Preface

Rather surprisingly, the autonomic nervous system in general finds itself in a difficult position. It is considered a central agent participating to the immense domain of humoral and metabolic functions and, as such, has been intensely explored by investigators who, at the time, were not really interested in the neurosciences as such, but rather in humoral mechanisms (in the French tradition “milieu intérieur”). In contrast, relatively few investigations are currently available on its refined organization and on the nervous processes that underlie its actions. One of the reasons probably lies in the (sometimes extreme) difficulties in assessing autonomic influences, not only at the synaptic level, but also at the systems level. Moreover, even the anatomy of autonomic innervations is often badly known and information is sometimes difficult to find. Jean-Jacques Puizillout's monograph is a very valuable effort to bring together, precisely, most of these refined structural data that are presently available on the organisation of the projections of the vagus nerve.

These refined data deal with the distribution of pathways with functional differences, afferents and efferents, often considered in a historical perspective, forming the basis for many explanations of the functions of this complex nerve. As well underlined by the author in his final comments, the research on central autonomic system functions has been focused for a long time on central structures which control the efferent centers, localized in the brain stem (parasympathetic system) and the medulla (sympathetic system). Beyond the short circuit reflex pathways that regulate cardiovascular or respiratory functions, it is essential to consider the great number and diversity of other functions the vagus supports, with the complexity of its connexions, both in the periphery, and in the central brainstem nuclei. The nucleus of the solitary tract (NTS) plays a key role. No one, nowadays, can explore vagal functions without a thorough knowledge of its connexions. The NTS is in fact composed of several subnuclei; those are stations for afferent impulses of various sources, and are in turn connected to higher brain centers, thus forming, despite its small size, a site of major importance for the maintenance of life. Puizillout also focuses on the nodose ganglion, where communication between the vagal primary cell bodies can occur, being the first stage of the integration process. Together with the visceral efferent, the vagus nerve represents a very complex system. No wonder therefore, that it plays a major role in autonomic control, and more generally, in somato visceral components of motivated behavior.

This book provides an extremely well documented source of information on what was designated, "in the older times", the pneumogastric nerve (a term that is apparently abandoned). Also, precisely based on this wealth of data, it should promote new studies, allow the raising of new questions and the exploration of new mechanisms, including neurochemical and refined synaptic ones, as well as those at the systems level. The author very wisely did not go beyond his own domain of anatomical competence. His monograph is an extremely helpful tool, not only for the anatomist and the histologist, but also for the physiologist in search of anatomical backgrounds. For all these reasons, Puizillout's book is a very appreciable and fine piece of work.

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Part 1

Introduction: the vagus nerve and the autonomic nervous system

1 - Historical background

The name “vagus”, which was more of a description than a name, refers to the wandering distribution and extensive ramifications of the tenth pair of cranial nerves originally observed at the periphery. The idea of arranging the cranial nerves in numbered pairs probably originated with Marinus of Alexandria (about 100 B.C.) (quoted in: Skandalakis et al., 1986) as Galen (130-201) wrote that his own description of the cranial nerves is that of Marinus (Galien, 1528; Galen, 1968; May, 1970; Galen, 1997; see translation in: Galien, 1994a).

Galen described seven paired of cranial nerves of which the sixth pair includes the glossopharyngeal (IX), the vagus (X) and the spinal accessory (XI). This was not due to an inability to distinguish them but an advisedly decision to treat them as one. Galen described a nerve trunk descending along the necks of the ribs (in fact it was in part the sympathetic trunk) which receives fibres from the thoracic and the lumbar portions of the spinal cord and gives off branches to the viscera. He regarded this nerve (now known as the tenth pair or vagus nerve) as the “costal” branch of the abducens nerve, the actual 6th pair of cranial nerves. He did not differentiate the cervical portion of the sympathetic trunk from the vagus nerve. He advanced the hypothesis that through this trunk the viscera received sensitivity from the brain and motor power from the spinal cord. Galen describes three swellings along the course of each “costal” nerve, one just above the level of the larynx (which was probably the superior cervical sympathetic ganglion), the second at the upper thoracic level (probably the stellate or inferior cervical sympathetic ganglion) and a third in the upper abdomen (probably the celiac or semi-lunar ganglion). Galen did not differentiate the inferior (nodose) ganglion of the vagus nerve as a separate entity, which was possibly included into the uppermost swelling, as the superior cervical sympathetic ganglion is located in the neck in close proximity to the nodose ganglion (Sheehan, 1936).

Galen also advanced the first theory, widely accepted at this time, that there was *"sympathy"* (word which prospered later), or *"consent"* between the different parts of the body. He rejected the teaching of Aristotle (384-322 B.C.) that the brain serves to cool the blood and thought that the blood, manufactured in the liver and carrying in it natural spirits, flowed to the heart where a change took place converting them into *vital spirits*. These travelled to the rete mirabile (terminal branches of the carotid arteries) where they were changed into *animal spirits* (which refer to the Latin word *anima,* meaning soul), a subtle fluid which then flowed out to the body through hollow nerves (Brazier, 1959). The peripheral nerves were regarded as tubular structures through which the *"animal spirits"*, materializing this *"sympathy"*, are distributed. This was a modification of the "humoral theory" which derived from views originally propounded by Empedocles (Stubbs and Bligh, 1931). Aristotle became a powerful advocate of this theory and recognized four bodily humours (blood, phlegm, black bile and yellow bile) as elemental factors influencing profoundly bodily functions. The "humoral" theory remained virtually unchanged until well after the Renaissance and its traces subsist in our modern language as we still speak of persons with sanguine, phlegmatic, melancholic or choleric temperaments (see ref. in: Mitchell, 1953 or Brazier, 1959).

Galen's description of the vagus nerve was put forward so authoritatively that it remained unchallenged for nearly 1500 years! Thus it was scrupulously followed by all the early anatomists including the great Vesalius. Andreas Vesalius (1514-1564) is credited with the first correct description of the vagus nerve in the first complete textbook of human anatomy *"de humanis corporis fabrica"* published in 1543, although anatomical dissection and even experimental vagotomy had been performed much earlier (see references in: Holle, 1974; Langley, 1916). Although the trochlear (IV) and abducens (VI) nerves were known to Vesalius (1543), they were included in the oculomotor nerve (the second pair of Galen). The vagus, together with the glossopharyngeal and the spinal accessory nerves still formed the sixth pair. Consequently, still at this time, the sympathetic trunk and the vagus nerve were regarded as a unit both anatomically and physiologically. The initial error arose perhaps because, in some domestic animals, such as the dog, the cat and the horse, the sympathetic trunk and the vagus travel in the neck in a common sheath. The sympathetic trunk probably was first differentiated anatomically from the vagus nerve by Etienne (or Stephanus) (1545) and Eustachius (1563, 1714), (whose plates engraved about 1552 were not published until 1714), who illustrated the sympathetic trunk as arising within the cranium from the abducens nerve, thus emphasizing its supposedly cerebral origin. This error was not corrected until the publication of Du Petit's (1727) who pointed out that the sympathetic trunk was a separate entity which was not directly connected to the brain.

In the 17th century, a new order was finally made by Thomas Willis who in "Cerebri Anatome" (1664) described nine pairs of nerves, instead of seven, beginning with the olfactory nerve which had never been counted as a nerve by Galen or Vesalius. The glossopharyngeal, vagus and the cranial portion of the spinal accessory nerves were counted together now as the 8th pair. The hypoglossal and the spinal portion of the accessory nerves formed the 9th pair. It remained to separate the auditory (VIII) from the facial nerve (VII) and to consider the glossopharyngeal, vagus and spinal accessory and hypoglossal nerves as individual pairs. This was finally accomplished by Soemmerring in 1778 but not completely accepted until the end of the 19th century! Effectively, the list of twelve pairs of cranial nerves, which is the one in use today, was only gradually accepted. In 1856, the Dictionary of Medical Science (Dunglison, 1883) carried a table with the numbering systems of both, Willis and Soemmerring. Anatomists were even slower to change. Gray's Anatomy of 1883, names the nine pairs from Cerebri Anatome of Willis and adds: "If, however, the 7th pair be considered as two, and the 8th pair as three distinct nerves, then their number will be increased to 12, which is the arrangement adopted by Soemmerring". In the next edition, published in 1887, the editor concluded that "…there can be no doubt that the arrangement of Soemmerring is the better of the two…" but still presented tables based on nine as well as twelve pairs of cranial nerves (Skandalakis et al., 1986)! Willis (1664) still adhered to the humoral theory. He called the ganglionated sympathetic trunk the "intercostal" nerve, reminding the "costal" branch of Galen, a name which persisted until the time of Winslow (1669-1760). He provided the first good description of the vagus nerve, even noting the branch supplied to the aortic arch and writing with great perspicacity "so, it may react to changes in the pulse", undoubtedly being the earliest reference to the aortic depressor nerve. He recognized the vagus innervation of the heart as an important factor in its functional regulation but discovered no specific reaction to vagus stimulation. Lower's (1669) observations of the effects of vagus nerve section and vagus stimulation on the heart beat, which were later amplified by Ens (1745), prepared the way for the final demonstration of the inhibitory action of the vagus nerve on the heart beat by the experimental studies of Weber and Weber (1845, 1846).

Winslow (1669-1760) discarded the term "intercostal nerves" which had been commonly applied to the sympathetic trunks. In accordance with his opinion that they are primarily concerned with the *"sympathies"* between various organs, he introduced the term *"grand sympathique"* (1732). This was the first use of the word sympathetic to describe the late intercostal nerves. In the general term "sympathique" he included two other nerves, the portio dura of the seventh nerve which he called the "small sympathetic" and the eighth pair (i.e. at this time, the vagus nerve or par vagum) which he called the "medium sympathetic". Except the word *"sympathique"*, this secondary terminology received little support and the names, small and medium sympathetic, were rarely referred to. At this time, he still supported the theory that the nerve was the principal means of bringing about the sympathies of the body and the idea that the ganglia were "small brains" (see Langley, 1916). One's have to wait 1751 when Whytt used the more neutral term "nervous power" or "influence" for animal spirits.
The detailed descriptions of the sympathetic ganglia and their relations to the nerves led Johnstone (1764) to the use of the terms "ganglionic nerves" and "*ganglionic nervous system"*, terms which subsequently did not really prosper. He supported the view, already advanced by Winslow, that the ganglia were independent nerve centers in which the effects of the will were intercepted, so rendering visceral movements involuntary, and in which visceral impulses were interrupted, so rendering the viscera relatively insensitive.

Early in the 19th century, the term "pneumogastric" for vagus began to appear in the French and Italian literature to disappear almost completely in the 1970's (see: Skandalakis, 1986).
During the 19th century rapid advances were made in the physiological and histological fields. In particular, the anatomical and

physiological studies of Bichat (1800, 1801, and 1802) contributed significantly to knowledge of the autonomic nervous system and stimulated further research. He conceived of life as made up of animal life (la vie animale) and organic life (la vie organique), a distinction which, later, finds expression in the current concepts of "somatic" and "visceral" functions or *"somatic nervous system"* versus *"visceral nervous system"*. He correlated the visceral nervous system with metabolic functions and pointed out the continuity of action, apparent in the organic life, in contrast to the intermittent activity, apparent in the animal life. He regarded the ganglia, as did Johnstone, as nerve centers entirely independent of the central nervous system (CNS). Although Bichat commonly used the term initiated by Johnstone *"ganglionic nervous system"* he may properly be regarded as the originator of the name *"organic nervous system"* because of his emphasis on the relation of the ganglionic nerves to organic life.

Reil (1807) in general reaffirmed Bichat's views, but he reverted to the ideas of Winslow and Johnstone about the interruption of motor and sensory impulses. However he localized this interruption in the rami communicantes (instead of the ganglia) which were considered as semiconductors because he believed that they did not conduct impulses under normal circumstances but could transmit the increased flow of sensory impressions only in diseased conditions, so allowing these impressions to reach consciousness. Reil also introduced the term *"vegetative nervous system"*, sometimes still used to-day.

The submucous plexus in the intestine was described by Meissner in 1857 and the myenteric plexus by Auerbach in 1864. At the middle of the 19th century the relationships of the vagus nerves to the "ganglionic" or "organic" nervous system still remained obscure, although a vagus influence on cardiac activity had been demonstrated. The ciliary, the sphenopalatine, the otic and the submandibular ganglia were regarded as components of the ganglionic nervous system, but their relationships also remained uncertain.

The significant anatomical and physiological studies leading up to Claude Bernard's (1858) discovery of the vasomotor function of the sympathetic nerves to the blood vessels, which was confirmed by Brown-Séquard (1852) had already been accomplished. Bichat's theory, according to which the sympathetic ganglia represent nerve centers which function independently of the central nervous system, could no longer be supported and Claude Bernard advanced the hypothesis that all sympathetic reflexes are mediated through the spinal cord. He also demonstrated the existence of centers in the brainstem which discharge impulses that are conducted through sympathetic nerves. The search for higher centers which exert their influence through the autonomic nerves was thus initiated.

Gaskell (1886) contributed greatly to a better understanding of the autonomic nervous system. He pointed out that the efferent fibres in the white communicating rami arise in the spinal cord and that corresponding fibres occur in certain of the cranial nerves and that there exist three outflows of nerve fibres of small calibre, the bulbar, the thoraco-lumbar and the sacral, through which the peripherally located efferent ganglion cells are connected with the CNS. In 1916 he used the term *"involuntary nervous system"* to designate the efferent neurons located outside the CNS that supply fibres to involuntary structures. He conceived this system as purely motor or efferent and referred to the outflows from the CNS as the "connectors". His terminology presented certain obvious difficulties; consequently it has never been widely used.

Langley and Dickinson (1890) discovered in the action of nicotine on the ganglia a new method of investigating the relationships of nerve fibres to peripheral ganglion cells. It became possible to determine the positions of the cell stations or synapses, and the "preganglionic" and "postganglionic fibres" terms were first used by Langley in 1893. The results led Langley (1898a, b) to propose a new terminology for the system of nerves in question which has been definitively accepted until now. He called it the *"autonomic nervous system"*, although he was not unmindful of its anatomical and functional relationships to the cerebrospinal nervous system. At that time it was known that the thoraco-lumbar outflow, through the sympathetic trunks, supplies fibres to all parts of the body when the cranial and sacral outflows supply fibres only to parts of the body. Following the work of Gaskell and others it was also known that, in general, stimulation of the fibres in the cranio-sacral and thoraco-lumbar outflows produced opposite effects. Langley therefore regarded the thoraco-lumbar outflow as a system distinct from the others outflows, and as he regarded the part of the cranial efferents supplying the eye as distinct from the bulbar part of this outflow, Langley divided (1898, 1903, 1916) the autonomic nervous system into four regions: tectal (mid-brain autonomic system), bulbar autonomic system, sympathetic system and sacral autonomic system. The two first were placed together under the heading of the "cranial autonomic system". Following the discovery that the effects produced by adrenalin apparently are similar to those produced by stimulation of sympathetic nerves and that other drugs produced effects apparently identical with those produced by stimulation of the tectal and bulbosacral nerves, he grouped the tectal and the bulbosacral autonomic nerves together as the *parasympathetic system* (Langley, 1905). He imagined the cells in the myenteric and submucous plexuses might be postganglionic neurons in the bulbar and sacral outflow, but in the absence of definite proofs he proposed (1900, 1903) to classify them in a separate system which he called the *enteric nervous system*.

NB: However as pointed rightly by Blessing (1997a, b), the "*system*" part of the term "*autonomic nervous system*" would be misleading as we do not speak of a "spinal nervous system" or a "brainstem nervous system", even though the isolated spinal cord or isolated brainstem do possess a degree of operational unity and integrated action; thus, the term "*autonomic nervous system*" should be abandoned and replaced simply by *visceral neurons*, both efferent and afferent. Moreover, although we must subdivide the organism or the nervous system in order to study it, each artificially subdivided portion must be reintegrated in the whole and we must keep in mind, as already underlined by Bichat (1800), that there is not one nervous system for la "*vie de nutrition"* and a separate nervous system for "*la vie de relation*". There is just only one individual and just one and unique nervous system.