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Research History and Current Concept of the Autonomic Nervous System

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Abstract: The term *jiritsu shinkei-kei* (autonomic or vegetative nervous system) has become well known in Japan due to the popularization of a concept particular to Japan of a disease called *jiritsu-shinkei shiccho-sho* (vegetative disorder). Despite the widespread use of the disease name, its actual meaning is often misunderstood. This paper describes the research history and development of concepts regarding the autonomic nervous system, and explains the current concept. This paper also presents the history and concept of *jiritsu-shinkei shiccho-sho*, which is often referred to inaccurately.

Key Words: autonomic nervous system, research history, anatomy, physiology

Introduction

In Japan, the term *jiritsu shinkei-kei* (autonomic or vegetative nervous system) is widely recognized by the general public. This may be because the distinct Japanese concept of a disease called *jiritsu-shinkei shiccho-sho* (vegetative disorder), proposed by Abe (1), has been adopted into common use by the general population. *Jiritsu-shinkei* means "autonomic nerves" in English, and *shiccho-sho* translates to "imbalance" or "dysregulation." However, the popularization of the term *jiritsu-shinkei shiccho-sho* seems to have muddled an accurate understanding of the autonomic nervous system. Healthcare professionals usually use the term to indicate a psychosomatic disease or medically unexplained symptoms, whereas the general public largely believes that it refers to a disease of the autonomic nervous system. This paper reviews the history of research concerning the autonomic nervous system and explains the development of the concepts regarding it. It also discusses *jiritsu-shinkei shiccho-sho*.

1. History of the Research on the Autonomic Nervous System (2-7)

The earliest description of the extant autonomic nerves is by Galen (Galenius or Galenos, 130-200)(Figure 1), the Roman-Greek physician. He served the Roman

Figure 1. Galen (line engraving by G. P. Busch), a Greek physician. The neuroanatomical graphic he drew in Roman times depicts the vagus nerve and the cervical sympathetic ganglion.
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emperor and wrote some 600 books. Included in his works is a description of the "sixth cranial nerve" and the cervical sympathetic ganglia. What Galen described as the sixth cranial nerve comprises what are now classified as the ninth (glossopharyngeal nerve), tenth (vagus nerve, including parasympathetic nerves), and eleventh (accessory nerve) cranial nerves. He noted that the sixth cranial nerve is distributed in the internal organs via the thoracic and abdominal cavities, and that sympathetic nerves have communicating branches (white ramus communicans). Galen thought that peripheral nerves, including the autonomic nerves, connected various parts of the body, and acted as channels through which the mind flowed and different parts of the body "sympathized." He believed that the sympathetic trunk (ganglionic chain) arose from the sixth cranial nerve, but the French anatomist Charles Etienne (1504-1564) revealed that the sympathetic trunk is separated from the sixth cranial nerve. In 1727, the French anatomist and ophthalmologist François Pourfour du Peti (1664-1741) recognized that the sympathetic nerves do not originate from the cranial nerves.

Thomas Willis (1621-1675), a British physician and anatomist, named the sympathetic trunk the "intercostal nerve" and the vagus nerve the "wandering nerve." He was able to depict the vagus nerve with accuracy (Figure 2). He thought that the cerebrum controlled voluntary movements, while the cerebellum controlled involuntary movements, coordinating both the intercostal nerve and wandering nerve. Later on, Jacques-Bénigne Winslow (1669-1760), a Danish anatomist, replaced the term "intercostal nerve" with "great sympathetic nerve." He also named the vagus nerve "middle sympathetic nerve," and the facial nerve "small sympathetic nerve." Winslow speculated that the sympathetic ganglion originated from the spinal cord rather than the cranial nerves, and regarded it as a "little brain" that functions independently.

Marie François Xavier Bichat (1771-1802), a French anatomist and physiologist, proposed that the body's vital systems could be divided into two categories: *la vie organique* (organic life) and *la vie animale* (animal life). The former is similar to the current concept of the autonomic nervous system. He considered *la vie organique*, meaning the life of plants, to be related to the "passions" and independent of education or habit. On the other hand, la vie animale was thought to account for externally directed activity of the body, to be formed through habit and education, and governed by the intellect. This understanding closely corresponds to the current concept of the somatic nervous system. Like Winslow, Bichat considered the sympathetic trunk to be the little brain. Currently, his idea that "the nervous system that controls internal organs is an independent system" is widely accepted.

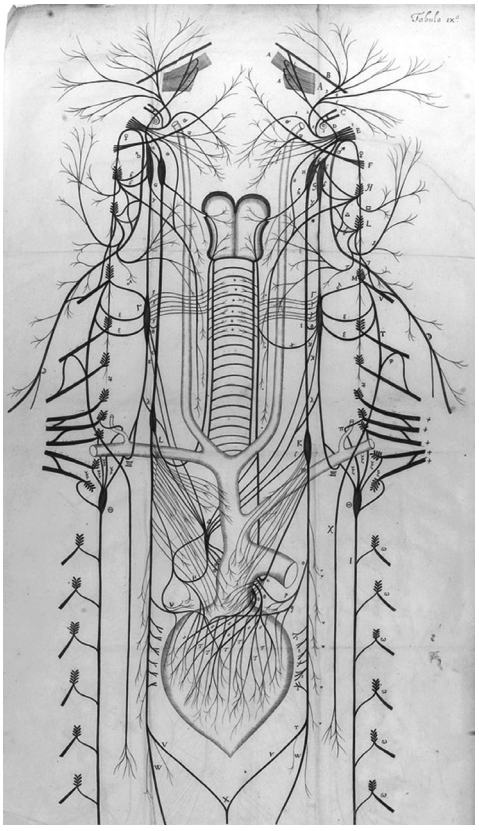

Figure 2. The vagus nerve, cervical sympathetic ganglia, splanchnic nerves and cardiac plexus in a figure from "Cerebri Anatome" (1664) written by Thomas Wills.
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German anatomist and psychiatrist Johann Christian Reil (1759–1813) proposed the term "vegetative nervous system" (1807), which is still sometimes used as an alias for the autonomic nervous system.

Histomorphology was established in the 19th century, with Christian Gottfried Ehrenberg (1795-1876) considered likely as the first to observe nerve cells in the sympathetic ganglion with the use of a microscope (1833); a more detailed observation of such cells was accomplished in 1836 by German physiologist Gabriel Valentin (1810-1883). Figure 3 shows a histological sketch of human sympathetic ganglion cells drawn by Fernando de Castro (1896–1967). Polish-German neurologist Robert Remak (1815-1865) discovered the presence of unmyelinated fibers of sympathetic nerves extending from the cell bodies of the sympathetic ganglia to the organs (1838). Regarding the enteric nerve, Georg Meisner (1829-1905) discovered the submucosal plexus of the gastrointestinal tract (1857), and Leopold Auerbach (1828-1897) discovered the intermuscular plexus (1864).

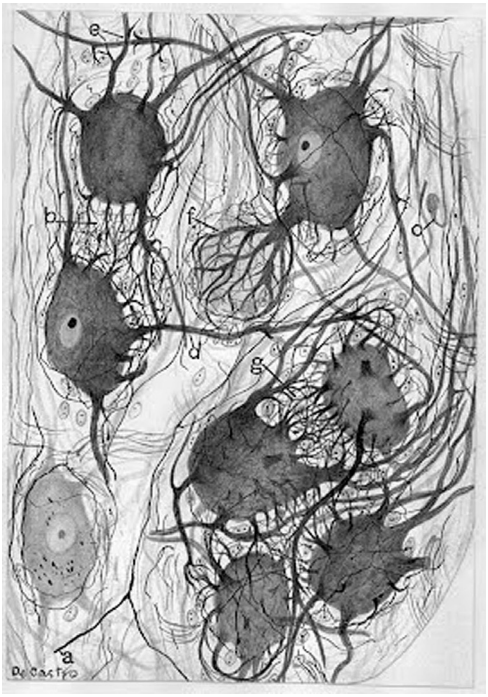

Figure 3. Histological sketch of human sympathetic ganglion cells by Fernando de Castro (1916) from Fernando de Castro Archives (http://www.neurodrawings.org/drawings-ii).

In physiological research, Claude Bernard (1813-1878), a French physiologist, found that excision of the sympathetic nerve resulted in blood vessels dilating (1851), and Brown-Séquard (1817-1894) found that sympathetic nerve stimulation induced constriction of blood vessels (1852). During this period, it became clear that the vagus nerve was involved in gastrointestinal function. German brothers Ernrst Heinrich Weber (1795-1878) and Eduard Weber (1806-1871) found that stimulating the vagus nerve caused cardiac arrest (1845). Claude Bernard noticed an association between heart activity stimulated via the vagus and the brain, i.e., the brain-heart axis.

The development of pharmacology in the late 19th century led to the discovery of hormones and neurotransmitters. English physician George Oliver (1841-1915) identified that the adrenal gland contained a certain substance with a strong pharmacological effect (1893). This discovery prompted further research focusing on the extraction and isolation of that specific component. American pharmacologist John Jacob Abel (1857-1938) was able to extract the active substance (1897) and named it "epinephrine." However, the process of purifying the substance remained incomplete and it was extracted as a form of benzoyl compounds. In 1900, using an extraction from the adrenal glands of cattle, Japanese chemists Jokichi Takamine and Keizo Uenaka successfully isolated the active substance as a form of a pure crystal and named it "adrenaline" (Takamine's father was a court physician of Kaga-han feudal domain). In Europe, the active substance became known as "adrenaline" in recognition of Takamine's work, while in the United States, it was called "epinephrine" following the evaluation and acceptance of Abel's work. At present, adrenaline is well known as a hormone that is closely correlated with the autonomic nervous system.

One of the most important neurotransmitters for the autonomic nervous system is acetylcholine, which is released from sympathetic and parasympathetic preganglionic nerves and sympathetic postganglionic nerves. Acetylcholine was first synthesized by Adolf von Baeyer, a German chemist, in 1867. Despite being synthesized, the pharmacological characteristics of acetylcholine would not be understood until much later. In 1911, Reid Hunt (1870-1948), an American pharmacologist, discovered that choline derivatives, especially acetylcholine, have a blood pressure-lowering effect. However, at the time of this discovery, Hunt was unaware that acetylcholine was a biological substance. Henry Hallett Dale (1875-1968), an English pharmacologist and physiologist, succeeded in isolating acetylcholine (1914), and noticed a similarity between the pharmacological effects of acetylcholine and parasympathetic nerve function. He then categorized the pharmacological effects of acetylcholine into muscarinic and nicotinic actions (1914). Otto Loewi (1873-1961), a German-born American physician and pharmacologist, asserted that "Vagusstoff" released by stimulating the vagal nerve was acetylcholine (1926), and his claim was later proved to be correct. Dale classified autonomic nerves as being adrenergic and cholinergic, based on pharmacological studies (1933).

In addition to acetylcholine, an important neurotransmitter for the autonomic nervous system is noradrenaline, which is released from sympathetic postganglionic nerves. Thomas Elliott (1877-1961) clarified that the form of adrenaline extracted by Takamine and Kaminaka has a sympathomimetic effect (1901), and identified that adrenaline can act as what is now known as a neurotransmitter (1904). In 1921, Loewi produced evidence that stimulating sympathetic nerves induces the secretion of adrenaline-like substances. Walter Cannon (1871-1945), an American physiologist, revealed that the substance secreted from the sympathetic nerve terminals is not adrenaline, but rather a different substance which he named "sympathin" (1931). Finally, Ulf von Euler (1905-1983), a Swedish physiologist and pharmacologist, identified that "sympathin" is noradrenaline in 1941. This achievement earned Euler the Nobel Prize in Physiology or Medicine in 1970.

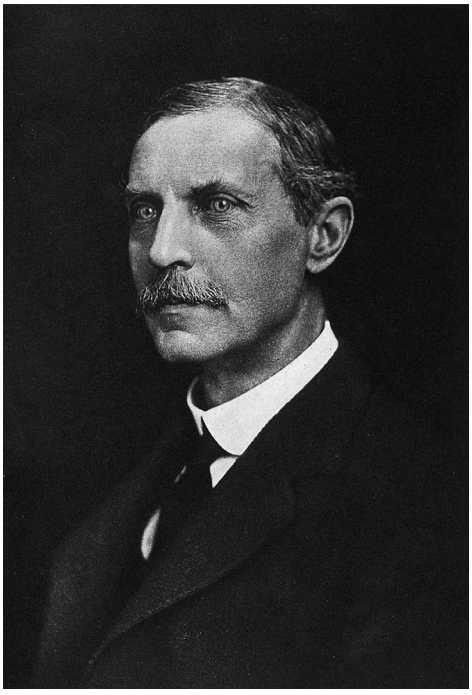

Figure 4. John Newport Langley.
He created the current concept of autonomic nervous system.
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Walter Holbrook Gaskell (1847-1914), a British physiologist, and John Newport Langley (1852-1925) (Figure 4), a British physiologist, played major roles in the development of modern autonomic neurology. Gaskell speculated that he had identified autonomic outflows into the thoracolumbar (sympathetic nervous system) and the craniosacral (parasympathetic nervous system) systems, and that the two antagonized each other. He named the autonomic nervous system "the involuntary system," whereas Langley called it the "autonomic nervous system," the name by which it is known today.

One of Langley's notable achievements was proposing the term "autonomic nervous system" and categorizing it into three systems: the sympathetic, parasympathetic, and enteric nervous systems. He assiduously investigated the autonomic nervous system using several pharmacological techniques, and revealed that nicotine has the property of blocking neurotransmission in autonomic ganglia. By blocking ganglionic neurotransmission with nicotine, it became possible to functionally distinguish the nerves ending in the autonomic ganglion, known as presynaptic or preganglionic nerves, from those located in the autonomic ganglion that directly innervate effector organs, known as postsynaptic or postganglionic nerves. Langley proposed dividing the autonomic nerve into preganglionic and postganglionic nerves. He also speculated the presence of a "receptive substance" between the sympathetic nerve endings and effectors (1905). In this sense, he is considered to have predicted the existence of neurotransmitters and receptors. Results from his body of research were summarized in the book "The Autonomic Nervous System" (1921).

Regarding the role of the brain in the functioning of the autonomic nervous system, C. Dittmar showed that a control center for blood pressure can be found around the caudal pons or the rostral medulla oblongata (1873). Based on the results of electrical stimulation experiments, S. W. Ranson (1880-1942) later proved that the vasomotor center is located in the medulla oblongata (1916). J. P. Karplus (1866-1936) and A. Kreidl (1864-1928) proposed that the hypothalamus may mediate sympathetic nerves (1909), and later revealed that the hypothalamus is involved in the regulation of blood pressure (1926). In the 1920s, Walter Rudolf Hess (1881-1973) determined that the hypothalamus is a control center of the autonomic nervous system (1936), and he was awarded the Nobel Prize in Physiology or Medicine in 1949 for this achievement.

Regarding Japanese researchers, in addition to Takamine (mentioned above), Yasu Kuno (1882-1977), a physiologist, made outstanding achievements in the field of the autonomic nervous system. He conducted multifaceted and extensive research on sweat, including the embryology and morphology of sweat glands, as well as the physiology of perspiration. He developed a device that can quantify perspiration, and conducted a study establishing the physiology of perspiration of humans. Results of his research were later compiled into the book "Physiology of Human Perspiration" in 1934 (8). He also clarified the difference between thermal perspiration and mental perspiration. Ken Kure (1883-1940) introduced Langley's concept of the autonomic nervous system to Japan in 1934.

2. The Current Concept of the Autonomic Nervous System

In a restrictive or classic sense of the term, the autonomic nervous system, also called the vegetative nervous system, indicates the peripheral efferent nerves that regulate internal organs such as the heart, lung, gastrointestinal tract, blood vessels, and glands. However, in a broader sense, it also encompasses several areas of the central nervous system and the visceral sensory nervous system. Based on Langley's classification (Figure 5), the autonomic nervous system is classified into three categories: the sympathetic, parasympathetic, and enteric nervous systems. However, under the current concept of the autonomic nervous

system, the enteric nervous system is often included in the parasympathetic nervous system (9). Organs are generally controlled by both the sympathetic and parasympathetic nervous systems, which work antagonistically in some organs, such as in the heart, which functions under dual control. However, sweat glands, arrector pili muscles, adrenal medulla, and blood vessels of the skin are considered to be mediated only by the sympathetic nerves, while gastrointestinal motility is mediated only by the parasympathetic nerves. Both sympathetic and parasympathetic nerves promote secretion in the salivary glands. Sympathetic and parasympathetic activities are not always antagonistic, and their roles are dependent on each organ.

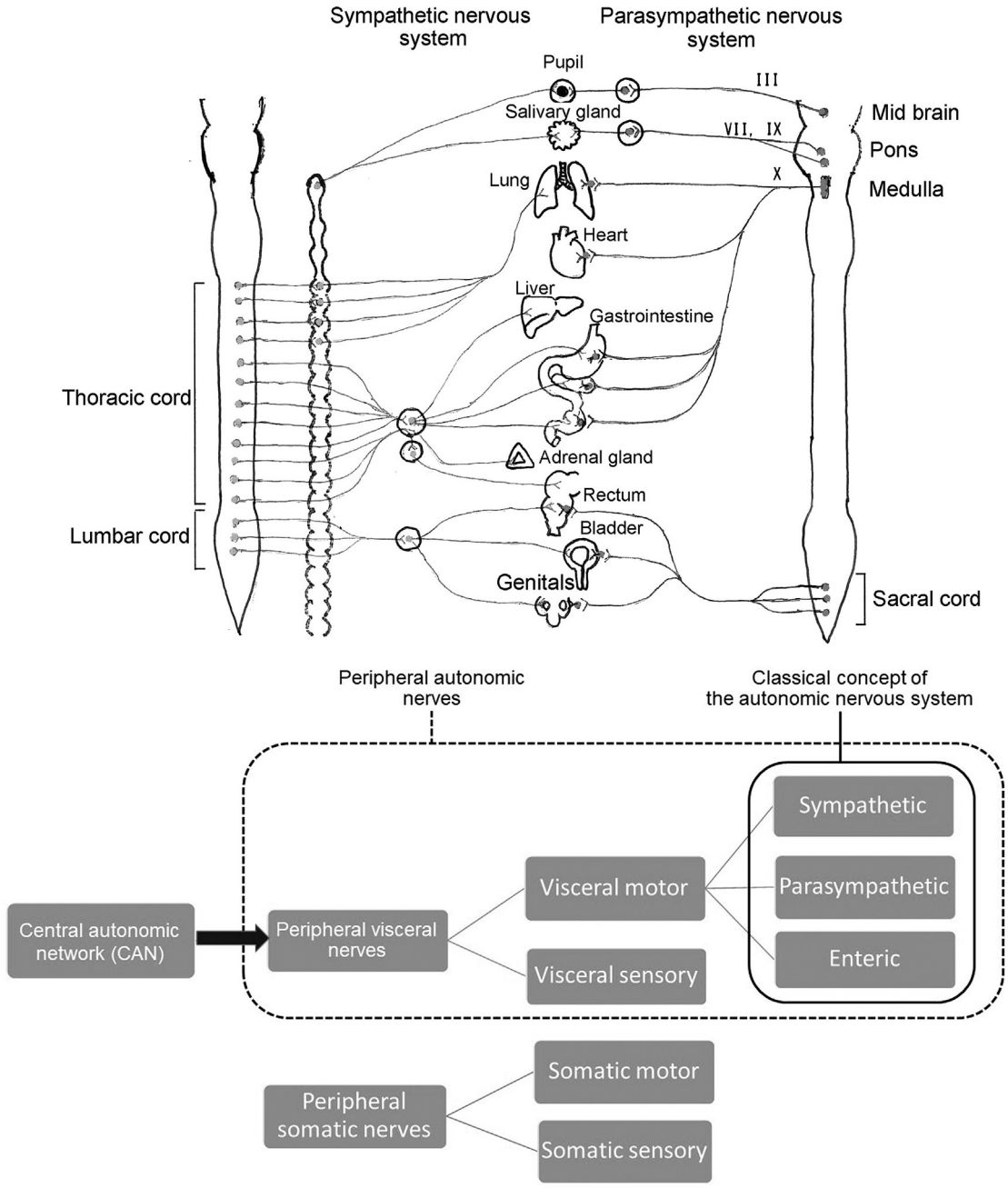

Figure 5. Sympathetic and parasympathetic innervation of organs (upper) and conceptual diagram of the autonomic nervous system (lower).
*Original chart

Several interconnected areas of the brain are involved in the control of the body's visceral function (10), and this network is called the central autonomic network (CAN). CAN consists of the anterior cingulate cortex, insular cortex, amygdala, hypothalamus, periaqueductal gray, brainstem reticular formation, etc. Sympathetic outflow from CAN descends through the spinal cord and reaches the thoracic intermediolateral column, where preganglionic sympathetic neurons are located. The axon of preganglionic sympathetic neurons reach postganglionic sympathetic neurons in the sympathetic ganglions, which directly innervate end-organs. Parasympathetic preganglionic neurons are located in the brainstem and sacral spinal cord, and parasympathetic postganglionic neurons are found in parasympathetic ganglions near end-organs.

The role of the autonomic nervous system is to control internal organs, such as the heart, lungs, alimentary tract, blood vessels, and glands. It works in close cooperation with the endocrine system to maintain the "internal environment (milieu intérieur)," and this mechanism is called homeostasis. Electrolytes, glucose, body temperature, oxygen, and pH in tissue fluid are kept at certain levels inside the body. Furthermore, the autonomic nervous system responds to rapid external and internal changes. Reflexive mediation by the reticular formation of the brainstem is important for short-term biological activities such as the regulation of blood pressure during standing load or postural change, and the respiratory response to CO_2 retention.

The autonomic nervous system and endocrine system are also involved in regulating biological fluctuations when changes occur within a certain range in the internal environment. For relatively long-term biological changes, such as those associated with circadian rhythm and the changing of seasons, the hypothalamus is considered to play an important role. Short-period fluctuations such as respiratory fluctuations in heartbeat involve the brainstem reticular formation. Furthermore, the autonomic nervous system works to assist physical functions. For example, perspiration of the palm acts as a way to prevent slipping when grasping objects, and secretion from Bartholin's glands aids in lubrication during sexual intercourse.

It is often thought that sole function of the autonomic nervous system is maintaining homeostasis. However, as mentioned above, it also works in cooperation with the endocrine system to help regulate physiological fluctuations in the internal environment, such as those associated with diurnal rhythm. In addition, autonomic and endocrine activities can intentionally and predictably change the internal environment. For example, cardiac sympathetic outflow increases when intending to stand up in preparation for postural change. Another example is perspiration of the palm induced by deep breathing. In this case, sympathetic sudomotor activities are elicited by intending to take a deep breath before actually doing so. This mechanism is referred to as "central command" (11).

Emotional and psychological stress strongly affect autonomic and endocrine activities, and this results in an impact to the internal environment. Sterling and Eyer proposed a concept of "allostasis," which emphasizes changes in the internal environment caused by mental stress in 1988 (12, 13). Humans and animals recognize external events and environmental changes with their five senses. When a stimulus is perceived as being potentially dangerous, there is an increase in heartbeat, respiratory rate, blood flow to the muscles, and perspiration of the palms and soles in preparation for escape. Such autonomic and endocrine reactions, in which the limbic system is involved, are related to emotional behavior, and are determined based on the individual's experience and learning as well as their instincts. Furthermore, when a dangerous stimulus reoccurs after initial or subsequent exposure, autonomic activity is markedly less responsive to that same stimulus. This phenomenon is called "habituation," and it results from cognitive processes mainly in the limbic system. These mechanisms cause poor reproducibility in autonomic function tests. From a different point of view, the instability of autonomic activities reflects activities of the limbic system, and is useful for the evaluation of emotion.

3. *Jiritsu-shinkei shiccho-sho* (Vegetative Disorder)

The term *jiritsu-shinkei shiccho-sho* was proposed by Tatsuo Abe in the early 1960s (1). He translated it as "vegetative disorder" in English, but in light of current research this translation may be considered inadequate. "Autonomic imbalance disorder" may be a more appropriate English term for Abe's concept of the disease. His ideas concerning the disease were based on his clinical experience with patients with beriberi and those with differential diagnoses. He noticed that there were certain patients who complained of beriberi-like symptoms without having beriberi or any of the associated disorders. He initially used the term *kakke-you shoukougun* (beriberi-like syndrome) for these patients, and later renamed it *futei-syuso shoukougun* (unidentified clinical syndrome). This syndrome was classified into three categories based on results from tests on autonomic function and psychogenic background. *Hontai-sei* (essential) *jiritsu-shinkei shiccho-sho*, one of the three categories of unidentified clinical syndrome, is defined as having an autonomic imbalance but no psychogenic background; in patients who do not have an autonomic imbalance but do have psychogenic background, the syndrome is classified as a neurosis; in patients with both an autonomic imbalance and

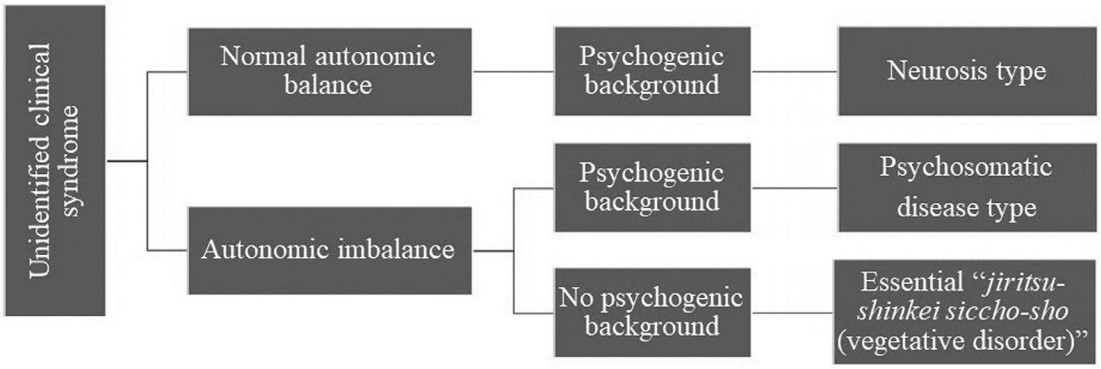

Figure 6. *Jiritsu-shinkei shiccho-sho* as a subtype of unidentified clinical syndrome. This figure is modified from the one in cited reference (1).

psychogenic background, it is classified as a psychosomatic disease (Figure 6). For the classification *hontai-sei jiritsu-shinkei shiccho-sho*, the prefix *hontai-sei* was eventually dropped as *jiritsu-shinkei shiccho-sho* became more prevalent as the preferred term.

Abe used a methacholine infusion test to evaluate autonomic imbalance, and he classified the findings as sympathetic-dominant, parasympathetic-dominant, and normal based on the specific pattern of changes in blood pressure. He judged the former two types to reflect an autonomic imbalance. However, both the sympathetic-dominant type and the parasympathetic-dominant type can be seen in healthy subjects and cannot be considered pathological. At present, *jiritsu-shinkei shiccho-sho* is not thought to be caused by autonomic dysfunction, but is regarded as form of somatic symptoms related to the functioning of the autonomic nervous system in mental disorders. This disorder may have to be classified as medically unexplained symptoms, functional somatic syndrome, or somatic symptom disorder.

Although Abe's idea that *jiritsu-shinkei shiccho-sho* is caused by autonomic dysfunction is not true, it should be appreciated that he noted the close relationship between emotion and autonomic response (emotional behavior). This relationship, such as seen between sweating on the palm and emotion (14), is well known at present. However, it is still debated whether the autonomic activity is triggered by emotion or whether emotions are recognized by feedback due to changes in autonomic activity. In my personal opinion, the expression of emotions and autonomic response could proceed at the same time.

Conclusion

Even physicians and researchers tend to understand the pathophysiology of autonomic diseases based on the classical concept of the autonomic nervous system, because of the greatness of Langley and Gaskell. However, in the last 100 years, knowledge about the autonomic nervous system has been accumulated. I hope this paper will help to understand autonomic disorders from a new perspective.

Conflict of Interest

The author report no disclosures relevant to the manuscript.

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