrations of acetylcholine in the human body, finding that sympathetic ganglia tended to be one such location [2]. Another of Dale's students, W. S. Feldberg, was able to demonstrate that acetylcholine was part of nervous messaging in presynaptic and postsynaptic neurons of ganglia. This led to the addition of all preganglionic nerves into Dale's cholinergic category [4]. Finally, in the 1950s, Dale's notion of chemical transmission of nervous signals between neurons became widely accepted [4].

The early twentieth century was also witness to several major advances in the understanding of the autonomic nervous system's center in the brain [2]. A. Kreidl and J. L. Karplus were able to demonstrate in 1909 that the hypothalamus exerted control of the cervical sympathetic [3]. In 1926, the pair caused hypertension via the hypothalamus after removing the adrenals and pituitary gland [2]. After Ranson destroyed the nuclear masses of the hypothalamus in 1939, the findings of these three scientists allowed the localization of the central autonomic ganglia to the diencephalon [3].

On a fundamental level, the autonomic nervous system persisted as a source of great mystery into the twentieth century. The confusion began early with Galen's assertion that the sympathetic trunk originated within the cranium itself and operated via "spirits." After a long period of stagnation, scientists soon regained interest. Following some speculation on the exact nature of the ganglia, including Johnstone's ingenious but inaccurate theories of the ganglion acting as a filter of impulses, Bichat offered a unifying principle that persisted for almost a century, challenged and supported by various anatomists and physiologists. Its refutation took decades of dissections, experiments, and observations. In the void where Bichat's doctrine once had been, Langley and Gaskell soon tied up many of the loose ends and brought the autonomic nervous system into the modern era of understanding. Dale then solved a mystery involving chemical transmission that affected not only the autonomic nervous system but the nervous system as a whole. When considering the future of the autonomic nervous system and what findings may yet be uncovered, a closing quote by Johnstone from 1795 admitting his own ignorance to the meaning of his anatomical findings must be appreciated: "In the next age, consequences of these truths will be unveiled to an extent not now to be conceived but of the greatest importance in the healing art: in the mean time, what is here proposed will furnish some direction to a sagacious searcher into the seat and nature of internal diseases" [1].

Conclusions

The evolution of our understanding of the autonomic nervous system has a rich history. Our current understanding is based on centuries of research and trial and error.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

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