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Sensory Innervation of the Viscera: Peripheral Basis of Visceral Pain

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> The commonest cause of gastritis—that is to say, an inflamed and irritable stomach—is worry and anxiety. I had it for fifteen years until I read Lenin and other writers who showed me what was wrong with our society and how to cure it. Since then I have needed no magnesia. But these pains may be due to gastric ulcer or even cancer. So it is better to consult a doctor, even though he will probably recommend magnesia.
>
> J. B. S. Haldane (1939)

I. INTRODUCTION

The ability to perceive pain from internal organs is part of the normal sensory repertoire of many animal species including humans. The afferent innervation of the viscera mediates the reflex control of internal organs and forms the peripheral end of the sensory link between the viscera and the brain. If pain can be perceived by the application of certain stimuli to internal organs, it follows that some of the afferent fibers that innervate the viscera must be sensitive to the painful stimuli.

This is the main prediction of Johannes Müller's often misquoted doctrine of specific nerve energies, namely, that the sensitivity of peripheral receptors to particular stimuli determines the general modalities of sensation that can be perceived by an individual. This principle is encapsulated in Müller's statement that "sensation is not the conduction of a quality or state of external bodies to consciousness but the conduction of a quality or a state of our nerves to consciousness, excited by an external cause" (287). Applying Müller's principle to visceral pain, the Russian physiologist Sechenov pointed out that "the existence of sensory nerves in the walls of intestines is being proven by the pains alone which accompany inflammation of the intestinal canal or its inflation by gases" (quoted in Ref. 75).

The existence of sensory receptors that respond to painful stimuli is only a small part of the visceral pain story. Many of the criticisms of the Müller's doctrine of specific nerve energies have been directed against its very extreme interpretation, whereby sensory receptor activity equals perception. The implication of such views is that the entire repertoire of sensory perceptions must be matched on a one to one basis with a similar range of specific sensory receptors. These interpretations play down the role of the central nervous system (CNS) in the modulation of the signals generated in peripheral receptors and do not take into account the fact that the final perception of pain, like that of any other sensation, depends on the central processing of peripheral activity.

Nevertheless, the fact remains that some peripheral receptors must be responsible for the generation of signals that will eventually lead to perception. In the case of visceral pain, this raises a fundamental question about the properties, and in particular about the encoding mechanisms, of the sensory receptors that signal this sensation, i.e., whether there exists a class of visceral sensory receptor concerned only with the signaling of events perceived as painful or whether visceral pain is signaled by the pattern of activity of nonspecific sensory receptors that are also involved in mediating regulatory visceral reflexes. The former interpretation requires the presence in the viscera of specific nociceptors similar to those found in the skin and other somatic structures (421). The latter proposes that low-intensity activation of nonspecific receptors evokes regulatory reflexes or nonpainful sensations, whereas high-intensity activity in the same receptors results in visceral pain. This question has been the subject of considerable debate, and to this day, there is no general agreement on the matter (but see Ref. 67).

This review aims to examine the literature on the afferent innervation of the viscera and to explore the relationship between discharges in visceral sensory receptors and the perception of visceral pain. Two main questions will be addressed: *1*) Which sensory receptors present in a given internal organ could be responsible for the pain sensations evoked from that organ? *2*) Are there separate populations of sensory receptors in internal organs responsible for regulatory reflexes and for the signaling of visceral pain, or are these two functions mediated by a single category of sensory receptor?

The apparent uselessness of many forms of visceral pain has generated numerous debates about its utility to the organism and about the relationship between internal injury and visceral pain. Disagreements about the meaning of some basic concepts, such as visceral noxious stimulation or visceral nociceptors, has often been the main reason for the differences of opinion about the interpretation of experimental data. Not many of the arguments have been satisfactorily resolved; therefore, a critical consideration of these basic concepts is included at the beginning of this review. Of necessity, many of the opinions expressed in this preliminary section are personal, although a survey of the different interpretations existing in the literature is also included.

The main body of the review contains a survey of the sensory innervation of most internal organs. The sensations that can be evoked by the stimulation of each viscus, the afferent innervation of the viscus, and the different kinds of sensory receptors found in the organ are described. In addition, current opinions about the properties of the sensory receptors thought to be mediators of nociceptive messages from each viscus are reviewed and critically discussed. This main section is followed by a discussion on the sensitization of visceral sensory receptors and by some comments on the possible role of receptor sensitization in mediating persisting and inflammatory visceral pain.

There are other aspects of the afferent innervation of internal organs and of visceral pain in general that are not covered by this review. The central mechanisms of visceral pain are not addressed here, and the reader can find information on this topic in other recent reviews (71, 295). The role of visceral afferent fibers in autonomic function and in the regulation of internal organs is only considered indirectly but has been the subject of detailed reviews elsewhere (75, 92, 109, 148, 233, 251, 252, 355, 356, 387, 400).

II. SOME BASIC CONCEPTS

A. What is a Noxious Stimulus?

A noxious stimulus is commonly defined as a stimulus whose intensity is damaging or potentially damaging to the integrity of the tissue. The origin of this concept can be traced to Sherrington (379–381), who used the alternative form *nocuous* to qualify stimuli that threaten immediate harm to the tissue and are capable of evoking pain sensations in the conscious animal. By using the term *nocuous* or *noxious*, Sherrington was trying to avoid calling these stimuli *painful* or *algesic*. Thus he emphasized that "excitants of skin pain have all a certain character in common, namely this, that they be-

come adequate as excitants of pain when they are of such intensity as threatens damage to the skin" (381).

The strength of Sherrington's concept is the removal of pain perception from the definition of the stimuli that can evoke it. It is clearly not possible to apply painful stimuli to animals that cannot feel pain because of anesthesia or decerebration. The use of the term *noxious* bypasses this problem by qualifying as potentially harmful the stimuli that would have evoked pain if the brain had been intact. For the purposes of neurophysiological analysis, the pain system thus becomes a nociceptive system, namely, a neural system that deals with the processing of injury-threatening stimuli.

Sherrington (380) used the term *nocicipient* to describe this neural system, "a term that has the advantage of greater objectivity," but changed it later to the better known *nociceptive* (381). He reserved the use of this term for the description of the motor activity evoked by noxious stimuli in animals devoid of perception by spinal transection or decerebration. The term *pseudaffective reaction* was also introduced by Woodworth and Sherrington (424) to describe the more complex reflexes triggered in these animals by noxious stimuli, including limb, mouth, and jaw movements, turning of the head and neck, vocalization, and transient increases in blood pressure.

Sherrington's definitions of noxious stimulus, nociception, and nociceptive systems also carry with them the seeds of potential trouble. By defining a noxious stimulus as one capable of producing injury and by regarding pain perception as the ultimate product of a nociceptive system, a very close correlation is implied between potential injury and pain. Thus pain becomes "the psychical adjunct of a protective reflex" (381).

Such close correlation between injury and pain is not always evident. It is well known that the emotional state of the subject or the presence of stressful circumstances determines whether a subject feels pain immediately after an injury (74). In these cases it can be argued that the potential for a close correlation between injury and pain is there but that the final perception depends on the central processing of injury-related information. There are other cases however when stimuli that can always produce an injury never evoke pain. For instance, the inhalation of carbon monoxide or the exposure to high doses of radiation are noxious stimuli in the sense that they produce injury and even death, but they evoke no sensations at all. Obviously we do not have a nociceptive system for all kinds of noxious stimuli.

We cannot approach this problem from our current standpoint, and therefore an extension to the strict application of Sherrington's concepts is necessary. The current definition of a noxious stimulus is deep rooted and widespread and should therefore be maintained. However, bearing in mind that not all noxious stimuli are detected by our sensory receptors, we could use the term *nociceptive* to qualify the subset of noxious stimuli capable of evoking pseudaffective reactions and pain. Thus the exposure of the skin to intense heat or to high doses of radiation are both noxious stimuli, but only the former is, in addition, a nociceptive stimulus. The adjective *noxious* qualifies the relationship between the stimulus and the integrity of the organism, whereas the adjective *nociceptive* qualifies the relationship between the stimulus and the nervous system of the subject.

B. What is a Visceral Noxious Stimulus?

The problems discussed above regarding the definition of noxious stimulus are magnified when it comes to the application of this concept to the visceral domain. Visceral pain cannot be evoked from all viscera, and there is often no relationship between internal injury and visceral pain (63). Some viscera, like the liver or the kidneys, are insensitive to all forms of stimulation so that no sensations can be evoked by even the most damaging stimuli. Hollow organs, like the bladder, the colon, or the ureter, are very sensitive to distension of the lumen or inflammation of the mucosa but totally insensitive to cutting or burning stimuli. A report of the International Association for the Study of Pain specifically states that the definition of noxious stimulus as one potentially damaging to the integrity of the tissue does not apply to all forms of visceral pain (342).

This insensitivity of the viscera to many forms of stimulation is very well documented. One of the most dramatic examples was the demonstration by William Harvey to King Charles I that touching the beating heart of the young Viscount Montgomery, who had sustained a large thoracic wound, produced no sensation (see Refs. 234, 236). Less spectacular and more detailed observations of visceral insensitivity to certain damaging stimuli are described in the works of Lennader (215), MacKenzie (232), and Hertz (156).

Cervero (63) has suggested that when studying the neurophysiological mechanisms of visceral pain, a noxious stimulus should be defined not as a stimulus than can produce injury but as a stimulus that can evoke pain. Although this approach has been followed by other authors (295, 297), it can also be argued that having different meanings for noxious stimulus depending on the site of application may contribute to increase, rather than to decrease, confusion.

The proposal put forward in the section IIA to use the word *nociceptive* to qualify the subset of stimuli that can trigger pseudaffective reactions and pain provides a useful alternative for both somatic and visceral stimuli. In the case of visceral sensitivity, nociceptive stimuli are few and restricted to certain internal organs. Many forms of noxious stimulation of the viscera are not nociceptive in the sense that they cannot excite the neural system that triggers pseudaffective reactions or leads to pain sensation. However, other visceral stimuli are both noxious and nociceptive, since they not only threaten the integrity of the tissue but are also detected by the nervous system and are thus capable of evoking reflex activity and pain. Cutting the wall of the small intestine is a noxious stimuli, but it is not nociceptive; overdistension of the bladder is both noxious and nociceptive.

This distinction between noxious and nociceptive stimuli can also help to qualify certain forms of visceral stimulation, like brief distensions of the gut, that may be painful but that are not damaging. The description of such stimuli as nociceptive does not necessarily imply injury to the tissue but, rather, that there are sensory receptors capable of detecting them and evoking pain perception.

C. What is a Nociceptor?

The word *nociceptor*, like nocuous and nociceptive, was also introduced by Sherrington (381). He was studying, in spinalized animals, the motor reflexes evoked by different types of skin stimulation and noticed that the nature and intensity of the stimulus determined the type of reflex evoked by its application. For example, a harmless contact with the skin evoked an extension reflex, but a needle prick to the same area caused a flexion withdrawal reflex. Sherrington (381) concluded that the skin was innervated by different kinds of sense organ, some sensitive to touch and some sensitive to harmful stimuli and produced the words *tangoreceptor* and *nociceptor* to designate these two types of sense organ (381). Both these words were used to describe sensory receptors for whose existence there was, at the time, no direct experimental evidence. Whereas the term *tangoreceptor* has been consigned to history, *nociceptor* has been used ever since to designate a special category of sensory receptor responding exclusively to noxious stimuli.

The earliest direct evidence for the existence of cutaneous nociceptors was provided by Zotterman (428), who recorded the electrical activity of sensory nerves and observed that intense heat stimuli evoked responses in presumably unmyelinated afferent fibers. During the 1960s, the work of Iggo, Perl, and colleagues (37, 55, 164, 165, 322) finally established that there was a category of sensory receptor in the skin, connected to small myelinated and unmyelinated fibers, that responded exclusively to noxious stimuli, a nociceptor in the Sherringtonian sense.

The main features of cutaneous nociceptors have been described as *1*) a high threshold to skin stimulation, *2*) an ability to encode stimuli in the noxious range, and *3*) a lack of background activity in the absence of previous insults to the skin (55a, 323). These features describe well the functional properties of the nociceptors found in the skin and can serve as useful linchpins for a general definition of nociceptor.

The essential attribute of a nociceptor is that it should be able to differentiate noxious from innocuous stimuli. This is achieved by the ability to encode the intensity of a noxious (or nociceptive) stimulus and by not responding to stimuli in the innocuous range. However, the threshold of a nociceptor should be defined in terms of the tissue innervated and not in absolute terms. The actual stimulus intensities that activate nociceptors in different tissues can be very variable and are determined by whether or not a particular stimulus intensity is noxious (or nociceptive) when applied to a specific tissue. Thus nociceptors in the cornea have much lower mechanical thresholds than those of skin nociceptors (27), since low-intensity mechanical stimulation of the cornea is both noxious and nociceptive (178).

The issue of whether or not nociceptors should be silent in the absence of stimulation has generated considerable debate. Cutaneous nociceptors do not have background activity in the absence of a previous stimulation, but after the application of a noxious stimulus, they can sensitize readily and thus develop spontaneous activity (55a, 323). Because of this it has been taken by some that absence of background activity should be a sine qua non property of any nociceptor (234), and criticisms have been raised against putative visceral nociceptors that show any level of background activity, however low (236).

Theoretically, it is not necessary for nociceptors to be silent in the absence of stimulation, since low levels of background activity can be filtered out by the CNS (67). In fact, it has already been demonstrated that low rates of firing of cutaneous nociceptors are insufficient to evoke a sensation and that temporal summation of impulses in nociceptors is necessary for pain perception (228). Therefore, the absence of background activity in nonsensitized nociceptors, while being a characteristic property of cutaneous nociceptors, cannot be used as an absolute condition for the identification of nociceptors in all tissues.

A nociceptor is, therefore, a sensory receptor that responds to and encodes nociceptive stimuli and that does not encode innocuous intensities of stimulation. The actual threshold for activation and the range of intensities encoded by a particular nociceptor are tissue dependent and are determined by the nature of the nociceptive stimulus. Nonsensitized nociceptors in the skin show no background activity in the absence of stimulation, but the presence of low levels of spontaneous activity is not an excluding criterion for putative nociceptors in other locations.

D. Afferent Versus Sensory Innervation of the Viscera

The poor correlation between internal injury and visceral pain and the apparent insensitivity of many viscera to noxious stimuli led some investigators to believe that internal organs lacked afferent nerves. Observations made on patients undergoing abdominal surgery under local or no anesthesia showed that many organs could be cut or burned without evoking any sensation or nociceptive reaction (215, 232). Lennander (215) believed that the viscera lacked innervation, whereas MacKenzie (232) thought that pain in visceral disease arises from the viscus itself via afferent impulses not related to pain. Along the same lines of thought, Morley (276) stated that abdominal pain is due to the spread of the visceral disease to the parietal wall or to branches of somatic nerves, thus supporting the view that viscera lacked a direct sensory innervation.

Anatomic and physiological studies in the first decades of this century demonstrated conclusively that the viscera were innervated by afferent fibers that projected to the CNS via sympathetic and parasympathetic nerves (249). Therefore, the question of the sensitivity of the viscera needs to be approached from the knowledge that all internal organs have an afferent innervation but that the activation of many of these afferent fibers evokes no sensations. Cervero (61, 62, 64) has discussed the conceptual differences between the afferent innervation of internal organs and their sensory innervation. The activation of visceral receptors such as the arterial chemoreceptors, the stretch receptors of the lungs, or the osmoreceptors of the liver evokes no sensations, and therefore, the term *afferent* is the most appropriate to designate their function. On the other hand, subsets of these afferent fibers have the capacity to evoke a sensation, for instance, some of the gut tension receptors, and hence the term *sensory* becomes an adequate qualifier of their function. Thus the sensitivity of a particular viscus depends on whether or not its afferent innervation includes fibers capable of evoking sensations. Some organs, like the liver or the lungs, have only an afferent supply, whereas others, like the ureter or the heart, have nerve fibers with both afferent and sensory functions.

Elements of this proposal can be found in Langley's (209) classification of visceral afferent fibers into autonomic fibers, i.e., those "which give rise to reflexes in autonomic tissues and which are incapable of directly giving rise to sensation" and somatic fibers, i.e., visceral afferent fibers mediating sensation and pain. Because of their sensory role, Langley (209) considered these fibers to he in all similar to the rest of somatic afferents.

Sherrington (379) also drew attention to the functional differences between afferent and sensory visceral fibers. "The impulses . . . from visceral nerves upon the central nervous system appear hardly at all to elicit ordinarily conscious sensations. When abnormally they do so, they seem almost invariably to produce pain as their result. It is as though particular afferent nerves, which usually are not in the strict meaning of the term *sensory nerves* at all, can on occasion become sensory even to the extent of convulsing the whole mind."

E. Sympathetic and Parasympathetic Afferents

The use of the terms *sympathetic* and *parasympathetic* to describe subsets of visceral afferents has been questioned because of the lack of an unequivocal correlation between pathway of projection and functional role. In the early part of this century, the dual afferent innervation of most internal organs was interpreted as an indication that visceral afferents in sympathetic nerves could subserve different functions from those in parasympathetic nerves. Clinical evidence obtained by removing or blocking the sympathetic innervation of internal organs suggested that afferent fibers in these nerves were concerned with the signaling of visceral pain, whereas those projecting in parasympathetic nerves were involved in regulatory autonomic reflexes (271, 348, 416). Current clinical practice is still based on the view that many forms of abdominal visceral pain are mediated by afferent fibers in sympathetic nerves (153, 158), although there are important exceptions to this rule particularly in regard to thoracic and pelvic viscera (255, 337).

Strictly speaking the terms *sympathetic* and *parasympathetic* should be reserved to qualify only the efferent component of autonomic nerves. Visceral afferents should be described by their anatomic, rather than their functional, pathway of projection, i.e., vagal, spinal, splanchnic, pelvic, hypogastric (see Ref. 173 and sect. XII*B*). When referring to whole groups of visceral afferents they should be called visceral afferents "in sympathetic nerves" or "in parasympathetic nerves."

However, the expressions *sympathetic* and *parasympathetic* visceral afferents are frequently used in the literature and provide a very convenient shorthand to the longer and more cumbersome alternatives described above. The use of these terms is justifiable when they are meant to describe generic pathways of projection of groups of visceral afferents without necessarily implying a division of function. Therefore, and taking into account this proviso, the expressions *sympathetic* and *parasympathetic* are used in this review to describe subsets of visceral afferents.

III. THEORIES ABOUT THE PERIPHERAL ENCODING OF NOXIOUS EVENTS

One of the fundamental questions of sensory physiology relates to the mechanisms used by the nervous system to discriminate between the different sensory modalities. For the special senses (vision, hearing, touch, olfaction, and taste), there is general agreement that there are receptor organs in the periphery and pathways in the CNS dealing with modality-specific information. However, there is still some disagreement about the peripheral encoding of nociceptive events, particularly in relation to the possible existence of specific nociceptors in internal organs and to the central mechanisms involved in the signaling of visceral pain states (67).

These questions have remained at the center of the classical controversy between the specificity and pattern interpretations of pain mechanisms. Both theories were originally developed to explain the encoding of noxious events in the periphery, and their main point of controversy has been the existence, or otherwise, of specific nociceptors. However, with the passage of time and the accumulation of new evidence, the positions have moved to discussions about central rather than peripheral mechanisms, something that obviously falls outside the scope of this review. Therefore, only those aspects of the specificity and pattern interpretations relevant to the peripheral encoding of nociceptive events are discussed here.

A. The Specificity Theory

The specificity theory originated as an extension of Müller's doctrine of specific nerve energies and attempted to establish a close correlation between individual sensory structures of the skin and individual sensory modalities. Thus Blix (41) found that the skin could be regarded as a mosaic of sensory spots such that stimulation of each spot evoked a distinct sensory modality of touch, warmth, cold, or pain. Max von Frey (412a) developed this concept further by suggesting that each morphological type of cutaneous sensory receptor was responsible for each of the elementary sensations evoked from the skin. In his view, the sense of pain was mediated by cutaneous afferent fibers without specialized sense organs, i.e., free nerve endings.

Modern electrophysiological studies in animals have clearly demonstrated the presence of distinct categories of cutaneous receptors including one of specific nociceptors (55a, 323). Moreover, microneurographic studies in humans have shown that elementary sensations of touch can be evoked by the stimulation of single afferent fibers connected to low-threshold mechanoreceptors (399) and that microstimulation of small groups of unmyelinated afferent fibers evokes only sensations of pain regardless of the pattern of impulses (228).

As for the viscera, a specificity interpretation of the peripheral encoding of noxious events has been maintained by Cervero (59, 61–64) based on his studies of the afferent innervation of the ureter and the biliary system. Thus he postulated that certain internal organs from which the only sensation that could be evoked is that of pain were innervated by a distinct group of high-threshold afferent fibers connected to receptors functionally similar to cutaneous nociceptors. The fundamental properties of such visceral nociceptors would be their ability to encode only noxious intensities of stimulation and their functional separation from a group of low-threshold visceral receptors concerned mainly with the regulation of internal organs.

B. The Pattern and Intensity Theories

Interpretations of peripheral pain mechanisms based on patterns of impulses have always run in parallel with those based on specific groups of sensory receptors. Two main lines of thought have been developed, known, respectively, as the pattern theory and the intensity theory. The former was presented in some detail in papers by Sinclair, Weddell, and colleagues (212, 382, 383, 413, 414) and states that individual sensations are the product of the temporal and spatial pattern of impulses in nonspecific sensory receptors. The main conclusion is that "activity in a given (afferent) fiber could at one time contribute towards the experience of a sensation of touch and at another towards the experience of pain, cold or warmth" (383). Because of the mounting evidence on the existence of specific sensory receptors in the skin, the pattern theory and its derivatives are nowadays almost totally restricted to central rather than peripheral mechanisms (see discussion in Ref. 46).

The intensity theory is usually traced to Goldschaider (137), who postulated that pain was not a specific sensation but that it resulted from excessive stimulation of touch and temperature receptors. Thus low rates of activity in tactile or thermal receptors evoked touch or temperature sensations, and high levels of activity in any of these receptors evoked pain. The intensity theory requires a central summation mechanism with a sensory threshold, whereby activity below this threshold is felt as nonpainful and activity above it can lead to the perception of pain.

The intensity theory acquired some experimental evidence with the discovery that sensory receptors encoded the intensity of the stimulus using a frequency code (6), which led to the proposal by Nafe (288) that pain resulted from high-frequency discharges in low-threshold receptors. However, the evidence in favor of the existence of specific nociceptors in the skin has confined the intensity-summation theory almost entirely to the visceral domain (167, 173, 234). The basic notion is that specific visceral nociceptors do not exist in the viscera and that all afferent activity leading to regulatory reflexes, nonpainful sensations, and visceral pain is mediated by a homogeneous group of nonspecific receptors that encode a wide range of stimulus intensities in the frequency of their responses. This requires a central decoding system for which several possible mechanisms were proposed (234, 319).

IV. SENSORY INNERVATION OF THE CARDIOVASCULAR SYSTEM

A. Heart

1. Cardiac sensations

It is generally acknowledged that the only sensation that can be elicited from the heart is that of pain (46). Some authors have expressed the view that sensations produced by mechanical events such as premature ventricular contractions and that are felt as palpitations and chest sensations may be due to the activation of cardiac afferents (128). However, this is unlikely for two reasons: *1*) it has been known for a long time that the heart and pericardium are insensitive to touch and other mechanical stimuli (218), and *2*) strong contractions of the heart produce shock waves that are transmitted throughout the chest and neck, where they can activate a variety of low-threshold mechanoreceptors. It is therefore more likely that the sensations associated with mechanical events in the heart are mediated by the

activation of somatic sensory receptors located in the chest wall.

Mechanical stimulation of the visceral pericardium and the heart itself is not painful (7, 218), and inflammatory processes such as acute endocarditis are also painless (311). The most commonly held view is that cardiac pain is produced by myocardial ischemia. However, the link between myocardial ischemia and cardiac pain is neither strong nor unequivocal (234), for cardiac pain can occur in the absence of ischemia, and conversely, episodes of myocardial ischemia can be painless.

Cardiac pain is known as angor pectoris or angina (meaning strangling, rather than pain), which describes its main characteristics: a feeling of tightness and constriction across the chest producing a strangling or crushing sensation (46). The pain often starts retrosternally and radiates to the left or both arms, to the neck and jaw, or to all of these areas.

The link between myocardial ischemia and cardiac pain was proposed by Sutton and Lueth (391) and White et al. (418). These authors produced controlled constrictions of the coronary arteries in conscious dogs and reported that the animals showed signs of severe pain a few seconds after coronary occlusion. Similar results were reported by Brown (52) using lightly anesthetized cats in which pseudaffective reactions were evoked by temporary coronary occlusion.

An alternative mechanism for cardiac pain was proposed by Martin and Gorham (241). They studied pain reactions in dogs following manipulations of the coronary arteries and reported that pain could be elicited by stretching the arteries in ways that did not alter coronary blood flow. They concluded that stretch of the coronary arteries rather than myocardial ischemia could be responsible for cardiac pain, a view recently supported by Malliani and Lombardi (235).

A proportion of patients with objective signs of severe ischemic heart disease do not experience angina pain. This absence of pain is usually referred to as silent or asymptomatic myocardial ischemia (90) and may be due to the destruction of nerve endings following myocardial infarction or to neuropathic alterations of peripheral nerves induced by a concomitant disease such as diabetes (4). It has also been suggested that the location of the nerve endings that signal cardiac ischemia can be important particularly when the ischemic area is restricted to subendocardial regions that do not appear to have a sympathetic afferent innervation (266).

On the other hand, extracardiac factors may also be important. Procacci et al. (330) have reported higher pain thresholds in patients with silent myocardial infarction. This has been explored in detail by Droste et al. (114), who demonstrated that patients with asymptomatic myocardial ischemia had significantly higher somatic pain thresholds than patients with anginal pain. They concluded that general inhibition of pain sensation, perhaps involving endogenous opioids, could be responsible for silent myocardial ischemia rather than a purely cardiac mechanism.

There is also a group of patients with angina pectoris in which exercise testing shows cardiac abnormalities, but coronary angiograms are normal. This condition, referred to as syndrome X, is a heterogeneous disorder in which alterations of myocardial metabolism probably play an important role. However, abnormalities of cardiac sensation may also be important. It has been reported that patients with syndrome X that were undergoing routine cardiac catheterization experienced pain sensation similar to that of which they had previously complained when the tip of the catheter touched the wall of the right atrium (374). Other parts of the heart such as the inferior vena cava, the right ventricle, pulmonary artery, and coronary sinus were not sensitive. Therefore, altered cardiac sensation whereby pain is evoked by changes in right atrial pressure during exercise could account for the anginal pain of these patients.

2. *Sensory innervation of the heart*

The heart has a dual afferent nerve supply mediated by the vagal and sympathetic nerves. Vagal afferent fibers have their cell bodies in the nodose ganglia and their central projections reach the brain stem, whereas afferents in sympathetic nerves have their cell bodies in the first three or four thoracic dorsal root ganglia and project to the lower cervical and upper thoracic spinal cord (236). The pericardium is innervated by vagal and sympathetic afferents and, additionally, by afferents running in the phrenic nerve (190).

In addition to these primary afferent fibers projecting to the CNS, there is also some electrophysiological evidence for the existence of short afferent fibers with cell bodies in the heart or in cardiac nerves and with centripetal projections that terminate in the stellate ganglion (48). These short afferents are presumably not involved in cardiac sensation but could mediate peripherally contained sympathetic reflexes similar to those of the enteric nervous system of the gut (181).

I) VAGAL AFFERENT FIBERS. Vagal afferent fibers innervating the heart are usually classified according to location (atrial or ventricular) and fiber type (myelinated or unmyelinated) (92, 148, 236, 396).

Atrial receptors connected to myelinated afferent fibers can be subclassified into several groups depending on their discharge properties (148, 313). These receptors are mechanically sensitive and respond to the stretch caused by changes in atrial volume. Their activation triggers a variety of regulatory reflexes that control blood volume (148).

Atrial receptors connected to unmyelinated fibers also respond to stretch, but with a higher threshold, and are often inactive at normal atrial pressures (93). They are mainly chemosensitive responding to veratridine, capsaicin, and phenyl diguanide. Activation of these receptors seems to be concerned with regulatory processes at high levels of atrial pressure (148).

The vagal afferent innervation of the ventricles is mainly mediated by unmyelinated fibers. These receptors are both mechano- and chemosensitive, and their activation appears to lead to inhibitory cardiovascular reflexes (236, 396).

Vagal chemosensitive afferents with receptor sites in the atria and the ventricles are not only excited by chemicals such as capsaicin and bradykinin but also respond to myocardial ischemia induced by coronary artery occlusion (92, 396). Because of these properties, it could be argued that they play a role in mediating anginal pain. However, it has been suggested that this is not the case for a number of reasons. First, intrapericardial injections in conscious dogs of nicotine, which excites vagal chemoreceptors, produces a vagally mediated depressor response but no signs of pain (384). Also, Kaufman et al. (177) and Clozel et al. (86) have argued that the role of vagal chemoreceptors is to mediate the coronary vasodilation that can be observed following myocardial ischemia. They speculate that during periods of coronary underperfusion ischemic stimulation of these chemosensitive afferents evokes a reflex dilatation of the coronary circulation that supplements the dilatation dependent on autoregulation (86).

II) SYMPATHETIC AFFERENT FIBERS. Afferent fibers in sympathetic nerves are also connected to mechano- and chemoreceptors in the heart and, like vagal afferents, can be myelinated or unmyelinated (92, 148, 233, 236).

Myelinated sympathetic afferents have mechanically sensitive receptor sites in the atria and ventricles (21, 53, 238, 409) and in the thoracic vessels (223, 237, 307, 403). The latter can signal changes in pulmonary or systemic blood pressure and thus trigger regulatory reflexes. Mechanoreceptors in the ventricles are also sensitive to chemicals such as bradykinin and to myocardial ischemia produced by coronary artery occlusion (395). The response properties of these receptors suggest that they can signal sudden changes in cardiovascular performance (92); however, they seem poorly designed to provide detailed and exact information about the mechanical events of the normal cardiac cycle.

All authors agree that unmyelinated sympathetic afferents are chemosensitive, but whether they are also mechanosensitive seems to be open to debate. Coleridge and Coleridge (92) and Baker et al. (21) divide the sympathetic afferent innervation of the heart into a large group of mechanically and chemically sensitive afferents (mostly myelinated) and a smaller group of purely chemosensitive afferents (mostly unmyelinated). Mechanically insensitive chemoreceptors with unmyelinated afferent fibers had previously been described by Uchida et al. (404) and Uchida and Murao (405–408).

In contrast, Casati et al. (58) have not found pure chemosensitive cardiac receptors connected to sympathetic unmyelinated fibers. They report that all chemosensitive receptors have some degree of mechanosensitivity, however small. In agreement with the other groups, they report vigorous responses of this type of receptors to coronary occlusion, ventricular fibrillation, and intracoronary administration of bradykinin (58, 222).

3. *Peripheral mechanisms of cardiac pain*

It is generally accepted that cardiac pain is mediated by the activation of afferents in sympathetic nerves (46) and that excitation of cardiac vagal afferents evokes no sensation (318, 319). Pseudaffective reactions in animals triggered by coronary occlusion are not abolished by vagotomy but disappear after thoracic sympathectomy (52, 418). Although no longer acceptable methods of treatment, thoracic sympathectomy, section of thoracic dorsal roots, and destruction of upper thoracic dorsal root ganglia have been used in the past as effective treatments for angina (155, 417).

Some authors still propose a role for vagal afferents in cardiac pain. For instance, it has been suggested that vagal afferents can mediate the anginal pain referred to the neck and the sensations of dyspnea that have been observed in sympathectomized patients (234, 236). Others (128, 337) have suggested an indirect role whereby vagal impulses modulate the transmission of sympathetically mediated nociceptive signals in the spinal cord. The case for a role of vagal afferents in cardiac pain has been discussed at length by Meller and Gebhart (255).

There are two fundamentally different views in the literature regarding the way in which cardiac sensory receptors signal anginal pain. One interpretation is based on the existence of cardiac nociceptors specifically activated by myocardial ischemia. The alternative view proposes a functionally homogeneous population of nonspecific receptors and a CNS mechanism that decodes their patterns of impulses.

The existence of specific cardiac nociceptors was suggested by the findings of Uchida and co-workers (404–408) and was proposed by the Coleridges and colleagues (21, 92). Cardiac nociceptors should not be activated by the mechanical events of the normal cardiac cycle but should be very sensitive to the chemicals known to be released by the ischemic myocardium, such as bradykinin (180). Their receptive fields should be widely distributed throughout the ventricles, and they should have little or no spontaneous activity in the absence of stimulation.

Baker et al. (21) claim to have found such a group of sensory receptors. They described a small population of chemosensitive receptors whose endings were mostly in the ventricles. The majority had unmyelinated fibers, and a few were connected to small myelinated afferents. They were insensitive to light touch, and virtually none of them fired in phase with the cardiac rhythm. Even large increases in ventricular pressure had little effect on impulse frequency. However, they were all very sensitive to bradykinin applied locally or injected into the left atrium.

In the same study, Baker et al. (21) described that the responses of low-threshold mechanoreceptors connected to sympathetic afferents were also greatly increased by the administration of bradykinin. They accepted the possibility that this increased responsiveness

could contribute to the sensation of cardiac pain and conceded that their cardiac nociceptors may not have an exclusive role in the signaling of ischemic pain.

The existence of specific cardiac nociceptors has been vigorously denied by Malliani and co-workers (58, 233-236). Casati et al. (58) recorded from cardiac receptors connected to sympathetic unmyelinated afferent fibers and concluded that they were all mechanosensitive and capable of responding to normal mechanical events in the ventricles. Lombardi et al. (222) argued that this group of receptors was not specific nociceptors but nonspecific sensory endings that could respond to a variety of stimulus intensities from innocuous to noxious. They proposed an "intensity" mechanism for the encoding of cardiac pain so that "when sufficient levels of afferent impulses are reached and an appropriate activation of the central ascending pathways is established, a breakthrough may occur giving rise to the conscious perception of pain" (235).

Malliani's objections to the existence of specific cardiac nociceptors are based on the observations that these receptors appear to have some spontaneous activity and that they are sensitive to the mechanical events of the normal cardiac cycle. However, examination of the original data shows that the levels of background activity reported in these afferents are extremely low (less than one impulse per second) and that their mechanosensitivity consists of not more than a single action potential per cardiac cycle and not even in all cardiac cycles. This contrasts with the more vigorous mechanosensitivity of the myelinated afferents and goes some way to explain the differences of opinion between Casati et al. (58) and Baker et al. (21).

A new twist in the story occurred as a consequence of another study from Malliani's laboratory. Pagani et al. (312) tried to reproduce the observations of Guzman et al. (142), who had reported pseudaffective pain reactions in lightly anesthetized dogs and cats following the injection of bradykinin into the coronary circulation. Pagani et al. (312) confirmed the presence of such reactions in conscious dogs when the animals were examined during the first week after surgery but were unable to observe signs of pain when they injected bradykinin into the coronary arteries of the same animals after they had made a full recovery. Although tachyphylaxis to bradykinin is known to occur, Pagani et al. (312) concluded that intracoronary injections of bradykinin in normal healthy animals were not painful.

This not only appeared to deny the existence of bradykinin-sensitive specific cardiac nociceptors but also called into question an intensity encoding by nonspecific afferents which would have also been maximally excited by the intracoronary injections of bradykinin. As a result, Malliani (234) proposed a different mechanism for the encoding of cardiac pain, this time also taking into account central mechanisms.

He suggested that when the activation of nonspecific afferents is widely and homogeneously distributed, as in the case of bradykinin injections or during exercise, central inhibitory modulations will prevent the onset of pain. However, extreme excitation of a spatially restricted population of these afferents, as during a myocardial infarction, will induce pain.

A similar interpretation based on the CNS decoding of a spatiotemporal code in nonspecific afferents has been put forward by Paintal (319). He suggested that during moderate or severe exercise most ventricular mechanoreceptors are activated but that this is not painful because of inhibitory inputs to the CNS generated in muscles and joints by the exercise. However, when the same ventricular receptors are activated at rest by ischemia in the absence of the inhibitory "exercise inputs," then anginal pain is felt.

B. Blood Vessels

1. Arteries

Pain can be evoked by mechanical stimulation of the arteries. Patients undergoing arterial punctures complain of dull and aching pain of a particularly unpleasant character similar to deep musculoskeletal pain (25). Often these sensations are accompanied by autonomic reactions such as nausea, sweating, or even fainting. As mentioned in section IV*A1*, stretch of the coronary arteries has been claimed to be an effective stimulus for the triggering of anginal pain.

Intra-arterial injections of irritants in lightly anesthetized animals result in pseudaffective reactions indicative of pain (272). These reactions can be evoked from all arteries, but according to Moore and Singleton (273), the arteries in the extremities are more sensitive to pain than those supplying the viscera. The afferent fibers responsible for these reactions run in spinal and sympathetic nerves and not in parasympathetic nerves such as the vagus.

Arteries receive their innervation via a perivascular plexus that runs in the adventitia of the vessels (220). Many unmyelinated nerve endings, some of them presumably sensory, can be found there, and it has been proposed that these endings are the sensory receptors responsible for the transmission of nociceptive signals (219). In fact, Lim et al. (220) have proposed that most forms of visceral pain result from the activation of these periarterial receptors by the localized release of substances such as bradykinin during visceral stimulation. The properties of some afferent fibers in the lumbar sympathetic nerves of cats, with mechanosensitive endings in the aorta and inferior mesenteric artery, have been reported by Bahns et al. (19).

2. Veins

There have been some differences of opinion as to whether or not veins are sensitive to pain. The classical view is that veins are not mechanosensitive and that the pain of venipuncture is entirely due to the stimulation of cutaneous nociceptors (25, 218). However, more recently it has been shown that veins are innervated by slowly adapting and rapidly adapting mechanoreceptors connected to small myelinated afferent fibers and responding to stretch and to direct mechanical stimulation of the vessel (101). The role of these afferent fibers in pain sensation or in the reflex regulation of venous blood flow remains poorly understood.

With the use of psychophysical methods, it has also been claimed that pain can be evoked from human veins by cold stimuli (130, 183) and that this sensation is mediated by polymodal nociceptors connected to small myelinated afferent fibers (16, 17, 184). Again, very little direct information is available on the functional properties of these cold-sensitive nociceptors in peripheral veins.

3. Vascular mechanisms of headache

A mention must be made here of the fact that one putative cause of migraine and other forms of vascular headache is the activation of sensory afferents innervating cranial vessels. Anatomic and clinical evidence supports such a role for cranial vascular afferents in headache (102, 282, 283); however, the precise mechanisms by which stimulation of these afferents triggers a headache and the properties of the vascular receptors involved are not fully understood. Factors outside simple mechanical or chemical events in cranial vessels are also thought to play an important role in the development of migraine. A full discussion of all the mechanisms implicated in vascular headache is outside the scope of this review.

V. SENSORY INNERVATION OF THE RESPIRATORY SYSTEM

A. Sensations From the Respiratory System

The only sensations that can be evoked by direct stimulation of respiratory afferent fibers are those of pain and discomfort. The nonpainful sensations that can be felt in association with respiratory functions are mediated by the activation of sensory receptors outside the respiratory system. For instance, human subjects are aware of the degree of distension of the lungs, but the sensation originates from proprioceptors in the chest wall (124). Also, sensations of breath-holding and resistance to breathing depend on the mechanical activity of the diaphragm and persist after bilateral vagal blockade (141).

Irritation of the larynx and upper respiratory tract produces sensations of rawness and burning (319, 420). These unpleasant sensations are triggered by the inhalation of irritants, by mechanical contact (i.e., endobronchial and endotracheal intubations), and by acute inflammation of the mucosa of the airways (124). The sensations are felt retrosternally and are usually restricted to the midthoracic region. On the other hand, constriction of the bronchi during acute asthma attacks produces general sensations of tightness of the chest and breathlessness. The visceral afferent origin of these sensations is indicated by the observation that they are relieved by bilateral vagal blockade (141).

The lung and the visceral pleura are usually regarded as being insensitive to pain. The passage of a needle through the lung for biopsy purposes produces no sensation, and extensive traumatic damage to the parenchyma of the lungs is also painless (46, 218). Lung cancer does not provoke pain until the parietal pleura or the bronchi are affected. In a small number of patients, lung cancer can cause pain referred to the face by way of a hypothetical mechanism that may involve vagal afferents (38). On the other hand, the sensations of breathlessness during exercise and of dyspnea (painful or difficult breathing) appear to be mediated by the activation of sensory receptors in the lungs (319). Pulmonary congestion and edema trigger these sensations by increasing the pressure around the alveoli and reducing gas exchange between the pulmonary capillaries and the alveoli (317, 318, 319). However, there is no direct evidence showing that the sensation of dyspnea is mediated exclusively by the activation of afferent fibers in the lungs.

B. Sensory Innervation of the Lungs and Airways

The lungs and the tracheobronchial tree are innervated by afferent fibers running in vagal and sympathetic nerves. However, virtually all the available information about the properties of respiratory afferents comes from studies of vagal afferent fibers.

1. Vagal afferent fibers

Vagal afferent fibers innervating the lungs and bronchi have their cell bodies in the jugular and nodose ganglia (46, 205). Those supplying the trachea have their cell bodies mainly in the nodose ganglion and less frequently in the jugular ganglion (205). Vagal afferent fibers reach the lungs via direct branches of the thoracic vagus and the trachea, particularly its upper region, via the recurrent laryngeal nerve.

There are numerous electrophysiological studies of respiratory afferents in the vagus nerve. Three main groups of sensory receptors in the lungs and airways have been identified in several animal species according to their functional properties and to the type of afferent fiber to which they are connected (29, 124, 317-319, 355, 356, 419, 420).

1) SLOWLY ADAPTING STRETCH RECEPTORS. These are mechanoreceptors connected to small myelinated afferent fibers. They respond to inflation of the lungs

and are thought to be located in the smooth muscle of the airways, particularly in the extrapulmonary and large intrapulmonary bronchi. These receptors are responsible for the Hering-Breuer reflex, that is, the inhibition of inspiratory activity during lung inflation that determines basic respiratory patterns (124, 185, 317-319, 355, 356, 419, 420). Although primarily mechanosensitive, they have some responsiveness to temperature (136) and chemicals such as histamine, acetylcholine, and CO_2 (318). However, these responses are probably mediated by the actions of the chemicals on the smooth muscle of the airways (420).

II) RAPIDLY ADAPTING STRETCH RECEPTORS. These receptors are also known as "deflation receptors," "cough receptors," and, most commonly, "irritant receptors." They are located in the lung parenchyma, the bronchioles, and the distal bronchi and are connected to small myelinated afferent fibers (124, 185, 265, 317-319, 355, 356, 369, 419, 420). They are mechanoreceptors that respond with irregular and rapidly adapting discharges to lung deflation, to large deformations of the airways, to gentle touch of the inner surface of the bronchi, and, in particular, to the inhalation of dusts and irritants. These properties suggest that they may be located in the mucosa of the airways. Irritant receptors are also excited by a number of chemical mediators such as serotonin, histamine, prostaglandins, and acetylcholine administered either as aerosols or intravenously (318, 353).

Irritant receptors are involved in the triggering of the cough reflex (189) and of reflexes associated with coughing, including bronchoconstriction and mucus secretion (327, 365, 427). In addition, they may play a role in the signaling of bronchopulmonary pain.

III) J-RECEPTORS. The third group of respiratory sensory receptors are connected to unmyelinated afferent fibers and are often described as C-fiber receptors (124, 355, 356, 419, 420). The term *J-receptors* was coined by Paintal (315), who studied pulmonary receptors at the alveolar level and suggested that they were located next to the pulmonary capillaries (juxtapulmonary capillary receptors or J-receptors). The authors who question the exclusive alveolar location of C-fiber receptors divide this group into two types called pulmonary and bronchial according to their location (355, 356, 419, 420) and state that the functional properties of the two types are broadly similar.

C-fiber receptors (or J-receptors) are mainly chemosensitive, although they can also be activated by mechanical stimuli. They respond to large inflations or deflations of the lungs and to a variety of chemicals such as bradykinin, prostaglandins, serotonin, histamine, acetylcholine, CO_2, phenyl diguanide, capsaicin, nicotine, lobeline, and others (94, 106, 318, 319, 326, 355, 356, 419, 420). They are also sensitive to pulmonary congestion and edema presumably as a consequence of the increase in interstitial volume produced by increased pulmonary capillary pressure (315, 317, 319, 339).

The C-fiber receptors are also involved in the triggering of the cough reflex (189) and a number of reflexes associated with defensive respiratory responses such as bronchoconstriction and mucus secretion (420). In addition, it has been suggested that they play an important role in the generation of dyspneic sensations during pulmonary edema (317, 319).

2. *Sympathetic afferent fibers*

There is virtually no information on the properties of the sympathetic afferent fibers that innervate the lungs and airways. These fibers are less numerous than their vagal counterparts and reach the upper thoracic spinal cord via the thoracic sympathetic chain (46, 205). An electrophysiological study by Kostreva et al. (191) reported the properties of some small myelinated sympathetic afferents responding, with slowly adapting discharges, to changes in transpulmonary pressure and to probing the lung parenchyma and the lumen of pulmonary veins and arteries. The functional significance of these afferents and their sensory role, if any, are obscure.

C. *Peripheral Mechanisms of Pain From the Respiratory System*

Two kinds of painful sensation can be evoked from the respiratory system: a burning retrosternal sensation due to the irritation of the airways and the sensation of dyspnea due to pulmonary congestion.

There is general, although not universal, agreement that pain due to irritation of the airways is due to the activation of the rapidly adapting stretch receptors also known as irritant receptors (124, 189, 355, 356, 419, 420). Because of their suggested intraepithelial location in the mucosa of the airways and their sensitivity to inhaled dusts and irritants, irritant receptors seem to be good candidates for the signaling of upper respiratory pain. However, it has been pointed out that hyperventilation excites irritant receptors to a high degree, yet this procedure does not evoke painful sensations (317, 319). Therefore, it could be that activation of irritant receptors is not sufficient to evoke upper respiratory pain but that summation at the periphery and central modulation of the message are necessary to trigger painful sensations.

Paintal (317, 319) has vigorously maintained that the sensation of dyspnea produced by pulmonary congestion is due to the stimulation of J-receptors (C-fiber receptors). The mechanism proposed for the activation of J-receptors is the increase in interstitial pressure due to the edema caused by the raise in pulmonary capillary pressure. This leads to dyspnea and breathlessness and, secondarily, to the triggering of the cough reflex. Paintal (319) has suggested that, in addition, general sensations of muscle weakness are evoked by the activation of J-receptors.

Because J-receptors can also be activated by normal increases in pulmonary pressure during exercise, Paintal (319) has put forward a hypothesis to explain why exercise does not normally evoke dyspneic pain. He suggests that inputs to the CNS from sensory receptors in the muscles and joints during exercise can block the sensory actions of J-receptors at central level. However, when J-receptors are activated at rest by pulmonary congestion and edema, then the lack of inhibitory "exercise inputs" results in the triggering of dyspneic pain (319).

Paintal's (319) interpretation is based on a central modulatory mechanism for the triggering of visceral pain and on the existence of visceral receptors that are activated by both normal and abnormal stimuli. According to this interpretation, J-receptors are not specific nociceptors but nonspecific sensory receptors that can trigger reflex actions when activated by exercise and pain when activated by pulmonary congestion.

VI. SENSORY INNERVATION OF THE GASTROINTESTINAL SYSTEM

A. *Esophagus*

1. *Sensations from the esophagus*

A number of nonpainful sensations can be evoked from the esophagus, particularly during swallowing (64, 156, 321). These include thermal sensations produced by drinking hot or cold fluids and mild sensations of distension evoked by the passage of food or during belching. An important characteristic of these sensations is their short duration. If the originating stimuli persist, they become first unpleasant, then painful (312).

Pain can be evoked from the esophagus by irritation of the mucosa, by distension of the lumen, and by intense contraction of the muscle layers. The most common form of mucosal irritation is produced by gastroesophageal reflux (46, 347). However, the fact that some reflux occurs in normal subjects in the absence of pain indicates that factors additional to the contact of the esophageal mucosa with the contents of the stomach must play a role in the genesis of the pain (347).

Motility disorders such as spasms and intense peristaltic contractions are also painful (46, 76, 347). The latter can be associated with the clearing of esophageal obstructions or occur spontaneously in the absence of a food bolus. Distension of the esophagus can also evoke painful sensations (156, 321). In humans, distensions above 40–45 mmHg applied for more than 10 s are perceived as painful (221). The belching of large amounts of gas, for instance, after the ingestion of carbonated beverages, can also evoke unpleasant sensations (76, 347).

Esophageal pain, often described as "heartburn," is usually retrosternal (232) and is commonly referred to the suprasternal notch, to the anterior chest wall and, less frequently, to the back (46, 328). Because of this pattern of referral, esophageal pain can often be mistaken by cardiac pain (76). The similarities between esophageal and cardiac pain suggest that the central organization of the afferent inputs from both organs share a common sensory representation.

2. *Sensory innervation of the esophagus*

The esophagus is innervated by afferent fibers running in the vagus nerve and in sympathetic pathways (80, 81, 231). Vagal afferent fibers have their cell bodies in the nodose ganglion, whereas those running in sympathetic pathways have their cell bodies in the dorsal root ganglia of the thoracic and upper lumbar segments. It is generally acknowledged that esophageal pain is mediated by the sympathetic innervation of the esophagus. However, vagal afferents are thought to contribute to other nonpainful esophageal sensations (12).

I) VAGAL AFFERENT FIBERS. Several studies have reported the functional properties of vagal afferent fibers from the esophagus of various animal species including rat, ferret, rabbit, dog, sheep, cat, and opossum (9, 15, 77, 84, 120, 122, 123, 151, 250, 357, 371). Two types of sensory receptor have been described: tension receptors and mucosal receptors.

Tension receptors have low levels of background activity and respond with slowly adapting discharges to imposed distensions of the esophagus. They are connected to small myelinated and unmyelinated afferent fibers and are thought to be located in series with the muscle layers of the esophagus. They discharge in phase with peristaltic movements of the esophagus and with the pressure changes imposed by respiratory movements.

A detailed quantitative study of vagal tension receptors in the esophagus of the opossum (371) has shown that these receptors have very low mechanical thresholds of ~10 mmHg and encode pressure changes in the range of 10–70 mmHg. Their maximum discharge rates at saturation pressure are between 45 and 60 impulses/s. These low-threshold mechanoreceptors respond to systemic injections of bradykinin, but this sensitivity appears to be secondary to contractions of the smooth muscle evoked by the peptide (373). Because of their response properties, vagal tension receptors are thought to be concerned mainly with the regulation of esophageal motility (12).

Mucosal receptors are connected to small myelinated fibers and respond with rapidly adapting bursts to light stroking of the esophageal mucosa and to the application of some chemicals including HCl, NaOH, and hypertonic NaCl. In addition, some mucosal receptors respond to temperature changes in the range of 10–50°C (120, 251). Mucosal receptors are well suited to detect the temperature of the food and drink as well as low levels of distension and the presence of gastroesophageal reflux (12).

II) SYMPATHETIC AFFERENT FIBERS. There are very few reports of esophageal afferent fibers running in sympathetic nerves. A study by Clerc and Mei (83) describes the responses of muscular and serosal receptors

connected to spinal afferents with cell bodies in the lower thoracic dorsal root ganglia of the cat. Their functional responses are described as being similar to those of the receptors connected to vagal afferent fibers but with higher thresholds for activation.

A comprehensive examination of esophageal mechanosensitive afferents running in the thoracic sympathetic nerves of the opossum has been published by Sengupta et al. (372). This study describes two types of mechanoreceptor connected to small myelinated and unmyelinated afferent fibers: *1*) "wide dynamic range" mechanonociceptors (~60% of the sample) and 2) "high-threshold" mechanonociceptors (~40% of the sample).

The first group of tension receptors have low thresholds to esophageal distension (~3 mmHg) and encode pressure stimuli monotonically in the range of 3-120 mmHg. Their maximum discharges at saturation pressure are of ~20 impulses/s. These receptors also respond to normal esophageal peristaltic contractions.

The second group of receptors have higher threshold to distension (~30 mmHg) and, like the previous group, encode pressure stimuli of up to 120 mmHg. They do not respond to normal peristalsis of the esophagus, but their maximum discharges at saturation pressure are similar to those of the previous group. In a separate study, Sengupta et al. (373) have also shown that both types of mechanonociceptor are activated by the systemic administration of bradykinin and that the mechanism of action involves a direct effect of the peptide on a B_2-receptor subtype on the fiber endings.

3. Esophageal pain

The series of studies by Sengupta and co-workers (371-373) on the sensory innervation of the esophagus has contributed greatly to our knowledge about possible mechanisms of esophageal pain. It seems clear that the main role of the low-threshold receptors connected to vagal afferent fibers is the control of esophageal motility and the triggering of regulatory reflexes concerned with the protection of the mucosa. On the other hand, the sympathetic afferent innervation contains two distinct types of receptors capable of encoding esophageal mechanical events in the noxious range and thus potentially concerned with the signaling of esophageal pain.

One possible role for the intensity-encoding mechanonociceptors would be the triggering of sensations of esophageal distension that are not painful at low pressure levels but that become progressively uncomfortable at higher intensities. A central summation mechanism would operate to add an unpleasant character to sensations of esophageal distension of increasing intensities. As for the high-threshold receptors, they could be involved in the triggering of acute esophageal pain evoked by intense mechanical activity of the esophagus or by spasms and contractures due to obstructions in the lumen. The important contributions of the studies of Sengupta and co-workers (371-373) are the clear demonstration that intensity-encoding and high-threshold receptors coexist in the same viscus and that both types of sensory receptor must therefore have a role in the processing of visceral nociceptive events.

B. Stomach

1. Gastric sensations

There is some controversy in the literature as to whether nonpainful sensations can be elicited by stimulation of the stomach. The availability of patients with exteriorized gastric fistulae has permitted the direct stimulation of the stomach in conscious human beings. The most comprehensive study was performed by Wolf and Wolff (423) on the patient Tom who had a large permanent gastric fistula surgically produced to treat a benign constriction of the esophagus. A number of mechanical, thermal, and chemical stimuli were applied directly to the stomach of this subject through the fistula, and the sensations evoked were carefully noted.

Wolf and Wolff (423) described that sensations of heartburn were reported when the mucosa lining the cardiac end of the esophagus was stimulated, the rest of the gastric mucosa being completely insensitive to touch. Thermal stimuli above 40°C were felt as heat and those below 18°C were perceived as cold. No thermal sensations were reported within this range, and thermal differences of 3°C were required above or below these thresholds for changes in the sensation to be felt. Painful sensations could not be elicited by pinching the mucosa with forceps or by electrical and chemical stimulation of the normal mucosa. However, pain could be evoked by strong and sudden distensions of the stomach and by large contractions of its muscle walls.

Another patient with a gastric fistula was examined by Nathan (293), who confirmed most of the observations of Wolf and Wolff (423) but stated that none of the stimuli was reported by this patient as being painful. The sensations evoked by distension of the stomach were described as a feeling of bloating or of fullness that became "worse" as the distension increased but that did not become unpleasant.

The performance of abdominal surgery under local anesthesia at the turn of the century led to the beliefs that pain was the only sensation that could be evoked from the stomach and that distension and irritation of the mucosa were the most effective stimuli to evoke pain. Cutting, burning, or clamping the stomach during surgery did not evoke any sensations in the patients (218). There are several reports in the literature showing that gastric distension is a very effective stimulus to evoke pain in normal subjects (42, 156). These studies examined the effects of gastric distension using orally introduced balloons and concluded that the reported sensations of bloating and fullness fell under the general heading of pain.

It can therefore be concluded that the stomach is insensitive to a variety of mechanical, thermal, and chemical stimuli and that sensations of fullness can be normally evoked by distension of its muscle wall (274). Most, but not all (see Refs. 12, 293), authors consider these sensations to be in the unpleasant and painful category with a range of intensities that matches the degree of distension of the stomach (179).

An interesting set of observations was reported by Wolf and Wolff (423) concerning sensations evoked from the inflamed gastric mucosa. Their patient Tom had suffered on several occasions from conditions resulting in a congested and inflamed mucosa, and on all these occasions it had become tender and painful even to light touch. To study this phenomenon in more detail, Wolf and Wolff (423) induced a localized area of acute inflammation on Tom's gastric mucosa. They were able to verify that whereas touch or chemical stimuli applied to regions of normal mucosa produced no sensations, all these stimuli evoked pain when applied to the inflamed area. This new sensitivity to pain that develops after inflammation of the gastric mucosa is probably the cause for the pain of gastric peptic ulcers (46, 320). Sensitization of gastric sensory receptors has also been claimed to be the cause for chronic idiopathic dyspepsia in subjects suffering from irritable stomach syndrome (213).

Gastric pain is usually referred to the midepigastric region but may radiate to the left flank and occasionally to the chest (42, 46, 232). It is felt as a dull aching sensation that is not very well localized and that can be accompanied by cutaneous hyperalgesia in the zone of referral. However, the pain of a gastric ulcer can sometimes be felt over a very small area and can be pinpointed by the patient with a fingertip (232). These differences in the extent of the referral are probably due to the number of gastric afferents activated by the originating stimuli rather than to genuine differences in localization accuracy. This interpretation is supported by the observation that changes in the position of the stomach during forced respiratory movements do not alter the superficial localization of the pain.

2. Sensory innervation of the stomach

Like the rest of the alimentary canal, the stomach receives a dual afferent innervation from sympathetic and parasympathetic nerves (54). The former have their cell bodies in the lower thoracic and upper lumbar dorsal root ganglia and reach the stomach via the thoracic sympathetic chain and the celiac plexus. The latter run in the vagus nerves and have their cell bodies in the nodose ganglion (390).

I) VAGAL AFFERENT FIBERS. There have been numerous studies of gastric vagal afferents in several animal species, particularly in relation to their functional roles in the control of gastric motility and secretion. Two main groups of sensory receptors have been distinguished according to their presumed location in the gastric walls.

A) "In series" tension receptors. These are sensory receptors thought to be in series with the smooth muscle of the stomach and thus responding to changes in the tension of its wall (12, 14, 40, 77, 160, 161, 163, 210, 211, 250, 314). They are connected mainly to unmyelinated afferent fibers, although some have small myelinated axons. They have some degree of background activity and respond to gastric distensions and contractions with a low threshold. These receptors are therefore capable of encoding motility changes of the stomach in the physiological range and are mainly concerned with the regulation of gastric motility and secretion.

B) Mucosal receptors. These are receptors presumably located in the gastric mucosa, connected mainly to unmyelinated afferent fibers and responding to light stroking of the mucosa, to the application of chemicals, and possibly to thermal stimuli (12, 78, 119, 162, 210, 211, 251). There is some argument as to whether some of these receptors are specifically chemosensitive or polymodal (see Ref. 12). On the basis of the sensitivity of some of these receptors to the application of acid solutions, they were thought to act as pH-sensitive receptors (162), but this view appears to be no longer tenable (211). The general consensus is that mucosal receptors are mainly concerned with the regulation of gastric motility and secretion rather than with the signaling of sensory events. Unlike tension receptors, mucosal chemoreceptors are excited by cholecystokinin (CCK), which suggests that they may play a role in the control of satiety (40).

II) SYMPATHETIC AFFERENT FIBERS. There are only a few studies of gastric sensory receptors with afferent fibers in sympathetic nerves. Ranieri et al. (338) describe that they are connected to unmyelinated afferent fibers and that they can be activated by gastric contractions particularly during their rising phase. Floyd and Morrison (127) examined mechanosensitive splanchnic afferents in dogs and described that they had receptive fields in the mesenteries consisting of up to eight punctate sites located along the blood vessels of the stomach. Finally, Longhurst et al. (225) studied in cats the chemosensitivity of splanchnic afferents with receptive fields in abdominal organs. They concluded that unmyelinated afferents required strong mechanical stimuli for their activation, whereas small myelinated afferents were more sensitive to local probing of their receptive fields. In addition, both types of receptor were found to be sensitive to the application of bradykinin and capsaicin.

Chemosensitive vagal and splanchnic afferents from the stomach have been implicated in the control of gastric mucosal blood flow by means of an axon reflex mechanism (105, 242). There is some evidence that vagal afferent fibers can have efferent functions in the stomach that could affect gastric motility (207), perhaps involving the antidromic release of neuropeptides.

3. Gastric pain

Although several research groups have examined the sensory innervation of the stomach, there are no

studies specifically concerned with the role of gastric afferents in the signaling of pain sensation. Most of the published evidence was obtained with the principal aim of studying the contribution of afferent nerves to the regulation of gastric motility and secretion.

A role for vagal afferents in gastric sensation has been proposed. Vagal afferents are known to mediate the feeling of satiety that follows food ingestion, a process that involves the peripheral release of CCK (152). Some of the nonpainful sensations that can be elicited from the stomach, particularly the initial feelings of fullness during gastric distension, could also be signaled by vagal tension receptors (12, 319).

On the other hand, clinical and behavioral evidence suggests that gastric pain is normally mediated by afferent fibers in sympathetic nerves (227, 416). Unfortunately, the lack of systematic studies of the functional properties of sympathetic gastric afferents makes it difficult to assess their specific contribution to the peripheral encoding of gastric pain. It would be of value to know if vagal or sympathetic gastric afferents can be sensitized by mucosal irritation in a way that would match the increased sensitivity to pain of the inflamed mucosa. Obviously studies of the role of vagal and sympathetic gastric afferents in pain sensation are much needed.

C. Liver, Biliary System, and Pancreas

1. Hepatic, biliary, and pancreatic pain

The only sensation that can be evoked from the liver, biliary system, and pancreas is that of pain. Biliary and pancreatic pains are frequently observed in medical practice and are dominant symptoms of common gastrointestinal diseases such as biliary colic or acute pancreatitis. Because of the immediate relevance of biliary and pancreatic pain to human medicine, numerous studies have been published on the clinical and behavioral aspects of these forms of pain. In sharp contrast, there are very few neurophysiological papers about the sensory innervation of the liver, biliary system, and pancreas, particularly in relation to the peripheral mechanisms of pain from these organs.

It is generally accepted that the parenchyma of the liver is insensitive to pain (46, 232). However, painful sensations can be evoked by hepatic congestion due to increases in venous pressure or by inflammatory processes such as hepatitis. This suggests that hepatic pain is secondary to processes affecting the biliary system and the parietal peritoneum or producing stretch of the liver capsule (46). On the other hand, some authors (340) have denied that the latter stimulus is capable of evoking pain.

Very intense painful sensations can be evoked from the biliary system particularly by its mechanical stimulation. In humans biliary pain is frequently associated with distensions and strong contractions of the gallbladder and ducts and with inflammation of the biliary system (46). The latter mechanism requires the involvement of the parietal peritoneum and is therefore not primarily triggered by afferents from the biliary system.

The most frequent cause of biliary pain is the presence of gallstones. Biliary pain is evoked by acute distensions of the gallbladder and ducts, by the increases in biliary pressure produced by obstructions of the ducts, and by the intense contractions resulting from increased peristalsis (39, 111, 131, 334, 256, 340). Pain sensations are intense, colicky, and referred to the epigastrium and right flank and occasionally to the back and to the top of the right shoulder (111, 232). Cutaneous hyperalgesia in the area of referral has also been observed (232).

Distensions of the gallbladder and biliary ducts evoke pseudaffective reactions in animals indicative of pain (103, 104, 364, 381, 389). Increases in systemic blood pressure and heart rate can also be triggered by distension of the biliary system (59, 381) or by the application of algesic chemicals to the gallbladder (240, 309).

Pancreatic pain is felt as a severe discomfort in the upper abdomen radiating toward the back and is reported to have a particularly unpleasant character (46). Malignant pancreatic tumors, acute and chronic inflammation of the pancreas, and obstructions of the pancreatic duct leading to increased pancreatic pressure produce intense pain (115, 334). A direct relationship between increased pancreatic pressure and pain has been demonstrated (115, 116, 308), but the mechanisms by which acute and chronic pancreatitis and pancreatic tumors evoke pain are obscure.

2. Sensory innervation of the liver, biliary system, and pancreas

The liver, biliary system, and pancreas are innervated by afferent fibers running in the vagus nerves as well as by fibers projecting through sympathetic pathways. The former reach these organs via branches of the abdominal vagus and have their cell bodies in the nodose ganglion. The latter run through the celiac plexus and reach the lower thoracic segments of the spinal cord via the splanchnic nerves.

A considerable amount of clinical and behavioral evidence suggests that hepatic, biliary, and pancreatic pain are mediated by afferent fibers in sympathetic nerves and that the vagal innervation does not contribute to pain sensation. In human patients, blocks or section of the sympathetic innervation, but not of the vagus, reduces or abolishes hepatic, biliary, and pancreatic pain (39, 46, 108, 139, 159, 333, 340, 388, 416). In animals, similar procedures abolish pseudaffective reactions to biliary distension as well as cardiovascular and other reflexes indicative of nociception (59, 103, 104, 289, 309, 364, 381, 389).

I) LIVER. Most of the electrophysiological data on the afferent innervation of the liver have been obtained from recordings of vagal afferents, and the results are therefore not immediately relevant to the mechanisms of hepatic pain (12). Reports by Niijima (300, 304, 305) and Adachi and Niijima (5) indicate that hepatic vagal afferents are sensitive to changes in the plasma concentration of glucose, to alterations in osmotic pressure of portal venous blood, and to temperature changes in the range of 35–39°C. These receptors are thought to be involved in processes associated with thermogenesis and glucose homeostasis or in the control of body fluids.

The liver is also innervated by afferent fibers with axons in the splanchnic nerves and cell bodies in the lower thoracic dorsal root ganglia (23). Morrison (278) reports that some of these receptors are mechanosensitive and respond to changes in portal venous pressure in the 5- to 50-mmHg range. Their afferent fibers are small myelinated or unmyelinated. These mechanosensitive hepatic afferents are probably concerned with the regulation of portal venous pressure.

II) BILIARY SYSTEM. The gallbladder and biliary ducts are innervated by vagal and sympathetic afferent fibers (8) and, like the rest of the gastrointestinal tract, by intrinsic neurons that are part of the enteric nervous system (243). The latter are not concerned with the signaling of biliary pain and, judging by the available clinical and behavioral evidence, neither are the vagal afferent fibers. In any case, there are no reports in the literature about the functional properties of the intrinsic neurons of the gallbladder or of biliary afferents running in the vagus nerve.

Several authors have examined the sensitivity of splanchnic biliary afferents to mechanical and chemical stimuli. Stulrajter et al. (389) reported responses to gallbladder distension in single and multiunit recordings taken from the right greater splanchnic nerve of the cat. No data on thresholds, stimulus-response functions, or type of afferent fiber were supplied. Morrison (278) described a population of mechanosensitive afferents with axons in the right splanchnic nerve and responding to distensions of the gallbladder. They had several mechanosensitive sites located along blood vessels and encoded biliary pressure in the range of 5–50 mmHg. These responses are similar to those of mechanosensitive afferents described by Floyd and Morrison (126, 127) in the serosal surfaces of other abdominal viscera. These afferents have also been found to be sensitive to algesic chemicals such as capsaicin and bradykinin (217, 225). Crousillat and Ranieri (100) examined the splanchnic innervation of the biliary system of the cat and described two types of mechanoreceptor: *1*) tension-sensitive receptors presumably located in the muscle layers of the gallbladder and ducts and *2*) peritoneal receptors with sensitive endings in the serosa and mesentery of the biliary system. They supplied no data on the thresholds and on the stimulus-response functions of these receptors, although they indicated that the tension receptors were connected to unmyelinated afferents and included both slowly adapting and rapidly adapting subtypes.

Cervero (59) carried out a study of the afferent innervation of the biliary system of the ferret to identify the types of afferent fibers that could be involved in the signaling of biliary pain. In this study, a technique for the natural stimulation of the biliary system which permitted the distinction between noxious and innocuous intensities of stimulation was developed. It involved the application of controlled distensions of the gallbladder and ducts while recording their effects on the systemic blood pressure of the animals. Raising the biliary pressure above physiological levels induced transient blood pressure increases that were not affected by bilateral vagotomy but were often abolished by bilateral section of the splanchnic nerves. This cardiovascular reflex, which since Sherrington (381) has been regarded as a nociceptive reaction, was used to assess the level of biliary pressure that could be interpreted as noxious.

Cervero (59, 61) reported that biliary afferents recorded from either the splanchnic nerve or the biliary plexus could be classified into two distinct groups according to their thresholds and their encoding ranges. About two-thirds of the afferents had low thresholds to increases in biliary pressure and encoded these stimuli within the physiological range. These afferents are probably involved in local or systemic reflexes related to gastrointestinal function. The other one-third was receptors with a high threshold to increases in biliary pressure and that encoded mechanical stimuli in the noxious range only. They had mechanically sensitive receptive fields in the gallbladder and ducts, showed no background activity, and did not respond to physiological changes of biliary pressure. Because of these properties they were classified as visceral nociceptors concerned with the signaling of events that could lead to pain perception.

III) PANCREAS. The afferent innervation of the pancreas includes vagal and sympathetic afferent fibers (346, 376). An anatomic study of the vagal afferent innervation of the rat's pancreas has shown that these afferents innervate almost exclusively pancreatic islets (299). Therefore, vagal afferents seem to be mainly concerned with the reflex regulation of the endocrine component of the pancreas (306).

Two studies of splanchnic afferents from the upper abdomen report the presence of some mechanosensitive afferents with receptor endings in the pancreas (127, 225). These are small myelinated and unmyelinated afferents with several punctate mechanosensitive sites located along blood vessels. Pancreatic afferents have been found to be sensitive to algesic chemicals such as capsaicin and bradykinin (225) as well as to ischemia and hypoxia (224).

The almost total lack of information about the functional properties of pancreatic afferents makes it very difficult to even speculate about the peripheral mechanisms of pancreatic pain. Whether or not there are mechanosensitive afferents responding to pancreatic pressure levels known to evoke pain is an open question. The fact that acute and chronic inflammation of the pancreas are usually the cause of intense pain would indicate that local changes in the environment of the sensory receptors may play a role. A report by Bockman

et al. (44) on the neuropathology of chronic pancreatitis describes abnormal and damaged nerve fibers supplying the fibrotic tissue that replaces normal pancreatic parenchyma. Unfortunately, the functional relevance of these structures is unknown.

3. *Biliary nociceptors*

The report by Cervero (59) on the afferent innervation of the biliary system of the ferret is the only study specifically undertaken to examine the kinds of sensory receptors that could be involved in the signaling of biliary pain. This study concluded that the biliary system was innervated by a group of high-threshold mechanoreceptors that was regarded as being functionally similar to cutaneous nociceptors and was thus labeled biliary nociceptors.

This conclusion was criticized by Jänig and Morrison (173) on the basis that these high-threshold receptors could represent the top end of a continuous spectrum of biliary afferents and that their mechanosensitive sites might not have been situated in the wall of the viscus but in the portal vein, thus responding indirectly to changes in biliary pressure. Notwithstanding the fact that these two criticisms are mutually exclusive, it is worth pointing out that high-threshold biliary receptors were regarded by Cervero (59) as primarily concerned with nociceptive events for three main reasons: *1*) their mechanosensitivity; their receptive fields were clearly located in the walls of the gallbladder and ducts, their thresholds for mechanical stimulation of the biliary system were above physiological levels, and they were able to encode biliary pressure increases in the noxious range. *2*) The existence of two populations of afferent fibers; there were clear differences between the thresholds and encoding ranges of the low-threshold and high-threshold populations so that two separate groups of mechanosensitive afferents could easily be distinguished (61). *3*) The clinical and behavioral data; the high-threshold receptors responded well to the type and range of mechanical stimuli known to evoke pain in humans and pseudaffective reactions in animals. Furthermore, in a later study of the afferent innervation of the biliary system, Cervero (60) showed that very large changes in biliary pressure induced only very small alterations of portal pressure so that an indirect activation of portal mechanoreceptors by changes in biliary pressure was very unlikely.

D. *Small Intestine*

1. *Sensations from the small intestine*

Ever since the comprehensive studies of Hertz (156) on the sensibility of the human alimentary canal, it has been known that discomfort and pain are the main sensations that can be evoked from the small intestine. The entire length of the small intestine is insensitive to touch, thermal changes, and traumatic stimuli such as cutting, burning, or clamping (156, 218, 232, 416). All authors agree that the main sensation elicited by stimulation of the small intestine is a vague feeling of fullness with more or less unpleasant overtones that evolve toward a sensation of painful distension. In addition, strong peristaltic contractions evoke the distinctive colicky pain that characterizes the response of the small intestine to acute irritation.

Mechanical events in the intestine are therefore the main triggers of intestinal pain. These include distension of the duodenum, jejunum, or ileum (3, 28, 39, 42, 156, 221, 275, 340, 352), traction and stretching of the mesenteries (210, 211, 276), and intense peristaltic contractions due to intestinal obstructions or acute inflammation of the enteric mucosa (46, 232).

Pain from the small intestine is felt vaguely around the umbilical region and is usually referred to the center of the abdomen, although it can extend to either flank and, more rarely, to the back (46, 275). Detailed examinations of the pain and the intestinal reflexes evoked by controlled distensions of the small intestine in human volunteers have demonstrated a clear dissociation between perception of pain and the triggering of intestinal reflexes (352). This has been interpreted to suggest that intestinal pain is mediated by a separate mechanism from that concerned with the regulation and control of intestinal motility.

Stimulation of the small intestine has also been shown to evoke pain and pseudaffective reactions in animals. Several forms of noxious stimulation of the small intestine including thermal and chemical stimuli have been reported to evoke pseudaffective reactions in anesthetized or decerebrate cats (113) and anesthetized rats (335). Acute distension of the duodenum or of the proximal jejunum in rats triggers nociceptive reflexes that are mediated by sympathetic afferents and reduced or abolished by the administration of opiates (91, 214, 284). Finally, injections of substance P into the splenic artery of conscious dogs evoke vocalization and other pain behaviors (329).

2. *Sensory innervation of the small intestine*

The small intestine receives its dual afferent innervation via sympathetic and parasympathetic nerves (46). The afferents traveling in sympathetic nerves have their cell bodies in the lower thoracic and upper lumbar dorsal root ganglia. The parasympathetic innervation is supplied by vagal afferents with cell bodies in the nodose ganglion (73). Both types of afferent fibers reach the small intestine by way of the mesenteric nerves, where they are intermingled with the efferent innervation and with centripetal projections of enteric nervous system neurons (181, 363). The latter terminate in the abdominal prevertebral ganglia and therefore cannot make a direct contribution to the mechanisms of intestinal sensation.

A large amount of clinical evidence indicates that intestinal pain is mediated by afferents in the sympathetic nerves. Unilateral section of the splanchnic nerve confines intestinal pain to the nonoperated side, and bilateral splanchnectomy abolishes intestinal pain completely (28, 39, 340, 416). On the other hand, vagal afferent fibers are involved in regulatory reflexes controlling intestinal motility and secretion (12) and play an important role in the triggering of the vomiting reflex (13). In this respect, vagal afferents may contribute to some of the general sensations that precede vomiting, such as nausea and malaise.

Electrophysiological recordings have been made from vagal and sympathetic afferent fibers with receptor endings in the small intestine. In addition, a number of studies have examined the functional properties of afferent discharges in mesenteric nerves. Because of the difficulty in tracing the pathway of projection of mesenteric afferent fibers, their properties are reviewed separately.

I) VAGAL AFFERENT FIBERS. Intestinal vagal afferents have been studied in a variety of different animal species including rat, rabbit, cat, and sheep. The most extensively studied segments of the small intestine have been the duodenum and the proximal jejunum. Two broad types of sensory receptor have been identified: tension receptors and mucosal receptors (12, 250, 251).

Tension receptors are connected to small myelinated and unmyelinated fibers and are similar to the in series tension receptors described in other parts of the gastrointestinal tract (97, 98, 210, 211, 250). They respond to passive distension of the walls of the intestine, compression, and contractions of the muscular layer. They also respond to the application of certain chemicals and gut peptides, but this sensitivity appears to be secondary to the motor activity evoked by the compounds (98). Because of their low mechanical thresholds, these receptors are thought to be concerned mainly with regulatory aspects of intestinal function.

Mucosal receptors are thought to be located superficially in the enteric mucosa and respond to mechanical stimuli, the application of chemicals, or both forms of stimulation (12, 78, 99, 210, 211, 252). They are sensitive to a variety of digestion-related compounds including acid and alkaline solutions, glucose and other carbohydrates, and amino acids. They are thought to be concerned mainly with the control of gastrointestinal motility and secretion and with the regulation of food and water intake (251, 252).

II) SYMPATHETIC AFFERENT FIBERS. Recordings from intestinal afferents in sympathetic nerves were first reported by Gernandt and Zotterman (134). They described responses to low-intensity mechanical stimulation of the mesenteries that they attributed to the activation of mesenteric pacinian corpuscles. In addition, they reported that noxious stimulation of the intestine, such as pinching the enteric wall, evoked activity in small-diameter afferent fibers that they interpreted as being related to the signaling of intestinal pain.

Other authors have described mechanosensitive afferents in the splanchnic nerves (127, 277, 338) as well as cold-sensitive afferents with receptor sites in the stomach and duodenum (140). Mechanosensitive splanchnic afferents are small myelinated or unmyelinated and have punctate receptive fields along the mesenteric blood vessels. Both slowly and rapidly adapting responses have been described.

A series of studies by Longhurst and co-workers (217, 224, 225, 226, 385) has described the functional properties of a group of splanchnic afferent fibers that are thought to be mainly concerned with nociception. These are sympathetic afferents that innervate the small intestine, stomach, liver, pancreas, and biliary system. Each individual afferent innervates only one of these organs and, very rarely, two of them. The afferents are either small myelinated or unmyelinated, with the former being mainly mechanosensitive and the latter either insensitive to mechanical stimulation or activated only by very intense mechanical probing of their receptive fields.

The main characteristic of many of these afferents is their sensitivity to algesic chemicals such as bradykinin and capsaicin as well as to pain-producing stimuli like ischemia and hypoxia (217, 225). Chemical stimulation sensitizes these afferents to subsequent stimuli, a process that involves the local release of prostaglandins and perhaps lactic acid (224, 226, 385, 386). Because of all these properties, these afferents are thought to mediate the intestinal pain evoked by ischemia and irritation of the alimentary canal.

III) RECORDINGS FROM MESENTERIC NERVES. Several authors have reported the responses of intestinal afferent fibers running in mesenteric nerves. Because vagal and sympathetic afferents travel together in the mesenteric nerves, their main pathway of projection is unknown. They could even be the centripetal projections of sensory neurons of the enteric nervous system (73). Both mechanical and chemical stimuli have been used to characterize their responses.

The few large myelinated afferents in mesenteric nerves are connected to pacinian corpuscles and are sensitive to very low-intensity mechanical stimuli of the mesenteries so that they can fire in synchrony with the arterial pulse (132, 378). Small myelinated afferents are mechanosensitive, can fire in phase with strong peristaltic movements of the intestine, and have receptive fields along branches of the mesenteric arteries (36). Specific mechanoreceptors, specific chemoreceptors, and polymodal receptors have also been described (10, 11, 73, 95, 96, 150, 377, 394).

The mechanical sensitivity of mesenteric afferents includes responses to distension of the small intensity, stroking of the mucosa, and congestion of mesenteric vessels. Their chemical sensitivity is shown by responses to the application of a variety of compounds including hexoses, bile salts, acid solutions, and bradykinin. Obviously many of these afferents are concerned with regulatory aspects of intestinal function.

Cervero and Sharkey (73) carried out an electrophysiological and anatomic study of mesenteric affer-

ents in the rat using an in vitro preparation of small intestine and associated vessels and nerves (375). They reported that most of the afferents were both mechano- and chemosensitive, although small populations of specific mechanoreceptors and specific chemoreceptors were also found. Some of the chemically evoked responses, such as those to bradykinin, were due to a direct sensitivity of the receptors to the drug, whereas others, most notably the sensitivity to substance P, were secondary to the increase in smooth muscle tension evoked by the peptide. Because the in vitro technique did not allow the application of intestinal distensions above 18 mmHg, the possible existence of high-threshold mechanoreceptors could not be examined.

3. *Intestinal pain*

The high-threshold mechanoreceptors with algesic chemosensitivity described by Longhurst and colleagues (217, 224–226, 385) qualify for a putative role in the signaling of intestinal nociception. They can be activated by strong mechanical events in the intestine and by chemicals known to evoke pain in humans and pseudaffective reactions in animals. In addition, they respond to ischemia and hypoxia and can be sensitized by these stimuli. However, the existence of this group of intestinal receptors does not exclude a possible contributory role of low-threshold mechanoreceptors to intestinal sensations, particularly to the initial feelings of distension that precede intestinal pain (173).

On the other hand, chronic intestinal pain associated with conditions such as the irritable bowel syndrome appears to be the expression of an increased gut sensitivity to physiological stimuli (275, 341). The sensitization of putative intestinal nociceptors by a variety of different stimuli offers a possible mechanism for the feeling of intestinal pain during the occurrence of normal digestive processes. This interpretation of the mechanisms of functional abdominal pain has been argued in recent years (65–67, 244) and currently forms the conceptual framework for experimental studies that address sensitization mechanisms in visceral sensory receptors.

E. *Colon and Rectum*

1. *Sensations from the colon and rectum*

The main functions of the colon and rectum are the formation and storage of feces and the regulation of their evacuation at behaviorally convenient times. The control of defecation and the maintenance of fecal continence depend on a highly complex set of autonomic and somatic reflexes and, to a large extent, on sensory feedback from the colorectal region and anal canal (176, 261–264). The afferent innervation of these viscera must thus mediate not only the regulation of their autonomic functions but also the sensations associated with the urge to defecate and the maintenance of continence. In addition, painful sensations can also be evoked by stimulation of the colorectum.

The sensitivity of the colon, rectum, and anal canal increases toward the anus. The only sensations that can be evoked by distension of the colon are vague feelings of distension and fullness that very soon become unpleasant (42, 156, 221). Distension of the sigmoid colon and rectum also evokes sensations of pressure and fullness that are accompanied by an initial urge to pass wind or to defecate and, if not relieved, by pain (138, 296, 340). Distension of the colorectum evokes aversive behavior and pseudaffective reactions in animals (175, 294, 295, 297) that are attenuated by morphine and other analgesic drugs. The human colon and rectum are insensitive to cutting, clamping, and burning (218) and to thermal stimuli in the 32.5–41.5°C range (261).

In contrast, the anal canal has a similar sensitivity to that of the perineal skin so that a variety of tactile and thermal sensations can be evoked from its lower portion (261–264). These sensations are essential for the maintenance of fecal continence, since they help to detect the presence of fecal material in the rectum and upper anal canal and to discriminate between solids and flatus (261–264).

The pain evoked by distension of the colorectal region is felt as a cramping and aching pain referred to the lower abdomen, the back, and the perineum (296). It is most easily triggered by mechanical stimuli that produce sudden distensions or sustained and intense contractions (138); therefore, it is thought that increases in colonic pressure rather than in volume are the most effective stimuli. Colorectal pain is often accompanied by cardiovascular and respiratory reflexes and by increases in the tension of abdominal wall muscles (296). Inflammation of the colorectal mucosa is also a powerful stimulus for the triggering of pain (46, 232). Common causes of inflammatory pain from the large intestine include acute appendicitis and conditions such as ulcerative colitis. In acute appendicitis, the appendix becomes extremely sensitive to light mechanical stimulation (182), and pain can be evoked by normal intestinal motility.

2. *Sensory innervation of the colon and rectum*

Afferent fibers reach the colon and rectum via sympathetic and parasympathetic nerves. The sympathetic innervation is mediated by afferents running in the lumbar colonic nerves. Their cell bodies are located in the upper lumbar dorsal root ganglia and their axons course in the lumbar splanchnic nerves, reach the inferior mesenteric ganglion, and project to the colon via the hypogastric and colonic nerves (46, 173). The parasympathetic afferent innervation of the ascending colon and of the right portion of the traverse colon is mediated by vagal afferents with cell bodies in the nodose ganglion (12, 46). Parasympathetic afferents innervating the left

portion of the transverse colon, the sigmoid, and the rectum project to the sacral spinal cord via the pelvic nerves and plexus (173).

The colon and rectum are also innervated by large numbers of intrinsic neurons of the enteric nervous system. A recent anatomic tracing study has shown that a few of those located in the walls of the rectum have centripetal projections that reach the lumbosacral spinal cord (110). The contribution of these neurons to the mechanisms of rectal sensation is unknown.

Colorectal pain is probably not mediated by afferent fibers in sympathetic nerves, since the colicky pain that can be evoked by balloon distensions of the colon and rectum persists in sympathectomized patients (416). Some authors (138) have argued that colonic pain, particularly from the ascending and traverse colon, can be mediated by afferent fibers in sympathetic nerves, whereas rectal pain is evoked by the activation of parasympathetic afferents. However, most of the clinical evidence points to the pelvic nerve as the pathway for the transmission of nociceptive signals from the colorectal region (46).

I) SYMPATHETIC AFFERENT FIBERS. Researchers from two laboratories have reported the functional properties of sympathetic afferent fibers with receptive fields in the colon. One of the groups (126, 127) described the properties of colonic afferents with axons in the hypogastric and splanchnic nerves in dogs and cats. These afferents were reported to have up to six punctate mechanosensitive sites located along the blood vessels of the colon, particularly at branching points. The afferent fibers were mostly small myelinated, and the mechanical thresholds were low.

Jänig and co-workers (43, 154) have also carried out a comprehensive examination of the sympathetic afferent innervation of the colon in cats. They recorded afferent fibers in the lumbar splanchnic nerves and the upper lumbar rami and studied their responses to controlled distensions of the colon and to the application of algesic chemicals. Two-thirds of the fibers were unmyelinated, and the remaining one-third was small myelinated. Most fibers had low levels of background activity of between 0.5 and 3 Hz.

Four types of mechanosensitive colonic afferents were distinguished according to the presence or absence of phasic components in their responses to a 60-s sustained distension of the colon. *Groups I* and *II* had only phasic responses to distension and formed just over 10% of the total sample. *Groups III* and *IV* showed, in addition or exclusively, a steady tonic discharge that lasted for the duration of the stimulus. Mechanosensitive sites were identified as punctate receptive fields along the vessels of the colon. Their mechanical thresholds formed a continuum spanning the innocuous and noxious ranges; all of the types I and II fibers and most of the type III fibers had thresholds below 25 mmHg, whereas 45% of the type IV had mechanical thresholds above 25 mmHg. In addition to their mechanical sensitivity, most sympathetic colonic afferents responded to ischemia of the colon and to the administration of algesic chemicals such as bradykinin and KCl. Virtually all afferent fibers excited by bradykinin were also activated by colonic distension.

II) PARASYMPATHETIC AFFERENT FIBERS. There is only one report on the responses of vagal afferents innervating the colon (250) in which they are briefly described as being sensitive to distensions and contractions of the colonic walls. On the other hand, the properties of parasympathetic afferents projecting to the sacral spinal cord via the pelvic nerves have been examined in greater detail in recordings made from dorsal and ventral root afferents.

Ventral root afferents with receptive sites in the sigmoid colon and anal canal are mostly unmyelinated and respond to intense mechanical and thermal stimulation of the mucosa or to distensions above 15–35 cmH_2O (85, 88). In a study of 245 sacral dorsal root afferents with axons in the pelvic nerve (20), it was reported that about one-half of them had mechanosensitive receptive fields in different pelvic viscera, of which some 20% were exclusively located in the colon. Most of these fibers were unmyelinated, had thresholds to mechanical distension of the colon in the range of 15–40 mmHg, and increased their rates of firing with increasing intraluminal pressure.

A separate study examined the functional properties of sacral dorsal root afferents with axons in the pelvic nerve and mechanical receptive fields in the colon (170). Thirty-six mechanosensitive colonic afferents were studied and were classified according to their adaptation characteristics into two groups of roughly equal sizes. One group of mostly unmyelinated afferents responded tonically to increasing distensions of the colon, and the other group of mostly small myelinated afferents responded phasically. Both groups of fibers were described as being part of a homogeneous population of afferents with low thresholds to distension and monotonic stimulus-response functions ranging from innocuous to noxious levels. The average mechanical threshold of the population, defined as the 10% value of the maximal impulse frequency, was given as 21 ± 12 (SD) mmHg.

The functional properties of colonic afferents projecting to the sacral spinal cord of the rat via the pelvic nerve have been reported (133, 370a). About three-quarters of the afferents had low thresholds to colonic distension, whereas the remaining showed high thresholds to this mechanical stimulus. Some of the afferents were reported to be sensitive to bradykinin administration.

3. *Colorectal pain*

Current interpretations of the peripheral mechanisms of colorectal pain are based on two hypotheses: *1*) the afferents responsible for the signaling of colorectal pain belong to a homogeneous population of intensity-encoding afferent fibers whose functions also include the triggering of autonomic reflexes and the signaling of