The spinal cord as organizer of disease processes: (II) The peripheral autonomic nervous system

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The neuromusculoskeletal system has been designated the "primary machinery" of human life. The visceral and endocrine systems, through their actions in and on the internal environment, serve logistical and maintenance roles that enable the primary machinery to function. The autonomic nervous system has a major role in "tuning" visceral, circulatory, and metabolic activity in accordance with neuromusculoskeletal demand. The sympathetic nervous system seems to respond to the rapid demands for energy and for heat exchange with the external environment, whereas the parasympathetic division focuses on the internal environment, being in charge of the long-term adjustments in accordance with more stable factors, such as age. The two divisions differ in basic designs, central origins, anatomic relations to the somatic nervous system, the tissues, organs, and systems that they innervate, and the sensory inputs to which they respond. The "effects" of the sympathetic nervous system on tissues and organs are as diverse as the tissues and organs that are innervated. Each tissue innervated responds in accordance with its specialized qualities. The sympathetic innervation modifies the intrinsic physiologic properties and processes of the component cells, each responding in its own way.

The first article in this series[1] presented some preliminary perspectives about the spinal cord's role in organizing disease processes. Reference was made to hyperactivity of the sympathetic innervation of various tissues and organs as a common feature in many syndromes. Evidence for the origin of sympathetic hyperactivity in somatic dysfunction was also briefly summarized.

Since the sympathetic nervous system (SNS) has its entire origin within the spinal cord, review of this aspect of pathophysiology seemed appropriate for the second article in the series. However, it has been my experience that understanding in this area is often impaired by the archaic and obfuscating myths and misconceptions that prevail about the autonomic nervous system (ANS). A prefatory review of fundamentals, therefore, seemed desirable, and that is the purpose of this article.

In this review I shall not be concerned with anatomic, physiologic, and pharmacologic details, those being abundantly available in many textbooks and monographs. Rather, my concern is with basic design, functional organization, and general role in the total body economy, perspectives that are often obscured by the very plethora of details as well as by hallowed and hoary concepts that are belied by the facts.

Myths and misconceptions

Among the most persistent myths is that the two divisions of the ANS, the sympathetic and parasympathetic, are equal and opposite moieties one being inhibitory where the other is excitatory, one positive, the other negative, one yin, the other yang. The implication usually conveyed is that normal life is a nicely balanced tug-of-war between these two divisions, and that it is the physician's function to redress "autonomic imbalance," usually with appropriately -lytic or -mimetic medications.

Although this view is widely held by physicians (and others), it will be shown that the two divisions are vastly different systems. Indeed, only one of them, the sympathetic, can truly be called a system. They differ in their basic design, central origins, peripheral distribution (overlapping though it is), and the sensory stimuli to which they respond. Accordingly, they differ fundamentally in mode of operation and in their roles in the total body economy. Another prevalent myth is that postganglionic neurons exert only two kinds of influence on their target organs: motor (regulation of contractile activity of smooth and cardiac muscle) and secretomotor (control of secretion by various exocrine glands). As will be shown, however, the repertoire of the ANS is a great deal larger and more diverse than that.

Relation of the ANS to the musculoskeletal system

I must confess that my own comprehension of the ANS remained quite turbid through years of teaching autonomic physiology despite a reasonably broad acquaintance with the growing knowledge *about* the ANS. A coherent perspective did not begin to emerge until I had acquired some understanding of the theoretical basis (as distinguished from the empiric) for osteopathic emphasis on the musculoskeletal system in maintaining and restoring health and in the care of the ill.

Throughout its history, medicine has emphasized the internal organs and their disturbances, and diagnostic and therapeutic methods have largely been directed at the origins and manifestations of those disturbances. In the absence of frank problems of the musculoskeletal system, that system has implicitly been regarded only as the vehicle for carrying the viscera about.

Rewarding as the visceral emphasis has been through the centuries, it is important to keep in mind, however, that human activity - behavior of the person - is not a composite of visceral functions, such as peristalsis, secretion, digestion, vasomotion, and glomerular filtration. Human activity is the continually changing composite of the activities of striated muscles, most of them pulling on bony levers, their contractions and relaxations orchestrated by the central nervous system, in response to external and internal stimuli and to volition.

Even those distinguishing features of the human species, related to intellect and affect, that are associated with unique cerebral development - ability to accumulate and transmit knowledge, reason, imagination, creativity, compassion, conceptualization, inquisitiveness about self, life, and the universe, et cetera - are important because they result in equally unique actions - all musculoskeletally mediated - that have led to the products (and problems) of human life, culture, and civilization as we know them. It is through the neuromusculoskeletal system that we act out our humanity and our individual personalities in the infinite variety of ways of being human. We are even recognizable by the idiosyncratic ways in which we stand and move; that is, by the ways in which we use our musculoskeletal systems.

Since even the highest moral, ethical, philosophical, and religious principles have value only insofar as they lead to appropriate behavior, they, too, must be acted out or communicated through the contractile activities of muscles. Similarly, it is through our musculoskeletal systems that we act out and communicate our attitudes, fears, hopes, aspirations, beliefs, and childhood conditioning. If, as has been said, education is the changing of behavior, then education has its ultimate expression in changed patterns of muscular activity.

It is for these and related reasons that I came to view the neuromusculoskeletal system as the primary machinery of life, the instrumentality through which we behave as human beings, each in his or her own way. [2]

What, then, are the functions of the viscera, with which the practice of medicine is so much concerned? Their role, from this perspective, is to maintain and service the "primary machinery" and to create the optimal circumstances for its operation. Such "service" includes: (l) providing and delivering, as rapidly (more or less) as they are consumed, the raw products, including oxygen, which serve as energy-laden fuels and as materials for cellular self-renewal; (2) removing the products of metabolism, more or less as rapidly as they are produced; (3) dissipating the heat that is produced; (4) otherwise controlling the composition and physical properties of the internal environment in which the component cells live; and (5) protecting against foreign substances and invading organisms. (In performing these services "for" the musculoskeletal system, the viscera are, of course, also doing the same for each other, in the course of maintaining homeostasis.)

By virtue of their mass, and their high and rapidly changing metabolic rate, the muscles are, in effect, the consumers of the body, and the total body economy is continually adjusted to meet their varying demands from moment to moment and in the long run. The "responsibility" for "tuning" visceral, circulatory, and metabolic activity to muscular (and environmental, especially thermoregulatory) demand rests with the ANS, in conjunction, of course, with the endocrine system. From the viewpoint presented here, the rapid, moment-to-moment adjustments in accordance with levels of exertion and posture (or anticipation conscious, or unconscious, of exertion) are orchestrated largely by the SNS. The parasympathetic division makes the long-term adjustments, according to customary muscular activity (and environmental demand), therefore, according to personality, temperament, occupation, habits, sports, recreation, age, climate, season, et cetera. It maintains and replenishes the stores of fuels, nutrients, and precursors from which the largest withdrawals are made under direction of the SNS.

It is for reasons such as these that Nobel laureate W. R. Hess used the term "ergotropic," signifying energy expenditure and exchange, to describe activity patterns in which the SNS plays a dominant role, and the terms "trophotropic" and "endophylactic," signifying nourishment, conservation, and guarding of the internal environment, to characterize those patterns in which the parasympathetic division participated.[3]

From this viewpoint, also, it becomes evident that illness results from - or even *is* - disparity between the demands of what I have called the "primary machinery" and the logistic meeting of those demands by the maintenance machinery. Indeed, that is the basis of therapeutic rest: In such disparity, the musculoskeletal system is less able to function and, when the disparity is sufficiently great, one takes to one's bed, thereby reducing the demand and the disparity until the basis for the disparity is corrected.

Traditional medicine has looked to the visceral part of the equation as the basis for disparity. Doubtless, this is frequently the case. However, I believe a more complete and balanced equation includes the following factors in the viscerosomatic disparity:

1. *Musculoskeletal.* Excessive, insufficient, or inappropriate musculoskeletal demand; somatic dysfunction; errors and problems of locomotion and posture
2. *Behavioral.* Inappropriate ("neurotic") behavior; hence, misuse of the musculoskeletal system; "psychosomatic" disorders.
3. *Communicative.* Impaired communication between visceral and somatic components, through nervous and vascular channels; "noisy," "garbled," incomplete, interrupted.
4. *Visceral.* Defect, dysfunction, or other visceral impairment.
5. *Multiple.* Any one of the previous may be the original or dominant factor in the somatovisceral "disparity," and therefore in a given illness. The disparity, however, soon involves one or more of the other factors, frequently culminating in a self-sustaining vicious cycle.

Functional organization of the ANS

In this section we shall examine, schematically, the design and structure of the two divisions of the ANS as related to their respective roles in the body economy. Figures 1 through 6 show the basic design of the peripheral ANS and the differences in functional organization between the sympathetic and parasympathetic divisions.

Central origin

The preganglionic neurons of the ANS, collectively represented in Figure 1, are situated within the central nervous system, where they receive the converging influences of a large number of presynaptic neurons. The presynaptic axons convey impulses from many neuronal and sensory sources. The preganglionic cell bodies are grouped into neuron pools known as nuclei and cell columns. The preganglionic neurons of the parasympathetic or craniosacral division occur in two main and widely separated populations, the cranial and the sacral. The cranial portion consists of four pairs of discrete nuclei, III, VII, IX, and X; the sacral portion occupies three (usually) sacral segments of the intermediolateral cell column of the spinal cord. The sympathetic preganglionic neurons are grouped into a pair of long, continuous "nuclei" - the intermediolateral cell columns of the cord, extending from T1 to L2.

Preganglionic outflow and the ganglia

The axons of the sympathetic preganglionic neurons issue from the cord via the ventral roots (together with axons of motoneurons in the ventral horn) and through the thoracic and upper lumbar intervertebral foramina, to synapse with postganglionic neurons, the cell bodies of which are grouped in the ganglia (Fig. 2). In the SNS, most of the synapses are with neurons in the paravertebral ganglia, linked in left and right chains extending over the entire length of the spinal column. Upon entering the chain at each level the preganglionic axons and their collaterals may turn upward or downward or both to synapse not only in ipsisegmental ganglia, but also in ganglia at higher and lower levels. Neurons in the cervical ganglia receive all of their preganglionic innervation from the upper thoracic segments, and those of the lower lumber and sacral segments, from cord level L2 and above.

Other preganglionic axons (T5 and lower), comprising the splanchnic nerves, proceed through the chain, without synapse, to terminate in outlying or collateral ganglia (for example, celiac and mesenteric) on left and right sides. Some of the preganglionic axons, however, terminate in the adrenal medulla. (Viscera are grouped into the four major regions, as shown in Figures 3-6, the organs of each region having certain innervational features in common.) The innervation of the adrenal medulla is shown in Figure 4.

The preganglionic axons issuing from cranial nuclei III, VII, and IX synapse in cranial ganglia (ciliary, sphenopalatine, otic, and submandibular) whereas those of the vagus nerve (X) synapse in small scattered ganglia lying in close relation to the innervated viscera.

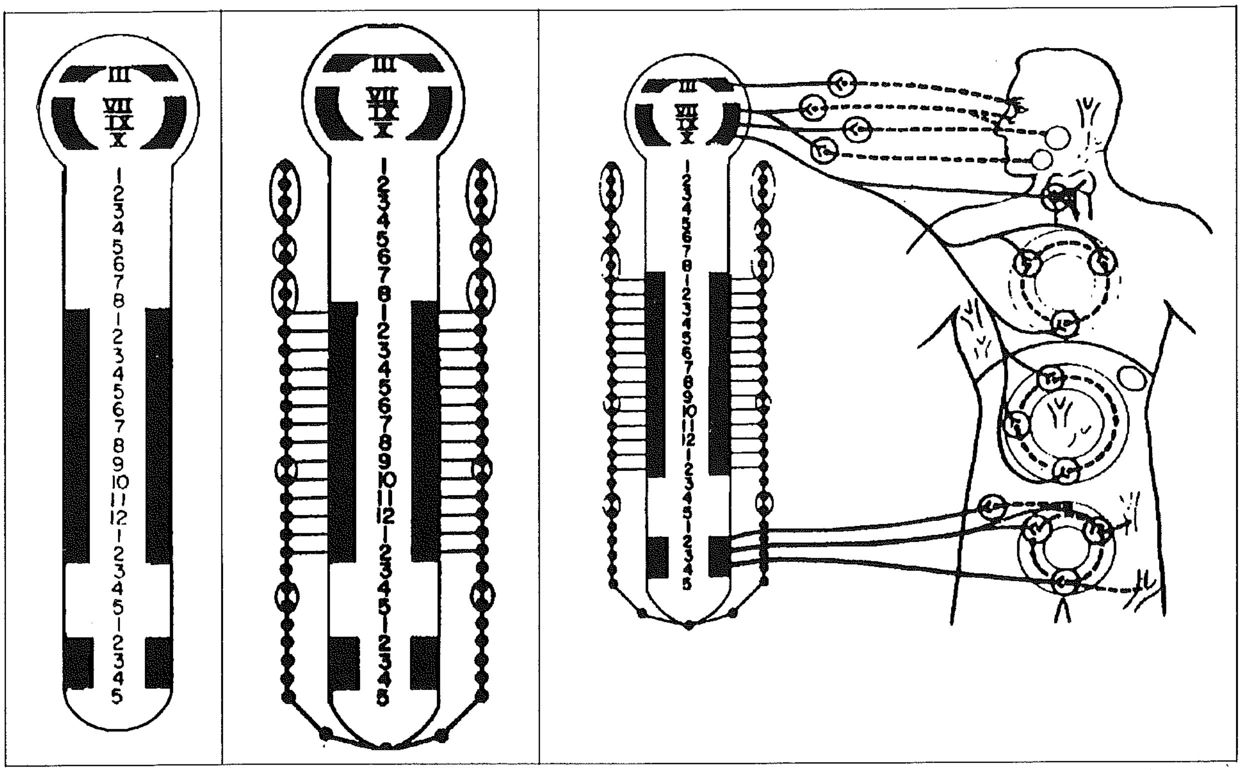

Fig 1. *Diagrammatic view of brainstem and spinal cord, representing origins of the ANS; that is, the location of the cells of origin (preganglionic neurons) in the central nervous system. These neurons are subject to a vast variety of presynaptic influences. In this and in all the diagrams the sympathetic division is in the center and the parasympathetic is at the top and bottom. Roman numerals represent parasympathetic cranial nuclei. Arabic numerals indicate cervical, thoracic, lumbar, and sacral segments of the spinal cord, and the segmental origins (intermediolateral cell columns) of the sympathetic division (T1 to L2), and the sacral portion of the parasympathetic division (S2 to S4).* Fig 2. *Paravertebral chains of sympathetic ganglia and the preganglionic fibers (leaving the spinal cord via the ventral roots and white rami between T1 and L2). Encircled pairs or groups of ganglia indicate fusions that are commonly found.* Fig. 3. *Visceral structures are represented within the human figure in four main groupings: those of head and neck; thoracic; abdominal; pelvic and genital. Only the parasympathetic innervation* is shown. *In this and the remaining figures solid lines represent preganglionic axons and interrupted lines represent postganglionic axons.*

(Parasympathetic ganglia and viscera are not individually identified in the diagrams.) Ganglia receiving the sacral outflow are of both the collateral and intrinsic types, as shown in Figure 4.

Distribution of postganglionic fibers

The postganglionic axons are, of course, those that deliver the autonomic influences to the end organs that they innervate. The respective innervation fields of the sympathetic and parasympathetic divisions are, therefore, related to their respective roles in the body economy. The parasympathetic ganglia provide innervation to all the viscera (Fig. 3). Those connected to the upper three cranial nuclei have a rather limited distribution to structures in the head, the impulses from each nucleus being rather specifically directed to one or two organs (for example, eye and lacrimal and salivary glands). The vagus, however, diverges to a wide innervation field including organs in the neck, thorax, and abdomen. The sacral outflow has its influence on the pelvic organs and genitalia. Blood vessels related to sexual (erectile) function also receive sacred parasympathetic innervation.

The sympathetic ganglia provide innervation to all of the organs supplied by the parasympathetic (Fig. 4). (Sympathetic and parasympathetic distribution to *parts* of a given organ may differ, however, as in the case of the eye and the urinary bladder.) It is in these dually innervated organs, all visceral with the exception of the eye, that sympathetic-parasympathetic "antagonism" may be expected. But even in these, it is at least as much a matter of delicate coordination of different tonic influences as it is of antagonism. Often, the sympathetic and parasympathetic influences are not so much *opposite*

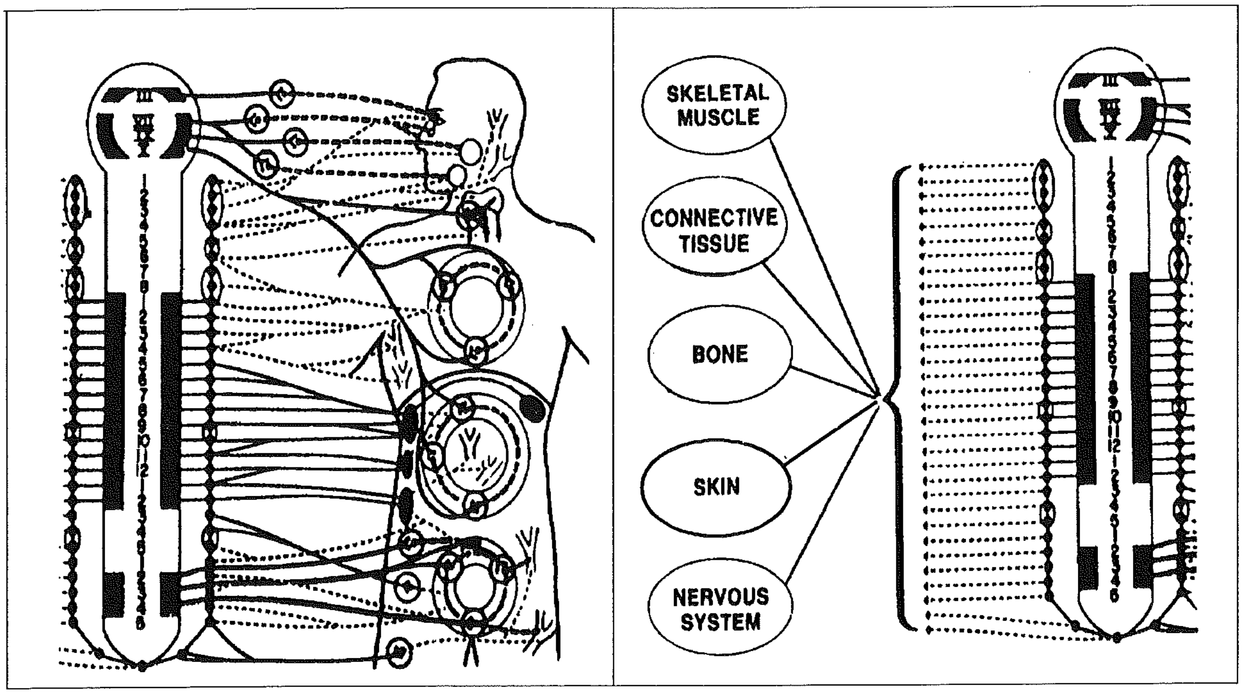

Fig 4. *Sympathetic innervation of visceral structures gas been added showing dual innervation of most viscera. Note that sympathetic postganglionic innervation in head and neck and the thorax originate in paravertebral ganglia. Those of the abdomen and some pelvic organs arise in outlying ganglia (for example, celiac and mesenteric). Note also that the adrenal medulla (shown under left side of diaphragm) is innervated by sympathetic preganglionic neurons, and that blood vessels receive their innervation predominantly from the sympathetic divisions.* Fig 5. *Somatic structures, including the musculoskeletal system (and the nervous system itself) are represented on the left side of the diagram. Note that somatic structures receive their autonomic supply exclusively from the sympathetic division (via the spinal nerves).*

in direction as *different* in quality (for example, in salivary secretion).

Dual innervation does not, however, extend to the vasculature. This is almost entirely the domain of the SNS (the major exception being the dual innervation of vessels in pelvic organs and genitalia). Through the control of the contractile activity of the smooth-muscle elements in arterioles, arteries, and veins (and even larger lymphatic vessels), the SNS can regulate the peripheral resistance, distensibility, vascular capacity, and arterial pressure, and, through these, the distribution of blood in the vascular tree, effective filtration pressure in the capillaries, and the apportionment of the cardiac output among the parts of the body, in accordance with their metabolic requirements or roles in the body economy. The SNS, therefore, is truly the vasomotor component of the nervous system.

The sympathetic innervation of the heart, through its chronotropic (rhythm) and inotropic (force of contraction) influence, has a major influence on the ventricular pressure-head and on cardiac output. The vagus profoundly affects the rhythm of the heart through its cardioinhibitory influence, but the degree and significance of any inotropic influences are still under debate. The SNS, therefore, may be said to mediate the central regulation of the entire cardiovascular system in accordance with what is going on in the body as a whole.

What is the innervation of the most massive parts of the body, namely, the musculoskeletal system and other somatic tissues? As is indicated in Figure 5, the autonomic innervation is exclusively sympathetic, via the chain ganglia and spinal nerves, the axons of which terminate in muscles, bones, articular structures, ligaments, tendons, other connective tissues, and skin. It is to be noted that the nervous system itself also receives autonomic innervation, and, as far as one can tell, this is also exclusively sympathetic.

As an example of prevailing perspectives of the ANS, this major outflow, to integument and neuromusculoskeletal system, which I have called the "primary machinery," is usually represented in the typical schema of the ANS by an inconspicuous little drawing of a blood vessel, a sweat gland, and a hair follicle at the outer edge of the diagram, as can be seen in one of the

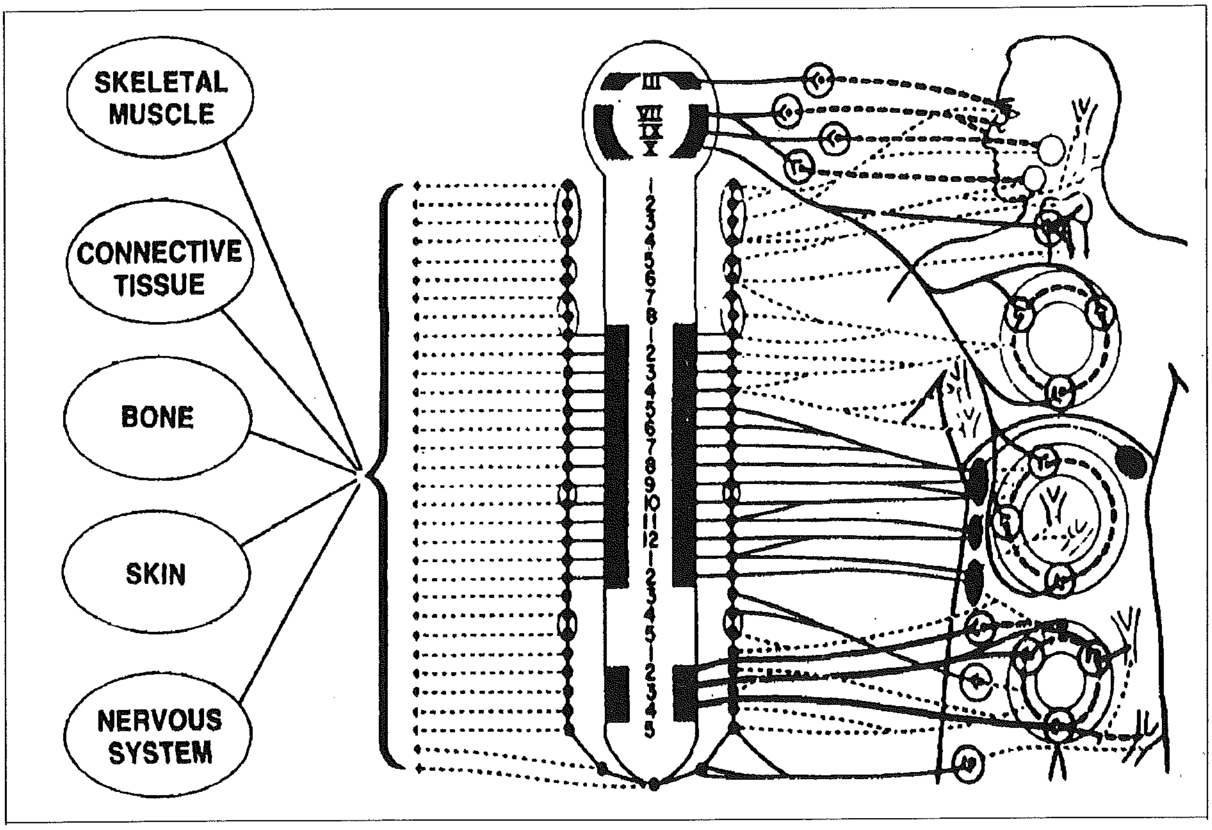

Fig 6. *Schema of the peripheral autonomic nervous system, completed. (Reprinted with permission.)*[2]

most frequently consulted schemata.[4] In keeping with the main sphere of medical practice, visceral innervation is the main subject of the typical diagram, while the largest part of the body, the musculoskeletal system, is scarcely identified.

Figure 6 summarizes the postganglionic distribution discussed heretofore, as well as the basic design of the ANS and its divisions. Certain features are immediately evident:

1. Unlike the parasympathetic division, whose sphere is almost entirely visceral, the sympathetic division provides autonomic innervation to every part of the body, including the nervous system itself.

2. Unlike the parasympathetic, which is really a collection of highly "private" lines to individual organs and tissues, divergence is a conspicuous feature of the SNS. Note, first of all, the rather extensive origin in the spinal cord, then the "fanning-out" of the preganglionic axons to ganglia along the entire length of the vertebral column and to the collateral ganglia and, from these, the spread of the postganglionic axons throughout the body.

3. To be emphasized again is the general vasomotor role of the SNS, which is part of its capacity for mobilizing resources throughout the body.

4. Finally, as is symbolized in Figure 6, the SNS is, in effect, strategically situated between the visceral and somatic tissues, whereby it can adjust function of the viscera (right side of the diagram) to the demands and requirements of the integumentary and neuromusculoskeletal systems (left side).

Obviously, unlike the parasympathetic division, the organization of the SNS provides for coordinated, body-wide broadcasting of sympathetic influences, reinforced and sustained by circulating epinephrine and norepinephrine from the adrenal medulla. Yet, like the parasympathetic, the SNS is also capable of selective, localized activity. Central activation of the entire sympathetic division, as in exertion, emergency (real or perceived), or environmental extremes, results in well-orchestrated, adaptive changes in visceral, circulatory, and metabolic activity throughout the body. The SNS, therefore, can be appropriately described as a system. In contrast, the unlikely event (fortunately) of central activation of the entire parasympathetic outflow, that is,

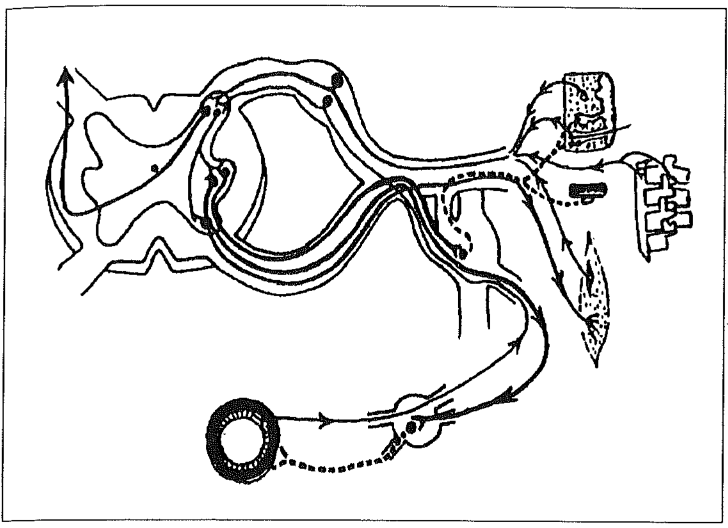

Fig. 7. *Cross-section of the spinal cord at thoracic or upper lumbar levels. Sensory (dorsal root ganglion) neurons and their fibers (black), convey impulses from receptors and endings in somatic and visceral tissues. Motoneurons (ventral horn cells) and their axons (green) supply motor innervation to skeletal musculature. Sympathetic neurons (red), the preganglionic neurons in the intermediolateral cell column, whose fibers (solid lines) synapse in ganglia with postganglionic neurons the axons of which (interrupted lines) innervate viscera and certain components of somatic tissues. A secondary sensory neuron (spinothalamic) conveys impulses to higher centers and mediates sensations of pain and temperature. (Reprinted with permission.)*[2]

simultaneous, intense activity of all four pairs of cranial nuclei and the sacral nuclei or the circulation of a (nonexistent) parasympathomimetic hormone corresponding to the adrenomedullary hormones, would result in utter physiologic chaos.

Relation of peripheral ANS to somatic innervation

In accordance with functional relations of the SNS to the musculoskeletal system, and its responsiveness to environmental changes (for example, in thermoregulation), the SNS is also intimately related anatomically to musculoskeletal innervation, both sensory and motor. As Figure 7 shows, SNS outflow and the motor supply to the skeletal muscles begin close together in the cord, where they are subject to many of the same presynaptic influences. The axons of the preganglionic cells and of the motoneurons then leave the cord together via the ventral roots, the motor axons proceeding to termination in skeletal muscles, the preganglionic axons proceeding to synapses in the ganglia. However, the motor axons are again rejoined by sympathetic fibers, namely the postganglionic axons entering the spinal nerves (via the rami communicantes), on their way to tissues of the neck, trunk, and extremities.

Because motoneurons and sympathetic preganglionic neurons are subject to similar presynaptic sensory, intraspinal, and supraspinal (that is, higher-center) inputs, they are also both vulnerable to disturbances via these inputs. Similarly, since their axons course together in the spinal roots and in the spinal nerves, which also include somatosensory fibers, somatic and sympathetic fibers are together vulnerable to deformation and other trauma of biomechanical origin. The clinical implications of these somatosympathetic disturbances were discussed in the previous paper,[1] and their mechanisms and manifestations will be the primary subject of the next.[5] It is nevertheless important to emphasize that every human action involves the simultaneous, coordinated activity of the somatic and autonomic nervous systems, and that dysfunction of one inevitably leads to dysfunction of the other.

Like the SNS, the sacral outflow of the parasympathetic division also has close functional relations with the musculoskeletal system, as in elimination, sexual intercourse, and parturition, in which coordination of visceral and motor activity is essential. Accordingly, this part of the parasympathetic outflow has its origin and course in close relation to the motoneurons. In contrast, the entire cranial outflow has little if any relation to motor function, in accordance with its remoteness from innervation of skeletal muscle.

Afferent pathways in relation to ANS

The sensory inputs to which they respond also reflect the respective roles of the two divisions of the ANS. The responses of the SNS to sensory input from receptors in skin, muscle, joints, et cetera, via segmental and suprasegmental pathways, in what have come to be called somatosympathetic reflexes, are highly organized and adaptive. Feedback from proprioceptors is important in local and regional adjustments according to site and kind of activity. These reflexes have been the subject of intensive study and excellent reviews in recent years.[6,8] Disturbances in these reflexes and their clinical manifestations have been previously reviewed,[9] and will be examined in Part III of this series.[5] I need only emphasize now that since this continual sensory feedback from the soma to the SNS is essential for normal function, somatic dysfunction will also be communicated to the SNS, with adverse effects on other sympathetically innervated structures.

Although both divisions are assemblages of efferent pathways, numerous sensory fibers run in "sympathetic" nerves such as the majority of the splanchnic and in parasympathetic nerves such as the vagi and pelvic splanchnic. Those in the sympathetic trunks are excited by noxious, painful states in the viscera, such as severe distention, chemical irritation, spasm, and ischemia. It is of interest that these "pain" fibers, through interneurons, not only stimulate sympathetic preganglionic neurons in the cord, thus producing changes in target organs (for example, viscera, blood vessels, sweat glands), but they also excite neighboring motoneurons, producing the sustained muscular contractions so often associated with referred pain of visceral origin.

In contrast, the sensory fibers running within parasympathetic nerves bring feedback from various reporting stations in the viscera. In vagal afferent pathways, for example, these signals serve mainly regulatory roles in respiration, circulation, digestion, and other visceral functions. In the sacral circuits, they signal such circumstances as fullness, that is, readiness for evacuation, of urinary bladder and rectum. In these sacral examples, muscular activity is invoked - to assist and help to execute primarily visceral activity. The converse is true of the SNS, which adjusts visceral function to support muscular activity.

Repertoire of SNS

In view of the divergence of the sympathetic outflow to virtually every tissue in the body, it is important to ask what effects impulse activity in these efferent pathways has on all these diverse tissues and organs. This is a key question to explore in preparation for a survey of the clinical effects of sympathetic *hyper*activity, which is the subject of Part III.[5]

As has already been mentioned, there seems to be a prevalent misconception in this regard, too. The traditional view is that whatever the effects of sympathetic activity (and, presumably, hyperactivity), they are mediated by regulation of contraction of smooth or cardiac muscle (the smooth muscle including that of blood vessels) and of secretion by exocrine glands, such as sweat glands and glands of the digestive tracts.

The truth is, however, that the sympathetic repertoire is a great deal more diverse than that, as the following few examples will indicate. (The experimental and clinical evidence for the following statements, and the corresponding bibliographic references, can be found in an earlier paper).[9]

1. *Muscle*. Stimulation of the sympathetic innervation of skeletal muscle increases the force of contraction, diminishes the fatigue of repetitively stimulated muscle or delays its onset, and facilitates neuromuscular transmission.

2. *Peripheral sensory mechanisms*. Sympathetic activity influences the function of various sensory organs, in most cases in the direction of increased excitability, that is, lowered thresholds and exaggerated frequency of discharge. Receptors and sensory organs in which this effect has been demonstrated include muscle spindles, tactile receptors, taste receptors, olfactory apparatus, chemo- and baroreceptors of the carotid sinus, pacinian corpuscles, retina, and cochlea.

3. *Central nervous system (CNS)*. Sympathetic influences, demonstrated by stimulation, ablation, interruption, ganglionic blockade, et cetera, have been shown on various parts of the CNS, including the cerebral cortex and subcortical structures, reticulospinal system, hypothalamus, cerebellum, and spinal cord. Effects have been shown on behavior (for example, alteration of established conditioned motor reflexes), electroencephalographic patterns, responses to various kinds of stimuli, motor reflexes, and many others, signifying a direct influence on neuronal excitability and activity.

4. *Development of collateral circulation*, following arterial occlusion, is impeded by sympathetic activity and is accelerated by sympathectomy.

5. Sympathetic activity exerts an important influence on *activity of bone cells and on longitudinal bone growth*.

6. Stimulation of the sympathetic innervation of *adipose tissue* favors lipolysis (release of free fatty acids and glycerol), whereas interruption of impulse traffic increases fat content, a result that suggests a tonic influence on fat metabolism. Indeed, the rapid lipolysis that takes place during cold exposure and the slow lipolysis during starvation do not occur in sympathectomized fat pads. These sympathetic influences on lipid metabolism have been shown to be quite independent of sympathetic influences on blood flow.

7. *Reticuloendothelial system*. Since bone marrow has a rich sympathetic innervation, it is not surprising to find effects of sympathetic activity not only on blood flow, but on erythropoiesis, phagocytic activity of reticuloendothelial cells, release and distribution of leukocytes, and endothelial permeability.

8. Sympathetic influences have been demonstrated on various *endocrine organs*, including thyroid, adrenal cortex, pancreas, testicle, and pineal body. The pineal body is of special interest in this

connection. Its elaboration of melatonin, which influences growth, gonadal development, and sexual activity, is controlled by sympathetic innervation from the superior cervical ganglion. The secretion of melatonin follows a diurnal cycle in that synthesis is increased in the dark (inhibiting growth and sexual development) and decreased in the light. When the sympathetic fibers to the pineal body are sectioned, the diurnal fluctuation of melatonin synthesis and the associated diurnal changes in behavior cease. Under these conditions, the animal kept in the dark is no longer subject to the antigonadal and growth-inhibiting influence of the pineal body.

9. Many other examples could be given of sympathetic influences on enzyme activity, mitosis, synthesis of nucleoproteins, growth and development, and on responses of various tissues to other factors (for example, hormones, parasympathetic stimulation, toxins).

The variety of the effects of stimulating peripheral sympathetic pathways does not lie in the sympathetic neurons or their influences, but in the responses of the organs that are innervated. These responses are as diverse as the target tissues and organs - virtually every tissue in the body. Sympathetic stimulation, rather than introducing new qualities, modifies the inherent physiology and molecular processes of the component cells, so that each tissue responds in its own way.

This provides the basis for understanding the diversity of clinical consequences (discussed in a succeeding paper)[4] of chronically exaggerated sympathetic influences associated with somatic dysfunction.[10-15]

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