The spinal cord as organizer of disease processes: (III) Hyperactivity of sympathetic innervation as a common factor in disease

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Musculoskeletal trauma or stress produces segmental sympathetic nervous system hyperactivity. The sympathetic nervous system also influences the response of tissues to noxious external agents as well as inflammatory and immune processes. Chronic sympathetic hyperactivity is an often critical factor in such diverse clinical syndromes as neurogenic pulmonary edema, peptic ulcer, arteriosclerosis, cardiac lesions, and osteodystrophies. Such clinical disturbances appear to be aberrant versions of local and regional feedback mechanisms. These abnormal reflexes become chronic and self-sustaining and often impair healing and recovery. Also, abnormal somatosympathetic reflexes produce dysfunctional, segmental coupling, resulting in "segmental relationships" as seen in referred pain. Effective manipulative therapy improves afferent input so that sympathetic hyperactivity is alleviated.

In the first article in this series[1] the human spinal cord was discussed as an organizer not only of normal adaptive behavior but also of disease processes. It was shown that pathogenic processes may be initiated in the cord by disturbances in afferent input from the musculoskeletal system or the viscera and by physicochemical disturbances in neuronal excitation and conduction. It was postulated that osteopathic manipulative therapy exerts its beneficial influence by correcting these disturbances, thus restoring adaptive behavior to the spinal cord.

Because of the role of the autonomic nervous system (ANS) in mediating visceral, circulatory, and metabolic manifestations of the cord disturbances, the second article was devoted to a review of the functional organization of the ANS and its role in the total economy of the body.[2] It was shown that the sympathetic and parasympathetic divisions are vastly different in their central origins, pathways, peripheral distribution, and responsiveness to various stimuli. Parasympathetic innervation is largely limited to the viscera, while components (vascular included) of *every* tissue of the body, including the somatic tissues, receive sympathetic innervation. Correspondingly, the two divisions have very different roles in the body.

The sympathetic nervous system (SNS) is mainly involved in moment-to-moment adjustments of visceral, circulatory, and metabolic functions according to the changing activity of the individual (carried out by the skeletal musculature) and to environmental demand. It is, appropriately, accessible and responsive to afferent input from the musculoskeletal system and skin as well as from supraspinal and viscerally related sources.

The parasympathetic division (which, unlike the sympathetic, is *not* a system, but a collection of private pathways) is more attuned to the internal environment, and regulates visceral activity according to such long-term, stable factors as *customary* activity of the individual, age, temperament, habits, occupation, climate, et cetera. Its afferent signals come mainly from sources related to the internal environment, and, other than at sacral levels, the parasympathetic receives no direct sensory input from musculoskeletal or other somatic tissues.

Finally, it was shown that sympathetic stimulation has a great variety of effects on tissue function, the effect varying with target tissue or organ. That is, the diversity is not diversity of sympathetic influences but of tissue responses, each of the body's many tissues responding in its own way. I interpret this as evidence that the sympathetic innervation modulates the physiologic properties and processes inherent in the component tissue cells; it does not impose new properties.

SNS and musculoskeletal function

The "ergotropic" function previously emphasized,[2] that of adjusting circulation, metabolism, and visceral activity according to musculoskeletal, postural, and environmental demand, includes changes in cardiac output, distribution, and blood flow by regulation of peripheral resistance, heat dissipation, and release of stored metabolites. These adjustments are of systemic nature, yet they have a high degree of localization according to the site and amount of muscular activity.

This function depends on continual and precise sensory input to the central nervous system (CNS) from the musculoskeletal system. Osteopathic clinical experience indicates that this feedback continues, though in modified form, under conditions of musculoskeletal dysfunction, and that this, in turn, may have a disruptive influence on the sympathetic outflow.

In a series of studies on human subjects and patients over a period of more than 20 years at the Kirksville College of Osteopathic Medicine, my associates and I showed that this was indeed a sound hypothesis.[3,8] Using the activity of sweat glands and cutaneous vasculature as physiologic indicators of sympathetic activity on the trunk, and employing a variety of methods to study topographic or dermatomal variations in SNS activity, we demonstrated that sympathetic hyperactivity was associated with venous types of somatic dysfunction and also with visceral pathologic alterations. We could induce segmental SNS hyperactivity with various types of musculoskeletal trauma or postural stress, usually slight and transient. The affected portions of the SNS *behaved* differently in that they made exaggerated responses to relatively minor stimuli applied to the person, whether of a physical, emotional, or environmental nature. These efferent pathways were said to be chronically facilitated, in the same way that Denslow and his coworkers[9,11] have shown for neuromuscular activity. The corresponding portion of the body seemed to respond as though in or bordering on a physiologic state of alarm. Since the sympathetic innervation of the skin is not fundamentally different from that of the viscera and blood vessels, it seems important to inquire about the possible effects of high-intensity sympathetic bombardment continuing over long periods.

What *is* the significance of sustained facilitation of this or that SNS outflow? The possible target tissues and potential clinical impact are determined by the segmental level of the affected outflow. The cervical and upper thoracic outflow, for example, would affect mainly structures of the head, neck, and thorax. Mid and lower thoracic outflow might affect abdominal viscera, etc.

Clinical significance of sympathicotonia

What does the sympathetic innervation do to these structures? The traditional view is that whatever the effects, they are mediated by regulation of contraction of smooth or cardiac muscle and of secretion by exocrine glands, such as sweat glands and glands of the digestive tract. As previously stated, however, the sympathetic repertoire is a great deal more diverse than that.[2] Effects were shown, for example, on the functional properties of skeletal muscle, peripheral receptors and sense organs, the central nervous system, bone cells, adipose tissue, reticuloendothelial system, endocrine organs, et cetera, and on the development of collateral circulation, enzyme activity, growth and development, synthesis of nucleoproteins, and on the responses of various tissues to *other* factors, such as parasympathetic stimulation, hormones, and toxins.

Evidence is presented in this paper of a corresponding diversity of clinical syndromes in which chronic sympathetic hyperactivity seems to be a major, often critical, factor. Yet, it is not readily perceived by clinical investigators because of the barriers that specialization causes. The specialist has difficulty enough staying current with the literature in his own field and is not usually aware that evidence for a sympathetic component in disease that has been gathered within his or her specialty has also accumulated in other specialty fields. The specialist therefore views the sympathetic role as peculiar to this or that syndrome, rather than as part of a general theme.

The evidence for the clinical impact of sympathicotonia lies in four areas: (1) symptomatology and pathophysiology; (2) effects of chronic experimental stimulation; (3) effects of interruption or reduction of sympathetic activity; and (4) morphologic changes in ganglia and other sympathetic components. This evidence was previously summarized in detail in a paper presented at a workshop on The Neurobiologic Mechanisms in Manipulative Therapy, held at Michigan State University in October 1977. The proceedings have been published in book form, and the original paper should be consulted for documentation and references .[12]

The production of *neurogenic pulmonary edema* by such factors as severe head trauma, lesions of various parts of the brain, hyperbaric oxygen, and localized pulmonary infarction is mediated by the sympathetic pathways to the lungs. All the manifestations, including vascular congestion, atelectasis, intra-alveolar hemorrhage, and protein-rich edema fluid, can be produced experimentally by stimulation of the stellate ganglia. Conversely, extirpation of the ganglia or adrenergic blockade, prior to the experimental trauma,

completely prevents the appearance of the syndrome.

Similarly, sympathetic components have been identified in *peptic ulcer* and *pancreatitis*. For example, sympathetic stimulation has converted mild, bile-induced pancreatitis to the lethal hemorrhagic and necrotizing form, whereas conduction block ameliorated the condition.

Sustained stimulation of the splanchnic nerve in unanesthetized rats produced the histologic features of *arteriosclerosis* in the aorta.

High activity of the peripheral SNS is known to be an important factor in some forms of *arterial hypertension*. It has been produced in dogs by chronic renal-artery nerve stimulation. Blockade of the innervation, on the other hand, reduced blood pressure in most eclamptic patients.

Hyperactivity of the sympathetic innervation of the heart, which has been shown to be provoked by myocardial infarction ("cardiocardiac reflex") has been found to be responsible for some of the *complications that follow myocardial infarction*, such as ventricular fibrillation and other arrhythmias. Even in the absence of myocardial infarction, sympathetic stimulation predisposes the heart to fibrillation, whereas chemical or surgical blockade protects the heart against these manifestations in experimental coronary occlusion.

Cardiogenic shock is also accompanied by high SNS activity, adversely affecting various visceral vascular beds, especially the renal and intestinal.

Severe *cardiac lesions* have been produced by intense stimulation of cardiac sympathetic pathways.

Increased activity of the sympathetic innervation of the kidney causes retention of sodium and water in *congestive heart failure*. Indeed, the augmented sympathetic tone is evident before failure develops. Conversely, blocking the adrenergic nerves has produced both diuresis and natriuresis.

A strong sympathetic component has been known for a long time in *post-traumatic pain syndromes* of a causalgia-like nature, usually produced by relatively minor injuries. Ganglionic blockade has been effective in many cases in relieving the extreme pain and other manifestations of an autonomic and trophic nature affecting bones, joints, skin, and other tissues of the injured extremity.

Sympathetic components have been demonstrated in other diseases involving *bones and joints*. Excellent results have been reported following lumbar sympathectomy in patients disabled by *arthritic pain* of either osteoarthritic or rheumatoid origin, in weight-bearing joints. Rheumatoid activity was affected only in the sympathectomized extremities.

Various *osteodystrophies* have resulted in the guinea pig from irritation of sympathetic fibers in the sciatic nerve. Treatment of patients with acute *anterior poliomyelitis* in one leg with a sympatholytic drug restored the rate of growth to that of the normal leg. Conversely, when the lumbar sympathetic chain in puppies was subjected to chronic unilateral stimulation, growth of the hind limb on the stimulated side was reduced.

When experimental animals that are to be subjected to traumatic or hemorrhagic *shock* are pretreated with adrenergic blocking agents or with sympathectomy, they are protected against the lethal effects.

The *liver pathology* caused by administration of carbon tetrachloride can be entirely ascribed to massive discharge of the peripheral SNS. The result is hepatic ischemia, hypoxic and necrotic changes around the central vein of the hepatic lobule as well as changes in enzyme activities.

Autonomic imbalance in the direction of sympathetic hyperactivity has been implicated in a variety of *obstetric and gynecologic conditions* in which uterine contractility was disturbed.

Sympathicotonia is involved, also, in several *affections of the eye*. Thus, the corneal ulceration that follows interruption of the trigeminal nerve can be prevented by prior stellectomy; stellectomy after the nerve section permits healing to occur.

Sympathectomy of the eye is protective in other ways also. For example, the severity of the ocular response to systemic bacterial endotoxin in rabbits, involving increased ocular vascular permeability, especially in the iridial portion of the ciliary process, with edema, hemorrhages, and thrombi, can be reduced by extirpation of the superior cervical ganglion. Other responses to systemic endotoxin elsewhere in the body are also suppressed or prevented by sympathetic denervation or α-adrenergic bloating agents.

Other clinical situations in which the sympathetic innervation has been implicated as playing a contributing, or even a critical, role include certain forms of colitis, dermatitis, megacolon, leg ulcers, peripheral vascular disease, postsurgical paralytic ileus, Dupuytren's contracture, and others.

In addition, it appears that SNS significantly influences the response, including resistance of tissues, to antigenic, infectious, irritative, toxic, and even carcinogenic agents. Processes such as allergic manifestations, anaphylaxis, and immune reactions, and the immunobiologic mechanisms that determine whether experimental implants "take" also seem to be under some

sympathetic influence.

Chronic exaggeration of the "normal" sympathetic influence may also be harmful. Thus, reflex regulatory mechanisms would be disturbed by distorted reports from sympathetically bombarded receptors, especially the regulatory chemo- and baroreceptors of the carotid sinus. Exaggerated sympathetic influences on CNS functions, the reticuloendothelial system, fat metabolism, enzyme activity, and endocrine function, and the tendency toward ischemia (due to vasoconstriction) may all be deleterious over long periods.

Further support of this hypothesis of a rather general role of chronic sympathicotonia in disease processes is in the neuropathologic changes observed in the neuronal and glial elements in ganglia removed at surgery in patients with various diseases and at autopsy. The changes seen reflect overstimulation of the ganglion cells, the type of change seen with prolonged experimental preganglionic stimulation.

Development and expression of sympathetic hyperactivity

In this section, a look is taken at factors that (1) contribute to the facilitation and exaggerated activity of sympathetic pathways, (2) sustain the activity over protracted periods, and (3) determine the clinical expression.

The sympathetic division of the ANS, unlike the parasympathetic, is capable of organizing widespread responses of the total organism in which it mobilizes the resources of the body for physical exertion and adaptation to environmental change. It is less well appreciated, however, that the SNS is also capable of considerable local and regional control. The capacity for localization is essential for organization and execution of the total body responses, so that changes in blood flow to each area, for example, can be adjusted according to circumstances in that area.

The local and regional components of the total pattern, especially in the somatic tissues, depends on sensory signals from participating and affected tissues for precise modulation. These continual streams of afferent impulses enter the CNS over segmental pathways and, through appropriate interneuronal connections, including those going to higher centers, influence the sympathetic preganglionic neurons in the spinal cord.

The clinical disturbances described in the foregoing section, which appear to be based on sympathetic hyperactivity, are, I believe, aberrant versions of these local and regional feedback mechanisms.[12] They are triggered, apparently, by patterns of sensory signals that have become "garbled" or "noisy" due to the input from injured, strained, or impaired tissues, or from irritative lesions in nerves and roots; that is, from sites of somatic dysfunction. The CNS, which "reads," not individual reports from this or that receptor, but the total "picture" collectively reported by all the receptors from a given area of the body framework, cannot possibly make an appropriate, adaptive response to conflicting, chaotic, and unintelligible reporting.*

How do these abnormal reflexes become self-sustaining and chronic? At least two factors seem to be implicated. One is the secondary afferent discharge from tissues subjected to the sympathetic bombardment. The other is an enduring increase in central excitability within the cord itself, which has also been shown to be induced by sympathetic hyperactivity[13] as well as other facilitative or sensitizing factors.[13] Either or both of these factors would contribute to a vicious circle of autogenic impulses. Although the initial trauma may not be painful, pain may arise because of the sympathetic discharge (causing ischemia, for example) and the "cross talk," at sites of irritative nerve deformation, between sympathetic postganglionic axons and neighboring unmyelinated "pain" fibers.**

What factors determine clinical expression? One important feature of the reflex responses to aberrant sensory input is that not only are they inappropriate to the situation, but that they are often detrimental to and disruptive of natural processes of recovery and healing. Thus, the SNS apparently makes no significant distinction, for example, between the sensory input from a painful laceration of an extremity and that from a painful joint in the same extremity.[12] Although

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*This situation might be looked upon as "vertigo" at the spinal level. In motion sickness, the reports from the labyrinth, the eyes, the proprioceptors, and other reporting stations may be so contradictory and confused that no appropriate postural and righting reflexes are possible. What results, instead, is excitation of pathways that are not ordinarily involved in maintenance of posture and equilibrium, such as those producing nausea, vomiting, and other violent visceral responses, as well as immobilization. For these reasons, I previously suggested that these disturbances in the cord appeared to be more a matter of segmental "consternation" than facilitation[1].

**Although not part of this review, it is important to point out that nerve deformation sufficient to cause local excitation (or conduction block) would probably also interfere with axonal transport of proteins and other substances between neurons and end-organs, and therefore with their trophic relations[14].

vasoconstriction may be an appropriate response for the laceration, SNS hyperactivity with ischemia is detrimental to a painfully irritated or inflamed joint. The pain from the ischemia heightens the sympathetic discharge. Thus, a vicious circle is set up, intensifying the pathologic condition.

Similarly, if the heart is already impaired by myocardial ischemia, intensified sympathetic discharge can only have a deleterious effect on the heart and on survival.

Other examples of inappropriateness are renal shutdown due to ureteral irritation[15] and the responses of viscera to chilling of overlying (or segmentally related) skin. The sympathetic response to chilling may be such as to predispose to infection or other illness as has been demonstrated in the upper respiratory tract, the intestines, and the kidney. (Presumably, the same pathways are utilized in therapeutic counter-irritation, with hot packs or rubefacients, to improve circulation, or with cold packs to reduce hyperemia and edema.)

Another feature of these abnormal somatosympathetic reflexes is that they produce abnormal synaptic connections that bring about "segmental relationships" not evident in normal activity.[12] As previously stated, "a segment in view is a segment in trouble."[1] Somatic and visceral structures that, in the course of normal body activity or adaptive response patterns, do not have a functional link become clinically coupled only because their innervating neurons are segmentally related. The structures which, in this manner, become reflexly entangled with each other, are adversely affected and the adaptive reflex patterns of these organs and tissues are disrupted. Referred pain of visceral and somatic origin, and the associated phenomena, are an example of dysfunctional segmental coupling. The distribution of referred pain and associated motor and sympathetic (sudomotor and vasomotor) reflexes in the reference zones ("Head's zones") are not related to normal functional patterns. Additionally, the reference zones may be the site of secondary pathologic change, such as in shoulder-hand syndrome after myocardial infarction. Also, the tissues affected may, themselves, produce abnormal afferent discharge, aggravating the sympathetic hyperactivity.

Although most reports have concerned referred pain and associated reflex patterns initiated from visceral structures, the same patterns have had their origin in deep somatic structures, as amply demonstrated by Travell [16] and others. Painful somatic or visceral stimulation elicits reflex activity through sympathetic pathways equally well and the manifestations are virtually the same. Indeed, it may be said that once viscus and soma have become linked in a vicious circle, it no longer matters, from the therapeutic viewpoint, in which of these the vicious circle started. What matters is the interruption of the circle.

Basis of manipulative therapy

In this final section I would like to offer hypotheses that show the relation between the clinical and experimental material that has been summarized here and the mechanisms involved in manipulative therapy. The spinal and supraspinal pathways allow a rich access of somatic afferents to sympathetic neurons. Therefore, when the motion of intervertebral or other joints is even slightly amiss, there will be autonomic effects, with resulting circulatory, metabolic, and visceral repercussions. With time and other adverse factors, these effects probably would increase.

The data that have accumulated, and my observations of clinical osteopathic medicine over a period of years, have led to the following conclusions:[12]

1. The clinical significance of local musculoskeletal dysfunction, particularly when it is in the axial and weight-bearing parts of the skeleton, lies not only in the impairments of motion and pain that may result, but also in its contribution to the sustained sympathetic hyperactivity that is a feature of many syndromes. Like those syndromes, somatic dysfunctions, with their sympathetic concomitants, appear to be aberrations of the somatosympathetic reflexes normally mediated by the spinal cord.

2. The disturbance in the cord is caused by distorted afferent impulse patterns from either (a) affected musculoskeletal tissues, (b) lesions of nerves, roots, and ganglia due to irritation, or both, preventing adaptive, appropriate responses.

3. Manipulative therapy is effective when it reestablishes coherent patterns of afferent input, permitting local reflexes to be an appropriate and well-integrated component of the total, supraspinally directed patterns of activity and adaptive response. The most critical clinical effect is the quieting of sympathetic hyperactivity with its deleterious effects.

4. The proper articular, interosseous, muscular, fascial, and ligamentous adjustments allow the tissues to report in logical proprioceptive patterns, thereby improving afferent input, and also relieve mechanical irritation or deformation of neural structures.

5. The same mechanisms are at work when the viscera produce the main disturbance of the cord and the somatic (musculoskeletal) involvement is secondary (as in referred pain). Manipulative therapy reduces the sympathetic discharge to the structures involved in this mutually detrimental reflex coupling, slowing the vicious

circle.

6. At this stage of medical history and in the foreseeable future, manipulative therapy, directed to the somatic component of disease, remains the only (certainly, the only noninvasive) effective and systematic approach to the management of local sympathetic hyperactivity, common to so many forms of human illness.

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