The Autonomic Nervous System and Pain

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THE TERM "autonomic nervous system" as applied by Langley[1] to the system of neurons supplying the viscera did not by definition include fibers giving rise to the sensation of pain. Only those afferent fibers operating at a reflex level were considered to be autonomic, and other afferent fibers were thought to be somatic. It has become increasingly evident over the years that nerves supplying viscera do contain pain fibers, and the narrower concept of the autonomic system is no longer pertinent. Most of the input from viscera is concerned with the maintenance of the "milieu interior" described by Claude Bernard in the latter part of the nineteenth century; few of these impulses penetrate to consciousness. If pain is felt it is probably because the integrity of some structure is being threatened, for pain is fundamentally a protective mechanism.

Characteristics of Visceral Pain

There is a striking difference between pain sensation originating in viscera and input from somatic sensory nerves. Somatic pain sensation is much more precise in its localization. It is concerned with our relationship to external factors, pleasant or unpleasant. Sight, sound, smell, taste, touch, and pain have a large representation at cortical levels due to the needs of the organism to adjust to the variety of situations necessary for maintenance of life in a complex environment. The peripheral sensory apparatus is developed to a high degree, and pain receptors are of prime importance in this relationship. Visceral pain, on the other hand, is often poorly localized due to the relative paucity of nerve endings and the infrequency of challenging stimuli from the internal environment. Pain, when it is felt, will in general be described as aching, cramping or colicy, squeezing, pulling, and the like, and will be located, in most instances, overlying the general area of the viscera involved.

Another notable difference between the two systems is that many of the stimuli which activate somatic sensory nerves do not elicit pain response when applied to viscera. For example the bowel can be cut or burned in the conscious patient without pain, yet distention will be quite uncomfortable. The intensity of the stimulus applied to autonomic afferents is of significance, but the type of stimulus is even more important. Pain is an adaptive function, and from the standpoint of developmental anatomy, the internal process which was life-threatening during evolution was much more likely to be distention of a viscus resulting from obstruction and not direct injury.

At times the sensation of pain arising from viscera is referred to an area of the body distant from the point where the stimulus originates. In addition to pain, hyperalgesia of the skin and muscle spasm may be noted in the area of referral. These observations led Lennander[2] and Mackenzie,[3] among others, to conclude that afferent impulses from viscera could not ascend directly via their own afferent pathways to the sensorium. It was MacKenzie's belief that all visceral pain was referred. The theory was advanced that impulses from the involved viscus overflowed into pain pathways of the somatic system in the posterior horn of the spinal cord, causing the development of an "irritable focus." Because of the involvement of somatic pain fibers at this locus, the pain was "referred" to the peripheral areas corresponding to the same somatic dermatomes from which the autonomic outflow to the viscera originated.

Angina pectoris is a good example to illustrate this theory, as often the pain experienced is referred to the inner aspect of the left arm.

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Weiss and Davis,[4] among others, lent support to the concept of referred pain by their observation that if the area of referral was made anesthetic by a procaine injection of the hyperalgesic skin, the pain of angina could be abolished. A number of observers have failed to substantiate the effectiveness of superficial anesthesia, particularly when the stimulus increases in intensity. Notable is the work of Theobald[5] on uterine pain following faradic stimulation of the cervix and fundus. The discomfort caused by mild stimulation, referred to the suprapubic area, could be abolished by procaine infiltration of the skin, but as the stimulation increased in intensity, pain always broke through to consciousness despite the anesthetic.

Morley[6] points out that the muscle spasm encountered in intra-abdominal disease usually results reflexly from a direct extension of an inflammatory process to the parietal peritoneum. For example, in acute appendicitis, the first colicy pain is a result of distention of the appendiceal wall, and is mediated by visceral afferents. Later, as the inflammatory process spreads, it involves parietal peritoneum, resulting in tenderness and spasm through irritation of the intercostal nerves innervating the lower right quadrant of the abdomen.

Attractive as the theory of MacKenzie is, it obviously does not explain the entire picture of visceral pain. It is now known that afferent fibers, identical in conduction characteristics to pain fibers elsewhere, travel centrally to the posterior horn from the viscera. Ruch[7] suggests that visceral and cutaneous "pain" afferents converge on cells of secondary afferent neurons in the posterior horn, and it is quite likely that the secondary spinal axons traveling in the spinothalamic tracts carry both visceral and somatic sensation to consciousness. "Thus when impulses of visceral origin reach the cerebral cortex, the interpretation is made which experience has built up—that of a pain arising from cutaneous pain neurons." The theory that all visceral pain is referred has long been discarded, and, according to White,[8] Lennander was misled into thinking that the viscera were insensitive because of the paucity of nerve endings and an absence of overlapping of pain fibers which made accurate localization impossible. White believes that the difference between somatic and autonomic afferent fibers is a quantitative rather than a qualitative one. Stimulation of the central cut ends of splanchnic nerves above the diaphragm has resulted in pain felt unmistakably in the abdomen or back on the side of stimulation. Stimulation of the central cut ends of upper thoracic ganglia has evoked pain in the precordium or chest and back, similar to the pain of angina. The weight of the evidence is conclusive, and no one now doubts the presence of autonomic pain fibers.

Before leaving a discussion of the characteristics of visceral pain it is appropriate to review the role of the autonomic nerves in pain arising from the extremities. Under certain conditions, the smooth muscle of blood vessels can give rise to pain apparently similar in mechanism to that occurring when spasm occurs in the smooth muscle of internal organs. It is a common observation that clamping or puncturing an artery can give rise to the sensation of pain, at times even during otherwise satisfactory spinal anesthesia. We have observed one patient undergoing hysterectomy under spinal anesthesia who complained of a vague pain in the right side of the pelvis throughout the operation. When a retractor which left its imprint on the right external iliac artery was removed, the pain disappeared. Postoperatively, thrombosis of the artery finally resulted in loss of the leg. It has also been noted that patients who have painful phantom limb sensations may have a marked exacerbation of pain when spinal anesthesia is given. One theory suggests that this is due to sudden loss of somatic sensory input, but it may also result from alteration in the caliber of blood vessels, in some way related to the paresis of vasoconstrictor fibers. Migraine headaches are thought to be due to arterial dilation; if so, the stimulus of distention causing the pain correlates with that of visceral pain resulting from distention of a hollow viscus.

Parasympathetic Pain Fibers

Considerably less is known about the role of the parasympathetics in the transmission of pain sensation. The vagus, the most prominent representative of the parasympathetic system, is a mixed motor and sensory nerve. It

does not have separate anterior and posterior nerve roots, characteristic of mixed somatic nerves. According to Larsell[9] the sensory fibers are present in four bundles which are readily distinguishable along much of their course in the solitary tract. Two ganglia along the nerve, the jugular and the nodosum, contain unipolar nerve cells which give rise to sensory fibers. Larsell describes the sensory components of the vagus as: (a) general somatic afferent fibers from cells in the jugular ganglion arising from the skin back of the ear through the auricular nerve; (b) general visceral afferent fibers, originating from cells in the ganglion nodosum, from the lungs, heart, digestive tract, and the mucosa of the pharynx and larynx; (c) special visceral afferent fibers originating from cells in the nodose ganglion from taste buds (in the infant) in the region of the epiglottis.

The sensory innervation of the main body of the larynx other than the mucosa and submucosal tissues properly seems to belong to the somatic system, yet there is evidence that some thoracic structures, notably the esophagus and possibly the bronchi, have pain afferents via the vagus. Morton, Klassen, and Curtis[10] stimulated the bronchial mucosa of the right and left mainstem bronchi and elicited an aching pain referred to the anterior chest wall on the same side, near the sternum, or to the neck within 2 cm. of the midline. They sectioned the vagus below the recurrent laryngeal branch and relieved pain apparently arising from the mucosa of the bronchi in a number of cases of invasive bronchogenic carcinoma. Grimson *et al.*[11] found that stimulation of the vagus above the diaphragm caused patients under spinal anesthesia to complain of "heartburn," and pain was referred to the neck. There is no experimental evidence to suggest that the vagus carries any pain fibers from its distribution below the diaphragm.

The numerous anastomoses of the vagus with the glossopharyngeal and hypoglossal nerves, as well as sympathetic fibers passing through or synapsing in the inferior cervical ganglion, make differentiation of pain afferents even more difficult. In this complex of somatic and autonomic fibers, some of the neuralgias of glossopharyngeal distribution may involve vagal pain afferents. Dandy[12] reported two cases where division of the upper two vagal rootlets was necessary to abolish pain after a rhizotomy of the glossopharyngeal nerve had been done for glossopharyngeal neuralgia. Robson and Bonica[13] suggest that involvement of the vagus can be demonstrated by failure of cocainization of the tonsillar fossa and pharynx to relieve pain arising in the ear, and cite two cases in which section of the anterior half of the upper vagal rootlets brought relief after the glossopharyngeal nerve had been sectioned.

Larsell[9] mentions that visceral afferent fibers for deep sensibility in the head and neck arise from cells in the geniculate ganglion and probably pass along through all branches of the facial nerve, including the chorda tympani. These fibers, forming the intermediate nerve of Wrisberg, have been shown to be involved in a type of neuralgic pain referred to the ear, usually localized deep in the external auditory canal, and also reported as present deep in facial muscles and the throat. White and Sweet[14] presented several cases to support the idea that this nerve is affected in certain cases of atypical facial neuralgia, but commented on the difficulty in distinguishing clinically between involvement of the nervus intermedius, the glossopharyngeus and the vagus. In summary, although the anatomy of sensory input via the cranial portion of the parasympathetics is incomplete, it is reasonable to assume that autonomic pain afferents are as much a part of this system as they are of the thoracolumbar division of the autonomic system. The sacral portion will be discussed in the section on abdominal viscera.

Pain and the Cardiovascular System

Knowledge of the autonomic regulation of blood vessels is of great importance to all anesthesiologists, and for those who are interested in problems of pain control, abnormalities of vasomotor regulation give rise to the most common area in which their special skills may be required.

Leriche[15] wrote, "There is no single act, no slightest organic function, not a mental effort, which is not accompanied by a vasomotor oscillation or sensation, no matter what the level of the point of action. Our lives, *in toto*, are little more than a succession of unconscious

acts of regulation of the vasomotor system. It is the perfectly harmonious interaction of these complex acts which results in our mental and physical equilibrium." A brief review of the distribution of the autonomic innervation of the blood vessels will show that while arteries are the most abundantly supplied with vasomotor fibers, veins[16] and precapillary sphincters[17, 18] are also under nervous system control. There is adequate evidence that parasympathetic and sympathetic efferents play a role in the regulation of blood vessel tone within the head and trunk, but little evidence that parasympathetic control extends to peripheral vessels or to the blood vessels of the extremities except in the distribution of the sacral division.[19] Stimulation of sympathetic nerve fibers to the extremities will produce vasoconstriction and the tone of vessels apparently is the result of the increase or decrease of such sympathetic vasoconstrictor impulses. However, the sensory innervation of these blood vessels is not clearly defined. The afferent fibers bearing information about pain may be somatic in origin, for nerve endings in and near arteries and veins resemble other sensory receptors. Kramer and Todd[20] have demonstrated that the blood vessels of the extremities receive sympathetic fibers at intervals from mixed nerves lying in the vicinity of the vessels. As these postganglionic fibers reach the vessels, they break up into smaller groups of fibers to reach the adventitia and media, and probably the intima. Sheehan[21] describes numbers of Pacinian corpuscles near vessels in the mesentery whose function may be sensory. Woolard's investigations[22] show that terminal nerves may divide, one branch to supply endings to skin, and the other branch to an arteriole. Apart from the presence of nerve endings that may transmit pain sensation from the walls of blood vessels by some as yet undetermined means, alterations in the tone of vessels can cause pain indirectly by affecting the oxygenation of tissue cells. The pain of intermittent claudication undoubtedly is due to the continued use of muscles receiving an inadequate supply of blood, as is that of angina pectoris.

Paravertebral nerve block, by blocking vasoconstriction, may be very helpful in a variety of conditions affecting the blood supply to the extremities. It should be pointed out that peripheral nerve blocks of, *e.g.*, the brachial plexus, anterior and posterior tibial nerves, ulnar nerve, or median nerve, will also block vasoconstrictor fibers. This perhaps should not require mention, but occasionally one meets with objections when planning an analgesic block in a patient with peripheral vascular disease.

The pain of angina pectoris has been the subject of much speculation. The referral of pain to the left shoulder and upper arm or, less frequently, to the right shoulder and neck, often accompanies the precordial pain so typical of myocardial vascular insufficiency. In this discussion it is assumed that sensory afferents from the heart arriving at the dorsal horn of the cord excite adjacent afferent systems from somatic areas of like dermatomal origin. Variations in anatomical development may account for the more unusual referral areas, but the observations of Cohen[23] are of interest in this regard. He observed an instance in which a peripheral focus such as a neuroma in the amputation stump of the left upper extremity in a patient with coronary arteriosclerosis, could, if stimulated, cause an anginal type of pain. Another patient, who had never before experienced referral to his arm, began to notice it in the region of a recent fracture whenever he had an anginal attack. In still another patient a mustard plaster was applied to the inner surface of the right arm, and after counter-irritation was well developed, anginal pain was now referred to the right arm where he had never felt it before. Possible mechanisms for these and other phenomena will be presented in the general discussion section.

In some cases of chronic coronary insufficiency, the so-called "shoulder arm" syndrome develops, and Kennard and Haugen[24] have described painful trigger spots in the upper thorax which occur in quite specific areas and which have a direct relationship to pain of cardiac origin. Injection of procaine into these areas may not only improve function of the arm, but also may alter the degree of anginal pain experienced by the patient. Livingston[25] has discussed the "trigger spot" mechanism, and Travell and Rinzler's[26] early work on relief of cardiac pain was also based on local block of such areas. White, Smithwick and

Simeone,[27] basing their conclusions on a large number of clinical observations, presented a now-generally-accepted schema of the pathway of sympathetic fibers to and from the heart. All cardiac fibers enter or leave the spinal cord through the first to fourth and sometimes the fifth thoracic somatic nerve roots. All pain of cardiac origin can be abolished by anesthetization or section of these dorsal roots bilaterally. Stellate ganglion block will be of temporary help in some instances and, conversely, it has been demonstrated that stimulation of the stellate ganglion may produce anginal pain in all its protean manifestations.[28] It is evident, then, that the syndrome of anginal pain and its referral may result from several sources of irritation, all related to the lower cervical or upper thoracic levels. It may be postulated further, that the referral need not involve only autonomic afferents with an effect on somatic afferents, but may conceivably take place solely on the basis of autonomic pain afferents, thus accounting for some of the more unusual referrals of cardiac pain, particularly those to higher cervical segments when lower cervical areas are unaffected.

Pain from Abdominal Viscera

Hertz,[29] writing in the early 1900's, claimed that visceral pain was produced by abnormal degrees of tension within the intestinal tract. Ryle[30] considered contraction of smooth muscle of any hollow viscus to be an adequate stimulus for visceral pain, and considered the referral phenomena to indicate the presence of an inflammatory process. Bentley[31] demonstrated that during operation for duodenal ulcer under field-block anesthesia direct pressure on the ulcer elicited pain similar to that resulting from pressure on the abdominal wall, and that transfixion of the ulcer by a needle also elicited pain. The pain was no longer felt when the splanchnic nerves were infiltrated with procaine.

These and other observations form the basis for the long-held belief that true visceral pain exists and that spastic contractions in the gastrointestinal tract will mediate pain sensation through its own autonomic afferents. Pain resulting from acute enlargement of an organ like the liver, on the other hand, may be due in part to increased traction on the parietal peritoneum. The same mechanism, that is, stimulation of somatic nerves, may provide the pathway for pain arising from kidney or spleen and such structures as the mesentery. However, it is evident that autonomic afferents transmitting pain from the kidney and ureter have pathways traveling with the sympathetic outflows from the tenth thoracic through the first lumbar dermatomes. Distention of the renal pelvis will not cause pain if the renal plexus has been divided, and the gallbladder, cystic duct and common bile duct are supplied by pain fibers that course primarily in the right splanchnic nerves.[32, 33]

A type of abdominal pain that has received little attention in textbooks is that due to postoperative adhesions. In our pain clinic we have seen patients who give a very accurate description of migrating pain in the small and large intestine that can be explained only by the presence of kinks or adhesions causing temporary distention in the gastrointestinal tract. There is probably a justifiable reluctance on the part of our surgical colleagues either to accept the obvious cause, or to attempt amelioration of pain by operation, because of the tendency for adhesions to re-form. Furthermore, chronic pain of this type seems to occur more frequently in patients who exhibit signs and symptoms of an anxiety state. It is no coincidence that these symptom complexes are indicative of an overactivity in the sympathetic nervous system, and therapy should be directed towards achieving a more relaxed outlook on life and its tension-producing situations. White and Smithwick[34] described the successful relief of pain of this type by splanchnicectomy. Sarnoff, Arrowood, and Chapman[35] reported on the value of differential spinal block with procaine as a diagnostic technique to predict the effectiveness of sympathectomy in the relief of the pain of small bowel adhesions.

The large bowel has its afferent pathways through the second, third, and fourth sacral nerves, as do the bladder and prostate, but presacral neurectomy has not proven to be of particular help in relieving visceral pain from these loci. In the female, the uterus has an afferent nerve supply from both the thoracolumbar outflow and the pelvic parasympa-

thetics. Cleland [36] demonstrated that the sensory supply from the body of the uterus passes centrally through the lowest thoracolumbar sympathetic nerves, and the cervix is known to be supplied by pain afferents by way of the sacral portion of the craniosacral division of the autonomics. Knowledge of this distribution aids in providing pain relief in obstetrics, and presacral neurectomy can effectively relieve the pain of dysmenorrhea.

Discussion

Whenever something happens to disturb man's normal equilibrium, be it mental or physical, a series of adjustments takes place to maintain or re-establish homeostasis. In this series of events the autonomic nervous system plays a very essential role. Vasoconstriction and vasodilation occur to provide an adequate blood supply to a particular organ complex or muscle mass. Pulse rate increases or decreases, respiratory rate increases or decreases, and countless adjustments which we recognize as autonomic functions take place. These adjustments obviously are infinitely complex and involve the entire central nervous system.

If we are to approach an understanding of pain and its role in providing sensory information to an organism, and particularly when pain has become a chronic process which no longer seems to perform a useful function, we should explore possibilities which, though not proven, may aid and not simply confuse the problem of understanding pain mechanisms.

Simply stated, sensory modalities of all types bring information to an organism upon which motor responses can act in an appropriate manner. In very elementary forms of life not much more than a stimulus and a response is required. But very soon in the phylogenetic scale the information from sensory input must have a storage or memory area, in order that the organism can profit from past experience. Coghill,[37] studying *Amblystoma* embryos from the earliest phase of development, identified what he called the "neuropil" as masses of small nerve cells interposed between the sensory and motor components of the salamander brain. He postulated that each incoming pattern of sensory input could diffuse through the neuropil so that the young animal could satisfy its primitive needs by utilizing the experience based on previous actions. Certainly other neurophysiologists who had philosophized on the role of the brain had come to similar ideas of its function, and such little-understood areas of the brain as the association areas, limbic lobe, and reticular formation are now generally considered to perform the functions of the "neuropil" described by Coghill.

Lorente de No's [38] concept of the internuncial pool at spinal-cord level, interposed between the sensory and motor components of simple reflex arcs, and Cajal's [39] description of this area implying a highly complex organization, led other investigators, using much more sophisticated techniques to demonstrate conclusively the interaction between the brain and the cord within this reticulum. It has been shown that a sensory stimulus may be subject to modification as far peripherally as the dorsal horn,[40] and that pre-existing background activity in the internuncial pool or influences reaching the cord from other parts of the central nervous system will condition the motor output resulting from the sensory neurons that are activated. All indications are that the reticular formation plays a very important role in coordinating function at all levels of activity—cerebral, brain stem and spinal cord.

We have found it convenient to view the functional organization of the central nervous system as a vertical arrangement (fig. 1) extending from the cord to the cortex with three longitudinal components: one for sensory input, one for motor outflow, and a "transactional component" between them represented by the reticular formation.[41] The latter embraces what Coghill called the "neuropil" and much more. We do not intend that this viewpoint should deny the usefulness of the concept of levels or centers proposed by Jackson,[42] but rather to extend his concepts to provide new meaning. Nor is this intended to deny the specificity of certain parts of the nervous system, but instead to define the specificity in terms of the functional whole. The concept, we believe, conveys the idea of a dynamic plasticity, wherein sensory input from any part of the nervous system can be accepted or ignored; accentuated or diminished; ascend directly to consciousness or, as in some chronic pain states, become hopelessly short-circuited

in a vicious circle of activity within the complex of short-chain internuncial neurons. It has been a most helpful concept in explaining bizarre patterning of pain, or its persistence long after the usefulness of the original sensory warning has passed. It would explain the referral of anginal pain in the case where Cohen applied a mustard plaster to the right arm, as described earlier in this paper. It helps to explain the part played by the autonomics in cases of causalgia. The pain of causalgia often can be relieved by sympathectomy. In fact, some go so far as to say it is not causalgia if sympathectomy fails to relieve the condition. But if the sympathetic nerve supply to an extremity is removed, and circulation visibly improves, and pain again becomes intolerable, one can only conclude that the autonomic control of blood vessels is only a part of the story. It was Livingston's [25] belief that injury to a somatic nerve exposed sensory fibers to scar compression or some other form of stimulation so that they became a focus of irritation. The sustained barrage of impulses from this focus resulted in a disorder in the internuncial pool within the cord, so that the pattern of excitation was changed and pain continued to be felt. The internuncials, related as they are to sensory and motor neurons, somatic as well as autonomic, now in abnormal activity, caused muscle spasm and vasomotor changes which resulted in new sources of pain input. Thus, as the intensity of this disorder increased, other systems of neurons were brought into the pathologic process. Livingston believed that although the autonomics played an important part in the developing picture it was not sufficient to state that they caused the process, and cure would not occur until the central perturbation of function had subsided. This might be accomplished in a number of ways, and sympathectomy is but one of them.

This hypothesis is the message this discussion hopes to convey. Central disturbance is the essential factor in many chronic pain states, and all involve to some extent somatic and autonomic nervous system functions. Bizarre patternings, nonexplainable by strict interpretation of sensory input, have more meaning if we accept the role of a self-sustaining process located in that "in-between" part of the central nervous system we have called

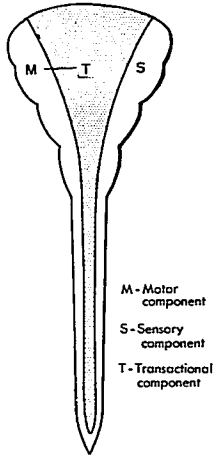

FIG. 1. The hypothetical "vertical" organization of the central nervous system as it relates to transmission and perception of pain.

"the transactional component." Efforts at treatment should be directed toward re-establishing a normal input-output relationship. This often can be accomplished by nerve block, by surgical excision of nerve components, by physiotherapy, by analgesic drugs, by tranquilizers, or by combinations of these. Anesthesiologists will find a challenging and intellectually-stimulating field of medicine if they undertake to treat the unusual pain problem. Their knowledge of analgesic drugs and regional anesthesia is unique among the specialties, and is particularly adapted to this area of medicine that all too often is shunted to one side by other physicians.

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