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For my parents, wife, and children.

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NEUROSURGICAL AND MEDICAL MANAGEMENT OF PAIN: TRIGEMINAL NEURALGIA, CHRONIC PAIN, AND CANCER PAIN

1. INTRODUCTION

Ronald Brisman, M.D.

This book will discuss three areas where the neurosurgeon may provide an important contribution to the relief of intractable pain: trigeminal and other facial neuralgias, chronic noncancer pain, and cancer pain. By one intervention, the neurosurgeon often may provide long-lasting pain relief. New techniques, which have developed since the 1970s and continue to evolve, dominate the neurosurgical armamentarium because they are not only effective, but safe. These include percutaneous radiofrequency electrocoagulation for trigeminal neuralgia, spinal stimulation for chronic noncancer pain, and intraspinal morphine infusion for cancer pain.

Sometimes a procedure relieves pain but the pain recurs; it may be necessary to repeat the procedure, which in the case of radiofrequency electrocoagulation for trigeminal neuralgia can be done without added risk and again with a reasonable probability that it will work well. Sometimes pain cannot be relieved by these safe maneuvers and another operation with a little more risk, but still a good chance of helping, may be recommended, such as the suboccipital operating microscope procedure for trigeminal neuralgia, deep brain stimulation for intractable noncancer pain, or stereotaxic ablations for cancer pain.

There are other operations that are indicated for specific circumstances: sympathectomy for causalgia, dorsal-root entry zone lesions for nerve root avulsion or herpes zoster radiculopathy, sacral rhizotomies, commissural myelotomy, or anterolateral cordotomy for certain kinds of cancer pains.

The multiplicity of procedures with varying degrees of risks and benefits sometimes requires a sequential approach, but always an individual one, matching an appropriate treatment plan or procedure for a particular patient at a specific time in his or her illness.

The neurosurgical chapters in this book represent my experience with several hundred patients during a 12-year period from 1975 through 1987. I have relied heavily on the works of others, which have been quoted from the neurosurgical literature, but this book is not meant to be encyclopedic.

At least as important as knowing when to operate is knowing when not to do so, and this is particularly true of the treatment of pain. Most patients with pain do not require neurosurgical intervention.

When a thorough diagnostic evaluation indicates that there is no further specific medical or surgical treatment that is likely to help, patients may still benefit from a variety of methods that are aimed at relieving pain, emotional distress, or harmful life styles. Experts from neurology, psychiatry, anesthesiology, and physical medicine and rehabilitation have written chapters on their respective roles in the treatment of pain.

Neurosurgical intervention is usually reserved for those patients who continue to have agonizing pain in spite of extensive nonsurgical management. It is remarkable that many in this highly selected but difficult group of patients will be helped by the proper neurosurgical procedure.

Advances in the treatent of pain have paral-

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leled developments in the basic sciences: neuroanatomy, neurophysiology, and neurochemistry. These are reviewed in detail. The neurosciences explain some of the fundamental principles behind current treatments and may help direct attention to new and improved forms of pain management.

I. BASIC SCIENCE OF PAIN

2. NEUROANATOMICAL, NEUROPHYSIOLOGICAL, AND NEUROCHEMICAL BASIS OF PAIN

Robert R. Goodman, M.D., Ph.D.

Introduction

Pain can be defined as the experience produced when a part of the body is physically damaged. The perception and discrimination of pain is distinct from distress or suffering, which may relate to an emotional experience. This chapter concerns itself with the neural substrate for the production of the sensation termed *pain*. Sherrington observed that pain usually accompanies tissue injury [1]. Tissue damage represented the common denominator for stimuli evoking pain, and he suggested the label *noxious* for these stimuli. The function of these neural systems was felt to be protective, and Sherrington thought that they were activated by the threat of damage. The proposed peripheral detectors of pain were termed *nociceptors*. Decades of study have determined a great deal regarding the mechanisms of nociception. First the peripheral nervous system and the mechanisms involved in the detection of the threat of tissue damage and the transmission of this information to the spinal cord will be discussed. Then the organization of the spinal cord with respect to its role in the transmission of the pain sensation to higher levels of the nervous system will be considered. Next, a summary of the present understanding of pain processing at higher central nervous system levels will be given. The final section will deal with the explosion of knowledge regarding the relatively recently discovered nervous system mechanisms involved in the modulation of the sensation/perception of pain and their relevance to the treatment of clinical pain syndromes. The discussion of the neural mechanisms involved at each level of nervous system processing will include their specific anatomical pathways, neurophysiology, and neurochemistry. Each of these aspects is particularly relevant to any attempts at the manipulation of pain processing.

The sensation of pain is necessary for survival, but diseases or injuries often produce an ongoing perception of pain without usefulness to the individual. These individuals represent the large population of chronic pain patients that have stimulated students of the nervous system to pursue their search for the mechanisms underlying the pathological processes involved, and methods to relieve their suffering. Our knowledge of the basic mechanisms involved in pain processing has resulted in numerous new and effective treatments for many of these patients. This chapter also reveals that the nervous system utilizes redundancy that allows adaptation to frustrate many of the attempts at its manipulation. Further study of pain mechanisms should yield

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many more improvements in our ability to help these patients.

Peripheral Nervous System

Originally there was a controversy concerning the way that pain processing was carried out in the periphery. Pattern theory held that all neurons were capable of conveying pain information depending on the pattern of their impulses. The alternative theory held that specialized peripheral neurons responded to specific types of stimuli and each might be associated with distinct specialized peripheral receptors. A large body of evidence supports the latter theory. Strong evidence for this includes the occurrence of nervous system lesions (peripheral and central) that can dissociate pain from other types of sensation. Studies in the early 1900s concerning the segregation of fine and coarse dorsal root fibers as they enter the spinal cord, and recovery of sensation after peripheral nerve damage, suggested that unmyelinated fibers particularly carried pain information [2, 3]. Pressure anoxia was used by some investigators [4, 5] to induce the loss of tactile and proprioceptive input before pain and temperature sensation. This was correlated with the preservation of the slower conducting components of the compound action potential. Electrical stimulation of only the slowest myelinated fibers produces pain in human subjects [6], while in animal experiments the unmyelinated (C) fibers and the thinly myelinated (A-delta) fibers provoke "pain" reactions [7]. Pinprick and heat evoke a double flash of pain in human beings that has been correlated to the separate input of the small myelinated and unmyelinated groups of fibers [8–11]. While it was becoming clear that these specific fiber subgroups carried the pain message, it was not known how they were specifically activated, or if a subset of these fibers represented specific nociceptors. It is known that 20% of ventral root fibers are C afferents, however, their function is not known [12]. Unmyelinated (C) fibers represent 70% of all afferents, and most of these appear to be involved in nociception.

A large body of research has concentrated on correlating noxious stimuli with unique responses. A class of myelinated fibers was defined (HTM fibers) that had a high threshold for injurious mechanical stimulation (e.g., responded only to noxious type stimulation), and then responded proportionally to increasing stimulus intensity [13, 14]. These fibers are poorly responsive or nonresponsive to temperature and chemical nociceptive stimuli. They innervate skin and subcutaneous structures (e.g., muscles and joints) and have a range of conduction velocities of 5-50 meters per second (mostly A-delta fibers). Electrical stimulation of many A-delta fibers elicits prolonged intense dorsal horn cell firing and pain in humans [12]. A-delta fibers carry the pain message in sunburn [15, 16]. A portion of the unmyelinated (C) fibers have high thresholds for all types of stimuli and graded responses to noxious levels of mechanical stimuli, heat, and irritant chemicals. Thus these fibers differ from the myelinated fibers in that they are *polymodal nociceptors* [17]. Interestingly, these fibers have almost no background activity until damaged, when they have markedly increased background firing rates. Also, the threshold for activation markedly decreases with repetitive activation, in contrast to the opposite response in low-threshold sense organs of the skin. The fact that this sensitization can spread to nonstimulated fibers, and can be prolonged, suggests that the mechanism may be the release of an algesic substance (possibly bradykinin, substance P, or another substance) [18]. However, some postulate that sensitization is due to nerve membrane damage [19]. It is important to note that not all C fibers are pain fibers. In the cat, 40% of C fibers respond to innocuous mechanical stimuli and in the primate, 10% re-

spond. Although several types of neurons are involved in the detection of tissue damage, humans are unable to differentiate pain of different chemicals [20] or pain caused by heat, cold, or mechanical damage [21].

Human skin C fibers have a low firing rate, intermediate adaptation, often have afterdischarges, and a velocity of 0.4 to 1.8 m/sec [22]. The activation of human C afferents that have nociceptor characteristics produces pain [11]. The study of both A-delta and C fibers confirmed that C afferents account for the second or dull pain, while A-delta afferents carry sharp pain [23]. The mechanisms for hyperalgesia (allodynia) and causalgic pain are not definitely known, however, the aberrant transfer of non-noxious impulses to nociceptor pathways via abnormal connections along axons, termed *ephapses*, is a postulated mechanism. Such ephapses have been demonstrated in peripheral nerves containing C afferents and sympathetic efferents [24]. The responses of C fibers (not A-delta fibers) to temperatures above 43°C in the monkey have been closely correlated with human reports of pain magnitude, and the duration of pain outlasts that of the C fiber response, possibly secondary to spinal cord integration [25].

The anatomical details of the peripheral [26] and central [27] terminations of nociceptors are important for our understanding of pain processing. The peripheral endings of C fibers have not yet been identified, while those of the A-delta HTM fibers lose their myelin as they enter the epidermis and are covered by a Schwann cell's basal lamina as they terminate between or invaginate into keratinocytes. It is not known by what mechanism they are activated. The A-delta mechanical nociceptors branch in the spinal cord, and the branches follow around part of the dorsal horn in the marginal zone (layer I) and give multiple terminal branches, with enlargements near or in the white mater. Most fibers also have terminals at the junction of layer I and the outer substantia gelatinosa (layer IIo). All have terminations ventral to the nucleus proprius in layer V, mainly at the lateral border of the dorsal horn. Many fibers have branches that terminate near the central canal, and some branches end in contralateral layer V. The layer I terminals contain clear, round vesicles and are often presynaptic in axodendritic and occasionally in glomerularlike arrangements (here they can be found postsynaptic in axo-axonic and dendroaxonic contacts). The low threshold mechanoreceptors (non-nociceptors) have a much different termination pattern, primarily in layers III and IV, not in layers I and II. The central termination of the C fiber nociceptors have been less well determined. They travel in Lissauer's tract (laterally) [28], make a major contribution to the primary afferent input of the substantia gelatinosa, and have some branches deep in this layer.

The chemical basis of neurotransmission in the peripheral nervous system is not yet very well understood. There are at least 16 functional classes of cutaneous afferents, each with a particular pattern of axon collateral arborization in the dorsal horn [12]. One approach to the determination of the specific neurotransmitters utilized by primary afferents has been the analysis of rat dorsal root ganglion cells in culture. The 25% of these neurons with a diameter greater than 30 microns share a particular type of neurofilament [29], but their neurotransmitter(s) is not known. The cell bodies of the 75% of neurons with 10–30 micron diameters do not contain this neurofilament, but have been identified to contain discrete and overlapping populations of neuropeptides considered to be putative neurotransmitters [30]. The most important neuropeptide for this discussion is substance P, an 11-amino-acid peptide. It is found in 15%–20% of rat sensory neurons (small-diameter afferents only), with terminations in layers I, II, III, and V. Nearly all of these

neurons also contain a peptide very similar to cholecystokinin. Small percentages of sensory neurons, with dorsal horn terminations, have been identified to contain somatostatin, vasoactive intestinal polypeptide, angiotensin II, gastrin-releasing peptide, dynorphin, enkephalin, and catecholamines [31]. A large body of evidence suggests that substance P is a sensory transmitter of primary afferents, particularly nociceptors [32]. The stimulation of C and A-delta fibers results in the accumulation of substance P in the CSF overlying the superficial dorsal horn, and this is blocked by opiate agonists such as morphine. Iontophoresis of substance P increases the firing rate of many dorsal horn neurons, and a substance-P antagonist abolishes a slow spinal reflex elicited by dorsal root stimulation. Also, substance P is particularly concentrated in peripheral terminals in the skin and tooth pulp. Tooth pulp afferents generate only pain with stimulation. Peripheral nerve injury results in significant changes within the spinal-cord dorsal horn, particularly a marked depletion of substance P. Capsaicin administered to neonates results in permanent loss of a large proportion of small-diameter primary afferent fibers, substance P depletion, and loss of thermal pain sensitivity. Capsaicin administered systemically or intrathecally in adults induces a massive primary afferent discharge and a reversible substance P depletion. Thus, substance P may be the major pain transmitter of the peripheral nervous system.

Recently there has been a great deal of work to determine the mechanism of the peripheral stimulation of nociceptors. This has particularly concentrated on the potent algesic (pain-producing) substances found in the periphery. The mechanism by which tissue damage elicits pain and hyperalgesia involves the activation of nociceptors [33]. Bradykinin potently sensitizes these nociceptors [34], and these sensory fibers contain high-affinity bradykinin receptors [35]. Recent work with selective bradykinin antagonist peptide analogues has demonstrated their ability to act as analgesics in certain animal tests [36]. These findings suggest that there may be an important clinical application for topically administered bradykinin antagonists in the treatment of certain types of pain (e.g., burns).

A very important aspect of pain perception concerns the change in activity that occurs within nociceptors in response to injury/activation. Following peripheral nerve injuries, a high percentage of regenerating axons fail to reach their physiologic target and may form a neuroma [37]. These sprouts often are spontaneously active, mechanically sensitive, and may contain adrenergic receptors that result in their activation by circulating epinephrine/norepinephrine [38]. Also, abnormal (ephaptic) connections between adjacent axons can result in the inadvertent activation of nociceptors by action potentials in other axons [39]. This mechanism has been suggested to explain reflex sympathetic dystrophy (causalgia). There is also evidence that central connections are altered by peripheral nerve injury, as well as descending inhibitory systems. These phenomena and others probably form the basis of many clinically encountered chronic pain syndromes.

Spinal Cord Mechanisms in Nociception

An overview of the anatomical organization of the dorsal horn is an essential prerequisite to understanding pain processing at the spinal cord level. In recent years, the combination of various techniques has dramatically broadened our knowledge of the morphology, physiology, and pharmacology involved. Intracellular recordings allow cell characteristics to be studied, and subsequently the morphology of that cell can be examined in detail, including its axon/dendrite distribution and types of synapses. Immunohistochemical methods and DNA/RNA techniques can provide information concerning the biochemical

specialization of these cells. These studies have greatly increased our appreciation of the complexity of spinal cord organization and are constantly expanding our understanding of spinal cord function.

The dorsal horn consists of a number of cytoarchitecturally defined layers [40]. The superficial portion of the dorsal horn consists of the marginal zone (layer I) at the surface and the substantia gelatinosa (layer II) just beneath. The marginal zone is a thin band with various neuronal types [41]. The Waldeyer cell is large and its dendritic arbor caps the dorsal horn. Many of the marginal zone neurons have long ascending projections to the reticular formation, thalamus, cerebellum, or to other parts of the spinal cord (propriospinal), and nearly all of the neurons in this layer are involved in nociception [42]. The layer I neurons either respond specifically to noxious stimuli or are so-called wide-dynamic-range neurons (responsive to innocuous stimuli, but more vigorously responsive to noxious stimuli). Essentially the sole excitatory input to most of these cells is by A-delta cutaneous HTM nociceptors. Some cells receive their major excitatory input from C-fiber polymodal nociceptors, while a small number of cells respond to non-noxious thermal stimuli. The substantia gelatinosa (layer II) can be divided into two layers [43]. The outer layer (IIo) receives a high density of high-threshold (nociceptive) inputs and contains small neurons responsive to both noxious and non-noxious stimuli. This layer is the major termination region for unmyelinated afferents (C fibers) carrying both nociceptive and non-nociceptive inputs. The inner layer (IIi) receives small-diameter, low-threshold inputs and contains cells that mainly respond to non-noxious stimuli. Morphologically there is no distinction between nociceptive and non-nociceptive neurons in the substantia gelatinosa, except that the specifically nociceptive neurons have their dendrites in the marginal zone and layer IIo, while cells that respond to low-threshold mechanical stimuli have their dendritic trees in layers IIi and III.

The substantia gelatinosa contains two prominent cell types. The stalk cell lies at the junction of layers I and II, with dendrites extending into layer III and its axon to layer I. It is felt to be an excitatory interneuron that transmits high-threshold mechanoreceptive input to the marginal zone. The islet cell has an unclear function. It is oriented longitudinally with the spinal cord and some are known to be GABAergic or enkephalinergic (e.g., inhibitory). Thus layer II neurons are almost exclusively interneurons, without distant projections.

The region of the dorsal horn termed the *nucleus proprius* consists of layers III, IV, and V. Many neurons in this area contribute to major ascending pathways (e.g., spinocervical, spinoreticular, spinothalamic, etc.), and few have dendrites extending out to the substantia gelatinosa. Layers III and IV particularly contain neurons with small receptive fields and relay mainly non-noxious information. Layer V represents a site of convergence for low and high threshold inputs, along with visceral input, and thus may be the site of origin for referred pain. Layer V receives some inputs directly from nociceptors (A-delta fiber collaterals), although much of its nociceptive input is via relays from layers I and II.

The remainder of the spinal cord gray matter, layers VI, VII, VIII, and the ventral horn, probably contribute in some way to nociceptive transmission. Some layer VII neurons respond specifically to high-threshold mechanical stimuli (probably without direct afferent input) and give rise to ascending spinal pathways (e.g., spinothalamic and spinoreticular). These neurons have complex receptive fields, often with bilateral input.

The distribution of primary afferents to these various spinal cord areas is quite distinct. The large-diameter, myelinated afferents of the dorsal roots take a medial course as they enter the spinal cord and either ascend in the

posterior columns or penetrate the superficial gray layers to end in the nucleus proprius or more ventrally. Few end in the substantia gelatinosa. The dorsal root A-delta HTM fibers arborize extensively in the marginal zone, with collaterals passing laterally down to layer V and some to layer X (the region around the central canal). The unmyelinated C-fiber afferents (including those that enter via the *ventral* roots) terminate almost exclusively in the outer substantia gelatinosa. Neurons within layers I and IIo respond differentially or exclusively to noxious stimuli [42, 44].

In recent years a large number of neuropeptides have been discovered and characterized as putative neurotransmitters or neuromodulators [45]. As described above, substance P may be the major neurotransmitter of the primary nociceptive afferents. Most of the other known neuropeptides occur in particularly high concentrations in the spinal cord dorsal horn. As mentioned previously, some of these are also associated with primary afferents, while the others occur either in local interneurons or in axon terminals of neurons projecting from the brain stem. The most extensively studied neuropeptides, and probably the most important relating to nociception, are the endogenous opioid peptide agonists, the enkephalins. Also, the study of their specific neuronal membrane receptors (the opioid receptors) has yielded very important information about the processing of nociceptive input. Enkephalin-containing neurons and axon terminals are concentrated in the superficial dorsal horn (layers I and II), layers V and VII, and around the central canal (46, 47). As noted above, these are all of the spinal cord regions that contain cells responsive to noxious stimuli. Also, opioid receptors are seen in all of these areas, although most are concentrated in layers I and II [48]. Most of the spinal cord enkephalin is located within local interneurons, although a small fraction is known to occur within terminals of bulbospinal axons [49]. The enkephalin neurons in the marginal zone most likely act as a local negative feedback circuit, since almost all layer I neurons are nociceptive. Systemically and intrathecally administered opiates markedly inhibit layer V nociceptors, but interestingly this may be via superficial opioid receptors, since this inhibition occurs with microinjection of opiates into the substantia gelatinosa [50]. These opioid effects may be mediated either by presynaptic inhibition of nociceptive primary afferents or by acting on dendrites of layer V neurons that extend up to layers I and II. Evidence exists supporting both mechanisms of opioid action. Anatomic and physiologic evidence most directly supports a traditional postsynaptic inhibitory effect. This includes the demonstration of some specialized synapses [51], opiate-induced hyperpolarization of postsynaptic membranes [52], and the blockade of glutamate-induced depolarization [53]. Opioid receptors have been demonstrated on primary afferents [54] and on neurites of cultured dorsal root ganglion cells [55]. Dorsal rhizotomies or ganglionectomies result in 40% to 60% reductions of opioid receptors in the dorsal horn [56]. Also, capsaicin-induced destruction of C fibers results in a similar partial loss of dorsal horn opioid receptors [57]. Physiological effects on primary afferents include direct effects of opioid agonists on membrane conductance in cultured dorsal root ganglion cells [58] and hyperpolarization of primary afferent terminals in the dorsal horn [59]. Although axoaxonic contacts with synaptic specialization have not been identified in the dorsal horn, arrangements of neurons in so-called glomeruli are seen that could explain endogenous opioid release at a short distance from primary afferent terminals and a neurohumoral type of action [21].

As noted above, opiates suppress the release of substance P in the spinal cord (the putative C-fiber afferent neurotransmitter). Systemic opiates selectively reduce dorsal horn neuron responses to A-delta/C afferent stimulation

and painful somatic and visceral stimuli without changing responses to A-beta afferent stimulation or innocuous stimuli [60, 61]. In addition, iontophoresed opiates suppress the activity in ascending nociceptive neurons (e.g., spinoreticular and spinothalamic) [62]. All of the above information helps to explain the potent and specific analgesia achieved by spinally administered morphine as demonstrated in rat, cat, primate, and humans [63–66]. Morphine selectively inhibits nociceptors without altering two-point discrimination or muscle tone. Interestingly, certain types of pain appear to be much more responsive to morphine than others. Continuous pain from visceral and deep somatic structures are potently relieved, while intermittent, incisional, and deafferentation pain syndromes are poorly responsive. This may be explained by opiates affecting C-fiber-mediated nociception (e.g., burning or "second" pain), more than A-delta fiber ("first") pain.

It is important to mention briefly here that multiple subtypes of opioid receptors have been identified and have unique distributions throughout the nervous system. The two most thoroughly studied subtypes are the mu, or alkaloid, and delta, or peptide, receptors. Extensive animal studies on spinal opiate action support the concept of separate mediation of potent analgesia by the mu and delta receptors [63]. An important aspect of this phenomenon is the relative lack of cross tolerance seen between the two systems. This provides a strong impetus for the search for specific mu and delta agonists and the investigation of their possible effectiveness as intrathecally administered analgesics in humans.

Many of the putative peptide neurotransmitters occur in relatively high density in the dorsal horn. Neurotensin terminals are dense in layer II, nearly exclusively from substantia gelatinosa neurons [67], and neurotensin selectively excites spinal nociceptors when applied iontophoretically [68]. Somatostatin-containing neurons occur in layer IIi [69] and the dorsal root ganglion [70], and somatostatin is known to inhibit spinal nociceptors [71]. Other peptides found in the superficial dorsal horn include bombesin, cholecystokinin, vasoactive intestinal peptide, avian pancreatic polypeptide hormone, and oxytocin [69, 72]. These peptides often occur in neurons along with nonpeptidergic neurotransmitters, and it is felt that they may function as neuromodulators. The actual relevance of these peptides to the processing of nociception is not known.

Another important class of neurons present in the dorsal horn utilizes GABA as its neurotransmitter [73, 74]. GABA is known to be inhibitory on spinal nociceptors, and intrathecal baclofen (a GABA-mimetic agent) is analgesic in animal studies [75]. Its physiologic role in nociception is not yet known.

Other neurotransmitter candidates (including substance P, enkephalin, somatostatin, thyrotropin releasing hormone, norepinephrine, and serotonin) are implicated in bulbospinal pathways that may modulate nociception. These will be discussed below.

Supraspinal Pain Pathways

It is classically held that the spinothalamic tract is the principal pain pathway. However, in actuality it appears that multiple parallel pathways carry important nociceptive inputs to several different supraspinal regions. Anterolateral cordotomies provide effective pain relief by severing the tracts that travel in the anterolateral quadrant of the spinal cord. These include the spinothalamic tract, and the spinoreticular, spinotectal and many propriospinal fibers. It is not known which, if any, of these individual tracts is most important for pain perception.

Most layers of the spinal cord have inputs to the thalamus [76, 77]. Primarily layers I and V give rise to the lateral thalamic inputs that carry localized pain sensations. However, there are also layer IV and VI inputs to the lateral thalamus that are not nociceptive, since

layer IV neurons respond only to non-noxious tactile stimuli and layer VI neurons to joint manipulation. Layers I, VII, and VIII provide inputs to the intralaminar nuclei of the medial thalamus. Layers VII and VIII of the ventral horn have neurons with wide receptive fields and respond to a wide dynamic range of stimuli (non-noxious and noxious). This type of input has been postulated to be the most relevant to clinically seen chronic pain syndromes.

Spinal inputs to the reticular formation are now felt to be very important for nociception and very possibly in chronic pain situations. They primarily originate from layers VII and VIII [78], and most medullary reticular formation cells respond to noxious stimuli with large, bilateral receptive fields. Reticular formation stimulation evokes pain behavior in the cat [79].

To summarize, the anterolateral tracts can be divided into two distinct systems as they reach supraspinal levels. The lateral system subserves pain, burning, and discriminative thermal sensations. This tract maintains a strict somatotopic organization and provides for the perception of sharp, well-localized painful stimuli. Peripheral nociceptive afferents reach nociceptive spinal cells (primarily layers I and V) and from there the neospinothalamic tract crosses and ascends to the ventral posterior and adjacent posterior thalamic nuclei, and from there is relayed to the primary sensory cortex along the posterior bank of the Rolandic fissure. Stimulation of this cortical region elicits well-localized pain sensations, and ablations produce small areas of analgesia [80]. The medial is the paleospinothalamic system, which originates in layers V–VIII and passes via multisynaptic relays to the mesencephalic region and the medial thalamic zone (the centralis lateralis, parafascicularis, and centrum medianum). It is not clear what if any important cortical connections exist. This system seems to be relevant to pain sensation only in deafferented patients, since in normal subjects stimulation in the mesencephalic portion yields only occasional pain/burning responses and in the medial thalamic zone produces no sensation. However, stimulation in this thalamic zone in patients with deafferentation pain syndromes yields severe pain and burning in the deafferented regions [81]. Thus, this system at least serves as an alternative mechanism for nociception.

Selective lesions of the lateral spinothalamic tract at the midbrain-thalamic junction can eliminate the localized pain sensation without altering diffuse, burning, and chronic pain. Thus the other two pathways described above, the medial spinothalamic and spinoreticular pathways, are likely to be primarily responsible for the conduction of diffuse or chronic pain inputs.

It is also known that anterolateral cordotomies only temporarily eliminate pain sensation, suggesting that an alternative pathway must at least have the potential to carry nociceptive input. While the dorsal columns can respond to noxious stimuli, under normal circumstances the anterolateral pathways are necessary for the perception of these stimuli as painful. The dorsal-column postsynaptic (DCPS) spinomedullary system is an ipsilateral ascending pathway involved in nociception that travels in the dorsal columns and terminates in the dorsal column nuclei [82]. The cells of origin are mostly in layers III and IV of the dorsal horn. As noted previously, these neurons almost exclusively respond to low-threshold (i.e., non-noxious) mechanical stimuli, however, the DCPS system contains equal numbers of wide dynamic range and low-threshold mechanoreceptive neurons [83]. It is not known to what extent this pathway is involved in pain sensation, but it is likely involved in the recurrence of pain subsequent to anterolateral cordotomies. The failure of bilateral spinal cord hemisections separated by

two root levels to abolish pain suggests that short-chain polysynaptic pathway(s) can relay pain [8].

The location and characteristics of the nociceptors of the thalamic and cortical levels are not well understood. Electrophysiologic studies reveal some nociceptors in the medial thalamic zone and many in the ventral posterior medial and lateral nuclei [85]. Although the ventral posterior medial (face) and lateral (body) nuclei carry nociceptive information with a strict somatotopic representation, the electrophysiologically identified nociceptors in the thalamus do not have a somatotopic organization. In primates, nociceptors are also found in the postcentral gyrus cortical projection area of the ventral posterior lateral nucleus [86]. There is some reason to think that much pain sensation becomes conscious at a thalamic level. Large cortical ablations, even including the postcentral gyrus, produce minimal changes in pain sensation [87]. Thus the actual cortical localization of the pain message is not definitely known.

Some studies have suggested certain physiologic changes that may underlie certain chronic pain syndromes. Chronic pain models convert lateral thalamic neurons from primarily non-nociceptors with very low spontaneous activity to neurons with much spontaneous activity, and a relatively high fraction become nociceptors [85]. The medial thalamic zone is of unclear importance as a pain relay, since some studies report pain relief with large lesions of this area, while others found no significant pain relief [88].

Pain Modulatory Systems

Over the past 20 years there has been rapid expansion of our knowledge regarding previously unknown nervous system mechanisms that appear to play an important role in modifying nociception. The first significant consideration of these mechanisms was the proposal of the gate control theory by Melzack and Wall [89]. Subsequently, empirical observations of profound inhibitions of pain induced by electrical stimulation of certain brain areas provided the first strong evidence that such mechanisms actually exist [90, 91]. Most importantly, it has been the exhaustive investigation of the endogenous opioid system and the detailed mechanism of action of exogenous opiates [92] that has led to our present understanding of these important neuronal mechanisms.

Briefly summarized, the originally proposed gate control theory held that the sensation of pain (i.e., nociception) depended on the balance of activity in the large- and small-diameter afferent fibers. This largely resulted from the observation that activity in large-diameter afferents appeared to significantly decrease pain perception under certain conditions. Melzack and Wall originally proposed that the key interaction occurred in the substantia gelatinosa, where large-diameter afferents would activate interneurons that would inhibit ascending nociceptive systems. Furthermore, small-diameter (nociceptive) afferents both activate ascending nociceptive systems and inhibit the inhibitory interneurons in the substantia gelatinosa. We now know that many of the mechanisms detailed in this theory are not in effect, however, there is strong evidence supporting the general proposition that large-diameter afferents inhibit nociception at the spinal cord level. The anatomical location and exact mechanism of this inhibition is not known. The large-diameter afferents have no direct input to the substantia gelatinosa so that if they inhibit substantia gelatinosa nociceptors, it must be via interneurons. Their spinal cord terminations are mainly in layers III and IV, but their activity could be relayed via interneurons to substantia gelatinosa neurons. Inhibitory interneurons have been identified in the substantia gelatinosa, including GABAergic and en-

kephalinergic neurons, which synapse either on the dendrites or cell bodies of second-order neurons or, in rare cases, on or near small-diameter afferent axon terminals (see above). Acupuncture analgesia is possibly the best example of the gate control theory. Two distinct types of electroacupuncture analgesia have been demonstrated. One type utilizes low-intensity/high-frequency stimulation and produces a non-naloxone reversible local analgesia, while the second type uses high-intensity/low-frequency stimulation to produce a naloxone-reversible relatively generalized analgesia [93]. Thus, the second type appears to involve an activation of the enkephalinergic spinal cord neurons. While both types involve the general mechanism of nociception inhibition via the activation of afferents, it is not known which afferents (i.e., large versus small diameter) mediate this inhibition. It may in fact not be solely the large-diameter non-nociceptive afferents, as proposed by the gate control theory.

These phenomena demonstrated the existence of a spinal mechanism of nociceptive modulation. The empirical observation that electrical stimulation in specific brain regions produces a profound analgesia revealed the existence of a distinct supraspinal mechanism for the modulation of nociception. These studies were initially carried out in animals [90, 91], and subsequently similar results were obtained in human patients [94, 95]. The regions that most effectively elicit analgesia are the diencephalic periventricular and midbrain periaqueductal gray matter (PVG and PAG). A large body of evidence supports the conclusion that the analgesia is mediated by multiple descending inhibitory pathways that utilize various neurotransmitters. Enkephalin neurons and opioid receptors play an important role in some of these processes.

Much is now known regarding the anatomy, physiology, and neurochemistry of brain-stem-activated descending modulatory systems. The PVG/PAG region exerts its influence on nociceptive processing in the dorsal horn indirectly via the region of the raphe nuclei [96, 97]. The descending pathway travels in the dorsolateral funiculus (DLF) of the spinal cord, since lesioning the DLF blocks PAG-stimulation-produced analgesia [98]. The neurons that compose the DLF are primarily in the ventral tegmentum of the rostral medulla and caudal pons, particularly the nucleus raphe magnus (NRM) and the adjacent reticular formation ventral to the nucleus reticularis gigantocellularis [99]. These neurons project mostly to layers I, II, and V of the dorsal horn, prime locations of nociceptive processing. Stimulation of the NRM can produce analgesia and decrease the firing of nociceptive dorsal horn cells [100]. In humans, stimulation of the ventrobasal complex of the thalamus can also produce analgesia [101]. In primates, this stimulation inhibits spinothalamic tract cell firing via descending pathways that travel in both the dorsolateral and the ipsilateral lateral funiculi [102]. The descending pathways have various specific origins, courses, and afferent innervation.

There is still significant controversy regarding the various neurotransmitters that appear to be utilized by various components of these pathways. At present the three most important neurotransmitters known to be involved in these modulatory pathways are enkephalin (endogenous opioids), serotonin, and norepinephrine. Others have been implicated as having roles, but only these will be considered here. The discovery of opioid receptors [92], and subsequently their endogenous ligands or neuromodulators (enkephalins, beta-endorphin, and dynorphin) (see review in [103]), resulted in a rapid expansion of our knowledge of the central nervous system's modulation of nociception. The various endogenous opioid ligands are generally termed *endorphins*. Opioid receptors and the endorphins are particularly concentrated in key anatomical regions that play a role in the inhibition of nocicep-

tion. As noted above, opioid receptors and endorphins are concentrated in the spinal cord regions involved in the processing of nociception. Also, they are concentrated in the periventricular and periaqueductal gray regions and raphe nuclei. This information led to extensive investigations into the mechanism of action of opioid agonists, such as morphine. It was discovered that microinjection of morphine into the PAG produces profound analgesia [103] and markedly depresses nociceptor responses in the dorsal horn [104]. Descending impulses from the brain stem via the DLF are necessary for systemic morphine analgesia at low morphine doses [105]. Additive analgesic effects are seen with selective morphine administration into the fourth ventricle and spinal intrathecal space, and spinal intrathecal naloxone blocks the analgesia induced by fourth ventricular administration [106]. Analgesia can also be produced by microinjection of morphine into the nucleus raphe magnus and adjacent ventral tegmentum (110). Analgesia produced by stimulation of this region is also naloxone reversible [108]. A small number of enkephalin neurons in the ventral medulla project to the spinal cord and may partly transmit inhibitory input to the dorsal horn [109]. While this knowledge helps us to understand the mechanisms by which opioid agonists produce analgesia, it is not yet known to what extent the endogenous opioid system is naturally active in influencing pain perception.

Investigations have been conducted both in animals and humans to determine what situations may activate endogenous analgesic mechanisms. The ability of naloxone to reverse acupuncture analgesia in some cases suggests the involvement of endogenous opioid neurons [110]. Naloxone reversal of placebo-induced analgesia has raised the possibility that this analgesia may be mediated by opioid neurons [111]. Certain stimuli in animals (such as foot shock) produce analgesia. For example, brief front-paw shock produces a naloxone-reversible analgesia that is cross tolerant with morphine, while hind-paw shock produces a non-naloxone-reversible analgesia [112, 113]. The front-paw-shock-induced analgesia is also blocked by medullary raphe nuclei and dorsolateral funiculus cord lesions and lumbar, but not thoracic, intrathecal naloxone, suggesting the existence of a critical opioid synapse in the lumbar spinal cord [114]. Naloxone prevents the analgesia but cannot reverse it, suggesting that activation of an endogenous opioid system produces a prolonged effect on nociception that is no longer dependent on continued opioid action. Opioids may thus be acting as neuromodulators (i.e., altering the response to classical neurotransmitters). Decerebration does not alter front-paw-shock-induced analgesia, however, classical conditioning can be used to provoke analgesia that is abolished by decerebration, PAG lesions, or naloxone [114]. Hind-paw, foot-shock-induced analgesia is only partially decreased by dorsolateral funiculus lesions, thus much of its analgesia is mediated by intraspinal mechanisms that are not opioid mediated. Also, serotonin and norepinephrine depletion do not alter this analgesia, while serotonin depletion markedly decreases front-paw, foot-shock-induced analgesia. To summarize, various neural mechanisms can be utilized to modulate nociception. Conditioned stimuli can activate a descending pathway via the PAG, the medullary raphe region, and the dorsolateral funiculus that has an important opioid synapse in the spinal cord. This same system can be directly activated at the medullary level by front-paw shock. Hind-paw-shock-induced analgesia is mediated by nonopioid systems that are either wholly intraspinal or supraspinal (descending via the dorsolateral funiculus).

The degree to which any of these endogenous analgesia mechanisms are important in humans is not known. Naloxone can decrease pain thresholds in subjects with relatively high baseline thresholds [115] and can increase pain

in certain clinical pain states. Two different forms of acupuncture analgesia are analogous to the front-paw and hind-paw foot-shock paradigms, respectively. Traditional acupuncture yields analgesia in areas distant from the point of stimulation and can be naloxone reversible [110], while electroacupuncture yields analgesia in adjacent areas only and is not naloxone reversible [116].

There is now a large body of evidence that a descending serotonin projection originating in the nucleus raphe magnus (NRM) plays a very important role in the modulation of nociception at the spinal cord level [98]. Stimulation of the NRM produces behavioral analgesia and increased serotonin synthesis and release [117, 118]. Repeated stimulation leads to diminished analgesia coincident with decreased serotonin release that is reversed by the administration of L-tryptophan (a serotonin precursor) [119]. This is also true of tolerance to PAG stimulation analgesia [120], which as noted previously appears to operate via the raphe nuclei. The front-paw, foot-shock-induced analgesia described above is markedly decreased by spinal cord serotonin depletion, while the hind-paw, foot-shock-induced analgesia is not altered by serotonin and norepinephrine depletion. Serotonin iontophoresed in the spinal cord dorsal horn decreases the responses of many cells to noxious stimuli, including spinothalamic tract neurons [121, 122]. Intrathecal serotonin or its precursor is analgesic in animals and this analgesia is blocked by serotonin antagonists [123]. Systemic morphine and microinjections of morphine into the PAG and nucleus raphe magnus both increase serotonin release in the dorsal horn of the spinal cord [124–126]. It is particularly significant that with morphine tolerance, increasing doses of morphine are needed both for analgesia and to increase the spinal cord release of serotonin [127]. Serotonin-induced analgesia is not mediated by spinal enkephalin neurons, since it is not naloxone reversible [128]. Thus many very different lines of evidence strongly support the important role of descending serotonin pathway(s) in mediating the nervous system's modulation of nociception.

There is a much smaller amount of evidence implicating a role for descending brain stem norepinephrine in the modulation of nociception [121, 129]. In fact some studies have suggested that norepinephrine may be more potent than serotonin in mediating spinal-cord-level analgesia. Antagonists of alpha-adrenergic receptors can markedly decrease analgesia produced by morphine injection into the PAG [63].

Certainly many other neurotransmitters have been implicated as having roles in nociceptive modulation. We have much to learn before we understand the various nervous system mechanisms involved in modifying nociception.

Summary

Pain is both a universal sensation/perception that is essential for survival and the source of tremendous suffering. The elimination or control of pain has been a prime objective of physicians throughout history. Our success in this endeavor requires a thorough understanding of the mechanisms by which we perceive pain. This chapter provides an overview of the anatomical pathways, with their physiology and chemistry, that are responsible for transmitting and modulating the awareness of pain. The pain message is initiated in specific peripheral nociceptors, passes through specific relays in the spinal cord, is carried via certain pathways through the brain stem and thalamus, and then reaches a conscious level within the thalamus and cerebral cortex. Endogenous systems exist at brain stem and spinal cord levels that are capable of powerful modulation of the pain message, either spontaneously or via exogenous activation. Our knowledge and understanding of these systems has been expanding rapidly over the past 20 years and has

greatly enhanced our ability to treat patients with pain. However, a great deal remains to be learned regarding this complex aspect of the human nervous system. Particularly, our expanding understanding of the neurochemistry of nociception has the potential to provide important new therapeutic modalities that will greatly improve our ability to relieve clinical pain syndromes.

References

1. Sherrington CS: The Integrative Action of the Nervous System. Charles Scribner's Sons, New York, 1906.
2. Head H, Rivers WHR, Sherren J: The afferent nervous system from a new aspect. Brain 28:99–15, 1905.
3. Ranson SW: Unmyelinated nerve fibers as conductors of protopathic sensation Brain 38:381–389, 1915.
4. Lewis T, Pickering GW, Rothschild P: Centripetal paralysis arising out of arrested blood flow to the limb, including notes on a form of tingling Heart 16:1–32, 1931.
5. Zotterman Y: Studies in the peripheral nervous mechanism of pain. Acta Med Scand 80:185–242, 1933.
6. Heinbecker P, Bishop GH, O'Leary J: Pain and touch fibers in peripheral nerves.
7. Clark D, Hughes J, and Gasser HS: Afferent function in the group of nerve fibers of slowest conduction velocity.
8. Lewis T, Pochin EE: The double pain response of the human skin to a single stimulus. Clin Sci 3:67–76, 1937.
9. Landau W, Bishop GH: Pain from dermal, periosteal, and fascial endings and from inflammation. Arch Neurol Pyschiat 69:490–504, 1953.
10. Sinclair DC, Hinshaw JR: A comparison of the sensory dissociation produced by procaine and by limb compression. Brain 73: 480–498, 1950.
11. Collins WF Jr, Nulsen FE, Randt CT: Relation of peripheral nerve fiber size and sensation in man. Arch Neurol 3:381–385, 1960.
12. Willis WD, Coggeshall RE: Sensory Mechanisms in the Spinal Cord. Plenum Press, New York 1978.
13. Burgess PR, Perl ER: Myelinated afferent fibres responding specifically to noxious stimulation of the skin. J Physiol (Lond) 190:541–562, 1967.
14. Perl ER: Myelinated afferent fibres innervating the primate skin and their response to noxious stimuli. J Physiol (Lond) 197: 593–615, 1968.
15. Campbell JN, Meyer RA, LaMotte RH: Sensitization of myelinated nociceptive afferents that innervate monkey hand. J Neurophysiol 42:1669–1680, 1979.
16. Campbell JN, Meyer RA, Jaffe SR: Comparison of the neural mechanisms of hyperalgesia in glabrous and hair skin. Pain (Suppl) 1:99, 1981.
17. Kumazawa T, Perl ER: Primate cutaneous sensory units with unmyelinated (C) afferent fibers. J Neurophysiol 40:1325–1338, 1977.
18. King JS, Gallant P, Myerson V, Perl ER: The effects of anti-inflammatory agents on the responses and the sensitization of unmyelinated (C) fiber polymodal nociceptors. In: Sensory Functions of the Skin in Primates, Vol 27, Zotterman, Y, ed. Pergamon Press, Oxford, 1976, pp 441–454.
19. Perl ER, Kumazawa T, Lynn B, Kenins P: Sensitization of high threshold receptors with unmyelinated C-afferent fibres. In: Somatosensory and Visceral Receptor Mechanisms, Progress in Brain Research, Vol. 43, Iggo A, Ilyensky DB, eds. Elsevier/North Holland, Amsterdam, 1976, pp 265–277.
20. Ong B, Singer G, Wallace M: Pain sensations produced by algogens in humans. In: Problems in Pain, Peck C, Wallace M, eds. Pergamon Press, Oxford, 1980, pp 34–43.
21. Chevy-Croze S, Duclaux R: Discrimination of painful stimuli in human beings. J Neurophysiol 44:1–10, 1980.
22. Torebjork HE, Hallin RG: Skin receptors supplied by unmyelinated (C) fibres in man. In: Sensory Function of the Skin in Primates, Zotterman Y, ed. Pergamon Press, New York, 1976, pp 475–487.
23. Torebjork HE, Hallin RG: Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact skin nerves. Exp Brain Res 16:321–332, 1973.
24. Devor M, Janig W: Activation of myelinated afferents ending in a neuroma by stimulation of the sympathetic supply in the rat. Neurosci Lett 24:43–47, 1981.
25. LaMotte RH, Thalhammer JG, Robinson CJ: Peripheral neural correlates of the magni-

tude of cutaneous pain and hyperalgesia: A comparison of neural events in monkey with sensory events in human. J Neurophysiol 50:1–26, 1983.
26. Kruger L, Perl ER, Sedirec MJ: Fine structure of myelinated mechanical nociceptor endings in cat hairy skin. J Comp Neurol 198:137–154, 1981.
27. Rethelyi M, Light AR, Perl ER: Synaptic complexes formed by functionally defined primary afferent units with fine myelinated fibers. J Comp Neurol 207:381–393, 1982.
28. Ranson SW: The tract of Lissauer and the substantia gelatinosa Rolandi. Am J Anat 16:97–126, 1914.
29. Wood JN, Anderton B: Monoclonal antibodies to mammalian neurofilaments. Biosci Rep 1:263–268, 1981.
30. Hokfelt T, Johansson O, Ljungdahl A, Lundberg JM, Schultzberg M: Peptidergic neurons. Nature 284:515–521, 1980.
31. Dodd J, Jahr CE, Jessell TM: Neurotransmitters and neuronal markers at sensory synapses in the dorsal horn. In: Advances in Pain Research and Therapy, Vol. 6, Kruger, and Liebeskind, JC, eds. Raven Press, New York, 1984.
32. Jessell TM: Substance P in the nervous system. In: Handbook of Psychopharmacology, Vol. 16, Iversen LI, Iverson SD, Snyder SH, eds. Plenum Press, New York, 1983, pp 1–105.
33. Campbell JN, Meyer RA: Primary afferents and analgesia. In: Spinal Afferent Processing, Yaksh TL, ed. Plenum Press, New York, 1986.
34. Khan AA, Raja SN, Campbell JN, Hartke TV, Meyer RA: Bradykinin sensitizes nociceptors to heat stimuli. Neurosci Abstr 12:218, 1986.
35. Manning DC, Snyder SH: 3H-Bradykinin receptor localization in spinal cord and sensory ganglia — evidence for a role in primary afferent function, Neurosci Abstr 9:590, 1983.
36. Steranka LR, DeHaas CJ, Varrek RJ, Stewart JM, Enna SJ, Snyder SH: Antinociceptive effects of bradykinin antagonists. Eur J Pharm 136:261–262, 1987.
37. Wall PD, Devor M: The effect of peripheral nerve injury on dorsal root potentials and on transmission of afferent signals into the spinal cord. Brain Res 209:95–111, 1981.
38. Wall PD, Gutnich M: Ongoing activity in peripheral nerves, II. The physiology and pharmacology of impulses originating in neuroma. Exp Neurol 43:580–593, 1974.
39. Seltzer Z, Devor M: Ephaptic transmission in chronically damaged peripheral nerves. Neurology 29:1061–1064, 1979.
40. Rexed B: The cytoarchitectonic organization of the spinal cord in the cat. J Comp Neurol 96:415–496, 1952.
41. Gobel S: Golgi studies of the neurons in layer I of the dorsal horn of the medulla (trigeminal nucleus caudalis). J Comp Neurol 180:375–394, 1978.
42. Light AR, Trevino DL, Perl ER: Morphological features of functionally defined neurons in the marginal zone and substantia gelatinosa of the spinal dorsal horn. J Comp Neurol 186:151–172, 1979.
43. Gobel S: Golgi studies of the neurons in layer II of the dorsal horn of the medulla (trigeminal nucleus caudalis). J Comp Neurol 180:395–413, 1978.
44. Bennett GJ, Abdelmoumene M, Hayashi H, Dubner R: Physiology and morphology of substantia gelatinosa neurons intracellularly stained with horseradish peroxidase. J Comp Neurol 194:809–827, 1980.
45. Krieger DT, Brownstein MJ, Martin JB (eds): Brain Peptides, John Wiley and Sons, New York, 1983.
46. Glazer EJ, Basbaum AI: Immunohistochemical localization of leucine-enkephalin in the spinal cord of the cat: Enkephalin-containing marginal neurons and pain modulation. J Comp Neurol 196:377–390, 1981.
47. Hokfelt T, Ljungdahl A, Terenius L, Elde R, Nilsson G. Immunohistochemical analysis of peptide pathways possibly related to pain and analgesia: Enkephalin and substance P. Proc Natl Acad Sci USA 74:3081–3085, 1977.
48. Moskowitz AS, Goodman RR: Light microscopic autoradiographic localization of mu and delta opioid binding sites in the mouse central nervous system. J Neurosci 4: 1331–1342, 1984.
49. Hokfelt T, Terenius L, Kuypers HG, Dann O: Evidence for enkephalin immunoreactive neurons in the medulla oblongata projecting to the spinal cord. Neurosci Lett 14:55–60, 1979.
50. Duggan AW, Hall JG, Headley PM: Morphine, enkephalin and the substantia gelatinosa. Nature 264:456–458, 1976.
51. Hamel E, Beaudet A: Electron microscopic

autoradiographic localization of opioid receptors in rat neostriatum. Nature 312:155–157, 1984.
52. Pepper CM, Henderson G: Opiates and opioid peptides hyperpolarize locus coeruleus neurons in vitro. Science 209:394–396, 1980.
53. Zieglgansberger W, Sutor B: Responses of substantia gelatinosa neurons to putative neurotransmitters in an in vitro preparation of the adult rat spinal cord. Brain Res 279:316–320, 1983.
54. Fields HL, Emson PC, Leigh BK, Iversen LL: Multiple opiate receptor sites on primary afferent fibres. Nature 284:351–353, 1980.
55. Hiller JM, Simon EJ, Crain SM, Peterson ER: Opiate receptors in cultures of fetal mouse dorsal root ganglia (DRG) and spinal cord: Predominance in DRG neurites. Brain Res 145:396–400, 1978.
56. LaMotte C, Pert CB, Snyder SH: Opiate receptor binding in primate spinal cord: Distribution and changes after dorsal root section. Brain Res 112:407–412, 1976.
57. Gamse R, Holzer P, Lembeck F: Indirect evidence for presynaptic location of opiate receptors on chemosensitive primary sensory neurons. Naunyn Schmiedebergs Arch Pharmacol 308:281–285, 1979.
58. Mudge AW, Leeman SE, Fischbach GD: Enkephalin inhibits release of substance P from sensory neurons in culture and decreases action potential duration. Proc Natl Acad Sci USA 76:526–530, 1979.
59. Carstens E, Tulloch I, Zieglgansberger W, Zimmerman M: Presynaptic excitability changes induced by morphine in single cutaneous afferent C- and A-fibers. Pfluegers Arch 379:143–147, 1979.
60. Einspahr FJ, Piercey MF: Morphine depresses dorsal horn neuron responses to controlled noxious and non-noxious cutaneous stimulation. J Pharmacol Exp Ther 213: 456–461, 1980.
61. Yaksh TL: Analgetic actions of intrathecal opiates in cat and primate. Brain Res 153:205–215, 1978.
62. Jurna I, Heinz G: Differential effects of morphine and opioid analgesics on A and C fibre-evoked activity in ascending axons of the rat spinal cord. Brain Res 171:573–576, 1979.
63. Yaksh TL: Opioid receptor systems and the endorphins: A review of their spinal organization. J Neurosurg 67:157–176, 1987.
64. Coombs DW, Saunders RL, Gaylor MS, Block AR, Colton T, Harbaugh R, Pageau MG, Mroz W: Relief of continuous chronic pain by intraspinal narcotics infusion via an implanted reservoir. JAMA 250:2336–2339, 1983.
65. Auld AW, Maki-Jokela A, Murdoch DM: Intraspinal narcotic analgesia in the treatment of chronic pain. Spine 10:777–781, 1985.
66. Penn RD, Paice JA: Chronic intrathecal morphine for intractable pain. J Neurosurg 67:182–186, 1987.
67. Seybold V, Elde R: Neurotensin immunoreactivity in the superficial laminae of the dorsal horn of the rat. I. Light microscopic studies of cell bodies and proximal dendrites. J Comp Neurol 205:89–100, 1982.
68. Miletic V, Randic M: Neurotensin excites cat spinal neurons located in laminae I–III. Brain Res 169:600–604, 1979.
69. Hunt SP, Kelly JS, Emson PC, Kimmel JR, Miller RJ, Wu J-Y: An immunohistochemical study of neuronal populations containing neuro-peptides or gamma-aminobutyrate within the superficial layers of the rat dorsal horn. Neuroscience 6:1883–1898, 1981.
70. Hokfelt T, Elde R, Johansson O, Luft R, Nilsson G, Arimura A: Immunohistochemical evidence for separate populations of somatostatin-containing and substance P-containing primary afferent neurons. Neuroscience 1:131–136, 1976.
71. Randic M, Miletic V: Depressant actions of methionine-enkephalin and somatostatin in cat dorsal horn neurons activated by noxious stimuli. Brain Res 152:196–202, 1978.
72. Swanson LW, McKellar S: The distribution of oxytocin- and neurophysin-stained fibers in the spinal cord of the rat and monkey. J Comp Neurol 188:87–106, 1979.
73. Barber RP, Vaughn JE, Saito K, McLaughlin BJ, Roberts E: GABAergic terminals in the substantia gelatinosa of the rat spinal cord. Brain Res 141:35–55, 1979.
74. Basbaum AI, Glazer EJ, Oertel W: A light and EM analysis of immunoreactive glutamic acid decarboxylase (GAD) in the spinal and trigeminal dorsal horn of the cat. Neurosci Abst 7:528, 1981.
75. Wilson PR, Yaksh TL: Baclofen is antinociceptive in the spinal intrathecal space of animals. Eur J Pharmacol 51:323–330, 1978.
76. Carstens E, Trevino DL: Laminar origins of spinothalamic projections in the cat as deter-

mined by the retrograde transport of HRP. J Comp Neurol 182:151–166, 1978.
77. Willis WD, Kenshalo DR Jr, Leonard RB: The cells of origin of the primate spinothalamic tract J Comp Neurol 188:543–574, 1979.
78. Abols IA, Basbaum AI: Afferent connections of the rostral medulla of the cat: A neural substrate for midbrain-medullary interactions in the modulation of pain. J Comp Neurol 201:285–297, 1981.
79. Casey KL: Somatosensory responses of bulboreticular units in awake cat: Relation to escape-producing stimuli. Science 173: 77–80, 1971.
80. Albe-Fessard D, Berkley RJ, Kruger L, Ralston HJ 3d, Willis WD Jr: Diencephalic mechanisms of pain sensation. Brain Res 356:217–96, 1985.
81. Tasker RR: Deafferentation. In: Textbook of Pain, Wall PD, ed. Churchill-Livingstone, London, 1984, pp 119–132.
82. Rustioni A, Hayes NL, O'Neill S: Dorsal column nuclei and ascending spinal afferents in macaques. Brain 102:95–125, 1979.
83. Lu G-W, Bennett GJ, Nishikawa N, Hoffert MJ, Dubner R: Extra- and intra-cellular recordings from dorsal column postsynaptic spinomedullary neurons in the cat. Exp Neurol 82:456–77, 1983.
84. Basbaum A: Conduction of the effects of noxious stimulation by short fiber systems in the spinal cord of rat. Exp Neurol 40:699–716, 1973.
85. Guilbaud G, Gautron M, Peschanski M: Electrophysiological responses of neurons of the thalamic ventrobasal complex to cutaneous and articular stimulation in rats exhibiting inflammatory polyarthritis. CR des Sciences 292:227–230, 1981.
86. Kenshalo DR Jr, Isensee O: Response of primate SI cortical neurons to noxious stimuli. Neurosci Abstr 6:245, 1980.
87. Lende RA, Kirsh WM, Druckman R: Relief of facial pain after combined removal of precentral and post-central cortex. J Neurosurg 34:537–543, 1971.
88. Cassinari V, Pagni CA: Central Pain. Harvard University Press, Boston, 1969.
89. Melzack R, Wall PD: Pain mechanisms: A new theory. Science 150:971–979, 1965.
90. Reynolds DV: Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science 164:444–445, 1969.
91. Mayer DJ, Liebeskind JC: Pain reduction by focal electrical stimulation of the brain: anatomical and behavioral analysis. Brain Res 68:73–93, 1974.
92. Goodman RR, Adler BA, Pasternak GW: Regional distribution of opiate receptors. In: The Opiate Receptors, Pasternak GW, ed. Humana Press, Clifton NJ, 1987.
93. Sjolund BJ, Ericksson MBE: The influence of naloxone and analgesia produced by peripheral conditioning stimulation. Brain Res 178:295–302, 1979.
94. Hosobuchi Y, Adams JE, Linchitz R: Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. Science 197:183–186, 1977.
95. Richardson DE, Akil H: Pain reduction by electrical brain stimulation in man. J Neurosurg 47:178–183, 1977.
96. Behbehani MM, Fields HL: Evidence that an excitatory connection between the periaqueductal gray and nucleus raphe magnus mediates stimulation produced analgesia. Brain Res 170:85–93, 1979.
97. Abols IA, Basbaum AI: Afferent connections of the rostral medulla of the cat: A neural substrate for midbrain-medullary interactions in the modulation of pain. J Comp Neurol 201:285–297, 1981.
98. Basbaum AI, Fields HL: Endogenous pain control mechanisms: Review and hypothesis. Ann Neurol 4:451–462, 1978.
99. Basbaum AI, Fields HL: The origin of descending pathways in the dorsolateral funiculus of the spinal cord of the cat and rat: Further studies of the anatomy of pain modulation. J Comp Neurol 187:513–532, 1979.
100. Fields HL, Basbaum AI, Clanton CH, Anderson SD: Nucleus raphe magnus inhibition of spinal cord dorsal horn neurons. Brain Res 126:441–453, 1977.
101. Turnbull IM, Shulman R, Woodhurst VB: Thalamic stimulation for neuropathic pain. J Neurosurg 52:486–493, 1980.
102. Gerhart KD, Yezierski RP, Fang ZR, Willis WD: Inhibition of primate spinothalamic tract neurons by stimulation in ventral posterior lateral (VPLc) thalamic nucleus: Possible mechanisms. J Neurophysiol 49: 406–423, 1983.
103. Yaksh TL: Narcotic analgesics: CNS sites

and mechanisms of action as revealed by intracerebral injection techniques. Pain 4:299–359, 1978.
104. Bennett GJ, Mayer DJ: Inhibition of spinal cord interneurons by narcotic microinjection and focal electrical stimulation in the periaqueductal central gray matter. Brain Res 172:243–257, 1979.
105. Yeung JC, Rudy TA: Sites of antinociceptive action of systemically injected morphine: Involvement of supraspinal loci as revealed by intracerebroventricular injections of naloxone. J Pharmacol Exp Ther 215:626–632, 1980.
106. Levine JD, Lane SR, Gordon NC, Fields HL: A spinal opioid synapse mediates the interaction of spinal and brain stem sites in morphine analgesia. Brain Res 236:85–91, 1982.
107. Dickenson AH, Oliveras JL, Besson JM: Role of the nucleus raphe magnus in opiate analgesia as studied by the microinjection technique in the rat. Brain Res 170:95–111, 1979.
108. Zorman G, Hentall ID, Adams JE, Fields HL: Naloxone-reversible analgesia produced by microstimulation in the rat medulla. Brain Res 219:137–148, 1981.
109. Hokfelt T, Terenius L, Kuypers HG, Dann O: Evidence for enkephalin immunoreactive neurons in the medulla oblongata projecting to the spinal cord. Neurosci Lett 14:55–60, 1979.
110. Mayer DJ, Price DD, Rafii A: Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. Brain Res 121:368–372, 1977.
111. Levine JD, Gordon NC, Fields HL: The mechanism of placebo analgesia. Lancet 2:645–657, 1978.
112. Mayer DJ, Watkins LR: The role of endorphins in pain control systems. Modern Problems of Pharmacopsychiatry: The Role of Endorphins in Neuropsychiatry, Emrich HM, ed. pp 68–96, S Karger, Basel, 1981.
113. Watkins LR, Cobelli DA, Faris P, Aceto MD, Mayer DJ: Opiate vs. non-opiate footshock-induced analgesia (FSIA): The body region shocked is a critical factor. Brain Res 242:299–308, 1982.
114. Watkins LR, Mayer DJ: Organization of endogenous opiate and non-opiate pain control systems. Science 216:1185–1192, 1982.
115. Buchsbaum MS, Davis GC, Bunney WE Jr: Naloxone alters pain perception and somatosensory evoked potentials in normal subjects. Nature 270:620–622, 1977.
116. Chapman CR, Benedetti C: Analgesia following transcutaneous electrical stimulation and its partial reversal by a narcotic antagonist. Life Sci 21:1645–1648, 1977.
117. Oliveras JL, Hosobuchi Y, Bruxelle J, Passot C, Besson JM: Analgesic effects induced by electrical stimulation of the nucleus raphe magnus in the rat: Interaction with morphine analgesia. Abstr 7th Int Cong Pharmacol 1:280, 1978.
118. Rivot JP, Chiang CY, Besson JM: Increase of serotonin metabolism within dorsal horn of the spinal cord during nucleus raphe magnus stimulation, as revealed by in vivo electrochemical detection. Brain Res 238:117–126, 1982.
119. Oliveras JL, Hosobuchi Y, Guilbaud G, Besson JM: Analgesic electrical stimulation of the feline nucleus raphe magnus: Development of tolerance and its reversal by 5-HTP. Brain Res 146:404–409, 1978.
120. Hosobuchi Y: Tryptophan reversal of tolerance to analgesia induced by central gray stimulation. Lancet 2:47, 1978.
121. Headley PM, Duggan AW, Griersmith BT: Selective reduction by noradrenaline and 5-hydroxytryptamine of nociceptive responses of cat dorsal horn neurones. Brain Res 145:185–189, 1978.
122. Jordan LM, Kenshalo DR Jr, Martin RF, Haber LH, Willis WD: Depression of primate spinothalamic tract neurons by iontophoretic application of 5-hydroxytryptamine Pain 5:135–142, 1978.
123. Yaksh TL, Wilson PR: Spinal serotonin terminal system mediates antinociception J Pharmacol Exp Ther 208:446–453, 1979.
124. Messing RB, Flinchbaugh C, Waymire JC: Tryptophan and 5-hydroxyindoles in different CNS regions following acute morphine. Eur J Pharmacol 48:137–140, 1978.
125. Vasko MR, Vogt M: Analgesia, development of tolerance, and 5-hydroxytryptamine turnover in the rat after cerebral and systemic administration of morphine. Neuroscience: 7 (5):1215–1225, 1982.
126. Yaksh TL, Tyce GM: Microinjection of morphine into periaqueductal gray provokes the release of serotonin from spinal cord.

Brain Res 171:176–181, 1979.
127. Godefroy F, Weil-Fugazza J, Bineau-Thurotte M, Besson JM: The relationship between morphine analgesia and the activity of bulbo-spinal serotonergic system as studied by tolerance phenomenon. Brain Res 226: 201–210, 1981.
128. Yaksh TL: Direct evidence that spinal serotonin and noradrenaline terminals mediate the spinal antinociceptive effects of morphine in the periaqueductal gray. Brain Res 160:180–185, 1979.

II. TRIGEMINAL NEURALGIA

3. TRIGEMINAL NEURALGIA AND OTHER FACIAL PAINS: DIAGNOSIS, NATURAL HISTORY, AND NONSURGICAL TREATMENT

Ronald Brisman, M.D.

Trigeminal neuralgia (tic douloureux) is an episodic condition of paroxysmal pain in the trigeminal distribution that is triggered by light touch. It is unilateral at any one time, is associated with a normal neurologic examination, and usually responds to carbamazepine and denervation.

Clinical Features

Trigeminal neuralgia is episodic, and patients may have weeks or months of remission interspersed with varying intervals of pain. An analysis of 155 patients seen at the Mayo Clinic in 1953 showed that

> 78 patients had experienced one or more spontaneous remissions lasting 6 months or longer and that 38 had had similar remissions of 12 or more months. [1]

Of these 38 patients, 8 had a remission lasting 3 to 5 years, and 2 had remissions of more than 5 years. Spontaneous remission may explain the apparently good responses from treatments that are probably ineffective,

> such as remissions lasting up to 4 years in 17 out of 39 patients after the extraction of apparently sound teeth [1].

It is possible that those patients seen at the Mayo Clinic may have represented a more intractable group of patients, and there may be others with even longer spontaneous remissions who do not seek further treatment for their condition.

According to Harris [2], trigeminal neuralgia becomes more chronic with the passage of time, and the intervals decrease between the episodes of pain, although some patients have periodic bouts of pain for several weeks or months every year. He describes one case where the pain disappeared with advancing age but says that is a very rare occurrence [2].

The pain is paroxysmal and is characterized by sudden bursts of extremely intense pain lasting from a few seconds to a few minutes [3] or 20–30 seconds [4]. The pain is like an "electric shock" and is followed by relative freedom from pain for a few seconds to a minute [4], to be followed again by another jab of severe pain. Attacks of these recurring pains may occur for hours. Sometimes milder forms of the pain are present.

The pain is triggered by light touch about

Modified from Medical/neurosurgical management of orafacial pain. In Handbook of Chronic Pain Management, C.D. Tollison, ed., Williams and Wilkins, Baltimore

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the face especially in the perioral area. Talking, eating, brushing the teeth, washing the face, a light wind, and, in severe cases, any movement of the body may precipitate the pain. The pain is followed by a refractory period of up to 2–3 minutes during which it is difficult to elicit pain [5].

At any one time, the pain is unilateral. The right side is more likely to be affected (58% of the time) than the left (see Chapter 5). Contralateral pain may develop sometime in the course of the illness in approximately 10% of patients (see Chapter 9).

The pain is in the trigeminal distribution, either the second or third divisions alone or in combination. The first division is affected less often, sometimes in combination with the second division (see Chapter 5).

The neurologic examination is usually normal in patients who have not had previous denervating procedures. Definite hypoalgesia in the absence of previous surgical denervation, or other neurologic abnormalities should raise the suspicion of a structural lesion involving the trigeminal nerve, such as a brain tumor or multiple sclerosis. Approximately 20% of patients with typical trigeminal neuralgia and normal computerized tomography may have abnormal areas of decreased sensation when the face is tested with careful sensory examination and the aesthesiometer [6].

Incidence of Trigeminal Neuralgia

Approximately 7000 new cases a year (3.5 per 100,000) were estimated to occur in the United States as of 1973 [7]. Older people are more likely to be affected than younger ones: The average age of onset is 55 years (see Chapter 5). As the population of this country gets older, it is probable that there will be more people with trigeminal neuralgia.

Patients with multiple sclerosis are more prone to develop trigeminal neuralgia than others [8].

The age-adjusted sex ratio is 1.17 females to 1.00 males [8]. Many series give a higher female preponderance but do not consider the age-adjusted factor, whereby there are more females than men in the older age groups.

Medical Treatment

CARBAMAZEPINE

Carbamazepine (Tegretol) is so effective in treating trigeminal neuralgia [9, 10] that the diagnosis should be doubted if the patient does not show some response to this medication. Treatment is usually begun at a dose of 100 mg twice a day. The daily dose is increased by 100 mg or 200 mg until the patient gets relief. The usual maintenance dose is a total of 400 mg to 800 mg daily, which is given in divided doses from 2 to 4 times a day. It is rarely necessary to give more than 1200 mg daily. After the patient is free of pain for several weeks, attempts should be made to reduce the dose gradually to the minimum necessary.

Many unpleasant side effects may occur from carbamazepine. The most common are dizziness, drowsiness, unsteadiness, nausea, and vomiting, and these are most likely to develop when carbamazepine is initiated or the dose is too high. They usually subside when the dose is lowered. Central nervous system toxicity is more likely to develop in the elderly (a common group afflicted with trigeminal neuralgia) and in those with multiple sclerosis. Carbamazepine is contraindicated in those with a known sensitivity to tricyclic compounds.

Other toxic effects may appear from the use of carbamazepine, these include skin rashes, bone marrow suppression, and liver or renal impairment. A complete blood and platelet count, and liver and renal chemistries should be done before beginning treatment, after 2 weeks, and at approximately 6 week intervals.

Substantial changes require that the medication be stopped.

Aplastic anemia is a rare but sometimes fatal complication of carbamazepine therapy; 20 cases (13 fatal) were reported between 1964 and 1982 [11].

BACLOFEN

If satisfactory relief cannot be obtained from carbamazepine, then baclofen (Lioresal) should be tried alone or in combination with carbamazepine (if the patient does not have a toxic reaction to carbamazepine and it is no longer effective by itself) [12]. The dose of baclofen is gradually titrated for each individual; an initial dose of 5 mg 3 times a day is given for 3 days then increased every 3 days by a total daily dose of 15 mg until the optimal dose (usually 40 mg to 80 mg) is achieved. The most common adverse reactions are drowsiness, dizziness, and fatigue.

PHENYTOIN

Although it is not effective in many patients, phenytoin (Dilantin) may be tried if treatment is not successful with carbamazepine or baclofen. The usual dose of phenytoin is 100 mg 3 or 4 times a day. In a study by White and Sweet, in only 5 of 70 patients was a medical regimen including phenytoin successful without surgical treatment, although another 8 patients were taking it as an effective supplement to surgical denervation [13]. Others have reported that phenytoin-induced pain relief was complete in 8 of 20 patients and partial in 6 [13].

Baclofen may act synergistically with either carbamazepine or phenytoin, and patients who do not respond to either medication alone may benefit from a combination of baclofen and either carbamazepine or phenytoin [12].

CLONAZEPAM

Clonazepam (Klonopin) is a benzodiazepine anticonvulsant that was effective in 65% of cases with trigeminal neuralgia [14]. The initial dose was 0.5 mg 3 times a day and was increased every 3 days by a total daily increment of 0.5 mg–1 mg until pain was relieved. Somnolence developed in 80% and unsteadiness of gait in 88%; these were severe and incapacitating in 9 of 25 patients.

MEPHENESIN

Mephenesin carbamate and chlorphenesin carbamate (Maolate) are muscle relaxants that are now used infrequently but have relieved pain in some patients with trigeminal neuralgia [4, 15]. Mephenesin carbamate provided sufficient comfort in 60% of 52 patients to make a surgical procedure unnecessary [15]. One gram to 3 grams were given orally every 3 hours. Patients who were unable to take oral medication were treated with intravenous mephenesin; 4 grams were added to 5% glucose in water, and this was given by slow intravenous drip over a 12-hour period. Some unpleasant side effects were light-headedness and unsteady gait. The dose of chlorphenesin carbamate was from 800 mg to 2400 mg per day [4], and drowsiness sometimes developed.

Related Conditions

Multiple sclerosis should be suspected in younger patients with trigeminal neuralgia (those whose symptoms began before they were 45-years-old) and those with bilateral symptoms [16]. Other diagnostic tests for multiple sclerosis such as cerebrospinal fluid examination for gamma-globulin and oligoclonal bands, visual-evoked responses, and magnetic resonance imaging should be pursued if multiple sclerosis is a possibility and microvascular decompression is being considered as treatment for the trigeminal neuralgia, because microvascular decompression is contraindicated in the presence of multiple sclerosis.

Only a few patients with trigeminal neuralgia will have a brain tumor (1%–5%), and

many of these will have other neurological abnormalities caused by the brain tumor [17]. Rarely, a patient with trigeminal neuralgia and no other signs or symptoms will have a brain tumor causing the trigeminal neuralgia. In those whose face pain symptoms are intractable enough to require a neurosurgical procedure, computerized tomography (with and without contrast) or magnetic resonance imaging [18] should be done to exclude the possibility of a brain tumor, even though most patients will not have one.

ATYPICAL TRIGEMINAL NEURALGIA

Some patients with triggered, paroxysmal pain in the trigeminal distribution have the atypical feature of constant pain that persists in between the paroxysms. These patients are often helped by the medications used for trigeminal neuralgia (carbamazepine, baclofen, phenytoin).

PRETRIGEMINAL NEURALGIA [19]

Some patients who later develop typical trigeminal neuralgia have a prodromal pain that is either dull and aching, or burning. The pain is localized to a part of one alveolar quadrant. Although it may occasionally be triggered by jaw movement, pretrigeminal neuralgia is not associated with a trigger area in the skin or mucous membrane. This pain may be episodic, and it may occur for weeks, months, or even years before the onset of true trigeminal neuralgia. A similar kind of pain occurs in association with multiple sclerosis. Pretrigeminal neuralgia does respond to carbamazepine.

TRIGEMINAL NEUROPATHY

Patients with trigeminal neuropathy show signs of trigeminal nerve dysfunction, such as hypoalgesia or hypoesthesia, or impairment of muscles of mastication and deviation of the opened jaw to the side of the lesion. There may also be pain in the distribution of one or more divisions of the trigeminal nerve; this pain may be paroxysmal and triggered by light touch, but sometimes it is continuous and not triggered. Other nearby cranial nerves may also be involved and may cause impairment of extraocular movement, facial weakness, or eighth nerve dysfunction. Tumors, infection, granuloma, vascular abnormalities, demyelinating disease, or viral infections are sometimes responsible for trigeminal neuropathy.

Peripheral tumors that involve the trigeminal nerve at the base of the skull are usually malignant and are more likely to be associated with atypical facial pains [17]. These can usually be biopsied via an otolaryngological approach and are treated with radiotherapy.

Other Facial Pains

GLOSSOPHARYNGEAL NEURALGIA

These patients have paroxysmal pain in the distribution of the glossopharyngeal and vagus nerves; the tonsillar pillars, base of the tongue, soft palate, and external auditory canal may be involved [20, 21]. Pain is triggered by swallowing or coughing, and temporary relief can be provided by spraying the throat with local anesthetics. Carbamazepine, baclofen, or phenytoin may help.

GENICULATE NEURALGIA

This has been described as pain in either the ear or the deeper structures of the face, orbit, posterior nasal, or palatal regions [22]. Sometimes there is evidence of a herpetic rash in the auricle or external auditory canal, with possible facial palsy, hearing loss, vertigo, and tinnitus. Geniculate neuralgia must be differentiated from glossopharyngeal neuralgia, which can also cause otalgia, although local anesthetics in the pharynx and tonsillar area may temporarily relieve the pain of glossopharyngeal neuralgia.

DENTAL PAIN

Pain of the dental and peridental structures is the most common cause for face pain and can usually be diagnosed by direct examination of dental structures. When diseased, these are frequently sensitive to direct percussion or cold temperature.

ATYPICAL FACIAL PAINS

These pains are often continuous, not triggered, and not confined to the distribution of one cranial nerve. Depression is frequently present [23, 24], and tricyclic antidepressants may help. Patients with atypical facial pain were significantly younger (mean 44.5 years) at onset than those with trigeminal neuralgia (mean 55.2 years) [25]. Although females outnumbered men by 2:1 in both conditions [25], the younger age of the atypical facial pain group suggests a stronger female preponderance if age-adjusted data were used. Usually there is no specific correctable underlying cause, and surgery is contraindicated because it is not likely to help and often makes the patient worse.

VASCULAR DYSFUNCTION

There are some conditions associated with face pain that are probably a result of vascular dysfunction and that respond to medications for migraine. These include cluster headache, lower-half face pain, and carotidynia. Ergotamine may abort an acute attack, and methysergide, lithium carbonate, prednisone, or propranolol may help prevent further episodes; indomethacin and calcium-channel blockers may also be helpful.

Cluster headache may involve the orbit and cheek as well as the head. Men are usually affected. During an attack there are autonomic manifestations with conjunctival congestion, lacrimation, stuffiness in nasal passages, and occasionally ptosis or myosis associated with facial sweating and ipsilateral erythema. During a cluster headache, patients often pace about. Pain lasts for 20 minutes to 2 hours and recurs at varying times every day for several weeks, then disappears and returns months or years later. (Some have suggested that cluster headache is mediated by the nervus intermedius, is a form of geniculate neuralgia, and may be relieved by section of the nervus intermedius [22, 26, 27]. However, the data are not conclusive enough to make this a standard recommendation.)

Lower-half headache is more typical of migraine, except that the pain is in the face. Women are involved more than men. The face pain is throbbing and unilateral, and may be associated with nausea, vomiting, and photophobia. Menstruation and alcohol are frequent precipitating factors, and there is usually a family history of migraine.

Carotidynia is a syndrome of lateral neck pain with radiation to the side of the face and tenderness over the carotid artery in the neck [28, 29]. The distribution of pain is not in the divisions of the trigeminal nerves, but rather along the branches of the external carotid artery. The pain is usually constant and dull with episodes of throbbing exacerbations. Pain is aggravated by palpation of the carotid artery and sometimes by turning the neck or swallowing.

A painful condition of the internal carotid artery associated with oculosympathetic paralysis and anhidrosis of the forehead is a pericarotid syndrome [30]. Pathogenetically associated conditions are migraine, cluster headache, infection, trauma, or dissecting internal carotid aneurysm; one of these is present in half the cases. In addition to treating the underlying condition when one is detected, symptomatic relief may result from the use of analgesics rather than vasoactive agents [30].

INFLAMMATORY VASCULAR DISEASES

Many patients with temporal arteritis will have pain and tenderness of the arteries of the scalp

and face in addition to systemic disease, which may present with fever, malaise, anemia, or other protean manifestations [31]. Vascular occlusion may cause blindness or infarction of the brain or facial structures. The elderly are affected, and the sedimentation rate is almost always elevated. The diagnosis is established by biopsy of the superficial temporal artery. A large segment of the artery (4–6 cm) should be obtained because pathologic abnormalities may be confined to short segments. A negative initial biopsy does not rule out the diagnosis, and contralateral biopsy is frequently positive. Corticosteroid therapy is beneficial.

Wegener's granulomatosis is associated with a systemic vasculitis but may cause pain of the paranasal sinuses, orbit, or palate [32]. Cranial neuropathy, mononeuritis multiplex, and infarction or hemorrhage of the brain may occur. Immunosuppressive therapy with cyclophosphamide is often effective.

REFLEX SYMPATHETIC DYSTROPHY [33]

Facial reflex sympathetic dystrophy may follow trauma to the face. Most of these patients have a constant burning that is exacerbated by light touch. Treatment is directed at sympathetic denervation, which can be produced by oral medication (phenoxybenzamine), repeated local anesthetic blocks of the stellate ganglion, or, rarely, sympathectomy.

POSTHERPETIC NEURALGIA

As in other forms of trigeminal neuropathy, analgesia or hypoalgesia is usually present when patients have postherpetic neuralgia of the trigeminal nerve. The appearance of vesicles establishes the diagnosis. The first division of the trigeminal nerve is usually involved, and the pain is continuous and not triggered. Occasionally there is also a paroxysmal pain.

Amitriptyline provides good to excellent pain relief in 67% of patients, as demonstrated by a double-blind crossover study [34]. The analgesia may be independent of the antidepressant effect. A single dose is given at bedtime, starting with 12.5 mg to 25 mg, and increased by half to one pill (25-mg size) every 2 to 5 days. Doses that are too high may sometimes result in increased pain, which is ameliorated after dose reduction.

Fluphenazine (Prolixin), 1 mg 3 times a day, is sometimes given in addition to amitriptyline, but the possibility of tardive dyskinesia that may develop from the use of phenothiazines (such as fluphenazine) plus the uncertainty of their benefit should temper their use.

Transcutaneous nerve stimulation is a safe technique and has helped some of these patients [4]; it is worth trying although it is frequently disappointing.

Neurosurgical procedures are rarely helpful but may be considered if there is a paroxysmal, triggered component in a patient who is not analgesic.

THALAMIC PAIN

Thalamic infarction can result in hemisensory dysfunction with agonizing, burning pain in the face as well as the rest of the body contralateral to the thalamic lesion. Tricyclic antidepressants and transcutaneous nerve stimulation [4] sometimes help. The pain may persist in spite of treatment.

EAGLE'S SYNDROME (ELONGATED STYLOID PROCESS)

Two clinical syndromes have been attributed to an elongated styloid process. The first typical form occurs after tonsillectomy and includes a sensation of a foreign body in the pharynx, pain in the ear, dysphagia, and a persistent sore throat [35]. The second atypical syndrome is similar to that described for carotidynia [36]. Tenderness in the distribution of the symptomatic pain is precipitated by palpation in the tonsillar fossa, and local anesthetics in this area abolish the pain temporarily. Panoramic radiographs demonstrate the elongated styloid process. Surgical reduc-

tion of the styloid process has been recommended if symptoms are severe [35, 36].

In a recent study [37], it was shown that the radiologic finding of elongated styloid process and/or ossification of the stylomandibular or stylohyoid ligaments occurred in about 30% of edentulous patients. There was a statistically significant relationship between facial pain and pain on turning the neck, and radiologic evidence of anatomic aberrations in the styloid-stylohyoid complex. This relation existed only in women and could not be demonstrated for the other Eagle symptoms of pain on swallowing or tinnitus. The authors concluded that the finding of elongated styloid processes is of minor clinical importance.

SINUS DISEASE

Chronic sinus disease does not usually cause face pain, although an expanding mass can produce a dull aching sensation. Sinus disease is much more likely to cause pain when it is acute. The pain of acute sinusitis is usually in the overlying face, which is often tender, although it may be referred in acute maxillary sinusitis to the eye or teeth. Acute involvement of the frontal sinus causes pain in the forehead, and acute ethmoiditis causes pain in the bridge of the nose and between and behind the eyes. Infection requires treatment with appropriate antibiotics; surgical drainage is sometimes necessary.

TEMPOROMANDIBULAR JOINT DISEASE [38, 39]

Face pain and disturbance of mandibular movement are characteristic of myofacial pain dysfunction (MPD) and temporomandibular joint (TMJ) dysfunction. The pain is a unilateral aching in the jaw with radiation to the face, ear, temple, and occasionally the lateral cervical or retroorbital region. Tenderness may be in the muscles of mastication (MPD) or joint (TMJ). In only a few patients with pain, impaired mandibular movement, and tenderness, are there organic abnormalities of the joint as demonstrated by imaging techniques; the term *TMJ disease* is restricted to these. TMJ disease may be caused by degenerative or rheumatoid arthritis, trauma, infection, or neoplasm; ankylosis or chronic dislocation may be present.

Treatment should usually be as conservative as possible. Excessive muscle contraction, if present, may be relieved by massage, moist heat, muscle-relaxing exercises, biofeedback, or psychological counseling. Obvious malocclusion should be corrected by dental maneuvers. Non-narcotic analgesics, anti-inflammatory agents, antidepressants, muscle relaxants, and minor tranquilizers may be helpful. Some physicians recommend local injections of trigger points in spastic muscles or intra-articular injections. Major surgical procedures on the joint may be required, but only for those rare patients with very advanced disease.

Summary

Trigeminal neuralgia is an episodic, paroxysmal, painful condition in the distribution of the trigeminal nerve, usually unilateral at any one time, which is associated with a normal neurologic examination or minimal hypoalgesia in untreated patients; it responds extremely well to carbamazepine and denervation; other medicines that may help are baclofen, phenytoin, clonazepam, and mephenesin carbamate.

Atypical trigeminal neuralgia, vagoglossopharyngeal neuralgia, and geniculate neuralgia are other facial neuralgias that respond to carbamazepine.

Non-neuralgic facial pains may be caused by infection, inflammation, or neoplasm The dentist or otolaryngologist may help diagnose these conditions.

Non-neuralgic pains are frequently atypical and may be constant, diffuse, or burning. They are not triggered by light touch and are beyond the distribution of one cranial nerve.

These pains are often associated with depression and are sometimes accompanied by myofacial or vascular dysfunction.

References

1. Rushton JG. MacDonald HNA: Trigeminal neuralgia: Special considerations of nonsurgical treatment. JAMA 165:437, 1957.
2. Harris W: Neuritis and Neuralgia. Oxford University Press, London, 1926, 418 pp.
3. White JC, Sweet WH: Trigeminal neuralgia. Tic douloureux. In: Pain and the Neurosurgeon. Charles C. Thomas, Springfield, 1969, pp 123–178.
4. Dalessio DJ: The major neuralgias, postinfectious neuritis, intractable pain, and atypical facial pain. In: Wolff's Headache and Other Head Pain, 4th ed. Dalessio, DJ, ed. Oxford University Press, London, 1980, pp 233–255.
5. Kugelberg E, Lindblom U: The mechanism of pain in trigeminal neuralgia. J Neurol Neurosurg Psychiat 22:36, 1959.
6. Terrence CF: Differential diagnosis of trigeminal neuralgia. In: The Medical and Surgical Management of Trigeminal Neuralgia, Fromm GH, ed. Futura Publishing, Mt. Kisco, NY. 1987, pp 43–60.
7. Kurland LT: Descriptive epidemiology of selected neurologic and myopathic disorders with particular reference to a survey in Rochester, Minnesota. J Chron Dis 8:378–418, 1958.
8. Rothman KJ, Monson RR: Epidemiology of trigeminal neuralgia. J Chron Dis 26:3–12, 1973.
9. Blom S: Trigeminal neuralgia: Its treatment with a new anticonvulsant drug (G-32883). Lancet 1:839–840, 1962.
10. Rockliff BW, Davies EH: Controlled sequential trials of carbamazepine in trigeminal neuralgia. Arch Neurol 15:129–136, 1966.
11. Hart RG, Easton JD: Carbamazepine and hematological monitoring. Ann Neurol 11:309–312, 1982.
12. Fromm GH, Terrence CF, Chattha AS: Baclofen in the treatment of trigeminal neuralgia: Double-blind study and long-term follow-up. Ann Neurol 15:240–244, 1984.
13. Braham J, Saiz A: Phenytoin in the treatment of trigeminal and other neuralgias. Lancet 2:892–893, 1960.
14. Court JE, Kase CS: Treatment of tic douloureux with a new anticonvulsant (clonazepam). J Neurol Neurosurg Psychiat 39:297, 1976.
15. King RB: The value of mephenesin carbamate in the control of pain in patients with tic douloureux. J Neurosurg 25:153–158, 1966.
16. Rushton JG, Olafson RA: Trigeminal neuralgia associated with multiple sclerosis: Report of 35 cases. Arch Neurol 13:383–386, 1965.
17. Bullitt E, Tew JM, Boyd J: Intracranial tumors in patients with facial pain. J Neurosurg 64:865–871, 1986.
18. Tanaka A, Takaki T, Maruta Y: Neurinoma of the trigeminal root presenting as atypical trigeminal neuralgia: Diagnostic values of orbicularis oculi reflex and magnetic resonance imaging. A case report. Neurosurgery 21: 733–736, 1987.
19. Mitchell RG: Pre-trigeminal neuralgia. Br Dent J 149:167, 1980.
20. Harris W: Persistent pain in lesions of the peripheral and central nervous system. Brain 44:557–571, 1921.
21. Weisenburg TH: Cerebello-pontile tumor diagnosed for six years as tic douloureux. The symptoms of irritation of the ninth and twelfth cranial nerves. JAMA 54:1600–1604, 1910.
22. Hunt JR: Geniculate neuralgia (neuralgia of the nervus facialis); A further contribution to the sensory system of the facial nerve and its neuralgic conditions. AMA Arch Neuro Psychiat 37:253–285, 1937.
23. Lesse SE: Atypical facial pain syndrome, Arch Neurol 3:122–123, 1960.
24. Engle GL: "Psychogenic" pain and the pain prone patient Am J Med 26:899–918, 1958.
25. Weddington WW, Blazer D: Atypical facial pain and trigeminal neuralgia: A comparison study, Psychosomatics 20:348, 1979.
26. Sachs E Jr: The role of the nervus intermedius in facial neuralgia. Report of four cases with observations on the pathways for taste, lacrimation, and pain in the face. J Neurosurg 28:54–60, 1968.
27. Solomon S, Apfelbaum RI: Surgical decompression of the facial nerve in the treatment of chronic cluster headache. Arch Neurol 43:479–481, 1986.
28. Fay T: Atypical facial neuralgia, a syndrome of vascular pain. Ann Otol Rhinol Laryngol 41:1030–1062, 1932.
29. Orfei R, Meienberg O: Carotidynia: Report of eight cases and prospective evaluation of

therapy, J Neurol 230:65–72, 1983.
30. Vijayan N, Watson C: Pericarotid syndrome. Headache 18:244–254, 1978.
31. Goodman BW: Temporal arteritis. Am J Med 67:839–852, 1979.
32. Wolff SM, Fauci AS, Horn RG, Dale DC: Wegener's granulomatosis, Ann Intern Med 81:513–525, 1974.
33. Jaeger B, Singer E, Kroening R: Reflex sympathetic dystrophy of the face. Report of two cases and a review of the literature. Arch Neurol 43:693–695, 1986.
34. Watson CP, Evans RJ, Reed K, et al.: Amitriptyline versus placebo in postherpetic neuralgia. Neurology 32:671–673, 1982.
35. Eagle WW: Elongated styloid process: Report of two cases. Arch Otolaryngol 25:584–587, 1937.
36. Eagle WW: Elongated styloid process: Further observations and a new syndrome. Arch Otolaryngol 47:630–640, 1948.
37. Keur JJ, Campbell JPS, McCarthy JF, Ralph WJ: The clinical significance of the elongated styloid process. Oral Surg 61:399–404, 1986.
38. Booth DF, Hagens GA, Altshuler JL: Facial pain. In: Evaluation and Treatment of Chronic Pain, Aronoff GM, ed. Urban & Schwarzenberg, Baltimore-Munich, 1985, pp 131–147.
39. Guralnick W, Kaban LB, Merrill RG: Temporomandibular-joint afflictions. Medical progress, N Engl J Med 229:123–129, 1978.

4. OVERVIEW OF NEUROSURGICAL TREATMENT OF FACIAL NEURALGIAS

Ronald Brisman, M.D.

Introduction

There are few situations in neurosurgery, and indeed in all of medicine, where the physician can relieve pain and suffering as dramatically and effectively as in patients with facial neuralgias. Two factors necessary for a successful outcome are recognition of which kinds of patients can be helped and persistence until the pain has subsided.

Trigeminal neuralgia is the most common facial neuralgia that can be helped neurosurgically. Glossopharyngeal neuralgia, which can also be treated successfully by the neurosurgeon (Chapter 11), is much less common.

Symptoms, Diagnostic Procedures, and Nonsurgical Treatment[1]

SYMPTOMS

Because there are so many other non-neuralgic face pains that not only cannot be helped neurosurgically but are often worsened by neurosurgical procedures, it is important to emphasize the diagnostic features that characterize trigeminal neuralgia (tic douloureux). This pain is paroxysmal, episodic, triggered by light touch about the mouth or face, and located in the distribution of the trigeminal nerve. The neurologic examination is usually normal in untreated patients, pain is unilateral at any specific time, and carbamazepine (Tegretol) relieves the pain.

NONSURGICAL TREATMENT

Some patients with trigeminal neuralgia will have very long spontaneous remissions and will not require medication or surgery; other patients can be managed well with medication; and the remaining patients who cannot be treated satisfactorily with medications are candidates for neurosurgical intervention.

One can err by hastening surgery, without giving carbamazepine a chance, or delaying unnecessarily and subjecting the patient to prolonged discomfort and unpleasant side effects of medications.

Carbamazepine is so effective for trigeminal neuralgia that the diagnosis should be doubted if patients do not respond to it. The dose can sometimes be decreased and even stopped, and a long remission may occur because of the episodic nature of the condition. Occasionally, an exacerbation may be controlled by increasing the dose temporarily.

Many people cannot tolerate carbamazepine. Others may find that larger doses are required after a period of time, often with less effective pain relief and with more unpleasant

[1] For details see Chapter 3.

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side effects. Other medications may be added or substituted for carbamazepine, but these are much less effective and have their own adverse effects. When carbamazepine is no longer effective, patients often benefit from a neurosurgical procedure; they find that medication can then be eliminated or reduced to more tolerable levels.

Neurosurgical Principles

Many procedures may relieve the pain of trigeminal neuralgia, but none results in a permanent cure for all patients. The longer the period of survival following a procedure, the greater the chance that recurrent pain will develop some time in that interval. There is a risk that the patient will be made worse from the treatment.

DENERVATION

Trigeminal sensory denervation frequently stops trigeminal neuralgia symptoms. Peripheral denervation that is further away from the brain stem than the sensory ganglion is less likely to be effective and more likely to be associated with early recurrence than denervation that is in the gasserian ganglion or in between the ganglion and the brain stem. When denervation, such as neurectomy or alcohol injection, is further out in the periphery, recurrence develops more rapidly. The more extensive the denervation, the longer the pain-free interval, but the patient is more likely to develop dysesthesias. Partial denervation may relieve the pain of trigeminal neuralgia with a lower incidence of dysesthesias but a greater chance of recurrence.

PERCUTANEOUS PROCEDURES[2]

The percutaneous approach to the gasserian ganglion and retrogasserian rootlets and the partial denervation induced by radiofrequency electrocoagulation (RFE) [1] or glycerol [2] is often associated with the relief of pain; except for the effects of trigeminal denervation, complications are rare.

MICROVASCULAR DECOMPRESSION[3]

Blood vessels are usually near the trigeminal nerve where it exits from the brain stem. Sometimes, these blood vessels indent the nerve. Microvascular decompression operations are often associated with relief of pain [3]. Surgical mortality occurs in approximately 1% of patients, major neurological morbidity occurs in another 1% or 2% of patients, and less severe complications occur in many others.

Choice of Procedure

A percutaneous procedure with either radiofrequency electrocoagulation (RFE) or glycerol should be done on patients with intractable trigeminal neuralgia in the second or third division and one of the following: age 65 years or older; a medical contraindication to suboccipital craniectomy and general anesthesia, such as marked obesity or severe cardiovascular disease; or multiple sclerosis.

There is more controversy regarding the neurosurgical management of those who are less than 65-years-old without multiple sclerosis or major medical illness, or patients with first division pain. Some physicians recommend percutaneous RFE or glycerol, others prefer microvascular decompression, and a few still advocate peripheral neurectomy or alcohol injection [4].

It is my practice to recommend a moderately denervating percutaneous RFE with or without glycerol (see Chapter 6) for almost all patients with intractable trigeminal neuralgia. I offer a milder percutaneous retrogasserian

[2] See Chapters 5 and 6.

[3] See Chapter 7.

denervation for those patients with contralateral facial anesthesia or those who are extremely fearful of dysesthesias and are willing to risk the likelihood of recurrence. With these percutaneous techniques, excellent relief of pain can be obtained in the vast majority of patients; the likelihood of a serious complication is extremely rare; and severe dysesthesias are infrequent. Recurrent pain may develop but can be handled successfully by repeating the procedure, which can be done without added difficulty and with a similar expectation of a good result.

For those few patients who cannot be managed well with percutaneous techniques, either because of technical problems or frequent recurrences, I favor a suboccipital craniectomy. During this procedure, I will do as much of a microvascular decompression as possible, but in addition, I will coagulate or cut the caudal quarter or third of the trigeminal sensory nerve.

There are a few patients who have pure trigeminal neuralgia restricted to the first division. Initially, I offer these patients a peripheral neurectomy or supraorbital alcohol injection, because this can avoid the undesirable consequences of corneal anesthesia. If pain recurs, which it usually does, then RFE or glycerol can be used.

Evaluating Results of Treatment — Methodology

In order to compare two or more treatments for trigeminal neuralgia, one must look not only at the safety of the procedures, but also at their effectiveness. The critical question is pain relief: What percentage of patients are relieved of pain and for how long? Ideally, patients should be randomly and prospectively allocated to different forms of treatment, followed in a uniform manner, and compared for parameters that might influence outcome. Such a study of the neurosurgical treatment of trigeminal neuralgia has not been done and would be very difficult to do because many patients and physicians have a definite preference for a particular kind of treatment.

Retrospective reviews can provide useful information, especially if certain methodological traps are avoided. Average duration of followup should be eliminated, because the constant accrual of new patients who have been followed for a short period of time falsely dilutes the data. Recurrence, with or without reoperation and with or without the resumption of carbamazepine, should be reported as a percentage of those who are at risk for recurrence per unit of time.

It is desirable, but often difficult, to follow all of the originally treated patients. When this is not done, it is likely that those who are followed are selected because they have recurred. If calculations are done using only those who are followed as the group at risk for recurrence, then the percentage of treatment failures will be falsely elevated; but if the entire group — including those who were not followed — is used as the group at risk for recurrence, then the recurrence rate will be spuriously lowered. The lack of uniformity in manner of followup among the different studies impairs the usefulness of one group of patients as a historical control for another.

Evaluating Dysesthesias — Methodology

Dysesthesias are one of the most common complications associated with trigeminal denervation, and their apparent incidence will be influenced by duration of observation, manner of inquiry, and recognition of the patient as his own control.

Dysesthesias frequently tend to diminish with time, as do other manifestations of denervation, and the longer the interval between surgery and followup, the less likely the patient is to notice and report them.

A casual history is less likely to elicit the presence and severity of dysesthesias than is a direct questionnaire that asks the patient to give a numerical score and choose the closest verbal description (see Appendix).

Some patients are bothered by an abnormal tightness, numbness, crawling, itching, or burning sensation in the face prior to the procedure being evaluated. These dysesthesias may have been caused by a previous manipulation of the trigeminal nerve, they may be associated with or linger after paroxysms of pain, or they may exist because of unexplained reasons.

The most reliable data regarding postoperative dysesthesias will be based on a comparison of the patient's responses to questions asked before and after the surgery; only those with postoperative dysesthesias who did not have similar unpleasant sensations prior to surgery should be regarded as having them as a result of the surgery.

Atypical Facial Pain

There are many more patients with atypical facial pains than true trigeminal neuralgia. The neurosurgeon must be particularly aware of the diagnostic characteristics of this group because these patients are usually not helped by neurosurgical procedures and are often made worse by them. These patients usually have constant, nonprovokable pain, which is not triggered by light touch, is not in the trigeminal distribution, and does not respond to carbamazepine.

There is a small group of patients who have some features of trigeminal neuralgia, but with atypical features. I have used a percutaneous approach to the gasserian ganglion in a few of these patients and have injected a small amount of bupivacaine (Marcaine 0.5%, 0.1 ml to 0.5 ml). This gives the patient an opportunity to see if the pain can be relieved by denervation and whether he or she is willing to accept permanent sensory alteration.

Summary

Trigeminal neuralgia is characterized by paroxysmal, triggered, episodic pain in the trigeminal distribution, which is usually relieved by carbamazepine.

Neurosurgical procedures are recommended for those who have intractable trigeminal neuralgia pain that cannot be managed with medications.

Partial trigeminal sensory denervation can relieve the pain of trigeminal neuralgia; less denervation increases the chance of recurrence but decreases the possibility of dysesthesias.

A moderate partial denervation of the gasserian ganglion and retrogasserian rootlets with radiofrequency electrocoagulation or glycerol is an extremely safe and effective way to treat trigeminal neuralgia, and is recommended for most patients with intractable pain. A light denervation is offered to patients with bilateral trigeminal neuralgia and contralateral facial analgesia, or those who are extremely fearful of dysesthesias and are willing to risk the likelihood of recurrence.

A suboccipital microneurovascular operation can also relieve the pain in many patients with trigeminal neuralgia; because of the added risks, this is advised only for those few patients who cannot be managed satisfactorily with percutaneous procedures.

Differences in methods of followup and groups at risk for recurrence make it difficult to compare the results in retrospective studies.

The reported incidence of postoperative dysesthesias will be influenced by the duration of followup, the use of a questionnaire, and a comparison with the patient's preoperative condition.

Patients with atypical facial pain are less likely to benefit from neurosurgical procedures and are more likely to have complications.

References

1. Sweet WH, Wepsic JG: Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers: Part 1. Trigeminal neuralgia. J Neurosurg 39:143–156, 1974.
2. Hakanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 9:638–646, 1981.
3. Jannetta PJ: Microsurgical approach to the trigeminal nerve for tic douloureux. Prog Neurol Surg 7:180–200, 1976.
4. Morley TP: Case against microvascular decompression in the treatment of trigeminal neuralgia. Arch Neurol 42:801–2, 1985.

5. TREATMENT OF TRIGEMINAL NEURALGIA BY RADIOFREQUENCY ELECTROCOAGULATION

Ronald Brisman, M.D.

Introduction

The radiofrequency electrocoagulation (RFE) of the gasserian ganglion and retrogasserian rootlets was performed in Europe in the 1930s [1] but was refined and popularized in this country by Sweet in 1974 [2] and others [3–5].

Using this technique, the surgeon can relieve the pain of trigeminal neuralgia in most patients. Damage to structures other than the fifth nerve is very unlikely if careful attention is given to surgical technique. The main drawbacks are dysesthesias and recurrence. Dysesthesias can be minimized by making small lesions, and recurrences can be controlled by repeating the procedure.

From July 1976 to November 1985, the author has performed 309 RFE procedures on 260 patients. One hundred fifty-seven consecutive patients with medically intractable trigeminal neuralgia, who did not have a brain tumor or multiple sclerosis and were treated with RFE alone (without glycerol) between July 1976 and December 1983, are the subject of this chapter.

Technique

The patient is positioned supine with a pillow under the knees to prevent back pain, which might otherwise occur during hyperextension of the neck for submentovertex skull x-rays. The face is prepped with alcohol so that erythema can be seen during heating, and Hartel coordinates are marked on the face with a sterile marking pen; these are 3 cm on the zygoma anterior to the tragus, just below the medial aspect of the pupil, and 2.5 (third division) to 3 (second or first divisions) cm lateral to the angle of the mouth. An intravenous infusion is started, and droperidol (2.5 mg to 5 mg) and fentanyl (0.05 mg to 0.1 mg) are given. The smaller doses are used for the elderly. During the procedure, more medication — usually small increments of fentanyl — may be necessary. Blood pressure is monitored, and nasal oxygen is administered. A disposable grounding plate is secured on the arm or upper chest.

The skin (2.5 cm to 3 cm lateral to the angle of the mouth) is infiltrated with local anesthetic, and a puncture is made with an 18-gauge needle. The Radionics straight cannula with a 7-mm uninsulated tip needle is inserted, and a gloved finger is held inside the oral mucosa. When correct placement in front of the midpoint of the foramen ovale or slightly anterior to this is confirmed by submentovertex and lateral skull x-rays, slumber is induced with methohexital (Brevital), and the foramen ovale is penetrated.

The target points are the midpoint of the foramen ovale, as seen on the submentovertex

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skull x-ray (Figure 5-1), and the angle between the petrous bone and clivus, on the lateral view (Figure 5-2). The mandible may obscure the foramen ovale on the submentovertex x-ray, especially in patients who cannot extend the neck fully. This may be overcome by turning the head 20° to the side of the needle (Figure 5-3).

Patients with severe cervical osteoarthritis may have difficulty extending the neck. As long as the x-ray cassette is placed tangential to the occiput and the x-ray tube is angled sufficiently, the foramen ovale will be seen on the submentovertex view, even if the neck is not completely extended. Under these circumstances the x-ray cassette will be at an angle to the x-ray table rather than flat on top of it, which is the usual position when the patient can extend the neck fully.

Skull x-rays in two projections are important because only one view can be misleading. The cannula may appear to be directed properly on the submentovertex view, but incorrect placement (usually posteromedial) may be demonstrated on the lateral. The lateral x-ray is necessary to determine depth of penetration. If the electrode is more than 5 mm anterior to the clivus, it will often be too shallow and a postganglionic lesion is more likely to develop. When the electrode is more than 5 mm posterior to the clivus, the danger of unwanted first division denervation is increased.

Final cannula placement within the trigeminal complex is determined by the response of the awake patient to stimulation at 100 cycles per second and 0.1 volts to 0.3 volts. Deeper insertion will often move the cannula tip from the third to the second or first sensory divisions. Sometimes, if second or first division denervation is desired, it is necessary to penetrate the foramen ovale in a more anteromedial location. If trigeminal motor response is obtained from stimulation, it is advisable to reenter the foramen ovale in a more posterolateral position. The conscious

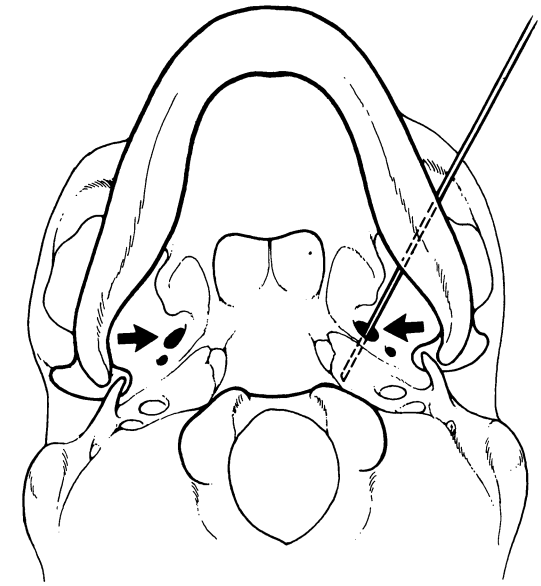

FIGURE 5-1. Submentovertex skull x-ray shows the cannula through the foramen ovale (arrow).

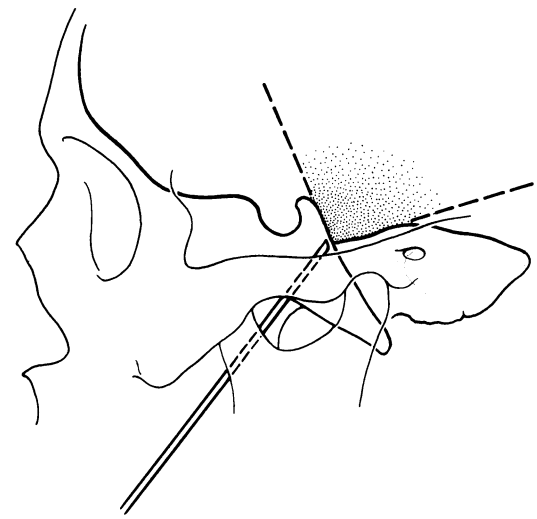

FIGURE 5-2. Target on lateral x-ray is the angle between the petrous bone and clivus.

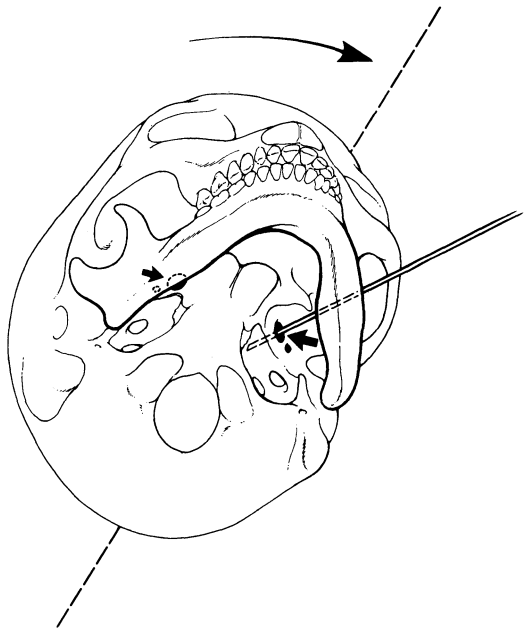

FIGURE 5-3. Turning the head 20° to the side of the cannula makes it easier to see the foramen ovale (large arrow) on the submentovertex skull x-ray, because the mandible is moved out of the way. The contralateral foramen ovale (small arrow) is obscured by the mandible.

patient's response to low-voltage heating and the location of facial erythema during more intense heating are further guides to the division that is being denervated.

During the first few years of this study, the author followed the standard description of the RFE and made an initial lesion at 60°C for 60 seconds and followed this with additional heatings for 60 seconds at 5°C increments until analgesia was induced in the desired division. In later years, mainly after 1979, most patients received two heatings — one at 65°C for 60 seconds, and, if analgesia did not develop, then a second lesion was made at 70°C–75°C for another 45–60 seconds.

A small dose of methohexital (20 mg to 25 mg) is given rapidly intravenously just prior to heating the nerve.

TABLE 5.1. Characteristics of 157 patients: 1976–83

Female	60.5%
Right-sided pain	58%
Bilateral face pain, by history	10%
Average age at first RFE	62 years
Median age at first RFE	64 years
Average duration of preoperative pain	86 months
Previous trigeminal surgery	13%

Results

PATIENT POPULATION (Tables 5-1 and 5-2) One hundred fifty-seven patients with trigeminal neuralgia were treated with at least one RFE between January 1976 and December 1983. The average age at the time of the first RFE was 62 years (Figure 5-4). Sixty percent were females. The right side was the side of initial RFE in 58%. In 10% of the total group, the other side was involved at some time, but simultaneous bilateral trigeminal neuralgia pain was present in only one patient. The second and third divisions were most frequently affected. The average onset of original pain was 86 months prior to the first RFE in the present study. Twenty-one patients had

TABLE 5-2. Division of pain in 157 patients: 1976–83

Division	2 & 3	3	2	1 & 2	1	1 & 3	1–3
Percent	37%	30%	19%	11%	2%	0.6%	0.6%

TABLE 5-3. Initial results in 157 patients: 1976–83

	No.	Percent
Initial technical success	152	97%
Initial good pain relief	143	90%

been operated previously for trigeminal neuralgia.

INITIAL RELIEF OF PAIN (Table 5-3)

Technically satisfactory RFE was performed in 97% of the patients, with initial relief of pain in 90% of the total group.

REOPERATION (Tables 5-4 and 5-5)

Repeat surgery was done in 38 patients (24%). The period at risk for reoperation ranged from 2 to 9 years, and the average followup was 25 months. Eighty-nine percent of the reoperated patients had their second procedure within 4 years of the first RFE (Figure 5-5). The Meier-Kaplan product limit curve was calculated, and an estimate probability of not being re-operated was constructed (Figure 5-6). After 72 months following RFE, the estimated chance of not requiring a repeat operation was 53%.

The reoperated and entire group with an initial technically successful RFE were compared to see if there were a disproportionately higher incidence in the reoperated group of certain characteristics (Table 5-5). The most statistically significant factor in the two groups ($p < .003$, chi-square with Yates' correction) was a tendency for the reoperated group to have been followed for a longer time (46 months as opposed to 26 months for the entire group). Also of statistical significance ($p = .04$), was the younger age (average 57 years) of the reoperated as opposed to the entire group (62 years). Although not statistically significant (< 0.1), but suggesting a possible trend, was the higher incidence of patients with previous surgery in the reoperated group (20%) as opposed to 11% in the entire group.

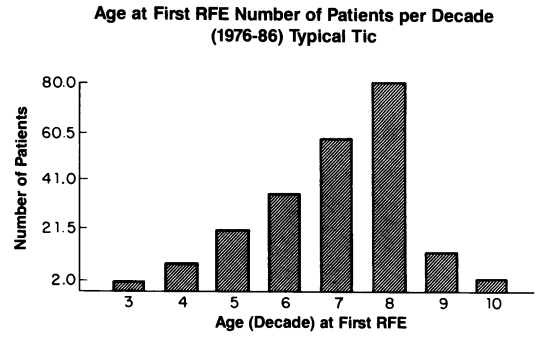

FIGURE 5-4. Most patients were in the 6th (50s), 7th (60s) or 8th (70s) decade at their first RFE.

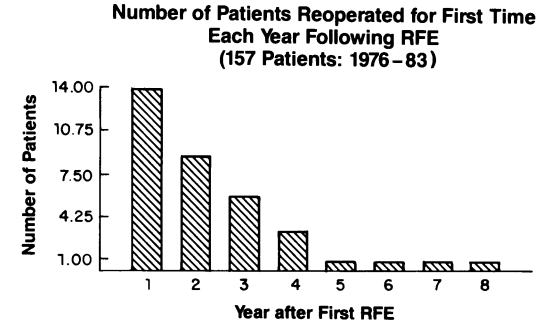

FIGURE 5-5. Most reoperations appeared to occur within the first 3 years of the original RFE.

TABLE 5-4. Reoperation in 157 patient: 1976–83

		Operations No.	Patients No.	Percent of 157
Reoperation:	By author	48	35	22%
	Other doctors		3	2%
	Total		38	24%

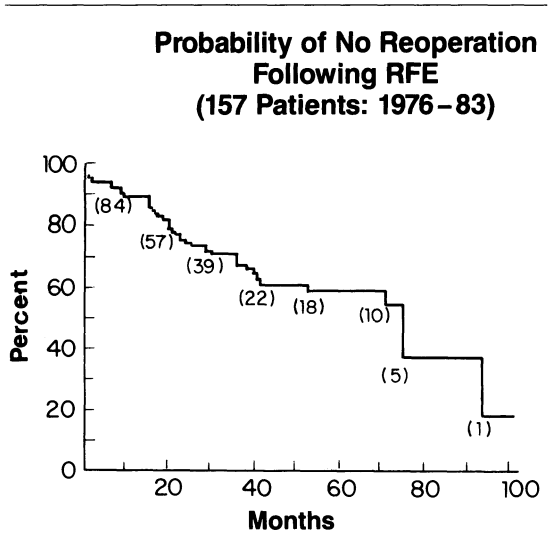

FIGURE 5-6. Estimated probability of not undergoing a repeat operation through any given period after RFE. The graph is a Meier-Kaplan product-limit estimate. The numbers in parentheses indicate how many patients who had not been reoperated were available for followup.

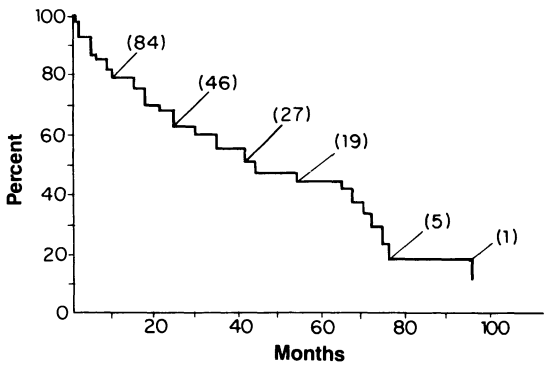

FIGURE 5-7. Estimated probability of not having recurrence after RFE. The numbers in parentheses indicate how many patients without recurrence were available for followup.

RECURRENCE (Figure 5-7)

The probability of recurrent trigeminal neuralgia pain, whether or not it resulted in reoperation, was plotted using the Meier-Kaplan product limit method. Estimated probability or recurrence for 50% of patients was between 40 and 43 months.

TABLE 5-5. Reoperated patients and entire group compared

	Re-operated	Entire group	p value
No.	35	152	
Mos. followed (average)	46	26	<.003[1]
Age (average)	57	62	.04[1]
Patients with previous surgery	20%	11%	>.1[2]
First symptom (Ave. mos. pre-first RF)	78	89	.42[1]
Female	57%	60.5%	>.1[2]
Right side	54%	58%	>.1[2]

[1] Two-tailed test on significance of mean
[2] Chi-square with Yates' correction

Factors associated with nonrecurrence were analyzed in 152 patients according to Peto and Peto's generalized Wilcoxon test and the two-sided alternative (Table 5-6). Patients who were followed for more than 48 months and those with postoperative, but not preoperative, analgesia had longer recurrent-free intervals (statistically significant, $p < .003$). There was a suggestion that the absence of previous surgery might be associated with less recurrence ($p = .095$). Sex, age, time of onset of the first symptom, and hypoalgesia (50%–89%) were not associated with an alteration in the recurrence-free interval.

FINAL PAIN RELIEF (Table 5-7)

At final followup (the last time that the patient was interviewed), pain relief was excellent (no pain and no medication) in 26.8%; good (either no pain or mild infrequent pain with small doses of medication or mild infrequent pain and no medication) in 51.6%; fair (bothersome pain in spite of medication but not so bad as prior to RFE) in 13%; and poor (as bad as before RFE) in 8.5%.

TABLE 5-6. Factors associated with nonrecurrence (152 patients)

	No.	p*
Followup > 48 months	14	<.003
Analgesia postop & not preop	23	<.003
No previous surgery	135	.095
Age < 75	132	.267
RFE before Jan 1 '80 & no postop analgesia	33	.285
Age > 40	142	.38
Male	58	.38
Without both preop & postop analgesia	146	.52
First symptom < 120 months preop	122	.653
Hypoalgesia (50%–89%) postop & not preop	25	<.795
First symptom > 12 months preop	141	.889

* Probability for the two-sided alternative based on Peto and Peto's generalized Wilcoxon test.

TABLE 5-7. Pain relief in 153 patients: 1976–83

Pain relief	No. patients	Percent
Excellent	41	26.8%
Good	79	51.6%
Fair	20	13.1%
Poor	13	8.5%

COMPLICATIONS (Table 5-8)

There was no mortality and no permanent neurological deficit other than in the trigeminal nerve. One patient developed meningitis with fever, increased cerebrospinal fluid (CSF) white cells, and low CSF sugar. Although bacterial cultures were negative, the patient was given a full course of intravenous antibiotics and made a full recovery. Following either the first or subsequent RFE procedures, dysesthesias were severe in 9% and moderately bothersome in 13%. Moderate or severe dysesthesias occurred in 24 of 152 patients (15.8%) after their first RFE. Dysesthesias developed in 8 of 32 (25%) of those who were analgesic post-RFE and in 14 of 120 (11.7%) of those who were not analgesic ($p > .1$ using chi-square test). Keratitis occurred in 2.6%.

TABLE 5-8. Complications in 157 patients: 1976–83

Mortality	0
Neurological deficit (not V)	0
Infection	1
Dysesthesia: moderate	13%
severe	9%
Keratitis	2.6%

Trigeminal motor (masseter and pterygoid impairment) that was not disabling occurred in six patients, and six others had postoperative herpes simplex eruptions on the face.

One patient developed mild bleeding from the external auditory meatus immediately following the procedure.

Discussion

HOW MUCH DENERVATION?

By repeating electrocoagulations until analgesia develops, the surgeon may cause excessive denervation with undesirable sequelae such as anesthesia dolorosa, corneal anesthesia, and keratitis. Many patients find it difficult to perceive or communicate the presence of analgesia to pin, and this difficulty is frequently worsened when they are under the influence of neuroleptanalgesia. In some patients, denervation may result in hyperpathia rather than analgesia, and further denervation may make the hyperpathia more profound. Lighter lesions, especially below 65°C for less than 1 minute, are much less likely to cause dysesthesias [6].

The first division is particularly senstitive to denervation, and special precautions should be taken to prevent an excessive first division lesion. The risk of first division denervation is increased when the cannula is 2 mm or more

posterior to the clivus, the patient feels stimulation at 50 Hz to 100 Hz per second or low-voltage heating (45°C to 48°C) in the first division, or a second division lesion is being made. Under these circumstances, it is advisable to make very small lesions at 5°C increments starting at 50°C for 10 to 15 seconds, preferably with the patient awake. The electrocoagulations should stop when mild first division hypoalgesia develops. It is also preferable to make a lesion in as shallow a position as possible (but not more anterior than 5 mm in front of the clivus). If a second division is desired, and a second division response is obtained at 4+ mm posterior to the clivus, it is wise to withdraw the cannula a few millimeters; if a second division response to stimulation is still obtained, then it is preferable to make the lesion here rather than at the deeper position.

WHAT INCREASES THE RISK OF RECURRENCE?

The duration of followup is an important factor increasing the likelihood of recurrence (Table 5-5). In the study with the longest followup period (average 12.7 years), 80% had a return of pain, but 96.7% ultimately attained freedom from pain after repeat electrocoagulation [7].

When a recurrence-free interval is calculated using the Meier-Kaplan product limit method, the final followup time is the time of recurrence, or in the absence of recurrence, the time of last patient contact. If patients are chosen on the basis of an arbitrarily long followup period (Table 5-6: followup > 48 months), they will automatically have a long recurrence-free interval, because those with earlier recurrences would have been excluded.

Patients with dense sensory deficits are less likely to have recurrence, as demonstrated in this study (Table 5-6) and elsewhere [6, 8].

Younger patients also appear to have a greater chance of requiring reoperation (Table 5-5), possibly because they are at risk for a longer period of time. This relationship was suggested by the two-tailed test on significance of the mean, but was not confirmed by the more sensitive Wilcoxon test (Table 5-6). Another study did not find any relationship between age and outcome [8].

The present data suggest that patients with previous surgery may possibly have a greater chance of requiring a repeat operation, but the data (Tables 5-5 and 5-6) are not statistically significant to the .05 level. In a different report, patients previously treated by open surgery also appeared to receive less benefit from subsequent RFE [8].

Other studies have shown a lower relapse rate with classical trigeminal neuralgia than with nonclassical neuralgia [8]. Although all patients in this study had paroxysmal triggered trigeminal face pain, and those who had primarily atypical facial pain were not included, some patients in this study may have had an atypical feature, such as a constant substrate of pain or a nontriggered component. The author's data do not allow for a subdivision within the category of trigeminal neuralgia for those with a partial atypical component.

There was no added risk of reoperation based on the side of the face pain, sex, or the duration of preoperative symptoms.

HOW SHOULD RECURRENCE BE CALCULATED?

Other series of RFE report great variations in recurrence rates (4.3% [9], 22% [2], 80% [7]). Recurrence is often defined differently — sometimes as reoperation, other times as return of pain. The interval of followup has ranged from 1 month [9] to 33 years [7]; average followup has varied from 15 months [9] to 12.7 years [7]. It is not always clear how patients who have been lost to followup were handled.

A more reliable technique for calculating and reporting recurrence is the product-limit

survival curve of Meier-Kaplan [8, 10–12]. This allows incorporation of data from patients during the period that they have been observed, even if subsequently they are lost to followup.

In a previous study where the product-limit method was used, 50% of patients were free of recurrence (reoperation or recurrent symptoms) at a 5- to 6-year interval [8]. In the present series (Figure 5-7), the estimated probability of recurrence of 50% of patients occurred at 40 to 43 months following the initial RFE. The discrepancy between the two series can be partly explained by the inclusion in the present study of all patients subjected to RFE, with a risk for recurrence starting with the initial RFE even if it was unsuccessful (which was the case in 5 of 157 patients); in the other study [8], 6 of 96 procedures were aborted due to difficulty in electrode positioning or patient anxiety, and the rescheduled procedure was treated as the patient's first. Even more important is the difference in analgesia, which was substantial in 34% and moderate in 55% in the other series [8], while in the present study analgesia occurred in only 15% and moderate hypoalgesia in another 16%.

OTHER TECHNICAL CONSIDERATIONS

The author has always used submentovertex and lateral skull x-rays and has rarely encountered a difficulty in locating the proper target point. If the foramen ovale cannot be seen on the submentovertex x-ray but the foramen spinosum is visualized, the foramen ovale may be estimated as being 1 cm anteromedial to the center of the foramen spinosum (Figure 5-1).

Direct fluoroscopic visualization of the foramen ovale with anteroposterior image intensifier has been described [4]. The extended head is rotated 20° away from the involved side until the foramen ovale appears as a rising sun over the petrous ridge.

An alternative target point is 9 mm medial to the lateral border of the internal auditory meatus, as seen on the anteroposterior projection, centered on the orbitomeatal line [13].

It has been suggested that a curved electrode may facilitate placement of the lesion in any particular division of the trigeminal nerve [5, 13]. The author has tried this on a few occasions with a curved cordotomy electrode but has not been successful in redirecting the electrode from the third into the desired second division. Repositioning the electrode through a more anteromedial portion of the foramen ovale is often effective in achieving a second (or first) division lesion, but this is not always possible to accomplish.

AVOIDING MAJOR COMPLICATIONS

The rare complication of cerebrovascular accident after RFE has been reported [14]. This occurs because of the proximity of the internal carotid artery in the foramen lacerum to the trigeminal ganglion in Meckel's cave [14]. It can be prevented by insisting on excellent position on both submentovertex and lateral x-rays prior to penetrating the foramen ovale. Usually there is minimal resistance when the foramen ovale is entered, and if much resistance is encountered it should be assumed that the position is probably incorrect. Good-quality x-rays in both views should be rechecked before proceeding.

Meningitis, with or without brain abscess, has occurred infrequently following RFE [15]. The author does not use prophylactic antibiotics for this procedure. Any suspicion of meningitis must be diagnosed promptly and treated vigorously. Although it is certainly possible to have aseptic meningitis following RFE [2], it is also possible to have a bacterial meningitis, even though bacteria do not grow from the initial cultures. The author is aware of such a case by another neurosurgeon, which progressed to brain abscess after original cultures of lumbar cerebrospinal fluid were negative. Because of this, the one case of presumed meningitis in the author's own experience was treated successfully with a 14-day course of

intravenous antibiotics because of a highly suspicious clinical and spinal fluid formula, even though initial spinal fluid cultures were negative.

Summary

RFE is a very effective method for treating intractable cases of trigeminal neuralgia. Good or excellent relief of pain can be obtained in most patients, although in some the procedure may have to be repeated.

RFE is an extremely safe procedure; mortality or damage to structures other than the fifth nerve are very rare and did not occur in any of the author's patients.

The main risks from the procedure are dysesthesias or corneal denervation. These are much more likely to develop if lesioning continues until analgesia develops. Lesser degrees of denervation, which this author prefers, are associated with less dysesthesias but a higher recurrence rate.

High-quality x-rays in two projections (submentovertex and lateral) are essential for safe identification of the target points, which should be determined just prior to penetrating the foramen ovale.

The product-limit survival curve is the preferred statistical method for estimating the probability of recurrence.

References

1. Kirschner M: Zur behandlung der trigeminusneuralgie: Erfahrungen an 250 fallen. Arch Klin Chir 186:325–334, 1936.
2. Sweet WH, Wepsic JG: Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers: Part 1 Trigeminal neuralgia. J Neurosurg 39:143–156, 1974.
3. Nugent GR, Berry B: Trigeminal neuralgia treated by differential percutaneous radiofrequency coagulation of the Gasserian ganglion. J Neurosurg 40:517–523, 1974.
4. Onofrio BM: Radiofrequency percutaneous Gasserian ganglion lesion: Results in 140 patients with trigeminal pain. J Neurosurg 42:132–139, 1975.
5. Tew JM, Tobler WD: Percutaneous rhizotomy in the treatment of intractable facial pain (trigeminal, glossopharyngeal, and vagal nerves). In: Operative Neurosurgical Techniques, Vol. 2, Schmidek HH, Sweet WH, eds. Grune & Station, New York, 1982, pp 1083–1106.
6. Salar G, Mingrino S, Iob I: Alterations of facial sensitivity induced by percutaneous thermocoagulation for trigeminal neuralgia. Surg Neurol 19:126–130, 1983.
7. Menzel J, Piotrowski W, Penzholz H: Long-term results of Gasserian ganglion electrocoagulation. J Neurosurg 42:140–143, 1975.
8. Latchaw JP, Hardy RW, Forsythe SB, Cook AF: Trigeminal neuralgia treated by radiofrequency coagulation. J Neurosurg 59:479–484, 1981.
9. Siegfried J: 500 percutaneous thermocoagulations of the Gasserian ganglion for trigeminal pain. Surg Neurol 8:126–131, 1977.
10. Lee ET: Statistical Methods for Survival Data Analysis. Lifetime Learning Publications, Belmont, California, 1980, pp 75–156.
11. Piatt JH Jr, Wilkins RH: Treatment of tic douloureux and hemifacial spasm by posterior fossa exploration: Therapeutic implications of various neurovascular relationships Neurosurgery 14:462–471, 1984.
12. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. Am Stat Assoc J 53:457–481, 1958.
13. Nugent GR: Radiofrequency treatment of trigeminal neuralgia Contemp Neurosurg 4:1–6, 1982.
14. Rish, BL: Cerebrovascular accident after percutaneous rf thermocoagulation of the trigeminal ganglion. Case report. J Neurosurg 44:376–377, 1976.
15. Apfelbaum RI: A comparison of percutaneous radiofrequency trigeminal neurolysis and microvascular decompression of the trigeminal nerve for the treatment of tic douloureux. Neurosurgery 1:16–21, 1977.

6. RETROGASSERIAN GLYCEROL INJECTION WITH OR WITHOUT RADIOFREQUENCY ELECTROCOAGULATION FOR TRIGEMINAL NEURALGIA

Ronald Brisman, M.D.

Percutaneous retrogasserian injection of pure sterile glycerol into the trigeminal cistern may relieve the pain of trigeminal neuralgia without major complications [1–3]. In the initial reports, there was little numbness and major dysesthesias were rare [1, 2]. As further experience developed, it became apparent that glycerol is a denervating agent and that it could cause analgesia with bothersome dysesthesias [3–5]. Larger doses of glycerol (more than 0.25 ml) are likely to cause more denervation and dysesthesias than smaller doses.

Another problem with glycerol is that initial pain relief cannot be obtained in all patients, and there is a substantial recurrence rate. Initial pain relief may be achieved in most patients (83%–96% [1–3]) and is more likely when there is flow of spinal fluid from the cannula. Recurrence occurred in 31% of those followed between 1 to 6 years [6], although most of these could be treated successfully with another injection.

Radiofrequency electrocoagulation (RFE) of the gasserian ganglion and retrogasserian rootlets appeared to cause less recurrence but more analgesia and dysesthesia [3] than glycerol. Perhaps the use of RFE and glycerol together could improve on the beneficial effects (pain relief) of either one alone with fewer complications (dysesthesias or corneal denervation). The author has explored this possibility with mild and moderate denervations in two consecutive series of patients with intractable trigeminal neuralgia who did not have multiple sclerosis or brain tumor.

Method (Tables 6-1 and 6-2)

1. *Mild Denervation* [(RFE + glycerol) mild]: Between December 1983 and January 1986, 61 patients received RFE for 62°C for 25 seconds followed by 0.15 ml glycerol [7].
2. *Moderate Denervation* [(RFE + glycerol) moderate]: Between February 1986 and December 1986, 32 patients received RFE for 60°C to 65°C for 45–60 seconds. If they were not analgesic and there was no CSF draining from the cannula or on the stylet, then another RFE was given for 70°C–75°C for 30 seconds. If they were not analgesic after the first RFE and there was CSF drainage, then glycerol 0.2 ml–0.25 ml was added.
3. *RFE*: The series of 157 patients treated

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TABLE 6-1. Three treatment groups

Group	No. of paients	Date of first procedure
RFE	157	1976–Nov.'83
(RFE + glycerol) mild	61	Dec.'83–Jan.'86
(RFE + glycerol) moderate	32	Feb.'86–Dec.'86

TABLE 6-2. Method of treatment

RFE	No standardization of number, degrees, or duration of coagulation. Originally (1976–1978) analgesia was sought, but later hypoalgesia was accepted.
(RFE + glycerol) mild	RFE (62°C for 25 seconds) plus 0.15 ml glycerol
(RFE + glycerol) moderate	RFE (60°C–65°C for 45–60 seconds). If not analgesic and no CSF, then another RFE (70°C–75°C for 30 seconds). If not analgesic after first RFE and CSF present, then glycerol (0.2 ml–0.25 ml) added.

with RFE and no glycerol between 1976 and November 1983 (see Chapter 5) was compared with the other two groups in which glycerol was used.

Final cannula position was determined by submentovertical and lateral skull x-rays and response to stimulation at 100 cycles per second, as described in Chapter 5. The straight electrode with 7 mm of uninsulated tip was used.

Results (Tables 6-3 through 6-5 and Figure 6-1)

There was less denervation and less anesthesia dolorosa in the mild denervation group [(RFE + glycerol) mild] than in those treated only with RFE, but the recurrence rate was higher in the mild denervation group. Meier-Kaplan survival curves showed a 50% probability of recurrence in the RFE group at 40 months and 14 months in those with RFE plus glycerol (mild). This difference was statistically significant to the 0.05 level (Peto and Peto's generalized Wilcoxon test). In patients with moderate denervation [(RFE + glycerol) moderate], the degree of denervation and incidence of anesthesia dolorosa was midway

TABLE 6-3. Degree of denervation

New postoperative hypoalgesia (% of patients)		
	Moderate[1]	Severe[2]
RFE	16%	15%
(RFE + glycerol) mild	10%	0%
(RFE + glycerol) moderate	12.5%	6%

[1] Moderate hypoalgesia was 50%–89% percent decrease in perception of pin.
[2] Severe hypoalgesia was 90%–100% percent decrease in perception of pin.

TABLE 6-4. Anesthesia dolorosa

Anesthesia dolorosa (% of patients)		
	Moderate	Severe
RFE	9%	13%
(RFE + glycerol) mild	5%	0%
(RFE + glycerol) moderate	6%	3%

TABLE 6-5. Recurrence

	Recurrent pain* Without Reop (%)	Reop (%)	Followup (years)
RFE	15%	24%	2–10
(RFE + Glycerol) mild	23%	15%	1–3
(RFE + Glycerol) moderate	6%	6%	0.1–0.9

* Includes those who were initially unsuccessful.

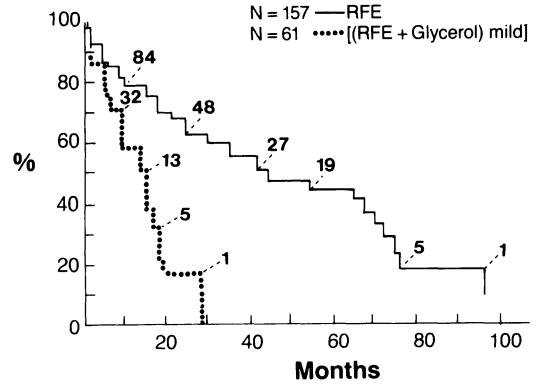

FIGURE 6-1. Meier-Kaplan survival curves show a 50% probability of recurrence in the RFE group at 40 months and 14 months in those with [(RFE + glycerol) mild].

between that of the mild denervation and RFE groups. It is anticipated that recurrence in the moderately denervated group will occur later than in the mildly denervated group, but sooner that in the more denervated RFE group; followup is not long enough at this time to determine this with certainty.

Discussion

The major factor affecting the frequency of anesthesia dolorosa and recurrence is the degree of denervation; the more denervation, the more likely is anesthesia dolorosa and the less likely is recurrence. If a mildly denervating lesion is made with RFE [8] or glycerol [1, 2, 5, 9] or RFE plus glycerol, there is likely to be a small incidence of anesthesia dolorosa and a great chance of early recurrence (Tables 6-6 and 6-7). Just as a mild, moderate, or severe denervation can be made with RFE, so can varying degrees of denervation be accomplished with glycerol [3]; larger volumes (greater than .25 ml or .3 ml) are more likely to cause more denervation.

Because of the relatively high recurrence rate following a mild denervation [(RFE + glycerol) mild], such a lesion should be recommended for those who are fearful of anesthesia dolorosa and are willing to risk the likelihood of recurrence, usually within 1 or 2 years. Patients with bilateral trigeminal neuralgia who have profound analgesia and anesthesia on the contralateral side may be appropriate candidates for a mild denervation [10]. Most patients with trigeminal neuralgia are best treated with a moderate denervation, which is unlikely to cause anesthesia dolorosa and will be associated with a longer remission.

Although we have been unable to prove that a combination of RFE and glycerol is better than either agent alone, there are still reasons to believe that under certain circumstances the use of one or the other technique, or perhaps the two together, may be better than either one alone. If CSF does not emerge from the cannula, it is unlikely that glycerol will be effective and RFE is preferred. If stimulation with low-voltage RFE at 100 Hz does not produce a response in the desired division (the site of the triggered pain), it is not an optimal condition for making a RF lesion, because that lesion will probably cause most denervation in the division of stimulation. One can advance the cannula, reposition it more medially (for second or first division lesions), or try a curved electrode [11], but such tactics do not always work. If there is free flow of CSF from the cannula, a situation often associated with a good response to glycerol, then the use of glycerol is a viable option. If the response to stimulation is in the desired division and a lesion for 60°C–65°C for 45 to 60 seconds is not followed by analgesia, then deepening the lesion by adding a modest dose of glycerol (0.2 ml) is an appropriate maneuver when there is flow of CSF from the cannula; it is unlikely to cause anesthesia dolorosa or keratitis. The surgeon who undertakes percutaneous denervation and is prepared to use either RFE or glycerol, or perhaps the two together, has an added flexibility in producing a safe and satisfactory moderate denervation.

TABLE 6-6. Other series. Glycerol volume, dysesthesia, and hypoalgesia

Authors	Yr	Patient no.	Glycerol ml	Dysesthesia major %	Hypoalgesia major %*
Hakanson	1981 [1]	75	.2–.4	0%	
Hakanson	1983 [6]	100	.2–.4	0%	
Lunsford	1982 [2]	30	.15–.35	0%	
Lunsford	1984 [9]	112	.15–.50	3.6%	
Sweet	1981 [3]	27	.2–.4	18.5%	59%

* 50% or greater reduction.

TABLE 6–7. Other series. Recurrence and final followup

Authors	Yr	Initial failure %	Pain recurs % of pts	Reop %	Final pain free	Followup mos
Hakanson	1981 [1]	1.3%	17%	6.7%	86	2–48
Hakanson	1983 [6]	4%	31%	16%	96	12–72
Lunsford	1982 [2]	17%			97	5–12
Lunsford	1984 [9]	10.7%	17%	17%	90	4–28
Sweet	1981 [3]	11.1%				

TECHNIQUE OF GLYCEROL INJECTION

In the original description of retrogasserian glycerol injection by Hakanson [1], the trigeminal cistern is punctured percutaneously by the anterior route via the foramen ovale, and contrast (metrizamide) is injected following spontaneous CSF drainage. Such drainage by itself does not always indicate proper placement because it may also occur when the needle tip is in the subtemporal subarachnoid space. Correct placement in the trigeminal cistern is confirmed when the proper configuration is identified fluoroscopically. The metrizamide is evacuated after the patient is placed in the recumbent or Trendelenburg position. The patient is then brought to the sitting position, the head is flexed, and pure sterile glycerol is injected. The volume of glycerol is between 0.2 ml and 0.4 ml and is determined by the estimated volume of the cistern; usually 0.20 ml to 0.30 ml of glycerol is sufficient [6]. To affect all three divisions, the cistern is completely filled; to treat the third division alone or the third and second divisions, 0.2 ml to 0.35 ml glycerol are injected. Metrizamide is heavier than glycerol, and a little may be left behind to protect the third division when the first or second divisions are affected; 0.15 ml to 0.25 ml glycerol is injected for these cases. A small amount of tantalum dust is added to the glycerol to help identify the cistern in case reinjection is needed.

Sweet described a few modifications [3]. Needle-electrode placement was guided by the response to stimulation by a square wave 50/second signal and by gentle radiofrequency heating. When these caused sensation in the main trigger zones or in the lowest division if the trigger zones affected more than one division, the final site for glycerol injection was selected. The response of the awake patient to the initial 0.05 ml to 0.2 ml of glycerol was used to indicate which fibers were first affected; localized pain, paresthesias, or

numbness were almost invariably present. The injection was stopped after 0.2 ml to 0.3 ml were instilled if analgesia was produced in the first division; otherwise, 0.4 ml was injected. Metrizamide was not given, and placement in Meckel's cave was established when low-voltage threshold was obtained — less than 0.15 volts for stimulation or less than 48°C for RF heating. This technique results in more analgesia and more dysesthesias (Table 6-6) than in other series, and Sweet has subsequently discontinued the use of glycerol in favor of RFE because of "too many initial failures, later recurrences, and major sensory losses or dysesthesias" associated with the use of glycerol [4].

Lunsford is enthusiastic about the use of glycerol but feels that contrast radiologic visualization of the trigeminal cistern is important [2, 9, 12]. He now uses iohexol as a nonionic contrast agent and not metrizamide, "thus considerably reducing the incidence of headache frequently associated with the use of metrizamide" [12].

A prospective, randomly allocated study performed by Arias has shown that equally good results can be obtained by percutaneous retrogasserian glycerol rhizotomy with and without metrizamide trigeminal cisternography [13]. Intraganglionic injection of the glycerol, which can cause marked denervation, is less likely if the needle tip is not too close to the floor of the middle fossa [13].

TYPE OF GLYCEROL

Two types of glycerol have been described, and different results have been obtained with each one [14]. Mallinckrodt glycerol is 76 times more viscous than water, while Sigma glycerol is 35 times more viscous than water. The osmolality of Mallinckrodt glycerol is 3753 mOsm per kilogram; Sigma glycerol osmolality is 3470 mOsm per kilogram. Sigma glycerol is less neurotoxic than Mallinckrodt glycerol and less likely to relieve trigeminal neuralgia pain.

MECHANISM OF ACTION

Light and electron microscopic studies of rat sciatic nerve showed that myelin disintegration and axonolysis occurred with glycerol application. The most striking histological changes were seen in the myelinated fibers, although myelinated and unmyelinated fibers were affected at random. Intraneural injection caused more damage than topical application [15].

The effect of topical anhydrous glycerol on both spontaneous firing from the neuroma and impulse propagation within the nerve was examined in rats that had undergone saphenous neurotomy [16]. Cessation of spontaneous action potential production from the neuroma was the earliest electrophysiological change noted, followed by loss first of C-fiber, then of A-fiber, conduction.

Electrophysiologic studies in humans showed disappearance of waves from slowly conducting, poorly myelinated fibers and some faster conducting ones [3]. In another study of patients with trigeminal neuralgia, the latency of the trigeminal evoked potential peak was reduced after glycerol injection; this was interpreted to indicate that glycerol more specifically affects damaged myelinated axons that may be responsible for trigeminal neuralgia [17].

Summary

Percutaneous injection of pure sterile glycerol into the trigeminal cistern may relieve the pain of trigeminal neuralgia in many patients. If relatively small doses of glycerol are used, complications such as anesthesia dolorosa are infrequent, but an early recurrence is likely. With larger doses of glycerol, there is more analgesia, more dysesthesias, a greater chance of corneal denervation, and less recurrence. Similar relationships between the degree of denervation, unpleasant sequelae, and recurrence exist for all known denervating agents, including glycerol, RFE, and surgical

manipulation or section.

A mild denervation, which can be done either with glycerol, RFE, or light RFE plus a small dose of glycerol, may be offered to patients who are extremely worried about postoperative dysesthesias or those who are profoundly analgesic on the face contralateral to the presently painful side. A moderate denervation is preferred for most other patients.

There are technical circumstances during the performance of a percutaneous denervation that are favorable for glycerol or RFE; free flow of CSF is often associated with a good result from glycerol; a response to low-voltage stimulation in the trigger zone of face pain is usually followed by a successful RFE. The surgeon who is prepared to use one or the other agent, or perhaps both, has an added flexibility in performing percutaneous denervation. The data presented in this chapter, however, are not sufficient to prove the superiority of a combined use of both glycerol and RFE over either agent alone.

Glycerol is a neurolytic agent that damages the unmyelinated and poorly myelinated, slowly conducting pain fibers, as well as the more heavily myelinated, faster conducting fibers, especially those that are already partially damaged.

References

1. Hakanson S: Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 9:638–646, 1981.
2. Lunsford LD: Treatment of tic douloureux by percutaneous retrogasserian glycerol injection. JAMA 248:449–453, 1982.
3. Sweet WH, Poletti CE, Macon JB: Treatment of trigeminal neuralgia and other facial pains by retrogasserian injection of glycerol. Neurosurgery 9:647–653, 1981.
4. Sweet WH: Current concepts. The treatment of trigeminal neuralgia (tic douloureux). N Engl J Med 315:174–177, 1986.
5. Sweet WH, Poletti CE: Problems with retrogasserian glycerol in the treatment of trigeminal neuralgia. Appl Neurophysiol 48:252–257, 1985.
6. Hakanson, Sten: Retrogasserian glycerol injection as a treatment of tic douloureux. Adv Pain Res Ther 5:927–933, 1983.
7. Brisman R: Treatment of trigeminal neuralgia: Radiofrequency electrocoagulation with/without glycerol. Contempor Neurosurg 8(3):1–5, 1986.
8. Menzel J, Piotrowski W, Penzholz H: Long-term results of Gasserian ganglion electrocoagulation. J Neurosurg 42:140–143, 1975.
9. Lunsford LD, Bennett MH: Percutaneous retrogasserian glycerol rhizotomy for tic douloureux: Part 1. Technique and results in 112 patients. Neurosurgery 14:424–430, 1984.
10. Brisman R: Bilateral trigeminal neuralgia. J Neurosurg 67:44–48, 1987.
11. Tew JM, Tobler WD: Percutaneous rhizotomy in the treatment of intractable facial pain (trigeminal, glossopharyngeal, and vagal nerves). In: Operative Neurosurgical Techniques, Vol. 2, Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1083–1106.
12. Lunsford LD: Letter to the editor. Glycerol rhizotomy for trigeminal neuralgia. J Neurosurg 66:151, 1987.
13. Arias MJ: Percutaneous retrogasserian glycerol rhizotomy for trigeminal neuralgia. A prospective study of 100 cases. J Neurosurg 65:32–36, 1986.
14. Waltz TA, Copeland BR: Treatment of trigeminal neuralgia. Letter to the editor. N Engl J Med 316:693, 1987.
15. Rengachary SS, Watanabe IS, Singer P, Bopp WJ: Effect of glycerol on peripheral nerve: An experimental study. Neurosurgery 6:681–688, 1983.
16. Burchiel KJ, Russell LC: Glycerol neurolysis: Neurophysiological effects of topical glycerol application on rat saphenous nerve. J Neurosurg 63:784–788, 1985.
17. Bennett MH, Lunsford LD: Percutaneous retrogasserian glycerol rhizotomy for tic douloureux: Part 2. Results and implications of trigeminal evoked potential studies. Neurosurgery 4:431–435, 1984.

7. SUBOCCIPITAL CRANIECTOMY AND TREATMENT OF TRIGEMINAL NEURALGIA

Ronald Brisman, M.D.

Suboccipital craniectomy and the operating microscope provide excellent exposure of the trigeminal nerve and nearby structures. The sensory part of the trigeminal nerve may be deliberately denervated by coagulation and/or section, usually of the caudal one third or one half [1]; an alternative maneuver is microvascular decompression [2]. Many patients with intractable pain from trigeminal neuralgia have had relief of pain following either of the above procedures.

Dandy operated on patients with trigeminal neuralgia via a posterior fossa "cerebellar route" [1]. He sectioned the caudal 50% of the trigeminal sensory root and found that this relieved pain "without loss of function" [3]. In 55% of the patients, he found compression of the nerve by tumors, arteries, or veins.

Gardner also believed that many cases of trigeminal neuralgia were caused by vascular compression [4, 5]. He used an extradural middle fossa approach to manipulate the nerve and obtained relief of pain in most patients [4]. He reserved posterior fossa exploration for those whose pain recurred after his middle fossa procedure. In one posterior fossa operation, he found an anomalous arterial loop lying against the trigeminal nerve, and completely relieved the pain after separating this vessel from the nerve root by the interposition of a piece of absorbable gelatin sponge (Gelfoam) [4].

Jannetta emphasized the prevalence of vascular compression as a cause of trigeminal neuralgia and used the operating microscope extensively for operating in the posterior fossa [2]. He developed a procedure of microvascular decompression that has become popular among many neurosurgeons [6].

The Operation

The patient is placed in the lateral position, which minimizes the need to retract the cerebellum and allows it to fall away from the fifth, seventh, and eighth nerves [7]. The head is secured with a three-pointed Mayfield headrest and is turned slightly to the side of the operation. A vertical retromastoid incision is made, followed by a circular craniectomy that is 4 cm in diameter. It is important that it extend superiorly to the transverse sinus and laterally to the sigmoid sinus. Mastoid air cells may be entered and should be waxed thoroughly. A cruciate dural incision is made, and the edges are tented up superiorly and laterally. The initial exposure is at the superior lateral aspect of the cerebellum, which is retracted medially. The operating microscope with a 275 mm objective is used.

The seventh and eighth nerves are usually encountered first. The trigeminal nerve is more superior and deeper, and a narrow brain retractor is required to expose it. The petrosal

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vein often has to be cauterized and divided. The arachnoid over the trigeminal nerve must be cut. Sometimes a blood vessel is found compressing the trigeminal nerve where it exits from the brain stem; this is usually a tortuous superior cerebellar artery. The trigeminal nerve may be surgically decompressed by placing a small prosthesis of either Ivalon foam sponge (Unipoint Industries, High Point, NC) or Teflon felt between the nerve and blood vessel [6].

When compression is not found, the caudal 30%–50% of the sensory part of the trigeminal nerve is divided. If a vein is found to be compressing the nerve, the vein is cauterized and divided. The caudal part of the nerve is also cut, because recurrence is more likely following microvascular decompression of a vein than an artery [8]. Section of the caudal part of the nerve is recommended for those who have had a previous denervation, because microvascular decompression alone is often followed by recurrence in these patients [9].

Personal Experience (Tables 7-1 through 7-5)

Although this series of patients with intractable trigeminal neuralgia who were treated with suboccipital craniectomy is small, it has provided the material for several impressions. The lateral position with the use of the operating microscope provides excellent exposure of the cerebellopontine angle. Blood vessels are frequently next to the trigeminal nerve and sometimes compress it. Decompression with a piece of Ivalon sponge can sometimes be carried out successfully. In one case (later shown to have multiple sclerosis), blood vessels pierced the trigeminal nerve and could not be successfully removed from the nerve. Microvascular decompression and/or section of the trigeminal nerve can be performed safely with a low complication rate.

In this series of suboccipital surgery for trigeminal neuralgia, patients had been treated with radiofrequency electrocoagulation (RFE), and most of these patients were offered suboccipital exploration only if pain recurred and could not be relieved by a repeat RFE. Denervation of the caudal part of the trigeminal nerve was carried out in all cases, and microvascular decompression was done when feasible. In most of these patients, excellent relief of pain resulted from the suboccipital procedure, but it is not certain how much the microvascular decompression added to the effects of denervation.

Patients who I treated for the first time were usually offered RFE. Several of these patients had been operated on previously with suboccipital craniectomy approaches, and most of

TABLE 7-1. Suboccipital craniectomy for trigeminal neuralgia

OR	Pts	Tic[1]	Tumor	Atyp[2]
15	14	10	3	1

[1] Trigeminal neuralgia.
[2] Atypical facial pain.

TABLE 7-2. Suboccipital Craniectomy (no tumor) 13 ORs on 11 Patients

Female	Left	RF[1]	Age[2]	V3	V2	V2,3	V2,1
8	8	11	53	6	2	2	1

[1] Patients who had previous RF lesion.
[2] Median age at time of first suboccipital operation.

TABLE 7-3. Operative findings: Suboccipital craniectomy (no tumor) 11 patients

Definite compression	Vessel contact	Denervate 1/3 to 1/2	Decompress
3 SCA	1 AICA 2 vein	11	4

SCA = Superior cerebellar artery.
AICA = Anterior inferior cerebellar artery.

TABLE 7-4. Complications/results

Anesthesia dolorosa	Other complications	Reop (Subocc)	Good result	Followup	
				<1 yr	1–3 yr
1*	0	2	12/14	11	3

* Following second suboccip and section of 70% of nerve (probable MS).

TABLE 7-5. Prior suboccipital craniectomy and subsequent RFE

Patients nos.	Results		Followup <1 yr
	Good	Fair	
7	5	2*	6

* One totally analgesic from previous section; one without analgesia per patient's request.

these patients had a good initial response from RFE (Table 7-5).

Discussion

VASCULAR COMPRESSION OF THE TRIGEMINAL NERVE IN OPERATED SERIES OF PATIENTS WITH TRIGEMINAL NEURALGIA (Table 7-6) [3, 5, 6, 10–12]

The frequency of trigeminal compression by a blood vessel at or near the root entry zone in patients with trigeminal neuralgia is disputed and has been reported to vary from 10.6% [10] to 95% [6] (Table 7-6), based on observations at posterior fossa exploration of the trigeminal nerve. All agree that blood vessels are frequently near the trigeminal nerve and often in contact with it; sometimes the blood vessel distorts the nerve. One study reported anatomical distortion by an artery in 14% of patients, arterial wedging into the crevice between the nerve and the pons in 23%, and distortion by a vein in 5%; there was nondistorting arterial contact in 33% and no arterial contact in another 30% [12].

ANATOMICAL STUDIES ON PATIENTS WITHOUT TRIGEMINAL NEURALGIA (Table 7-7) [13–16]

Arterial contact with the trigeminal nerve was found in 30% to 60% of trigeminal nerves examined at autopsy in patients without trigeminal neuralgia [13, 14, 16]. Arterial compression was found in 7%–11% of nerves [13, 16] and 15% of cadavers [16]. Venous contact was noted in another 8%–10% of nerves [13, 16] and 20% of cadavers [16].

Because of differences between cadavers and living patients, it is difficult to draw firm conclusions from autopsy studies regarding the causal relationship between vascular contacts and trigeminal neuralgia. The lower incidence of arterial compression of the trigeminal nerve in autopsy specimens of patients without trigeminal neuralgia than in operated patients with trigeminal neuralgia has been offered as support for the theory that vascular compression causes trigeminal neuralgia [13]. An equally reasonable conclusion from the autopsy data is that the high incidence of neurovascular contacts in non-trigeminal-neuralgia cadavers implies that the finding at operation of similar neurovascular contacts is coincidental [14].

RESULTS OF MICROVASCULAR DECOMPRESSION (Table 7-8) [6, 8, 11, 12, 17, 18]

Persistent relief of trigeminal neuralgia pain following one microvascular decompression occurs in 72% to 83% of patients who are

TABLE 7-6. Vascular compression causing trigeminal neuralgia (percent)

No. Patients	215 [3]	18 [5][1]	57 [10]	414 [6][2]	50 [11][3]	105 [12]
Aneurysm	2.8	5.6	1.8	.24		
Angiomas	2.3					2
Artery	30.7	33.3	8.8	58.5	28	37 (33)
Vein	14.0			13.0	6	5
Mixed arterial and venous				23.2	12	
AVM				.24		
Total	48.8	56.9	10.6	95.18	46	44 (33)

All are series of posterior fossa exploration.
[1] Recurrent trigeminal neuralgia following middle-fossa neurolysis.
[2] Operative findings, excludes MS.
[3] 82% had neurovascular contacts, but only 46% had compression.
(33) Arterial contact without clear distortion of the nerve.

TABLE 7-7. Vascular contact in autopsy series of patients without trigeminal neuralgia

No. of cadavers	65 [13]	25 [14]	56 [15]	20 [16]
No. root entry zones	130	50		40
Average age of patient (yrs)	65			
Nerve artery contact	30%	60%[1]		35%
Nerve artery compression	7%	Uncommon	0	10%
Nerve vein contact	9%			22.5%
Nerve vein compression	0.8%			10%
Nerve vessel contact or compression	40%			67.5%[2]

All percentages are calculated using the number of root entry zones as the denominator.
[1] Only arterial relationships were studied. Six of 50 had arterial contact at the pontine entry zone of the trigeminal nerve.
[2] Seventeen of 20 patients (85%) had nerve vessel contact or compression.

TABLE 7-8. Results of microvascular decompression for trigeminal neuralgia

Number	103[1] [12]	200 [17]	400 [6]	23 [11]	51 [18]	72 [8]
Followup (mos)	48.3[2]	36	?	36	1–53	59
Excellent/good (%)	77	72	79.8	83	72	78
Failure/recurrence (%)	23	28[3]		17	28[4]	22

[1] Includes 22 patients who had partial sensory rhizotomy at suboccipital OR.
[2] Average followup.
[3] 20% had pain but it was medically controlled; 8% failed (refractory pain).
[4] 15% had no initial relief or significant return of pain within 1 month, and 13% had return of pain 1.5 to 33 months after surgery.

followed for an average of 36 to 59 months (Table 7-9) [6, 8, 11, 12, 17, 18]. It is not certain how much of the relief is due to denervation or to decompression. Purposeful denervation caused by partial sensory rhizotomy in the posterior fossa produces pain relief that is as good as microvascular decompression [12]; the two procedures have a similar incidence of postoperative dysesthesias [12]. Minor manipulation of the trigeminal nerve may cause relief of pain without detectable sensory change [4].

TABLE 7-9. Factors that influence results of microvascular decompression

	No. pts	Recur %	Followup Months
Arterial compression [8]	59	19	59[1]
Venous compression [8]	7	47%	59[1]
Arterial contact [12]	68	22%	54[1]
No arterial contact [12]	13	46%	54[1]
Arterial distortion [12]	37	17%	50[2]
Other arterial contact [12]	31	38%	40[2]
No previous procedure [9]	23	9%	43[1]
Previous procedure [9]	14	57%	43[1]
Symptoms 3–9 yrs [9]	88	12%	43[1]
Symptoms 10–50 yrs [9]	42	58%	43[1]
Paroxysmal pain only [20]	44	5%	12–60
Paroxysmal & permanent pain [20]	24	25%	12–60
Male [19]	35	11%[3]	55.8[1]
Female [19]	46	37%[3]	55.8[1]

[1] Average for total series.
[2] Estimated recurrence at 50 and 80 months for anatomic distortion and 40 and 70 months for other arterial contact.
[3] Failure or recurrence.

FACTORS THAT INFLUENCE RESULTS OF MICROVASCULAR DECOMPRESSION (Table 7-9) [8, 9, 12, 19]

Certain factors are associated with a greater chance of recurrent pain following microvascular decompression. These are venous rather than arterial compression [8], no arterial contact rather than arterial contact [12], nondistorting arterial contact rather than arterial distortion [12], a previous procedure [9], symptoms longer than 9 years [9, 19], and female rather than male patient [8, 19]. Less recurrence following cases where arterial distortion is found may be explained by the greater denervation that occurs from the extra manipulation required in these cases; an alternative explanation is that the arterial distortion is causing the pain and its decompression may be effective independent of denervation. The inability of microvascular decompression to relieve trigeminal neuralgia in some patients, and reduced success of microvascular decompression in patients who have had previous procedures, indicate that in many patients there are factors other than vascular compression responsible for trigeminal neuralgia.

COMPLICATIONS (Table 7-10) [6, 8, 17, 18]

Although most patients can undergo suboccipital craniectomy and trigeminal nerve exploration safely, there is a small risk of major complications and a greater risk of milder problems. The reported incidence of postoperative death or major stroke is 0%–1.5% or 0%–2.5%, respectively [6, 8, 12, 16, 18, 20]. Less severe complications occur in 10%–60% [6, 8, 12, 17, 18, 20], and many of these are transient. Aseptic meningitis occurred in 30% of patients in whom Teflon felt was used for decompression [6]; Jannetta favors Teflon because of the ease with which the blood vessel can be manipulated. Ivalon sponge was associated with aseptic meningitis in 10% of his cases [6].

Complications of cranial neuropathies are most likely from permanent damage to the fifth (11%) [8, 12, 18] or eighth nerves

TABLE 7-10. Complications of microvascular decompression (percent)

No. patients	800 [6]	72 [8]	200 [16]	52 [17]	
Cranial neuropathy	2.9[4]				
Hearing loss		19.5[1,4]	4.5[4]	13.4[3]	7.7[4]
Facial numbness		11.1		5.8[3]	11.5[4]
Facial weakness		1.4[4]	1.5[3]	9.6[3]	5.8[4]
Diplopia		2.8	5.5[3]	1.9[3]	1.9[4]
Occipital analgesia				1.9	
Aseptic meningitis	30.0[2]			3.8[3]	
CSF leak				1.9	
Gait disturbance		2.8[4]		11.5[3]	
Cerebellar hematoma			1.5		
Stroke			1.0		
Death	0.52	0	1.5		

[1] 7% of the total series were total deafness (ipsilateral).
[2] With Teflon felt.
[3] Transient.
[4] Permanent.

(4.5%–19.5%) [8, 18]. In one series, persistent unilateral hearing loss occurred in 19% of patients and complete deafness in the ipsilateral ear in 7% [8]. Patients should be warned of these possibilities, especially those with contralateral hearing loss. A few patients may develop permanent facial palsy (0%–6%) [8, 17, 18] or diplopia (0%–3%) [8, 17, 18].

It has been suggested that intraoperative auditory monitoring may lessen the chance of eighth nerve damage [21].

Summary and Conclusions

Many patients with trigeminal neuralgia have blood vessels in contact with the trigeminal nerve, and sometimes there is distortion of the nerve, most often by the superior cerebellar artery. Excellent exposure of the nerve and blood vessels can be obtained at posterior fossa exploration when the operating microscope is used. The lateral position is preferred.

Arteries may be decompressed from the nerve by interposing a soft prosthesis; veins are cauterized and divided. The caudal part of the trigeminal sensory root is divided when arterial compression is not found or when the pain has recurred following a previous procedure.

There are several advantages associated with the suboccipital operation. It can relieve the pain of most patients with trigeminal neuralgia, including many of that small group who cannot be managed satisfactorily with percutaneous denervation. Most patients treated with suboccipital techniques do not develop disabling dysesthesias. Posterior fossa tumors associated with trigeminal neuralgia, although rare, may be treated successfully during suboccipital exposure; these tumors include those extremely rare ones that are not suggested by the preoperative clinical examination or imaging tests.

The disadvantages of suboccipital operations are: not all patients are relieved of their pain; recurrence may occur; complications are frequent; although most complications are temporary and relatively minor, occasionally they are very serious and permanent; and suboccipital reoperations are more difficult and more likely to be associated with complications than are the initial operations.

References

1. Dandy WE: The treatment of trigeminal neuralgia by the cerebellar route. Ann Surg 96:787–793, 1932.
2. Jannetta PJ: Microsurgical approach to the trigeminal nerve for tic douloureux. Prog Neurol Surg 7:180–200, 1976.
3. Dandy WE: Concerning the cause of trigeminal neuralgia. Am J Surg 24:447–455, 1934.
4. Gardner WJ, Miklos MV: Response of trigeminal neuralgia to "decompression" of sensory root. Discussion of cause of trigeminal neuralgia. JAMA 170:1773–1776, 1959.
5. Gardner J: Concerning the mechanism of trigeminal neuralgia and hemifacial spasm. J Neurosurg 19:947–958, 1962.
6. Jannetta PJ: Trigeminal neuralgia: Treatment by microvascular decompression. In: Neurosurgery, Wilkins RH, Rengachary SS, eds. McGraw-Hill, New York, 1985, pp 2357–2362.
7. Mount LA: The lateral position for operations in the cerebellopontine angle. J Neurosurg 2:460, 1945.
8. Kolluri S, Heros RC: Microvascular decompression for trigeminal neuralgia: A five year follow-up study. Surg Neurol 22:235–240, 1984.
9. Barba D, Alksne JF: Success of microvascular decompression with and without prior surgical therapy for trigeminal neuralgia. J Neurosurg 60:104–107, 1984.
10. Adams CB, Kaye AH, Teddy PJ: The treatment of trigeminal neuralgia by posterior fossa microsurgery. J Neurol Neurosurg Psychiat 45:1020–1026, 1982.
11. Loveren H, Tew JM, Keller JT, Nurre MA: A 10-year experience in the treatment of trigeminal neuralgia: Comparison of percutaneous stereotaxic rhizotomy and posterior fossa exploration. J Neurosurg 57:757–764, 1982.
12. Piatt JH Jr, Wilkins RH: Treatment of tic douloureux and hemifacial spasm by posterior fossa exploration: Therapeutic implications of various neurovascular relationships. Neurosurgery 14:462–471, 1984.
13. Klun B, Prestor B: Microvascular relations of the trigeminal nerve: An anatomical study. Neurosurgery 19:535–539, 1986.
14. Hardy DG, Rhoton AL Jr: Microsurgical relationships of the superior cerebellar artery and the trigeminal nerve. J Neurosurg 49: 669–678, 1978.
15. Jannetta PJ: Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg 26:159–162, 1967.
16. Haines SJ, Jannetta PJ, Zorub DS: Microvascular relations of the trigeminal nerve. An anatomical study with clinical correlation. J Neurosurg 52:381–386, 1980.
17. Apfelbaum RI: Surgical management of disorders of the lower cranial nerves. In: Operative Neurosurgical Techniques, Vol 2, Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1063–1082.
18. Breeze R, Ignelzi RJ: Microvascular decompression for trigeminal neuralgia. Results with special reference to the late recurrence rate. J Neurosurg 57:487–490, 1982.
19. Piatt JH Jr, Wilkins RH: Correspondence. Microvascular decompression for tic douloureux. Neurosurgery 15:456, 1984.
20. Szapiro J Jr, Sindou M, Szapiro J: Prognostic factors in microvascular decompression for trigeminal neuralgia Neurosurgery 17: 920–929, 1985.
21. Moller AR, Jannetta PJ: Monitoring auditory functions during cranial nerve microvascular decompression operations by direct recording from the eighth nerve. J Neurosurg 59: 493–499, 1983.

8. TRIGEMINAL NEURALGIA AND BRAIN TUMORS

Ronald Brisman, M.D.

Introduction

Trigeminal neuralgia is caused infrequently by brain tumors. The tumor may be upon but extrinsic to the trigeminal peripheral divisions, the gasserian ganglion, the retrogasserian rootlets (in between the gasserian ganglion and the brain stem) [1] or in the trigeminal pathways in the brain itself [2]. In any of these locations, the facial pain may be typical trigeminal neuralgia (paroxysmal, provokable, episodic, unilateral, distributed in one or more divisions of the trigeminal nerve, and associated with a normal neurologic examination) or it may be atypical trigeminal neuralgia [3] (paroxysmal, triggered face pain associated with one or more atypical features: a continuous pain in between the paroxysms, an abnormal neurologic examination, or distribution that is not precisely trigeminal) [1]. It is important to recognize the presence of a tumor because treatment should often be directed at the tumor rather than just the pain.

Results (Tables 8-1 and 8-2)

Between January 1976 and February 1987, the author has treated 10 patients with face pain caused by tumor. Nine of these patients had either trigeminal neuralgia or atypical trigeminal neuralgia, and eight were operated on for this condition.

Data accumulated between January 1976 and February 1986 were used to compare patients with trigeminal neuralgia and tumor with those who had trigeminal neuralgia without tumor (or multiple sclerosis) (Table 8–2). During this period, 219 patients with trigeminal neuralgia (or atypical trigeminal neuralgia) without tumor or multiple sclerosis were also treated surgically, usually with percutaneous radiofrequency electrocoagulation (RFE: either alone or with glycerol). Although patients with tumors were younger and more likely to be males, these differences were not statistically significant.

Two patients had posterior fossa epidermoid tumors. Both had paroxysmal-triggered trigeminal pain, but one had the atypical feature of constant pain during some of the intervals between paroxysms. This patient had a normal neurologic examination and a normal CT scan. The tumor was found unexpectedly during posterior fossa exploration. Two days prior to this, the patient underwent a percutaneous RFE for second division trigeminal neuralgia. The procedure was done without a technical problem, and moderate hypoalgesia was induced in the second division, but the patient continued to have such severe paroxysmal pain, which was uncontrolled with carbamazepine, that posterior fossa exploration was done. The characteristic pearly white epidermoid tumor was encountered, removed, and the posterior third of the sensory part of the trigeminal complex was divided, with excellent relief of pain.

The second patient with an epidermoid

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TABLE 8-1a. Patients with tumor and face pain

No.	Sex	Age	Location	Tumor type	Pain	Surgery	Result (months)
1	F	55	R V3>2	Epidermoid	ATN	RF; SO	E An Dolar 26
2	M	42	R V3	Epidermoid	TN	SO	E 11
3	F	55	L V2	Meningioma	TN	SO	E 24
4	F	66	R V2	CP angle	TN	RF	E Keratitis 17
5	M	23	L 3>2	Intraaxial	TN	RF	E 72
6	M	62	R V3	Nasopharynx	TN	RF	G 9
7	M	56	R V1,3	Pituitary	ATN	RF; NU	P 11
8	M	66	R V3	CP angle	TN	None	G 36
9	M	40	R V1–3	Sarcoma	AFP	RF; SO	G 5
10	F	75	R V3	CP angle	TN	RF*	G <1

TN = Trigeminal neuralgia: paroxysmal, triggered, episodic.
ATN = Atypical trigeminal neuralgia: triggered but continuous.
AFP = Atypical facial pain: continuous and not triggered.
RF = Radiofrequency electrocoagulation.
SO = Suboccipital craniectomy and tumor removal (total in Nos. 1 & 2; partial in No. 3).
NU = Neurectomy of supraorbital and supratrochlear nerves.
E = Excellent relief of pain; no medications.
G = Good relief of pain; occasional medication.
P = Recurrent pain not well controlled with medication.
* After February 1986.

TABLE 8-1b. Patients with tumor and face pain

No.	Comment
1	Normal CT; no relief from RF; tumor removal and partial section (caudal third) sensory part of V.
2	Tumor removal and section caudal third of sensory V.
3	Large tumor in middle and posterior fossae.
4	Giant unoperated contralateral CP angle tumor.
5	Intraaxial mass either astrocytoma or syrinx.
6	Pain occurred 9 years after successful radiotherapy for nasopharyngeal carcinoma. No apparent recurrence.
7	Pain developed 2 years after radiotherapy of pituitary.
8	Unoperated CP angle tumor, probably acoustic neurinoma.
9	Right temporalis muscle sarcoma 3 years after radiotherapy and surgery for left frontal glioma.
10	Giant unoperated contralateral CP angle tumor in posterior and middle fossae; shunted hydrocephalus.

tumor had classical trigeminal neuralgia and a normal neurologic examination. A percutaneous RFE was planned, but a CT scan unexpectedly showed a large cerebellopontine angle radiolucent mass (Figure 8-1). Suboccipital exploration was carried out instead, with removal of a typical epidermoid tumor and section of the lower third of the trigeminal sensory nerve. Postoperatively, the patient was free of pain.

Another patient with typical trigeminal neuralgia and a normal neurologic exam was found on CT scan to have a large meningioma involving much of the base of the skull in the posterior and middle fossae. At surgery, a vascular meningioma was encountered; only a small amount could be removed, and the caudal third of the trigeminal sensory nerve was cut. Postoperatively the patient was free of pain and had a normal neurologic examination except for hypoalgesia in the lower part of the face. She has remained asymptomatic for the duration of followup, which is now 2 years.

TABLE 8-2. Comparison of patients with trigeminal neuralgia (TN) and tumor with those without tumor or multiple sclerosis

	Tumor		No Tumor		p*
Number of patients	8		219		
Average age at first (TN) OR	53		63		.064
Female	3	37.5%	130	59%	>.1
Right-side pain	6	75%	131	60%	>.1
Location: V2,3 or 2 & 3	7	87.5%	188	89%	>.1
Reoperation, ipsilateral	2	25%	40	19%	>.1

All patients had first TN procedure prior to Feb. 1986.
* Probability was determined by the chi-square test with Yates' correction for all data except average age, which was based on the two-tailed test on significance of mean.

Unoperated cerebellopontine angle tumors were encountered in three patients who refused direct surgery. Two of these patients had giant posterior fossa tumors on the side contralateral to their face pain. These two responded well to RFE.

Discussion

INCIDENCE (Table 8-3)

Approximately 5% of patients with trigeminal neuralgia have a brain tumor [4]. This incidence is derived from Dandy's series of

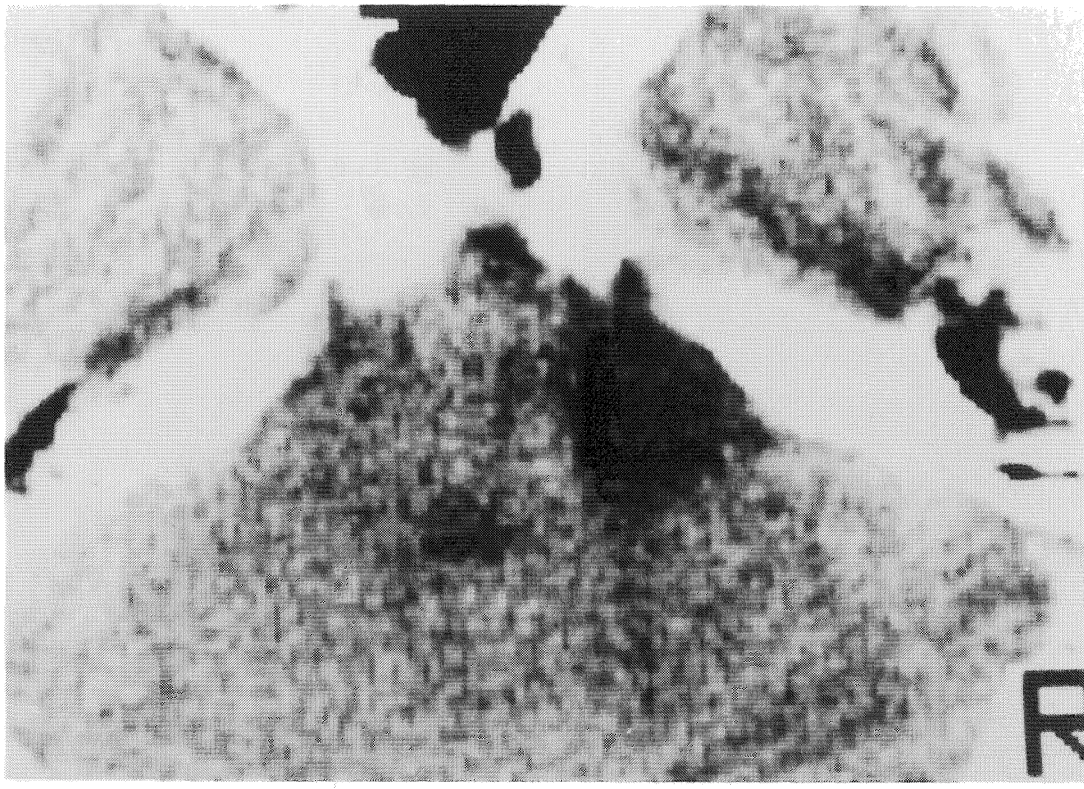

FIGURE 8-1. CT scan in a patient with trigeminal neuralgia and epidermoid tumor reveals a large lucency in the right cerebellopontine angle.

TABLE 8-3. Incidence of brain-tumor-associated trigeminal neuralgia

	Years	Patients total no.	Tumors No.	Tumors %
Dandy [4]	1925–45	473[1]	24	5.1%
Jannetta [5]	–76	100[1]	4	4.0%
Brisman	1976–87	252[2]	9	3.6%
Apfelbaum [6]	1977–82	200[1]	6	3.0%
Bullitt et al. [7]	1976–86	2000[3]	16	0.8%

[1] All operated via the posterior fossa
[2] All operated; most were RFE
[3] Operated and non operated cases; radiofrequency electrocoagulation (RFE) was the most frequent procedure.

patients with trigeminal neuralgia who had posterior fossa surgery. Patients with contralateral posterior fossa tumors or middle fossa tumors may have been missed. The figure of 5% is for operated patients who have a more intractable pain and probably reflects a higher incidence of brain tumor than in those with milder forms of trigeminal neuralgia who do not require a surgical procedure.

CLINICAL FINDINGS

Most patients with trigeminal neuralgia and brain tumor are reported in series where face pain is the chief complaint. Some of these patients may have signs and symptoms of other cranial nerve abnormalities and sometimes noniatrogenic hypoalgesia or hypoaesthesia, which may alert the physician to the possible presence of a structural lesion such as a brain tumor (or possibly demyelinating disease). Hearing loss from an acoustic neurinoma is one of the more common cranial neuropathies in brain-tumor-associated trigeminal neuralgia [4]. This can easily go undetected because many patients, especially the elderly, may have hearing impairment due to causes other than a brain tumor.

Peripherally located tumors, which are usually about the base of the skull, are more likely to cause an atypical kind of facial pain associated with sensory loss [7]; these tumors are frequently carcinomas, and multiple cranial neuropathies may be present.

Middle fossa tumors are usually meningiomas or fifth nerve neurinomas. Three groups of patients, with different kinds of meningiomas of Meckel's cave involving the gasserian ganglion, have been described [8]. The largest group of patients have typical trigeminal neuralgia and an excellent prognosis after removal of the easily detachable mass that is impinging on the ganglion. A second group of patients, with meningiomas "en plaque," have atypical pain without neurologic deficit; the prognosis for pain relief is not so good as in the first group. Patients in a third group have face pain, dysesthesias, objective trigeminal sensory loss, multiple cranial nerve deficits, histological signs of mitotic activity, and a poor prognosis.

The posterior fossa tumors, which can also cause atypical trigeminal neuralgia pain [3], are more likely to cause pure trigeminal neuralgia, although initially mild abnormalities in nearby cranial nerves (especially the eighth) may be present. These tumors are frequently neurinomas, epidermoids, or meningiomas [4].

DIAGNOSTIC TESTS

Although skull x-rays may show erosion about the base of the skull or abnormalities in the internal auditory meatus, the CT scan is much more sensitive for diagnosing brain tumors [9]. CT scanning without and with contrast or magnetic resonance imaging (MRI) are recommended for those with intractable trigeminal neuralgia requiring neurosurgical intervention, especially if they are healthy enough to be considered candidates for direct surgical intervention should a tumor be found. Imaging should include the base of the skull and middle and posterior fossae. A CT scan (or MRI) will be a very low-yield procedure, however, in patients with classical trigeminal neuralgia and a normal neurologic examina-

tion. An unsuspected brain tumor will be found in only 1% of such patients.

Even with CT scanning, some brain tumors may be missed, especially small epidermoids [10]; this occured in one of our cases (Table 8-1 Case 1). CT cisternography with a water-soluble contrast agent may help define such a problem [11]. Magnetic resonance imaging is an excellent noninvasive technique for visualizing cerebellopontine angle lesions and is sometimes more sensitive than CT scanning [12]. Posterior fossa exploration for those who do not respond to technically satisfactory RFE is another alternative, but only after a CT scan (or MRI) to exclude either a middle fossa or contralateral tumor.

CONTRALATERAL BRAIN TUMOR

Although rare, brain tumors contralateral to the side of the trigeminal neuralgia may cause such face pain [13, 14]. Explanations that have been offered are: distortion and displacement of the brain stem [13]; stretching of the trigeminal nerve around the lateral margin of the dural foramen through which it leaves Meckel's cave [15], or vascular cross compression [3, 14]. Contralateral brain tumors were present in two of our patients (Table 8-1, Cases 4 and 10). These tumors are usually very large. Although they frequently cause other signs and symptoms, these may be subtle.

THERAPEUTIC CONSIDERATIONS

Trigeminal neuralgia associated with a brain tumor frequently responds to carbamazepine [7] or RFE. Four of the five patients that we treated with RFE had a very good result. Percutaneous RFE may not always be technically successful in patients with malignant tumors of the skull base [7].

Patients with malignant tumors may have pain beyond the confines of just the trigeminal nerve. This may require denervation of the ninth, tenth, and/or upper cervical dorsal nerves as well as the trigeminal nerve, depending on the exact location of the pain. This occurred in one of our patients (Table 8-1, Case 9) who had pain in the side of the face, temporal area, and angle of the jaw. Percutaneous RFE did not relieve the pain, but open section of the fifth and dorsal roots of the three upper cervical nerve roots did.

Radiation therapy is often indicated for malignant tumors of the skull base after biopsy, which is usually obtained from the nasopharynx or appropriate paranasal sinus. Neurosurgical denervation may be indicated if radiotherapy does not control the pain.

Direct surgery with removal of the tumor is indicated for most patients with benign tumors. I chose to cut the caudal one third to one half of the sensory part of the trigeminal sensory nerve to ensure good relief of pain, which occurred in each case; none of these patients was bothered by the postoperative hypoalgesia. Some patients may obtain good relief of pain with removal of the tumor and no nerve section, although it is not always clear how much denervation may occur from the surgical manipulation, even though the nerve is not purposefully cut.

The epidermoid tumor is a rare tumor but one of the more common ones to cause trigeminal neuralgia that is unassociated with other neurologic abnormalities [4]. This tumor is avascular and readily removable by neurosurgical techniques. Many neurinomas and meningiomas can also be totally removed safely, but occasionally these tumors (especially meningiomas) may be very extensive and invasive; total resection may be hazardous and sometimes impossible. It is sometimes wise to do a partial removal and cut the lower part of the trigeminal nerve (Table 8-1, Case 3).

Summary

Five percent of patients with trigeminal neuralgia will have a brain tumor.

In addition to paroxysmal, unilateral, triggered trigeminal pain, these patients some-

times have atypical features such as a constant nontriggered pain, hypoalogesia, or other neurologic abnormalities.

The tumor may be at the base of the skull (carcinoma), where atypical features are likely; in the middle fossa (neurinoma or meningioma); or in the posterior fossa (neurinoma, epidermoid, or meningioma), frequently with subtle neurologic abnormalities such as hearing loss (neurinoma), but sometimes with no other signs or symptoms (epidermoids). Occasionally the tumor may be contralateral to the pain.

CT scanning without and with contrast or MR are the preferred imaging tests.

Although carbamazepine and RFE may help the pain, direct surgical removal is recommended for healthy younger patients with benign resectable lesions.

References

1. Sweet WH: Comment on trigeminal root neurinomas. Neurosurgery 6:273–277, 1980.
2. Epstein N, Epstein F, Allen JC, Aleksie S: Intractable facial pain associated with a ganglioglioma of the cervicomedullary junction: Report of a case. Neurosurgery 10:612–616, 1982.
3. Yonas H, Jannetta PJ: Neurinoma of the trigeminal root and atypical trigeminal neuralgia: Their commonality. Neurosurgery 6:273–277, 1980.
4. Revilla AG: Tic douloureux and its relationship to tumors of the posterior fossa. Analysis of twenty-four cases. J Neurosurg 4:233–239, 1947.
5. Jannetta PJ: Microsurgical approach to the trigeminal nerve for tic douloureux, Prog Neurol Surg 7:180–200, 1976.
6. Apfelbaum RI: Surgical management of disorders of the lower cranial nerves. In: Operative Neurosurgical Techniques, Vol 2, Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1063–1082.
7. Bullitt E, Tew JM, Boyd J: Intracranial tumors in patients with facial pain. J Neurosurg 64:865–871, 1986.
8. Nijensohn DE, Araujo JC, MacCarty CS: Meningiomas of Meckel's cave. J Neurosurg 43:197–202, 1975.
9. Gorelick PB, Masdeu JC: Use of CT to uncover underlying brain tumor. Trigeminal neuralgia. IMJ 160:225–227, 1981.
10. Cusick JF: Atypical trigeminal neuralgia. JAMA 245:2328–2329, 1981.
11. Fein J, Lipow K, Taati F, Lansem T: Epidermoid tumor of the cerebellopontine angle: Diagnostic value of computed tomographic metrizamide cisternography. Neurosurgery 9:179–182, 1981.
12. Tanaka A, Takaki T, Maruta Y: Neurinoma of the trigeminal root presenting as atypical trigeminal neuralgia: Diagnostic values of orbicularis oculi reflex and magnetic resonance imaging. A case report. Neurosurgery 21:733–736, 1987.
13. Florensa R, Llovet J, Pou A, Galito E, Vilato J, Colet S: Contralateral trigeminal neuralgia as a false localizing sign in intracranial tumors. Neurosurgery 20:1–3, 1987.
14. Snow RB, Fraser RAR: Cerebellopontine angle tumor causing contralateral trigeminal neuralgia: A case report. Neurosurgery 21:84–86, 1987.
15. O'Connell JEA: Trigeminal false localizing signs and their causation. Brain 101:119–142, 1978.

9. BILATERAL TRIGEMINAL NEURALGIA

Ronald Brisman, M.D.

Bilateral trigeminal neuralgia has been reported to occur infrequently. This disorder is difficult to treat because of the unpleasant sequelae of bilateral denervation. The present report demonstrates a higher incidence of bilateral involvement than in other series (32 cases or 11.9%) in a group of 269 patients with trigeminal neuralgia. Percutaneous radiofrequency electrocoagulation (RFE) of the retrogasserian rootlets and gasserian ganglion either alone or with glycerol proved to be an excellent therapeutic technique.

Clinical Material

PATIENT POPULATION AND CLINICAL SYMPTOMS

In this series of 269 consecutive patients with trigeminal neuralgia, 32 had bilateral symptoms. There were 25 females and 7 males. The median age of patients was 58 years (33–86 years) at the time of the first operation. First division trigeminal pain was a prominent feature on one side in two patients, while the others had second and/or third division pain. The median interval between the appearance of the first symptom on one side and the first symptom on the other side was 5 years (range <1 to 45 years in 23 patients for whom these data were available). Bilateral trigeminal neuralgia occurred simultaneously in two patients. Six of the 32 patients had multiple sclerosis. Computerized tomography demonstrated a cerebellopontine angle tumor in one patient and hydrocephalus in another.

OPERATIVE PROCEDURES

Thirty-two patients underwent 87 operations between 1952 and 1986 (Table 9-1). Forty-four radiofrequency electrocoagulations were done by this author on the 32 patients. Ten of these radiofrequency procedures were light coagulations (62°C for 25 seconds) combined with 0.15 ml to 0.20 ml of glycerol [1]. Seven of the RFE were a moderate denervation (65°C for 45 to 60 seconds) combined with 0.2 ml to 0.25 ml of glycerol. The straight Radionics cannula with a 7-mm uninsulated tip was used for the RFE. Final placement was based on lateral and submentovertex skull x-rays and the response of the awake patient to low voltage stimulation at 100 Hz. Glycerol injections were done without contrast injection for identifying Meckel's cave. [2] Most patients did not develop significant hypoalgesia (50% or greater reduction of pin sensation over preoperative condition) (Table 9-2).

Sixteen patients required bilateral surgery; seven of these were treated with bilateral RFE. The interval between the first operation on one side and the second on the other ranged from 0.4 to 25 years (median 7 years).

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TABLE 9-1. Operations

	Patients	Operations	Before 1976
Subtemporal	10	15	13/15
Suboccipital	4[1]	9	2/9
Neurectomy (supraorbital)	2	7	4/7
Radiofrequency	32	54[2]	10/54
Total	32	87	29/87

[1] In three of these patients, the trigeminal nerve was cut during the suboccipital procedure.
[2] In 10 of 54 operations, a small combined lesion was made (62°C for 25 seconds followed by 0.15 ml–0.20 ml glycerol). In 7 of 54 operations, a moderate combined lesion was made (65°C for 45–60 seconds followed by 0.20 ml–0.25 ml glycerol).

COMPLICATIONS (Tables 9-3)

Moderate discomforting dysesthesias developed in two patients following RFE (without glycerol). A third patient sustained undesired first division analgesia and mild keratitis following RFE. Chewing problems from weakness of the trigeminal motor nerve was not a major problem in any patient, even though the entire trigeminal nerve was cut bilaterally in one patient.

RECURRENCE

Immediate relief of pain was obtained in 31 of the 32 patients in whom RFE was done by this author. Pain recurred in eight patients, in one

TABLE 9-2. Degree of RFE[1] (with or without glycerol) denervation in patients with bilateral trigeminal neuralgia and total series

Operation	No. of Operations[2]	Hypalgesia[3] Moderate	Hypalgesia[3] Severe
Bilateral trigeminal neuralgia (32 cases)			
RFE (no glycerol)	20	5%	30%
Moderate (RFE + glycerol)	7	14.3%	28.6%
Mild (RFE + glycerol)	10	0%	0%
Total series (249 cases)[4]			
RFE (no glycerol)	157	16%	15%
Moderate (RFE + glycerol)	31	6%	13%
Mild (RFE + glycerol)	61	10%	0%

[1] For details of coagulation and glycerol dosage see text. RFE = radiofrequency electrocoagulation.
[2] Data available for 37 operations on 32 patients.
[3] Hypalgesia is the postoperative reduction of sensitivity to pinprick (moderate, 50% to 89%; severe, 90% to 100%).
[4] Of the total 269 patients, the 20 with multiple sclerosis were excluded.

TABLE 9-3. Complications

	No. Pts.	Operation	Year
Dysesthesias: moderate	2	RFE	1980, 1982
severe	1	Suboccip	1981
Keratitis: mild	1	RFE	1982
severe	2	Subtemporal	1952, 1958
Palsy: third & eighth nerves	1	Suboccip	1969

TABLE 9-4. Recurrence (or persistence) of trigeminal neuralgia following initial RFE

Recurrence	Other Condition	Time	No. Pts.	Division[1]
Early		(within 1 month)	2[2]	Same
Later		7 mos	1	Same
		9 mos	1	Same
		24 mos	1	Same
		48 mos	1	Same
		72 mos	1	Same
	Multiple Sclerosis	7 mos	1	Different
	Multiple Sclerosis	24 mos	1	Different

[1] Division of recurrent pain was either the same or different from the division of original pain.
[2] The first RFE never relieved pain in one of these patients.

TABLE 9-5. Patients with bilateral trigeminal neuralgia compared with unilateral group

	Bilateral	Unilateral Group	p
Prior surgery[1]	8/24 (33%)	22/197 (11%)	$<.01$[2]
Multiple sclerosis[1]	5/28 (18%)	11/213 (5%)	.04[2]
Female[1]	16/22 (73%)	114/197 (58%)	$>.1$[2]
Analgesia postop but not preop[3]	3/16 (19%)	20/136 (15%)	$>.1$[2]
Average age at first RFE in this series[1]	61	62	
Recurrence ipsilat[3]	5/16 (31%)	53/136 (39%)	$>.1$[4]

[1] Series from 1976–Feb 1986. Twenty-four sides operated in the bilateral group were at risk for prior surgery.
[2] Chi-square with Yates' correction.
[3] Series from 1976–1983.
[4] Probability for the two-sided alternative based on Peto and Peto's generalized Wilcoxon test.
Data for prior surgery, female, age, analgesia postop but not preop, and recurrence ipsilat exclude patients with multiple sclerosis or tumor.

within the first month and later than 1 month in the other seven (Table 9-4). Following RFE, eight patients (25%) were eventually reoperated, all successfully. The period at risk during which patients were at risk for recurrence varied from 1 month to 10 years.

COMPARISON BETWEEN THOSE PATIENTS WITH BILATERAL TRIGEMINAL NEURALGIA AND THE ENTIRE GROUP (Table 9-5, Figure 9-1)

Patients with bilateral trigeminal neuralgia had a greater incidence of multiple sclerosis (18%) than the entire group (5%) (statistically significant: chi-square $p < 0.05$). Excluding those with multiple sclerosis, there was still a higher incidence (statistically significant) of prior surgery in the bilateral group (33%) than in the unilateral group (11%). There was no significant difference in the two groups regarding the percentage of female patients, age at time of first RFE, development of post-RFE analgesia, or recurrence (determined by Peto and Peto's generalized Wilcoxon test) [3].

Recurrence was defined as the development of bothersome ipsilateral trigeminal neuralgia in spite of medication following initial RFE, whether or not there was reoperation. The recurrence-free interval was calculated on the basis of the Kaplan-Meier product limit estimate (Figure 9-1) [3] using the consecutive series of 157 patients with trigeminal neuralgia who were treated between January, 1976 and December, 1983. All of these patients received

RFE without glycerol. Patients with multiple sclerosis were excluded from this analysis.

Discussion

INCIDENCE

There was an 11.9% incidence of bilateral trigeminal neuralgia in the present study, in contrast to a 3% incidence reported in other series. In a review of the literature prior to 1966, White and Sweet accumulated 14,692 cases of trigeminal neuralgia of which 486 (3.3%) were bilateral [4]. The incidence of bilaterality in several series that they reviewed ranged from 1 of 322 (0.31%) in Cushing's series [5] to 85 of 1433 (5.93%) reported by Harris [6].

Several factors will influence the incidence of bilaterality. Important among these is the presence of multiple sclerosis, where the incidence of bilaterality has varied from 11%–30% in other studies, an incidence which is much higher than in those patients without multiple sclerosis [7, 8].

The duration of the followup period also affects the incidence of bilaterality. The longer that patients with unilateral trigeminal neuralgia live, the more likely it is that they may develop contralateral symptoms; and the longer that they are monitored, the more likely it is that the contralateral symptoms will be noticed and reported. Peet and Schneider [4, 9] reported that the incidence of bilaterality in their patients increased from 2.7% when they were first seen to 5.9% at their latest followup examination. Some patients in the present series, which started in 1976, have been followed for 10 years. The actual period at risk is much higher for some of these patients who were treated initially at the Neurological Institute from 10 to 30 years ago and have continued to seek medical attention at the same institution.

Retrospective reviews of hospital records are less likely to detect bilaterality than are prospective studies like the present series, where all patients were questioned about bilateral symptoms. Studies that consider only those with bilateral symptoms severe enough to require bilateral surgery will demonstrate a lower incidence of bilaterality than those (such as the present one) that include patients with even mild paroxysmal, triggered, and episodic trigeminal pain contralateral to an operated side.

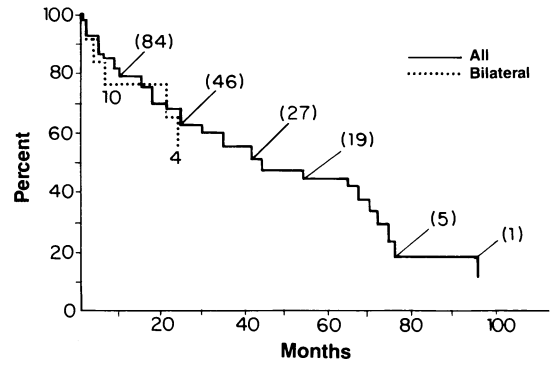

FIGURE 9-1. Estimated probability of not having recurrence after RFE. The graphs are Kaplan-Meier product-limit estimates. The numbers in parentheses indicate how many patients without recurrence were available for followup. There was no statistically significant difference ($p > .1$) between those with bilateral trigeminal neuralgia and the entire group. The entire group of 157 patients with trigeminal neuralgia includes five patients in whom the initial RFE was unsuccessful. None of the patients in the bilateral or entire group had multiple sclerosis.

BILATERAL AND UNILATERAL GROUPS COMPARED

There was a statistically higher incidence of prior surgery as well as multiple sclerosis in the bilateral group. Perhaps the higher incidence of prior surgery can be explained by the reluctance of surgeons to make a profoundly denervating lesion in a patient with bilateral trigeminal neuralgia. Since lesser degrees of denervation are associated with a

higher incidence of recurrence [10, 11], this may explain why many patients with bilateral disease had previous surgery. An alternative possibility is that patients with bilateral disease have a greater chance for recurrent disease. This seems less likely, because the recurrence rate in the bilateral group in this series was not greater than in the entire group (Figure 9-1).

Although a statistically significant difference could not be determined between the likelihood of ipsilateral recurrence in those with bilateral and unilateral trigeminal neuralgia, it is still possible that such a difference exists. Longer followup periods with a larger series might show this difference, which is suggested by the 55% nonrecurrence at 24 months in the bilateral group as compared with 55% rate of nonrecurrence at 34 months in the total group (Figure 9-1).

Many surgical maneuvers have been tried in patients with trigeminal neuralgia, and most of these have also been used to treat patients with bilateral involvement [2, 4, 12–15]. A partial denervation using RFE with or without glycerol provides a very satisfactory solution. This procedure has the advantages of preserving much facial sensation and trigeminal motor function, of having a very low morbidity, and of being repeatable without added risk or difficulty. These are particularly important in patients with bilateral trigeminal neuralgia who may need multiple procedures and are at risk for the especially disabling effects of bilateral trigeminal sensory and motor denervation.

GUIDE FOR TREATMENT

The degree of denervation can be controlled to a certain extent by varying the temperature, duration of heating, volume of glycerol, and by monitoring the response of an awake patient to incremental lesions. Placing further lesions until the patient becomes analgesic in the trigger zone may produce too much denervation in some patients and may cause a higher incidence of anesthesia dolorosa; such a tactic may be appropriate in those with unilateral disease who are reluctant to accept a repeat procedure and are willing to take the added risk of dysesthesias. A more moderate lesion may increase the possibility of recurrence, but will lessen the chance of dysesthesias and is preferable in most patients. A lighter lesion is indicated if the patient has profound denervation on one side and is about to undergo treatment on the other side, and in those who are very fearful of dysesthesias and are willing to risk the likelihood of an early recurrence.

Summary

Bilateral trigeminal neuralgia occurred in 32 (11.9%) of 269 consecutive patients who were treated with radiofrequency electrocoagulation. This is a higher incidence than has been reported before and may be explained by the prospective nature of the present study, the long followup, and the inclusion of patients with even mild bilateral symptoms. Multiple sclerosis is the most common predisposing factor and occurred in 19% of those with bilateral trigeminal neuralgia. Although patients with bilateral trigeminal neuralgia were more likely to have had prior surgery than those with unilateral neuralgia, they did not have a higher recurrence rate. The percutaneous radiofrequency trigeminal electrocoagulation with or without glycerol is very effective for managing those patients whose pain has been intractable to medical therapy. The preservation of most trigeminal sensory and motor function, low morbidity, and ease of repetition are particularly advantageous for patients with bilateral involvement.

References

1. Brisman R: Treatment of trigeminal neuralgia: Radiofrequency electrocoagulation with/without glycerol. Contemp Neurosurg 8(3):1–5, 1986.

2. Sweet WH, Poletti CE, Macon JB: Treatment of trigeminal neuralgia and other facial pains by retrogasserian injection of glycerol. Neurosurgery 9:647–653, 1981.
3. Lee ET: Statistical Methods for Survival Data Analysis. Lifetime Learning Publications, Belmont, California, 1980, pp 75–156.
4. White JC, Sweet WH: Bilateral trigeminal neuralgia. In: Pain and the Neurosurgeon. Charles C. Thomas, Springfield, 1969, pp 251–256.
5. Cushing H: The role of deep alcohol injections in the treatment of trigeminal neuralgia. JAMA 75:441–443, 1920.
6. Harris W: An analysis of 1433 cases of paroxysmal trigeminal neuralgia (trigeminaltic) and the end-results of gasserian alcohol injection. Brain 63:209–224, 1940.
7. Henderson WR: Trigeminal neuralgia: The pain and its treatment. Br Med J 1:7–15, 1967.
8. Rushton JG, Olafson RA: Trigeminal neuralgia associated with multiple sclerosis: Report of 35 cases. Arch Neurol 13:383–386, 1965.
9. Peet MM, Schneider RC: Trigeminal neuralgia: A review of six hundred and eighty-nine cases with a followup study of sixty-five percent of the group. J Neurosurg 9:367–377, 1952.
10. Latchaw JP, Hardy RW, Forsythe SB, Cook AF: Trigeminal neuralgia treated by radiofrequency coagulation. J Neurosurg 59:479–484, 1983.
11. Salar G, Mingrino S, Iob I: Alterations of facial sensitivity induced by percutaneous thermocoagulation for trigeminal neuralgia. Surg Neurol 19:126–130, 1983.
12. Jannetta PJ: Microsurgical approach to the trigeminal nerve for tic douloureux. Prog Neurol Surg 7:180–200, 1976.
13. Stookey B, Ransohoff J: Bilateral trigeminal neuralgia — Surgical treatment. In: Trigeminal Neuralgia: Its History and Treatment. Charles C. Thomas, Springfield, 1959, pp 214–234.
14. Sweet WH, Wepsic JG: Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers: Part 1. Trigeminal neuralgia. J Neurosurg 39:143–156, 1974.
15. Velasco-Siles JM, Ouaknine GE, Mohr G, Molina-Negro P, Hardy J: Bilateral trigeminal neuralgia. Surg Neurol 16:106–108, 1981.

10. TRIGEMINAL NEURALGIA AND MULTIPLE SCLEROSIS

Ronald Brisman, M.D.

Although there are similarities between trigeminal neuralgia associated with multiple sclerosis (TNMS) and trigeminal neuralgia without multiple sclerosis (TN), there also are differences. In both conditions, paroxysmal, episodic triggered face pain occurs in the trigeminal distribution and is relieved by carbamazepine (Tegretol) and trigeminal denervation. As opposed to TN, TNMS usually occurs in younger patients and is more frequently bilateral; in patients with multiple sclerosis, carbamazepine is less well tolerated and microvascular decompression is contraindicated. It has been suggested that recurrence is more likely following radiofrequency electrocoagulation of the gasserian ganglion and retrogasserian rootlets (RFE) in TNMS than in TN [1].

In the following chapter, a consecutive experience with RFE in 219 patients with TN will be compared with 16 patients with TNMS. Particular attention will be directed towards the relative effectiveness of RFE in each group.

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Results

COMPARISON OF PATIENT GROUPS: TRIGEMINAL NEURALGIA WITH MULTIPLE SCLEROSIS (TNMS) AND TRIGEMINAL NEURALGIA WITHOUT MULTIPLE SCLEROSIS (TN) (Table 10-1)

Between January 1976 and December 1983, all patients were treated with RFE as described in Chapter 5. RFE and glycerol were used between December 1983 and February 1986, as described in Chapter 6.

Bilateral trigeminal neuralgia was much more likely to occur in patients with multiple sclerosis (31%) than in those without MS (10.5%). The patients with MS were younger at the time of their first RFE (average age 50 years)(Figure 10-1) than patients without MS (average age 63.5 years) (see Figure 5-4 in Chapter 5). Patients in the TNMS group were more likely to be female (81%) than those without MS (59%); right-sided pain occurred more frequently in those with TNMS (87.5%) than TN (60%). Most patients in both groups had pain in the second or third divisions, but first division pain was seen in 11% of TN and in none of TNMS.

The probability of recurrence was calculated using Kaplan-Meier product-limit esti-

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TABLE 10-1. Comparison of trigeminal neuralgia patients with and without multiple sclerosis

	MS		No MS		p[5]
RFE (1976–Dec. 1983)	10		157		
RFE & glycerol (Dec '83–Feb '86)	6		62		
Total no. of patients	16		219		
Female	13	81%	130	59%	>.1
Average age at first RFE	50		63.5		.003
First tic symptom, months pre-first RFE	61		93		.089
Bilateral	5	31%	23	10.5%	.042
Right-sided pain[1]	14	87.5%	131	60%	.055
Previous trigeminal surgery[2]	2	12.5%	30	13.9%	>.1
Division of pain: V3	6	37.5%	67	31%	>.1
V2 & 3	5	31%	77	35%	>.1
V2	5	31%	44	20%	>.1
V1 & 2		0%	24	11%	>.1
Analgesia after, not before, RFE	1	6%	24	11%	>.1
Hypoalgesia (50%–89%) after, but not before, RFE	2	12.5%	29	13%	>.1
Reoperation, ipsilateral	4	25%	40	18.7%[3]	>.1
Recurrence same division[4]	3	75%	37	92.5%	>.1

[1] Only cases with unilateral pain included.
[2] Ipsilateral to first RFE.
[3] Based on 214 patients; excludes 5 with initially technically unsatisfactory RFE.
[4] Only reoperated cases.
[5] Probability was determined by the chi-square test with Yates' correction for all data except average age and first symptom months pre-RFE, which were based on the two-tailed test on significance of mean.

mates [2]. When recurrent pain was used as the endpoint, whether or not reoperation was performed, there was no significant difference between TN and TNMS (Peto and Peto's generalized Wilcoxon test with two-sided alternative [2]) (Figure 10-2). Only patients from 1976 to December 1983 were included for this analysis. There is a suggestion that ipsilateral reoperation may occur more often in TNMS (25%) than in TN (18.7%); the entire series (1976–1986) is included. Recurrent RFE was more likely for pain in the same division as the original RFE in TN (92.5%) than in TNMS (75%). Analgesia was more likely following RFE in TN (11%) than in TNMS (6%).

Thirteen of the 16 patients with TNMS had evidence of brain-stem involvement other than trigeminal neuralgia. This was internuclear ophthalmoplegia in four, nystagmus in

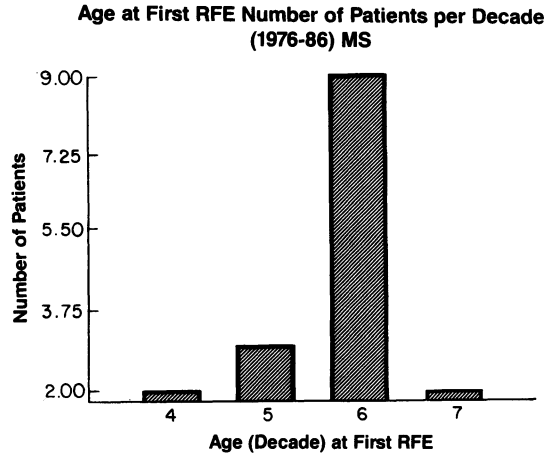

FIGURE 10-1. Most frequent age at first RFE in total of 16 patients with trigeminal neuralgia and multiple sclerosis was sixth decade (50 to 59 years) in nine patients.

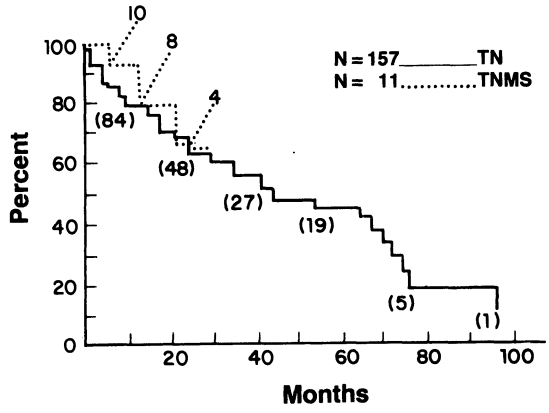

FIGURE 10-2. Kaplan-Meier product-limit estimates of probability of ipsilateral recurrence. There were 157 patients with trigeminal neuralgia without multiple sclerosis (TN) and 11 sides in 10 patients with trigeminal neuralgia and multiple sclerosis (TNMS) treated with RFE between 1976 and 1983.

eight others, and abnormal brain-stem auditory evoked responses in one patient who had no other clinically detectable brain-stem findings.

Discussion

PATHOLOGY

Autopsies on patients with TNMS has shown a demyelinating plaque in the posterior root or descending tract of the trigeminal nerve [3]. The plaques involving the sensory root at its entrance to the pons probably play a role in the pain of TNMS [4].

INCIDENCE AND BILATERALITY

Patients with multiple sclerosis are at added risk for developing trigeminal neuralgia, which may occur in about 1% to 2% of patients with multiple sclerosis [5]. The incidence of multiple sclerosis in trigeminal neuralgia was 7.2% in the present study, but has varied from 1% to 8% in other series [5–11]. Our finding that TNMS is more often bilateral and more likely to occur in younger patients than TN agrees with other reports [5].

RESPONSE TO TREATMENT AND RECURRENCE

The present series confirms that trigeminal neuralgia associated with multiple sclerosis responds well to denervation as induced by RFE either alone or with glycerol. Others have also shown this response to various forms of denervation [5, 10], including RFE [1, 12–14] and glycerol [15, 16].

There is little in the literature regarding recurrence following RFE in patients with TNMS [1, 13], and followup has usually been short. One study reported a 12.5% recurrence (1 of 8 patients) following RFE for TNMS, with an average followup of 26 months [13]. Another group found a 40% recurrence in TNMS followed for 1 to 4 years after RFE, which was much higher than 9% recurrence in their previously reported series (TN) [1]; however, the much shorter followup in the TN group (3 to 12 months) [17] could easily explain the lower recurrence rate.

A number of factors may explain the higher recurrence rate in TNMS than in TN. Patients with multiple sclerosis tolerate carbamazepine less well and are more likely to develop unpleasant symptoms of central nervous system malfunction such as dizziness or incoordination; non-surgical management of recurrence is therefore more difficult and they are more likely to seek another surgical intervention. Patients with MS are more likely to have bilateral trigeminal neuralgia, and our data suggest (although the numbers are too few to be certain) that ipsilateral recurrence in TNMS is more likely to be in a different division than in patients with TN. In addition, those with MS are more likely to have atypical rather than classical trigeminal neuralgia [14], and recurrence is more likely following RFE [18] (as well as all other kinds of treatments) in patients with atypical features.

The present data do not show a statistically different ipsilateral recurrence rate following RFE in TNMS than in TN, but the 25% ipsilateral reoperative rate in the MS group is higher than the 19% rate in those without MS and suggests that such patients are more likely to require reoperation.

SURGICAL IMPLICATIONS

RFE with or without glycerol is a very effective technique for treating TNMS that does not respond to medical treatment. Since MS patients are particularly sensitive to carbamazepine, which often causes adverse symptoms of CNS malfunction, these patients are especially helped by the percutaneous denervation of the gasserian ganglion or retrogasserian rootlets. Although recurrence may occur, the procedure can be repeated without added risk or difficulty.

Because many of these patients will develop bilateral trigeminal neuralgia and may require a contralateral procedure, it is very desirable not to produce excessive denervation during the initial RFE or glycerol injection.

Demyelinating plaques in the trigeminal system and not blood vessel compression are etiologically related to the trigeminal neuralgia in MS. Microvascular decompression is clearly contraindicated.

Patients may develop trigeminal neuralgia as the first symptom of MS; this occurred in two of our cases and in 4 of 35 patients in another series [5]. Diagnostic tests to identify MS in younger patients (those whose symptoms of trigeminal neuralgia begin before the age of 50) should be done, especially if the patient is otherwise being considered for microvascular decompression.

Summary

Patients with multiple sclerosis (MS) are at added risk for developing trigeminal neuralgia, which occurs in 1%–2% of those with MS.

Approximately 5% of patients with trigeminal neuralgia also have MS.

Those with trigeminal neuralgia and multiple sclerosis (TNMS) tend to be younger and are more likely to have bilateral face pain than those with trigeminal neuralgia without multiple sclerosis (TN). Patients with TNMS tolerate carbamazepine less well because of CNS side effects and are more likely to have atypical features associated with their pain.

The percutaneous partial denervation of the gasserian ganglion and retrogasserian rootlets with RFE and/or glycerol is recommended for those with TNMS that is intractable to medical therapy.

There is a suggestion that ipsilateral recurrence following RFE with or without glycerol may be higher for TNMS than TN, but a statistically significant difference could not be demonstrated.

References

1. Broggi G, Franzini A: Radiofrequency trigeminal rhizotomy in treatment of symptomatic non-neoplastic facial pain. J Neurosurg 57:483–486, 1982.
2. Lee ET: Statistical Methods for Survival Data Analysis. Lifetime Learning Publications, Belmont, California, 1980, pp 75–156.
3. Loeser JD, Calvin WH, Howe JF: Pathophysiology of trigeminal neuralgia. Clin Neurosurg 24:527–537, 1977.
4. Olafson RA, Rushton JG, Sayre GP: Trigeminal neuralgia in a patient with multiple sclerosis. An autopsy report. J Neurosurg 24:755–759, 1966.
5. Rushton JG, Olafson RA: Trigeminal neuralgia associated with multiple sclerosis: Report of 35 cases. Arch Neurol 13:383–386, 1965.
6. Adson AW: The diagnosis and surgical treatment of trigeminal neuralgia. Ann Otol 35:601–631, 1926.
7. Harris W: Rare forms of paroxysmal trigeminal neuralgia and their relation to disseminated sclerosis. Br Med J 2:1015–1019, 1950.
8. Ruge D, Brochner R, Davis L: A study of the treatment of 637 patients with trigeminal neuralgia. J Neurosurg 15:528–536, 1958.
9. Peet MM, Schneider RC: Trigeminal neural-

gia: A review of six hundred and eighty-nine cases with a followup study of sixty-five percent of the group. J Neurosurg 9:367–377, 1952.
10. Chakravorty BG: Association of trigeminal neuralgia with multiple sclerosis. Arch Neurol 14:95–99, 1966.
11. Stookey B, Ransohoff J: Paroxysmal trigeminal pain in multiple sclerosis. In: Trigeminal Neuralgia: Its History and Treatment. Charles C. Thomas, Springfield, 1959, pp 124–127.
12. Siegfried J: 500 percutaneous thermocoagulations of the Gasserian ganglion for trigeminal pain. Surg Neurol 8:126–131, 1977.
13. Brett DC, Ferguson GG, Ebers GC, Paty DW: Percutaneous trigeminal rhizotomy. Treatment of trigeminal neuralgia secondary to multiple sclerosis. Arch Neurol 39:219–221, 1982.
14. Sweet WH: Treatment of facial pain by percutaneous differential thermal trigeminal rhizotomy. Prog Neurol Surg 7:153–179, 1976.
15. Hakanson S: Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 9:638–646, 1981.
16. Sweet WH, Poletti CE, Macon JB: Treatment of trigeminal neuralgia and other facial pains by retrogasserian injection of glycerol. Neurosurgery 9:647–653, 1981.
17. Broggi G: Thermorhizotomy in trigeminal neuralgia: Preliminary considerations on 46 cases. Brain Hypoxia. Pain. Advances in Neurosurgery, Vol 3. Springer-Verlag, Berlin/Heidelberg/New York, 1975, pp 297–300.
18. Latchaw JP, Hardy RW, Forsythe SB, Cook AF: Trigeminal neuralgia treated by radiofrequency coagulation. J Neurosurg 59: 479–484, 1983.

11. NEURALGIA OF THE SEVENTH, NINTH AND TENTH NERVES

Ronald Brisman, M.D.

Geniculate Neuralgia

Geniculate neuralgia has been used to refer to two kinds of facial pain caused by impairment of the sensory part of the seventh cranial nerve: otalgic and prosopalgic [1]. In the otalgic form, pain is primarily in the ear, although it may radiate towards other parts of the face. It may be constant or intermittent and is sometimes associated with herpes zoster infection. It is sometimes triggered by light touch in or near the ear. The prosopalgic type of geniculate neuralgia involves mainly the deeper structures of the face, including the posterior orbit, posterior nasal, malar, and palatal areas.

PROSOPALGIC GENICULATE NEURALGIA

The prosopalgic form of geniculate neuralgia that was described by Hunt [1] is probably a migraine variant sometimes called *histamine cephalgia*. It has also been named *nervus intermedius* neuralgia [2], and surgical section of the nervus intermedius has been done [2, 3]. The surgical results have been unpredictable [2, 3], and neurosurgical denervation for this condition is not recommended.

TREATMENT OF OTALGIC GENICULATE NEURALGIA

There have been a few reports of successful treatment of the otalgic form of geniculate neuralgia by cutting the sensory part of the seventh nerve (nervus intermedius) in the posterior fossa [4–6]. In one of these earlier cases, the seventh, the pars intermedia, and the upper fascicles of the eighth nerve were also cut, and the patient developed a facial palsy as well as relief of pain [4]. Sometimes a discrete nervus intermedius may not be identified in the posterior fossa and it may be so closely combined with the vestibular nerve that section of the latter may be necessary to relieve the pain [2]. Autopsy studies show that the nervus intermedius is usually adherent to the eighth nerve for a variable distance distal to the entrance of these nerves into the brain stem; the nervus intermedius often consists of two or more filaments as it leaves the eighth nerve before joining the seventh; and in approximately one fifth of cases there is no separate nervus intermedius in the posterior fossa, in which cases it is found only within the internal acoustic meatus [7].

After section of a "tiny" nervus intermedius by Jefferson failed to relieve pain, White and Sweet obtained relief by a medullary tractotomy [8].

In the largest series of 15 surgically operated patients with otalgic geniculate neuralgia, Pulec showed that total sensory denervation of the seventh nerve may require excision of the nervus intermedius, geniculate ganglion, and the anterior 20% of the diameter of the motor portion of the facial

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nerve, which he did via a middle cranial fossa approach. There was no postoperative facial paralysis [9].

One difficulty in treating neuralgic ear pain arises from the multiple sensory innervations of the ear, which may be supplied by the upper cervical, fifth, ninth, and tenth cranial nerves, as well as the seventh. By using local anesthetics to block the trigger zone, the physician may clarify which nerve is responsible. Local anesthetics applied to the back of the throat may temporarily relieve the pain of glossopharyngeal (ninth nerve), but not geniculate, neuralgia. Intraoperative stimulation of the awake patient during posterior fossa surgery has been advocated as a method for determining which nerve is responsible for the pain [5]. Multiple, sequential denervations may be necessary of part of the fifth as well as the sensory part of the seventh nerve, before complete pain relief is obtained [9].

Surgical treatment of geniculate neuralgia should be reserved for those rare patients with idiopathic paroxysmal otalgic pain that is incapacitating and unrelieved by carbamazepine. Documented cases are so rare that new ones should be reported.

Vagoglossopharyngeal Neuralgia

CLINICAL FEATURES (Table 11-1)[10–14]

Paroxysmal triggered pain in the distribution of the ninth and tenth cranial nerves occurs from one-seventieth to one-hundredth times as frequently as trigeminal neuralgia [11, 15, 16]. The pain is located in the ear, tonsil, larynx, and/or posterior aspect of the tongue, with occasional spread to other parts of the face [12]. The pain is triggered by swallowing, chewing, or coughing, but definite trigger zones are identified less frequently than in trigeminal neuralgia. The pain is rarely associated with syncope [11, 12, 17].

CLINICAL MATERIAL (Table 11-2)

Between January 1967 and February 21, 1987, the author performed neurosurgical proce-

TABLE 11-1. Trigeminal and vagoglossopharyngeal neuralgia compared

	Trigeminal	Vagoglosso pharyngeal
Incidence per 100,000/yr	4.0 [10]	.04 [11]
Age at onset > 50 years	65%[1]	57% [12], 78% [11]
Bilateral	5% [12], 10%[1]	2% [12], 11% [11]
Left side	42%[1]	83% [11]
Episodic	Yes	Yes [11, 12]
Triggered	Yes	Sometimes [12][2]
Night pain	Rare	Not uncommon [11]
Burning pain	Atypical	Frequent [11]
Location of pain	V 1, 2, 3	Ear, tonsil, larynx, posterior tongue
Syncope with pain	No	2% [12]
Multiple	2% [12]	< 0.3% [13]
Tumor	5% [14]	15%–25% [14]

[1] Brisman's series of 157 patients with trigeminal neuralgia without brain tumor or multiple sclerosis.
[2] Swallowing often precipitates the pain.

TABLE 11-2. New cases of vagoglossopharyngeal neuralgia

No.	Age	Sex	Location	Procedure	Result
1	53	M	L V3, IX	RF V3	No relief; refused reop
2	90	F	R V3, IX	RF IX	Relief
3	47	F	L IX, X	Suboccipital[1]	Relief

[1] Cut ninth and upper 15%–20 percent of tenth cranial nerve. Followup in cases 2 and 3 was one month.

dures on 255 patients with trigeminal neuralgia and three patients (1.2%) with vagoglossopharyngeal neuralgia.

Case 1. This 57-year-old man had paroxysmal triggered pain in the left lateral aspect of his tongue and jaw. A percutaneous radiofrequency electrocoagulation was done in 1977 and hypoalgesia was produced in the third division of the trigeminal nerve, but his pain was not relieved. He was seen in 1980 and had his original pain and pain in the back of the throat that was provoked by swallowing. Surgical section of the ninth (and upper part of the tenth nerves) was advised, but the patient declined further surgery.

Case 2. This 90-year-old woman had paroxysmal triggered pain in the second and third divisions of the trigeminal nerve for several years. She had peripheral alcohol injections in the past with some relief. During the past several weeks she had paroxysmal pain in the throat and back of the tongue that was precipitated by swallowing and talking. Carbamazepine (200 mg twice a day) helped a little but it made her more forgetful. The patient was mildly hoarse. Computerized tomography (CT) showed a contrast enhancement in the left cerebellopontine angle that was consistent with a tortuous vertebrobasilar artery (Figure 11-1).

On July 20, 1983, the patient underwent percutaneous radiofrequency electrocoagulation of the glossopharyngeal nerve. The pars nervosa of the jugular foramen was penetrated with the aid of submentovertical and lateral x-rays (Figure 11-2); fluoroscopy was also used. Stimulation at 100 Hz caused the patient to feel discomfort in the lower jaw but not clearly the ear or pharynx. Radiofrequency lesions were made for 65°C and then 70°C for 60 seconds. Each time, monitoring of the electrocardiogram and blood pressure showed no bradycardia and no hypotension. At the conclusion, the patient was able to swallow well and had no pain. The patient was discharged home the morning following the procedure, at which time she was asymptomatic.

When last seen in followup 1 month later, the patient had mild paroxysmal triggered pain in the third division of the left trigeminal nerve but had no difficulty swallowing. The preoperative pain in the posterior aspect of the tongue and back of the throat was gone. Gag reflex was present bilaterally.

Comment: This elderly patient with trigeminal and glossopharyngeal neuralgia and a prominent vertebrobasilar artery, which may possibly have been causing compression of the fifth and ninth nerves, had an excellent result from percutaneous electrocoagulation of the ninth nerve.

Case 3. This 47-year-old woman had agonizing paroxysmal pain deep in the anterior aspect of her left neck for several weeks. The burst of pain lasted for 30 to 60 seconds and occurred every 5 to 10 minutes. The pain radiated towards the angle of the jaw and infrequently to the ear and back of the throat.

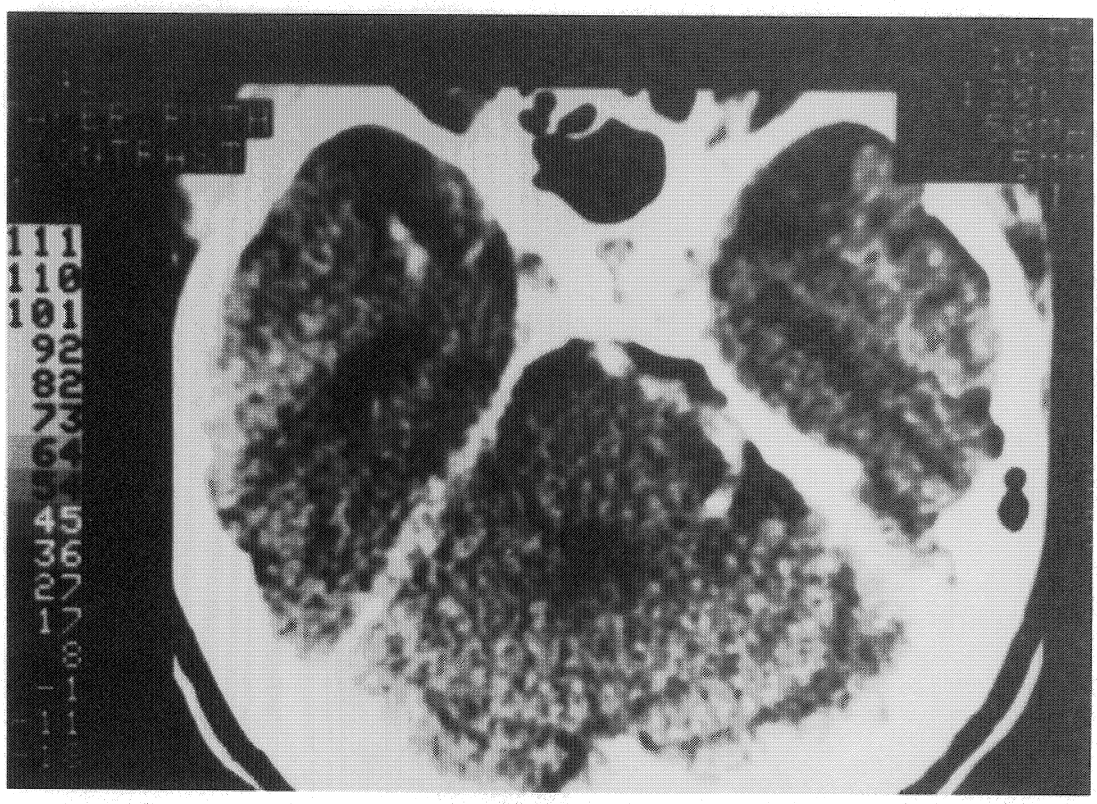

FIGURE 11-1. (Case 2) CT scan shows contrast enhanced tortuous vertebrobasilar artery in the left cerebellopontine angle.

The pain occurred spontaneously, although it rarely was brought on by swallowing. The patient had been hoarse for an indeterminate time. CT scan and neurologic examination (in between the frequent paroxysms of pain) were normal.

Carbamazepine (200 mg every 4 hours) did not provide any relief. The blood level of carbamazepine was subtherapeutic. When the dose of carbamazepine was increased to 400 mg every 4 hours, the patient noticed definite, but partial, relief of pain; blood tests now showed therapeutic levels.

Suboccipital craniectomy was done in January 1987 with the aid of the operating microscope. The ninth and upper two filaments of the tenth nerve were cut. No changes in pulse or blood pressure occurred during these maneuvers. No blood vessels were found compressing these nerves.

Postoperatively, the patient noted immediate relief of pain. She was aware of some discomfort in the right (contralateral) part of the throat, which diminished within a few days. One month later, the patient complained of a mild sticking sensation in the right side of the throat that was not bothersome; neurological examination was normal. There was no recurrence of the left-sided pain, and she had stopped taking carbamazepine.

Comment: This patient's pain had a prominent vagal component in that it was localized primarily in the neck. Unusually large doses of carbamazepine were necessary to get a therapeutic blood level and clinical benefit. Surgical section of the ninth and upper parts of the tenth nerves resulted in dramatic relief of pain.

CAUSES

Most cases of glossopharyngeal neuralgia are idiopathic [18], although in some cases a structural lesion has been found compressing

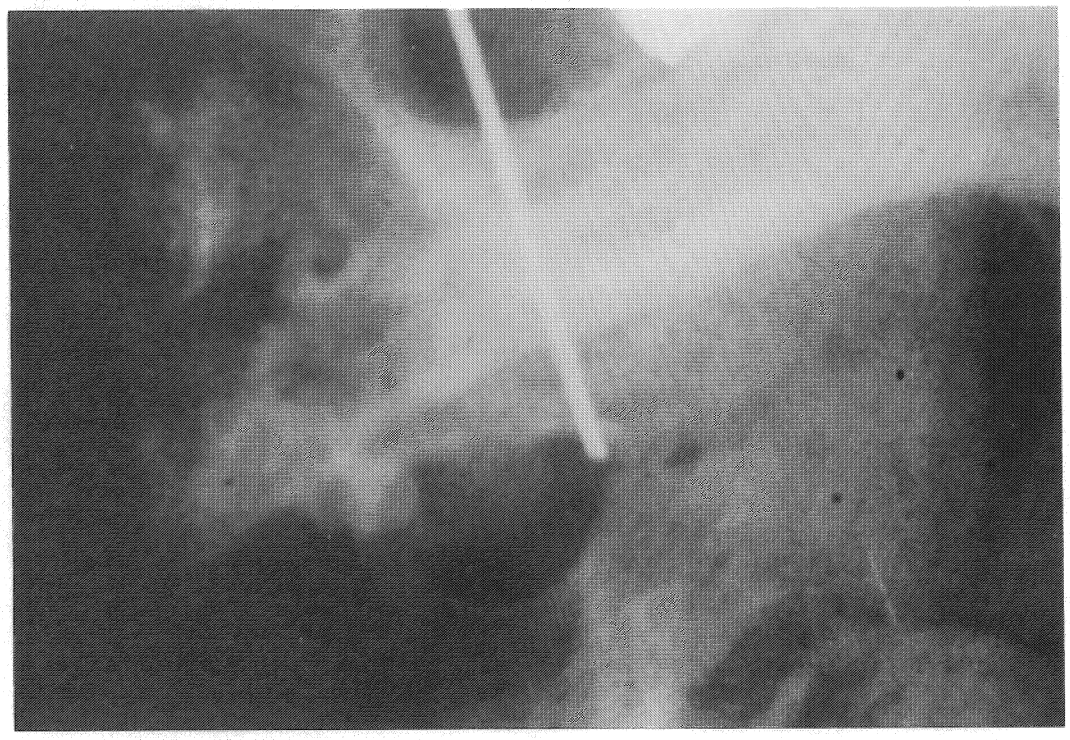

FIGURE 11-2A. (Case 2) Submentovertical x-ray shows needle through the anteromedial aspect of the jugular foramen.

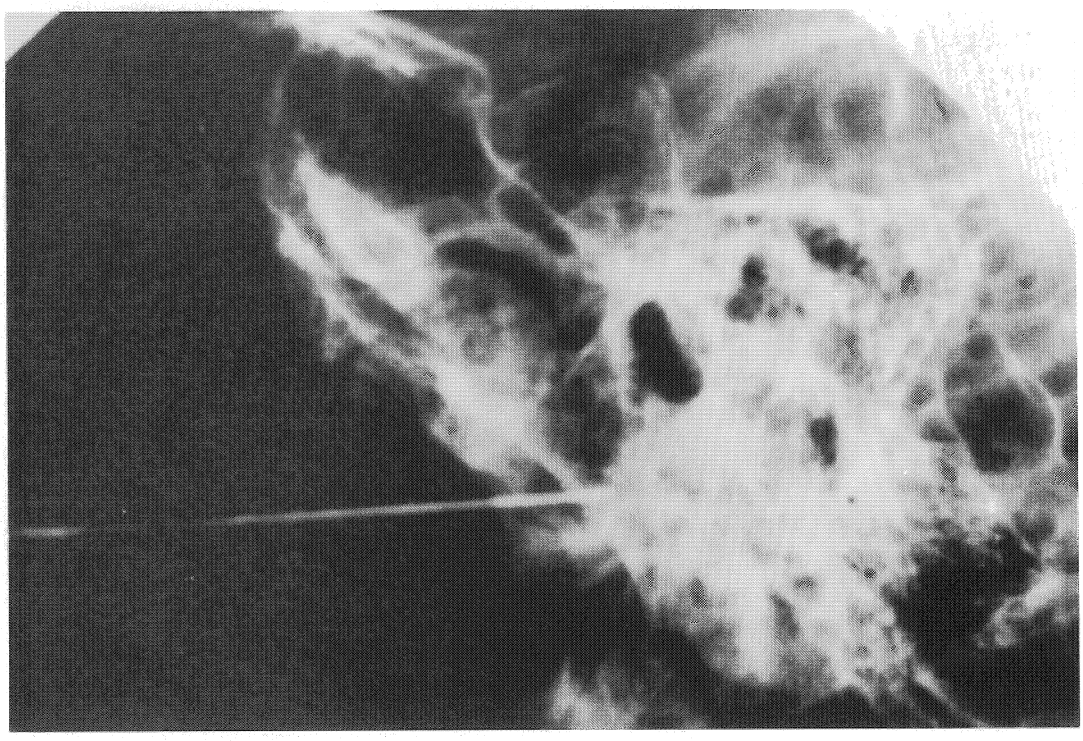

FIGURE 11-2B. (Case 2) Lateral x-ray shows proper position of needle.

the ninth nerve and a causal relationship has been suggested. Nasopharyngeal and cerebellopontine angle tumors [14, 19], ossification of the stylohyoid ligament [20], an atheromatous vertebral artery [21], and compression at the root entry zone of the ninth and tenth nerves by a tortuous vertebral artery or posterior inferior cerebellar artery [22] have been implicated.

There is some disagreement as to the importance of these structural compressions. Dandy added 2 of his cases to 18 from the literature and found that 3 (15%) were definitely associated with tumors and 2 more may have been, which gave a "probable incidence of at least 25% [14]." Vascular compression was found in 5 of 6 cases (83%) by Laha and Jannetta [22]. According to Onofrio, "almost all cases of glossopharyngeal neuralgia are idiopathic [23]."

TREATMENT

Patients with intractable pain from glossopharyngeal neuralgia who cannot be managed with carbamazepine are appropriate candidates for neurosurgical intervention. Section of the ninth and upper 15%–20% of the rootlets of the tenth cranial nerve provides excellent relief of pain with minimal morbidity. Although initially only the ninth nerve was cut [14], it subsequently became apparent that the vagus (tenth) nerve is often involved as well as the ninth and that sectioning the upper part of the tenth nerve in addition to the ninth is more likely to provide better relief than just sectioning the ninth nerve [24].

SUBOCCIPITAL CRANIECTOMY

The initial suboccipital approach for treating glossopharyngeal neuralgia is similar to that for trigeminal neuralgia (see Chapter 7) except that the bony opening for glossopharyngeal neuralgia extends a little lower. Just below the seventh and eighth nerves, the nerves at the jugular foramen have a characteristic configuration that makes them easy to identify. Most rostrally, the ninth nerve leaves the posterior fossa as a single nerve (in most cases [25]) through a separate dural opening. Multiple filaments of the tenth nerve are caudal to the ninth. The eleventh nerve, which is most caudal, has at its lowest portion the vertically elongated spinal accessory nerve.

RADIOFREQUENCY ELECTROCOAGULATION (RFE)

RFE of the neural (anteromedial) portion of the jugular foramen can relieve the pain of glossopharyngeal neuralgia that is idiopathic [26–29], tumor related [26, 28, 30, 31], or associated with tortuous blood vessels (Case 2). The needle is directed 14° posterior to the lateral roentgenographic target point used for penetration of the foramen ovale [26]. A percutaneous lateral cervical approach has also been described [32]. Complications such as bradycardia with hypotension, and impaired phonation and deglution can result from excessive vagal denervation [26, 33]. These can be prevented by proper x-ray localization in the anteromedial part of the jugular foramen, continuous monitoring of electrocardiogram and blood pressure [29], and small incremental lesions [27].

MICROVASCULAR DECOMPRESSION

There are reports of microvascular decompression of the ninth and tenth nerves associated with relief of pain [17, 22, 34]. Not all patients can be treated successfully by this technique and care has to be taken to prevent medullary compression during the procedure [22].

SURGICAL TREATMENT RECOMMENDATION

Elderly patients or those who have severe medical illness that precludes suboccipital craniectomy should have RFE. Other patients are best treated with sectioning of the ninth and upper 15%–20% of the tenth nerve. The results of direct rhizotomy are too good and

the risks too few to recommend microvascular decompression.

Trigeminal neuralgia occurs in 11.5% of patients with vagoglossopharyngeal neuralgia [12, 16], and surgical attention may have to be directed to the fifth as well as ninth and tenth nerves in some of these patients.

Summary

Otalgic geniculate neuralgia, a very rare condition, is characterized by paroxysmal ear pain. Local anesthetics applied to the back of the throat may temporarily relieve glossopharyngeal, but not geniculate, neuralgia. Intractable pain from geniculate neuralgia may be relieved by cutting the sensory part of the seventh nerve; this may be accomplished by cutting the nervus intermedius, but sometimes the vestibular nerve and geniculate ganglion may have to be excised.

Patients with vagoglossopharyngeal neuralgia have paroxysmal pain in the throat, ear, tonsil, larynx, or neck. For elderly patients who do not respond to carbamazepine, percutaneous RFE with continuous electrocardiogram and blood pressure monitoring is advised. Younger patients are treated with suboccipital craniectomy and surgical section of the ninth and upper 15%–20% of the vagus nerve.

References

1. Hunt JR: Geniculate neuralgia (neuralgia of the nervus facialis): A further contribution to the sensory system of the facial nerve and its neuralgic conditions. AMA Arch Neuro & Psychiat 37:253–285, 1937.
2. Sachs E Jr: The role of the nervus intermedius in facial neuralgia. Report of four cases with observations on the pathways for taste, lacrimation, and pain in the face. J Neurosurg 28:54–60, 1968.
3. Apfelbaum RI: Surgical management of disorders of the lower cranial nerves. In: Operative Neurosurgical Techniques, Vol 2, Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1063–1082.
4. Clark LP, Taylor AS: True tic douloureux of the sensory filaments of the facial nerve. I. Clinical report of a case in which cure was effected by physiologic extirpation of the geniculate ganglion. II. Report of surgical treatment JAMA 53:2144–2146, 1909.
5. Furlow LT: Tic douloureux of the nervus intermedius (so-called idiopathic geniculate neuralgia). JAMA 119:255–259, 1942.
6. Wilson AA: Geniculate neuralgia: Report of a case relieved by intracranial section of the nerve of Wrisberg. J Neurosurg 7:473–481, 1950.
7. Rhoton AL, Kobayashi S, Hollinshead WH: Nervus intermedius. J Neurosurg 29:609–618, 1968.
8. White JC, Sweet WH: Pain, its mechanisms and neurosurgical control. Charles C Thomas, Springfield, 1955, 736 pp.
9. Pulec JL: Geniculate neuralgia: Diagnosis and surgical management. Laryngoscope 86: 955–964, 1976.
10. Kurland LT: Descriptive epidemiology of selected neurologic and myopathic disorders with particular reference to a survey in Rochester, Minnesota. J Chron Dis 8:378–418, 1958.
11. Bohm E, Strang RR: Glossopharyngeal neuralgia. Brain 85:371–388, 1962.
12. Rushton J et al.: Glossopharyngeal neuralgia. Arch Neurol 38:201, 1981.
13. Kahana E, Leibowitz U, Alter M: Brainstem and cranial nerve involvement in multiple sclerosis. Acta Neurol Scand 49:269–279, 1973.
14. Dandy WE: Glossopharyngeal neuralgia (tic douloureux). Its diagnosis and treatment. Arch Surg 15:198–214, 1927.
15. Spurling RG, Grantham EG: Glossopharyngeal neuralgia. South Med J 35:509–512, 1942.
16. Brzustowics RJ: Combined trigeminal and glossopharyngeal neuralgia. Neurology 5:1–10, 1955.
17. Tsuboi M, Suzuki K, Nagao S, Nishimoto A: Glossopharyngeal neuralgia with cardiac syncope. A case successfully treated by microvascular decompression. Surg Neurol 24: 279–83, 1985.
18. Harris W: Persistent pain in lesions of the peripheral and central nervous system. Brain 44:557–571, 1921.
19. Weisenburg TH: Cerebello-pontile tumor

diagnosed for six years as tic douloureux. The symptoms of irritation of the ninth and twelfth cranial nerves. JAMA 54:1600–1604, 1910.
20. Graf CJ: Glossopharyngeal neuralgia and ossification of the stylohyoid ligament. J Neurosurg 16:448–453, 1958.
21. Brihaye J, Perier O, Smulders J, Franken L: Glossopharyngeal neuralgia caused by compression of the nerve by atheromatous vertebral artery. J Neurosurg 13:299–302, 1956.
22. Laha RK, Jannetta PJ: Glossopharyngeal neuralgia. J Neurosurg 47:316–320, 1977.
23. Onofrio BM: Glossopharyngeal neuralgia. In: Neurosurgery, Wilkins RH, Rengachary SS, eds. McGraw-Hill, New York, 1985, p 2363–2366.
24. Robson JT, Bonica J: The vagus nerve in surgical consideration of glossopharyngeal neuralgia. J Neurosurg 7:482–484, 1950.
25. Rhoton AL, Ruza R: Microsurgical anatomy of the jugular foramen. J Neurosurg 42:541–550, 1975.
26. Tew JM, Tobler WD: Percutaneous rhizotomy in the treatment of intractable facial pain (trigeminal, glossopharyngeal, and vagal nerves). In: Operative Neurosurgical Techniques, Vol 2, Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1083–1106.
27. Arias MJ: Percutaneous radio-frequency thermocoagulation with low temperature in the treatment of essential glossopharyngeal neuralgia. Surg Neurol 25:94–96, 1986.
28. Lazorthes Y, Verdie JC: Radiofrequency coagulation of the petrous ganglion in glossopharyngeal neuralgia. Neurosurgery 4:512–516, 1979.
29. Isamat F, Ferran E, Acebes JJ: Selective percutaneous thermocoagulation rhizotomy in essential glossopharyngeal neuralgia. J Neurosurg 23:575–580, 1981.
30. Pagura JR, Schnapp M, Passarelli P: Percutaneous radiofrequency glossopharyngeal rhizotomy for cancer pain. Appl Neurophysiol 46:154–159, 1983.
31. Giorgi C, Broggi G: Surgical treatment of glossopharyngeal neuralgia and pain from cancer of the nasopharynx. A 20-year experience. J Neurosurg 61:952–955, 1984.
32. Salar G, Ori C, Baratto V, Iob I, Mingrino S: Selective percutaneous thermolesions of the ninth cranial nerve by lateral cervical approach: Report of eight cases. Surg Neurol 20:276–279, 1983.
33. Ori C, Salar G, Giron G: Percutaneous glossopharyngeal thermocoagulation complicated by syncope and seizures. Neurosurgery 13: 427–429, 1983.
34. Morales F, Albert P, Alberca R, de Valle B, Narros A: Glossopharyngeal and vagal neuralgia secondary to vascular compression of the nerves. Surg Neurol 8:431–433, 1977.

III. CHRONIC BENIGN PAIN

12. ANESTHESIOLOGIC MANAGEMENT OF CHRONIC BENIGN PAIN

Howard L. Rosner, M.D.

Introduction

It can be argued that the first anesthetic procedure was described in the Bible, when God put Adam to sleep to remove a rib for the creation of Eve. This very early reference to what has since become a common procedure typifies man's long struggle to reduce or abolish pain. Since the dawn of civilization the desire to deaden pain has been an ongoing and frequently frustrating preoccupation. From the far corners of the ancient globe come various formulae: the poppy from the Far East; opium, mandrake, and henbane from the Greece of Galen and Hippocrates; hashish from the Middle East; and alcohol, the universal analgesic. The Assyrians used strangulation to produce unconsciousness and also described methods of nerve compression and applications of intense cold to help alleviate pain.

Modern methods of analgesia and anesthesia began in the eighteenth century with the works of Faraday on the stupefying effects of ether and Hickman on the anesthetic potential of nitrous oxide. Mesmer first described hypnosis in the late eighteenth century and soon thereafter these techniques found their way into the operating room. In the nineteenth century, ether was introduced into the operating room, first by Crawford Long in 1842, then by William T.G. Morton in 1846.

The latter half of the nineteenth century saw two separate but concurrent developments that altered and improved the abilities of physicians to treat patients for their pain problems. The glass syringe and hypodermic needle and the local anesthetic, cocaine, allowed physicians to inject nerve trunks for the relief of neuralgic pain. Local anesthesia for minor surgical and dental procedures soon followed. The twentieth century saw the synthesis of procaine, less toxic and not addictive like its predecessor. The development of regional techniques such as spinal (1885) and caudal (1901) anesthesia allowed patients to have many surgical procedures without running the risks of general anesthesia. Many other regional techniques followed in rapid succession, and these procedures are now used in operating rooms around the world.

The formalization of anesthesiology in the middle of the twentieth century presaged the involvement of anesthesiologists in the area of pain management. As surgical procedures became more complex and surgical patients more ill, the science of life support was born. Anesthesiologists began using their training outside the operating rooms in diverse areas: intensive care and respiratory care, pain control in labor and delivery, and the management of acute and chronic pain. By the mid-1940s,

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Emery Rovenstine had established a nerve block clinic at Bellevue Hospital in New York City for patients suffering with pain. This fascinating and exciting subspecialty of anesthesiology has grown in the ensuing years and has become a needed and valuable component of the multidisciplinary approach to the treatment of patients with chronic pain.

Techniques

The various modalities of pain management and their applications are the subjects of much discussion. Disciplines cross and recross, each with its own applications of techniques. To the anesthesiologist, pain management began simply in nerve block clinics to which patients came periodically for their injections. This approach alone led to many successes, but also to many failures. Therefore, the concept of pain management has expanded to a multimodality approach, much of which lies within the province of the anesthesiologist.

NERVE BLOCKS

Nerve blocks, the area where the anesthesiologist makes the major contribution in a multidisciplinary clinic, can be divided into three different categories: 1) diagnostic, 2) prognostic, and 3) therapeutic.

1. Diagnostic blocks can help render an anatomic diagnosis by differentiating a level of nerve involvement, i.e., peripheral nerve versus spinal root versus central pain, and can differentiate between somatic and sympathetic origins. Saline injections can also help differentiate between organic and functional pain.
2. Prognostic blocks acquaint a patient about to undergo neurablative procedures with the expected results and sensory deficits, previous to the surgery. Many patients find the numbness as uncomfortable a sensation as the pain they are having, although many more find numbness a blessed relief to continual pain.
3. Therapeutic blocks include all injections, single or in series, that provide a patient with long-lasting relief from pain. Relief of pain outlasting the duration of the anesthetic is a favorable sign and often an indication for repetition of the injection. Single nerves, plexuses, the epidural space, the subarachnoid space, muscles, ligaments and tendons, and other connective tissue can be injected. The most common substances injected include local anesthetics, steroids, and neurolytic agents (phenol or alcohol). Spinal injection of opiates for postoperative, chronic malignant, and chronic nonmalignant pain can also be placed in this category.

DRUG THERAPY

Some of the major advances in pain management over the past several years have been in the area of drug therapy. The uses of newer analgesics, neuroactive agents, and vasoactive medications are widespread and growing. Depending on the problem being treated, these medications can be considered as adjuvant therapy or as the mainstay of treatment. These medications are useful for the management of both malignant and nonmalignant pain of all varieties.

Current research into the physiology of pain transmission has revealed a highly complex and hitherto unexplored area. The elucidation of the importance of neurohumoral transmitting agents such as dopamine and serotonin, opiate receptors, enkephalins, and endorphins is opening new vistas in therapy for many highly complex and previously untreatable disorders. Agonism or antagonism of these central pathways and receptors can now be safely accomplished with medication therapy [1–3].

Treatment

The judgment that a patient has an organic basis for pain may be rendered on the basis of

physical examination, diagnostic testing, diagnostic nerve blocks, and whatever other means are available. Once this diagnosis has been established, treatment may commence.

MYOFASCIAL PAIN

Those syndromes that are listed together under the terms *myofascial syndrome*, *fibromyalgia*, *myofibrosis*, and other synonyms have as their source of discomfort a process involving musculature, ligaments, tendons, and other soft tissue structures. Discrete trigger points may be present, which when palpated can provoke or worsen the pain complaint. Diffuse spasm of the involved muscle groups is usually present with or without trigger points.

Muscular Trigger Points and Spasm. As yet, there is no widely accepted pathologic or physiologic explanation associated with muscular trigger points. A range of theories has been advanced, including local areas of fibrosis in muscle to discrete areas of severe spasm. The concept of stretch-treatment of the involved muscles has been the mainstay of therapy for trigger points and in the short term has been quite effective. However, more lasting relief is frequently not obtained due to reactivation and perpetuation of trigger points by unrecognized or unknown factors [4].

Stretching the involved muscles containing trigger points in conjunction with injections of local anesthetic agents into the trigger points can produce more lasting relief [5]. The use of these agents produces a local area of pain relief and reduces local muscular spasticity. This in turn can relieve spasm in a larger uninvolved area of the same muscular group due to a decreased need for splinting. This process allows the patient to flex and extend these muscles, thus stretching them and decreasing the chances for recurrence of the spasm. Often the injections and subsequent stretching need to be done repeatedly as a series to break down severe trigger points and spasm.

Muscular spasm without the presence of trigger points can also be treated with local anesthetic infiltration into the involved muscles. Although there is no single point where the injection of local agents will produce a specific reduction in the pain, diffuse infiltration throughout the muscle will reduce the spasm and allow the patient to move about more comfortably. This process, done in conjunction with a vigorous graded exercise program, can reduce the pain from myofascial trigger points and spasm dramatically. A useful adjuvant to consider when doing a series of local anesthetic injections is the concomitant use of a transcutaneous nerve stimulator, which will also serve to reduce the areas of local spasm [6]. If trigger points are present, the stimulator should be placed over the tender points themselves.

Ligamentous Strain. The ligaments and joints, integrally associated with body function, motion, and support are under constant stress in daily movement and exercise. Acute strain of these structures produces pain in their associated distributions and can also cause referred pain into an involved limb. Tender points may be palpable over the structures involved and may indicate a potential source for the pain problem. Infiltration of these points with local anesthetics is helpful in diagnosis of the problem, and the prompt relief of pain may last several weeks to months. Repeated injections over the course of the problem can keep patients comfortable, active, and exercising while the strained ligaments heal.

Many clinicians advocate the use of long-acting steroids along with local anesthetic agents in injections of the ligaments and joints of the posterior pelvic girdle as well as myofascial trigger points. While the rationale behind this is often unclear, they report an

increase in duration of benefit with the concomitant use of these agents.

LOW BACK PAIN

Whatever the precipitating problem, low back pain can be grossly divided into two broad categories: sciatica and lumbago. While both can involve pain and tenderness in the low back, decreased range of motion of the lumbar spine, and spasm of the paraspinous musculature, sciatica also involves pain radiating below the knee. There are other precipitating problems that may mimic the symptoms and signs of sciatica or lumbago. It is therefore important to try to establish a differential diagnosis prior to instituting treatment with nerve blocks. While the conservative management of these problems is essentially the same, the nerve blocks used to approach the various problems differ greatly.

Sciatica. The influence of the intervertebral disc on the symptom complex known as sciatica was demonstrated over 50 years ago [7]. Over the course of those 50 years, surgical intervention became the standard treatment for patients with lumbar radicular pain. It had been assumed that mechanical compression by disc material on the nerve roots was responsible for the pain of sciatica. However, it was also noted that many patients failed to demonstrate anatomical changes on myelography that would indicate root compression. Furthermore, many patients with obvious pathology on myelography did not benefit from surgical intervention.

Even before the relationship of ruptured disc material and nerve root compression was established, physicians were injecting local anesthetics into the epidural space via the caudal hiatus to relieve radicular pain [8]. With the introduction of techniques to inject directly into the epidural space, physicians were presented with an alternative to surgical intervention in acute discogenic pain. Many studies have shown good results in the management of acute discogenic pain by introducing local anesthetic agents and long-acting steroids into the epidural space at the level of the involved nerve root [9]. The results of the use of this technique further show that the optimal time to recommend epidural injections for sciatica is in the first 3 months of symptoms. The therapeutic results for epidural injection after 3 months of pain are not as encouraging [10].

The exact mechanism for the beneficial results of epidural injections remains unclear. Several mechanisms for the etiology of radicular pain have been advanced. Direct nerve root compression by herniated nucleus pulposus and mechanical irritation of the surrounding tissue have been implicated along with chemical irritation of the surrounding tissues by the disc material. The direct action of nucleus pulposus on laboratory animal tissue has been shown to produce inflammatory reactions. Therefore the antiinflammatory action of the corticosteroids would be highly beneficial to treat this problem. In the case of patients with mechanical irritation and possible adhesion formation in the epidural space, the injection of a volume of any material would be beneficial (as it would serve to break up adhesions and allow free movement of the nerve roots in their sheaths). The addition of a dilute local anesthetic to the mixture with the steroids serves two purposes. First, it documents that the steroid has advanced to the root in question. Secondly, it enables the patient to perform straight-leg raising painlessly, thereby enabling any adhesions present to be broken by the mechanical stretching of the nerve roots.

Lumbago. While sciatica usually refers to a specific pain problem with an indentifiable etiology, *lumbago* is a vague term meaning pain in the lumbar region. In contemporary English, *backache* is the more simple term for the more elegant Latin word. There is no implication in this diagnosis of a specific anatomic or pathologic etiology for the pain, nor is there

usually the justification for the expense of major diagnostic testing.

Regardless of the causative factor (which may often be impossible to establish) the symptoms of lumbago are usually consistent. Most patients describe an ache in the low back at or near the lumbosacral or sacroiliac junctions. The pain is most often midline, with occasional radiation outward to one or both sides, into the buttock and the thighs. The intensity can vary from tolerable, allowing virtually full activities, to incapacitating, preventing all but the most necessary of movement.

The muscular, ligamentous, and bony structures of the low back are complex. The influence of posture in standing and sitting, the interplay of muscle groups in movement, and the effect of occupation and personality on the use of the low back have all been topics of discussion and controversy for many years. However, even with a vague diagnosis of lumbago and without a specific precipitating factor for pain, there are several things that can still be done for these patients including TENS, trigger point injections, exercise, and physical therapy.

Piriformis Syndrome. The piriformis is a deep-seated muscle forming a portion of the posterior wall of the pelvis, from its origin along the anterolateral sacrum to its insertion on the greater trochanter of the femur. As in any other skeletal muscle, trigger points and spasm of the piriformis can result from trauma or occur spontaneously. The resultant pain complex is usually indistinguishable from other causes of lumbago. Pain is most often midline over the lumbosacral junction and down the thighs, with a particularly tender area in one buttock. Pressure on the piriformis muscle should reproduce the patient's pain complaint. Often this can be elicited by deep palpation of the buttock along a line drawn from the greater trochanter to the midpoint of the sacrum. There are also transrectal and transvaginal approaches to this muscle [11]. Injection of the muscle transgluteally through the sciatic notch or from the perineum will produce prompt relief of pain. Care must be taken to avoid injection of the sciatic nerve, which lies deep to the piriformis.

Facet Joint Arthropathy. In a number of cases, arthropathy of the intra-articular surfaces of the facet joints can produce symptoms that mimic those of myofascial syndrome or sciatica. The diagnosis is difficult to establish, particularly if no roentgenographic changes are present to document the problem. In these patients, injection of local anesthetic and steroid mixtures into the intra-articular space produces prompt and complete relief of the pain. These blocks often require fluoroscopic guidance to be effective [12].

SYMPATHETIC DYSTROPHY AND CAUSALGIA

Pain radiating into the arm or leg may be neither myofascial nor radicular in origin. Injury to the limb or to one of the nerves leading to that limb may result in reflex dystrophy or causalgia. In its initial or acute phase, many of the sequelae associated with reflex dystrophy, such as a diminution of temperature with hypovascularity, may not be present. The limb can appear normal to hyperemic without the trophic changes associated with this disorder. The pain may be sharp, aching, or burning in nature, with hypersensitivity of the skin in the involved area. A diagnostic cervicothoracic (stellate ganglion) or lumbar paravertebral sympathetic block should be performed if the question of causalgia has been raised. Pain relief is profound following local anesthetic blockade of the sympathetic chain in reflex dystrophy, with duration of pain relief outlasting the duration of the local agent by days to weeks. Often, a series of local anesthetic blocks is needed to produce a complete cure [13].

More recently, therapy by intravenous re-

gional sympathetic blockade with guanethidine using the Bier technique has been described to be effective in the treatment of sympathetic dystrophy and causalgia. This technique has achieved a growing popularity in the treatment of these syndromes and other vasoconstrictive disorders in the extremities [14].

PHANTOM LIMB PAIN

Likened by many to sympathetic dystrophy and causalgia, phantom limb, or stump pain, may take several forms. Following an amputation, particularly if the limb was especially painful prior to amputation or the amputation was traumatic, the ensuing pain may take one of several forms [15].

Most amputees develop a "painless" phantom limb with sensation from the amputated extremity diminishing over a period of weeks. These patients require nothing but supportive intervention and usually do very well.

Stump pain may be sympathetic or nociceptive in origin. In these patients, the entire stump may be sore diffusely with small trigger zones of intense burning sensation. Injection of local anesthetics into the trigger zones often relieves neuromas or entrapped nerves. Several blocks into these areas can be performed as a therapeutic trial and often produce favorable results.

Should no trigger points be palpable and the patient has other signs and symptoms of phantom limb pain, e.g., diffuse burning, hyperesthesia, vasospasm, trophic changes, intense burning, or shooting in the missing limb, all of which may be exacerbated by emotional stimuli, then a major sympathetic component can be implicated. In these patients, the appropriate sympathetic block should be performed for diagnosis and treatment. Often a series of sympathetic blocks is curative of the problem. Should local agents not be sufficient, neurolytic or surgical approaches may be necessary [16].

Transcutaneous nerve stimulation may also be effective in the treatment of reflex dystrophy, causalgia, and phantom limb pain. Most often it is useful as an adjuvant to sympathetic blockade. However, TENS alone has been shown to be adequate treatment for these entities only in a pediatric population [17].

VISCERAL PAIN

Visceral pain remains one of the "gray" areas of pain physiology and pathophysiology. Is the pain nociceptive or sympathetic, peripheral or central, in origin? Patients complaining of visceral pain have often had numerous surgical explorations searching for an acute cause for their pain only to find apparently normal anatomy. After several attempts at proving an anatomical diagnosis, the patient is given a psychiatric diagnosis and sent on for psychotherapy. Commonly the first surgical procedure discloses some anomaly: hernia, gall stones, endometriosis, etc. However, after a period of weeks to months the pain returns. Subsequent operations reveal nothing new or unusual. These often do little to improve the pain of which these patients are complaining.

As has been described here and elsewhere, nociceptors are not the only transmitters of pain impulses. In the limbs, the sympathetic nervous system is responsible for many pain problems. The same may hold true for the viscera [18].

All visceral afferent fibers pass through the celiac plexus. Furthermore, many authors feel that the sympathetic nervous system is the primary pathway for visceral pain in many patients. With these facts in mind we can describe *abdominal causalgia*: pain of sympathetic origin in the abdomen with little or no anatomic abnormality seen at surgery. Yet, as in the cases of reflex dystrophy and phantom limb, this pain is real, discomforting, and sometimes disabling.

Diagnosis of this entity is difficult. Many patients presenting with visceral pain complaints have a psychiatric etiology as the

source of their pain. Separating out those patients whose pain complaints are consistent with a diagnosis of abdominal causalgia can be impossible at history and physical examination. Some patients may be dismissed from the outset, however, the majority will require a diagnostic nerve block [19].

Celiac plexus blockade with neurolytic agents has been a mainstay of the treatment of pain due to pancreatic carcinoma and to a lesser extent the pain of chronic pancreatitis. These blocks are preceded with a diagnostic blockade of the celiac plexus with local anesthetic to determine if there is indeed pain relief from the block. Similarly the "chronic visceral pain of unknown etiology" patient could receive a diagnostic celiac plexus blockade. Unlike the more unfortunate patient with carcinoma, this patient with chronic nonmalignant pain should not receive a neurolytic blockade. After the determination that a celiac plexus block alleviates the pain, the patient should receive a series of celiac plexus blocks with local anesthetics similar to a series of sympathetic blocks of the limbs. Just as in the limbs one would hope to see an increasing duration of pain relief from subsequent injections, so too the relief of visceral pain should increase in duration with subsequent injections.

NEURALGIAS

The protean etiologies of pain disorders characterized as neuralgias are multifaceted and diverse. So, too, their therapies differ depending on the diagnosis. Treatment for these disorders can often be frustrating due to the tenacity of the neuralgia.

Occipital Neuralgia. Neuralgic-type pain of the occipital nerve is one of many diverse reasons for headache. Although the possible causes of occipital neuralgia are many, the patients' presenting complaints are similar. It is an aching pain, usually occipital and/or temporal in location. The pain can be either unilateral or bilateral. There are no visual, auditory, or olfactory auras prior to the onset of the headache. It is usually constant, with unpredictable waxing and waning. Often there is accompanying pain down the back of the neck. In many cases there is a sensation of pressure or pain in the retrobulbar region on the ipsilateral side of the head. Most times, a trigger point can be found on the occiput corresponding to the emergence point of the occipital nerve as it pierces the semispinalis capitus and spreads over the scalp. Palpation of this trigger point can reproduce the symptoms, causing a flash of pain outward over the course of the occipital nerve and often into the ipsilateral orbit [20].

This symptom complex may present as a single or series of acute attacks. During the acute phase, patients may complain of severe sequelae of headache including photophobia, nausea, and vomiting. In intermittent occipital neuralgia, the patient is pain-free between acute attacks. In its chronic form, pain and tenderness are almost always there.

The conservative management of occipital neuralgia should progress in a stepwise fashion. Once the diagnosis is established and no overt or gross pathology is overlooked, a local anesthetic block of the occipital nerve at its emergence from the muscles of the occiput should alleviate the pain. Sometimes a single injection will be sufficient to produce long-lasting analgesia, however, these patients usually require a series of injections with local anesthetic agents. Often, long-acting steroids are mixed with the local anesthetics for injection into the nerve. Furthermore, the concomitant use of centrally acting medications such as antidepressant, antiseizure, and antipsychotic agents has also been recommended. Relaxation therapy and biofeedback play an important role in cases where cervical muscle spasm is due to tension.

Trigeminal Neuralgia. Tic douloureux or trigeminal neuralgia has been one of the most

feared of pain syndromes. The major characteristic of this syndrome is blinding paroxysms of pain in the face along one or more branches of the trigeminal nerve. Often the precipitating cause of the trigeminal irritation is unclear, however, the complaint is the same: lancinating, debilitating facial pain. Often there is a trigger point that sets off the remainder of the pain syndrome: other patients have no trigger points but the same pain complaints [21].

In the past, the only therapies available were narcotic analgesics or neuroablation. Prior to many technologic advances in thermocoagulation of nerves, neuroablation was done with injections of absolute alcohol into the affected branch of the trigeminal nerve or into the ganglion itself. The necessity for this procedure was rendered obsolete by the discovery that antiseizure agents, particularly carbamazepine, cured the vast majority of these patients. Advances in neurosurgical approaches, including thermocoagulation, also rendered alcohol injections obsolete in recalcitrant cases, as this procedure is more certain to achieve the desired results [22].

Local anesthetic injection of the trigeminal nerve remains an important nerve block for prognostic purposes, both to determine the efficacy of neuroablation in relieving pain and to demonstrate the extent of numbness to patients contemplating the procedure.

Herpes Zoster and Postherpetic Neuralgia. Herpes zoster, an infectious disease, is most commonly associated with its sequelae of severe pain [22]. The disease is caused by the herpes virus varicellae, commonly known as varicella zoster. It is a DNA virus in the same group as herpes simplex, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). It is the causative agent of both varicella (chicken pox), the primary infection in the nonimmune host, and zoster (shingles), the infection in the partially immune host. It is believed that on initial infection, the virus travels to the dorsal root or extramedullary cranial nerve ganglion. There it becomes dormant until its host develops a period of decreased cell-mediated immunity, when it then can become reactivated. At the time of reactivation, the virus travels along peripheral or cranial sensory nerves to produce active disease.

Zoster is a disease of adults. Only 5% of all cases can be found in people under the age of 20. However, in the population over the age of 60, the incidence is higher than in younger age groups. Suppression of cell-mediated immunity is responsible for the reactivation of the disease. Immunosuppression due to carcinoma, chemotherapy, and systemic steroid therapy can also lead to reactivation. The elderly have a diminished cellular immune response and hence cannot manifest the appropriate proliferation of lymphocytes in response to viral infections such as zoster.

Diagnosis of early zoster may be difficult to make. In its initial stages it may present with headache, malaise, fever, and lymphadenopathy prior to the appearance of the characteristic rash. Additionally, pain may precede the appearance of the rash by as many as 14 days. The pain is segmental, usually unilateral and bandlike, following a specific dermatomal distribution. When the rash appears it is macular and erythematous. It then progresses through papular, vesicular, and pustular stages before crusting and scarring take place. The scars themselves may be painful for several months after the initial outbreak and can take many years to fade into the surrounding skin. The rash may appear over any part of the body. However, a recent series reported more than half the rashes located in a thoracic distribution, with the other half divided equally between cranial nerves, cervical, and lumbar distributions, with only a small number in the sacral dermatomes. Only 1% of this population had bilateral manifestations. Rarely, the disease can be disseminated throughout the body. In these cases it can resemble other diseases with vesicular eruptions such as primary varicella, coxsakie virus, echo virus,

herpes simplex, mycoplasma, rickettsia, or impetigo. In these cases, correct diagnosis might entail diagnostic testing such as culturing of varicella virus from vesicular fluid, a Tzanck preparation of the base of the vesicle, or counterimmunoelectrophoresis of vesicular fluid. Acute and convalescent antibody titers can confirm the diagnosis in retrospect but are usually too slow to help diagnose an acute case.

One of the most feared complications of a herpes zoster infection is the development of the long-standing chronic pain condition, postherpetic neuralgia. Patients over the age of 60 years are at greater risk for developing this syndrome than those in younger age groups. Up to 10% of those individuals in a recent series who were over the age of 60 went on to develop postherpetic neuralgia.

Characteristically, the involved area is hyperesthetic to light touch but has decreased sensation to pin prick. Tactile stimulation of this area can lead to severe paroxysms of pain, which is usually burning and sharp [24]. Several authors have postulated small fiber destruction with unimpeded large fiber impulses. Others have postulated a central mechanism to account for the prolonged pain. Whatever the etiology, postherpetic neuralgia is a severe and prolonged complication of an acute zoster infection that can lead to severe depression and sometimes suicide unless steps are taken to prevent or treat it.

Of the multitude of modalities offered for the prevention or treatment of postherpetic neuralgia, few if any have been sufficiently studied to report that there is a definite means by which this problem can be avoided.

Traditionally, the patient with zoster has been given a course of oral narcotic or nonnarcotic analgesics and told to wait out the course of the disease. However, newer methods of pain control for the acute phase have been described. Altering the outcome of an acute herpetic attack, that is, prevention of postherpetic neuralgia, has been attempted through many methods. Radiation therapy to the involved dorsal root ganglia has been advocated by some. Antiviral medication such as cytosine arabinoside (ARA-C), vidarabine (ARA-A), interferon, and, most recently, acyclovir has been used with some success. Zoster immune globulin has been used for prevention of infection in high-risk individuals, but as yet it has not been demonstrated to be of benefit in prevention of postherpetic neuralgia after an acute zoster attack. A short course of high-dose oral steroids had also been used to some success both in shortening the course of acute zoster and in decreasing the incidence of sequelae [25].

The use of nerve blocks for the treatment of pain in the acute phase of zoster and the prevention of postherpetic neuralgia has been a focus of controversy. Many authors argue that the pain of acute zoster is similar to causalgia. Sympathetic blockade of the involved area for the treatment of this pain was first performed in the early 1940s and has many advocates [26]. Many papers have discussed the benefits of these procedures and report prompt relief of the pain of early acute zoster and further report a decreased incidence of postherpetic neuralgia.

Stellate (cervicothoracic) ganglion blockade is the procedure of choice for sympathetic blockade of the head, neck, and upper thorax. This method provides easy access and can be performed on outpatients. Thoracic epidural anesthesia has been advocated for pain in lower thoracic roots and can be performed as single-shot or continuous (catheter) techniques [27]. Sympathetic blockade below L1 can be performed by paravertebral techniques or epidural injection. A series of three to five injections has been described as sufficient for maximum benefit. Again, it is important to emphasize that therapy starting earlier in the course of the disease has a greater chance of success than anything begun later on.

Local infiltration of the affected skin areas with solutions of dilute steroid in saline or

local anesthetic has also been described as decreasing the acute pain and altering the outcome. These injections of 60 mg to 80 mg of triamcinalone or similar steroid are injected daily subcutaneously at the sites of pain or eruption for up to 2 weeks. However, most patients require far fewer than 14 days of treatment [28].

Postherpetic neuralgia also presents a major problem in treatment. Here, too, the mainstay of therapy had been chronic narcotic or nonnarcotic analgesics for the duration of the pain syndrome. In many cases, this would be for the lifetime of the patient. More recently, alternative methods of treatment have been attempted with some success.

Neuroactive medications have been used recently to treat patients with postherpetic neuralgia. Most notably is the use of a tricyclic antidepressant in combination with a phenothiazine and/or an antiseizure medication [29, 30]. Although this is fairly effective treatment for many people, the side effects are often difficult to live with. The typical sufferer of postherpetic neuralgia is over the age of 60 and often has some other systemic illness. These patients can become dysphoric, disoriented, oversedated, or hyperactive from these medications. Often they will describe that the treatment is worse than the disease. Here, again, the alternative treatments are more effective when begun earlier in the course of the disease.

Although not as helpful as in acute zoster, local infiltration of the painful areas with dilute solutions of steroids in saline or local anesthetics can be helpful in this situation as well. Sympathetic blockade, through the aforementioned techniques, have also been described as helpful. Additionally, transcutaneous electrical nerve stimulation (TENS) can be a useful adjuvant to the above techniques and in some patients can result in ablation of pain by itself [31].

Often, the pain of postherpetic neuralgia is worsened by stress, anxiety, depression, or sleep deprivation. Psychological counseling can help in this regard. Progressive relaxation therapy, hypnosis, and behavior modification are neglected but useful aids in the treatment of this painful and potentially disabling disorder.

Peripheral Neuropathy. Peripheral nerves are not immune from the development of neuropathy. As in cranial nerve and cervical neuralgias, pain is the major presenting complaint. It is usually paroxysmal, sharp, and often debilitating. Discomfort may be chronically present throughout the distribution of the involved nerve, punctuated by episodes of severe lancinating pain. Often the involved nerves have had a previous injury of some sort, however, the history of trauma may be difficult to establish.

Local anesthetic injections into the involved nerves are helpful in establishing a diagnosis. Treatment is often difficult, as series of local anesthetic injections do little more than give temporary relief. Sometimes, centrally acting medications are helpful in controlling the paroxysms, but rarely in controlling the underlying pain complaints. Neuroablation with alcohol or phenol is often necessary. A greater degree of permanence and reliability can be obtained with surgical neurectomy.

Summary

Pain is an almost universal problem of the human condition. It is likely that it will afflict most members of the population at some point during their lives. The problem can range from mild discomfort to complete debilitation, yet the causative factors may remain obscure. Extremely conservative therapy with bed rest, heat, and analgesics works well for a majority of cases given sufficient time and patience. The select use of nerve block techniques, well described in the literature [32], applied in the right fashion can hasten a return to comfort and functioning. These techniques can and

should be added to the armamentarium of the conservative, nonsurgical approach to the treatment of pain. Their use, joined in a total pain management program with psychological and pharmacological intervention, allows the patient to move about with greater comfort and confidence and can increase his or her exercise tolerance for muscle strengthening and return to functioning. Nerve blocks can be performed for both diagnostic and therapeutic functions and are usually safe in the hands of a physician experienced in their techniques.

References

1. Halpern LM: Analgesic drugs in the management of pain. Arch Surg 112:861–869, 1977.
2. Ward NG, Bloom VL, Friedel RD: The effectiveness of tricyclic antidepressants in the treatment of coexisting pain and depression. Pain 7:331–341, 1979.
3. Sternbach RA, Jarowsky DS, Huey LY, et al.: Effect of altering brain serotonin activity on human, chronic pain. Adv Pain Res Ther 1:601–606, 1976.
4. Simon DG: Myofascial trigger points: A need for understanding. Arch Phys Med Rehabil 62:97–99, 1981.
5. Rubin D: Myofascial trigger point syndrome: An approach to management. Arch Phys Med Rehabil 62:107–110, 1981.
6. Shealy CN, Taslitz N, Mortimer JT, Becker DP: Electrical inhibition of pain: Experimental evaluation. Anesth Analg 46:299–305, 1967.
7. Mixter WJ, Barr JS: Rupture of the intervertebral disc with involvement of the spinal cord. N Engl J Med 211:210–215, 1934.
8. Goebert HW, Jallo SJ, Gardner WJ, Wasmuth CE, Bitte EM: Sciatica: Treatment with epidural injections of procaine and hydrocortisone. Cleve Clin Quart 27(4):191–197, 1960.
9. Benzon HT: Epidural steroid injections for low back pain and lumbosacral radiculopathy. Pain 24:277–295, 1986.
10. Brown FW: Management of discogenic pain using epidural and intrathecal steroids. Clin Orth 129:72–78, 1977.
11. Wyant GM: The piriformis syndrome. Canad Anaesth Soc J 26:4, 1979.
12. Carrera GF: Lumbar facet joint injection in low back pain and sciatica. Radiology 137:661–667, 1980.
13. Bonica JJ: Causalgia and other reflex sympathetic dystrophies. In: Advances in Pain Research and Therapy, Bonica JJ, Liebeskind JC, Albe-Fessand D, eds. Raven Press, New York, Vol 3, 1979.
14. Glynn CJ, Basedon RW, Walsh JA: Pain relief following post-ganglionic sympathetic blockade with IV guanethidine. Br J Anes 53: 1297–1301, 1981.
15. Melzack R: Phantom limb pain: Implications for treatment of pathologic pain. Anesthesiol 34(4):409–419, 1971.
16. Reid W, Watt JK, Gray TG: Phenol injections of the sympathetic chain. Br J Surg 57(1): 45–50, 1970.
17. Richlin DM, Carron H, et al.: Reflex sympathetic dystrophy: Successful treatment by transcutaneous nerve stimulation. J Pediatr 93(1):84–86, 1978.
18. Hollinshead WH: Textbook of Anatomy, 3rd ed., Harper & Row, Hagerstown, MD, 1974.
19. Thompson GE, Moore DC, et al.: Abdominal pain and alcohol celiac plexus nerve block. Anesth & Analg (Current Researches) 56(1):1–5, 1977.
20. Rosner HL, Schwartz A, et al.: Occipital neuralgia: An often missed cause of headache. Reg Anesth 11(1):34–38, 1986.
21. Kerr FWL: Etiology of trigeminal neuralgia. Arch Neurol 89:15–25, 1963.
22. Voorhees R, Patterson RH: State of the art: Management of trigeminal neuralgia (tic douloureux). JAMA 245:2521–2523, 1981.
23. Rosner HL, Yerby JT, Brand L: Herpes zoster: Can we change the outcome? J Pain Sym Manag 1(3):168–170, 1986.
24. Frengley JD: Herpes zoster, a challenge in management. Prim Care 8(4):715–31, 1981.
25. Reular JB, Chang MK: Herpes zoster: Epidemiology, clinical factors and management. South Med J 77(9):1149–56, 1984.
26. Colding A: The effects of regional sympathetic block in the treatment of herpes zoster. Acta Anaesthiol Scand 13:133–141, 1969.
27. Perkins HM, Hanlon PR: Epidural injection of local anesthetic and steroids for relief of pain secondary to herpes zoster. Arch Surg 113:253–254, 1978.
28. Epstein E: Treatment of herpes zoster and post-herpetic neuralgia by subcutaneous injection of triamcinalone. Int J Dermatol

20(1):65–68, 1981.
29. Gerson G: Studies on concomittant use of carbamazepine and cloripramine for the relief of postherpetic neuralgia. Postgrad Med J 53(Suppl 4):104–109, 1977.
30. Weis O, Sriwatanakul K, Weintraub M: Treatment of postherpetic neuralgia and acute herpetic pain with amitriptyline and perphenazine. S Afr Med J 62:274–275, 1982.
31. Nathan PW, Wall PD: Treatment of postherpetic neuralgia by prolonged electrical stimulation. Br Med J 3:645–647, 1974.
32. Cousins MJ, Bridenbaugh PO (eds): Neural Blockade in Clinical Anesthesia and Management of Pain. JB Lippincott, Philadelphia, 1980.

13. PSYCHIATRIC MANAGEMENT OF CHRONIC BENIGN PAIN

Ralph N. Wharton, M.D.

Chronic Pain and Pain-Complaining Behaviors

Chronic pain and pain-complaining behavior in patients challenge physicians and surgeons in every specialty. The challenge is both diagnostic and therapeutic. The subtypes and species variability from patient to patient defy simple classification or categorization at this time. Although several models have been under consideration, no one model is being utilized in various clinics throughout the country. The models make efforts to integrate somatic, psychical, and social factors. Mathematical models or computer models may ultimately help the clinician to develop a format as specific as a fingerprint to define the individual afflicted. Until such time, we shall have to settle for the assessments of pathology and behavior as the current subspecialties permit.

International Pain Association Classification Effort

A scheme for coding chronic pain disorders has been recently published in the journal, *Pain* (Supp. 3, 1986) and edited by Harold Merskey, a member of the International Association for the Study of Pain (IASP). Description of chronic pain syndromes and definitions of pain terms are within and appropriately codeable according to a five-axis system that includes regions, systems, temporal characteristics of pain pattern, patients' statements of intensity, and etiology when known. As a reference text, it is an excellent beginning for the International Association for the Study of Pain (IASP) to find some common grounds for meetings and research. The IASP is attempting to bridge the gaps in communication among all diverse specialties (from dentistry to neurosurgery), as well as to promote international understanding for research into the different cultural aspects of diverse treatments.

American Psychiatric Pain Classification

In psychiatry, there is also an ongoing effort toward reclassification of pain. Chronic pain disorders, according to the *1987 Diagnostic and Statistical Manual* of the American Psychiatric Association, may be considered under 1) hypochondriasis (300.70), 2) somatization disorder (300.81), 3) somatoform pain disorder (307.80), or 4) undifferentiated somatoform disorder (300.70). Conversion reactions when limited to pain or primarily dominated by pain are *now* classified as somatoform pain. The other common psychiatric entity associated with chronic pain is, of course, 5) major (296.2) or 6) unipolar depression.

The generalized anxiety disorder (300.02) is a less frequent and less well-studied psychiatric entity seen in many pain clinics. The diagnostic criteria include chronic muscle aches (or pains) along with other features. The essential feature is unrealistic or excessive anxiety or

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worry about two or more life circumstances for 6 months or longer. There may be signs of motor tension, easy fatiguability, autonomic hyperactivity with vigilance, palpitations, exaggerated startle response, irritability, trembling, and twitching.

Pure forms of depression or generalized anxiety disorders do not often exist and may also overlap when found in chronic pain patients. It is important at the outset to make a thorough mental examination to determine the extent and nature of a concomitant psychiatric entity, personality disorder, or psychosis with hallucinatory pain.

Once a psychiatrist's diagnosis is established, a treatment plan must be formulated.

Psychogenic Overlay versus Pain Amplifier

Chronic pain problems are often referred to psychiatrists for advice in management. Often, the referring physician asks about "psychogenic pain versus real pain" or a "psychogenic overlay." The legitimate patient who is *not* involved with compensation or litigation is often clearly fearful and uncertain himself/herself and may be easily offended when aware of any implied critical overtones in the consultation request. It is best to try to avoid adding resentments in the style and manner of referral or negative implication in "overlay" or malingering. Pain is mainly in the brain, so "overlay" is a mythic concept that deserves to be permanently interred. A better concept is that of a pain amplifier.

Psychiatric Assessment

The psychiatrist's repertoire in evaluation for treatment should include the following options:

First: Test for hypnotizability.
Second: Mental examination repeatedly at as low drug intake level as possible.
Third: Amytal interview for assessment of possible conversion phenomena.
Fourth: Thorough evaluation of prominently involved family members and/or coworkers when possible.
Fifth: Detailed family history.
Sixth: Assessment of medical risks for use of MAOI drugs and/or possible ECT.
Seventh: Absolutely no placebo studies. Use of cold pressor test, thermal, and pressure testing to assess pain amplifiers, averages, or stoics.

1. The medical use of hypnosis in treatment centers throughout the U.S. is a welcome sign of the multimodel approach to chronic pain. The ability to go into a deep trance still is a capacity that may be utilized at anytime in a patient's treatment. Focal areas of anesthesia or coldness may be induced; the reduction in intake of drugs or increase in acitivity or both may be accomplished with three sessions of hypnotherapy in the highly suggestible individual.
2. Drug-abusing chronic pain patients cannot be properly assessed psychiatrically in an outpatient setting. Whenever there is a significant question of brain dysfunction, especially in older patients, several mental exams must be done with minimal drugs on board. Urine and blood screening tests for toxicology must be done before establishing a treatment agenda.
3. An Amytal interview in a hospital setting may establish rapid rapport. A climate of trust is established, with reduction in pain and fear early in the course of evaluation. During the course of the interview, marked relaxation may be seen. Often, there may be additional revelations about personal and family history of traumas, sexual abuse, etc.
4. Decision about treatment invariably involves significant partners. When the patient is living alone, the hazards of drug overdose, error, and suicide are greatest. The hazards of disappointment and rejection after another "last" series of consultations are great. Large medical centers are

often seen as the court of last resort. Anger, protest, or profound despair may be the emotional response to a set of recommendations depending on the tone of proffered hope or the setting of treatment goals in an outpatient or inpatient context. In an inpatient or outpatient evaluation, involved "significant others" must be seen.

5. Family history with notation as to alcoholism, depression, and/or suicide is extremely important. Identification with friends or others in chronic pain, or with amputees or deformed individuals, may give clues as to hoped-for resolutions with health or death.
6. Medical assessment in terms of cooperation with diet and/or other drug restriction is necessary when considering MAOI drugs. Attitudes and fears about ECT for treatment of concomitant depression should be addressed early in the treatment.
7. Placebo use is to be decried. Placebo injections or pills are given by some physicians to assess "real" pain. Over 40% of postoperative patients will respond positively to placebo injections with significant pain relief. In a variety of inpatient and outpatient settings, most likely one-third or more individuals are positive placebo responders. Hence so-called positive responses to placebo does *not* imply there is no "real" pain; it validates the concept of the power of positive placebo responsivity. The cold pressor test, a high-pressure tourniquet (up to 250 mm Hg), and thermal discriminability have been used by Clark, Wharton, and others to assess stoicism and/or pain-amplifying personality types.

Specific Treatments To Achieve

General Goals

1. Reduce pain and suffering
2. Reduce drug intoxication
3. Avoid unnecessary surgery
4. Improve work and social capacities
5. Consider financial costs
6. Control pain behaviors but not necessarily aim for or promise complete relief

All of these goals may need to be addressed in the course of treatment, but the priorities will vary greatly from patient to patient. In order to reduce pain and suffering, a prolonged relationship of support at fixed intervals will be necessary to provide a sense of relief and emotional security. Most patients with chronic nonmalignant pain have chronic needs for dependency — either iatrogenic or as an aspect of their premorbid personality. Often a patient will insist on an explanation as to the cause of his difficulty; however, there may be none. Invariably *all* pain is in the brain; there is no need to make simplistic dichotomies between mind and body. It is important to agree that there is recognition by the physician of suffering and that it can clearly be reduced by appropriate and constant attention to that realistic need.

Medications should *not* be abruptly changed or altered without a cooperative mind set and agreement between the physician and the patient. Substantive therapies or activities should be introduced slowly.

Special attention must be paid to changes in pain patterns in anticipation of, or in contact with, loved or hated family members. Simple reduction of anxiety through verbalization or expressions of anger, guilt, and fear may lead to lessened pain or demand for pain medications. It is important not to promise or hint that one can deliver more complete relief too early in the treatment. Often, lowering expectations for cure and dramatic relief is an essential first step.

There are several excellent studies demonstrating the value of antidepressants for chronic pain in a variety of painful illnesses [1–11] ranging from headaches to pain associated with malignancy. It is difficult to separate pain relief from the antidepressant effect, although usually clinicians have noted the more rapid onset of analgesia. In certain drug trials, the variety of pain patient groups confounds generalization about efficacy and specificity. In one review [3], 13 of 17 trials

Specific Medications for Chronic Pain:

TABLE 13-1. Tricyclic antidepressants for pain relief [1–14]

Brand name	Generic name	Average daily dose for pain relief (mg)	Maximum daily dose for antidepressant effect (mg)
Tofranil	Imipramine	100–150	300
Elavil	Amitriptyline	100–150	300
Aventyl	Nortriptyline	75–100	150
Pamelor	Nortriptyline	75–100	150
Norpramine	Desipramine	50–100	300
Sinequan	Doxepin	50–100	150
Prozac	Fluoxetine	10	20

showed clear efficacy of drug over placebo. The results of studies on diabetic neuropathic pain have been mixed, but blood level assays were not done in any study to control for possible poor absorption or inconsistent intake.

Most studies of patients with cancer pain have shown that tricyclics are beneficial. In one pharmacological assay study, amitriptyline's analgesic potency was clearly well above aspirin and close to the range for codeine. Studies on several groups of patients in England [10] reported clear reduction in joint pain and tenderness in sufferers with arthritis. Another study demonstrated limited relief.

Almost invariably, patients with chronic pain suffer sleep disturbances [7–9]. The use of tricyclics at bedtimes generally shortens REM latency and improves total sleep time. After adequate sleep, most patients are less irritable. However, in a study by Ward [12], he was unable to document that the more sedating antidepressants were more effective in relieving chronic back pain. In his study, baseline cerebrospinal fluid levels of beta endorphin did not predict pain outcome and did not change with treatment. There was also no change in pain tolerance as measured in a laboratory paradigm.

There had been a hypothesis that the tricyclic medications relieved pain via a descending inhibitory serotonergic mechanism [4]. Presumably, the greater the serotonergic activity, the more likely relief. However, clinical practice has not confirmed this. The biochemical theoreticians remain baffled by the clinical efficacy of these drugs — both in their capacity to relieve pain as well as in their antidepressant effectiveness. This is not entirely surprising, inasmuch as there have been many drugs of clinical widespread use available for more than 30 years (duration of use of tricyclics) whose mode of action is not unequivocally known or accepted (TABLES 1 and 2).

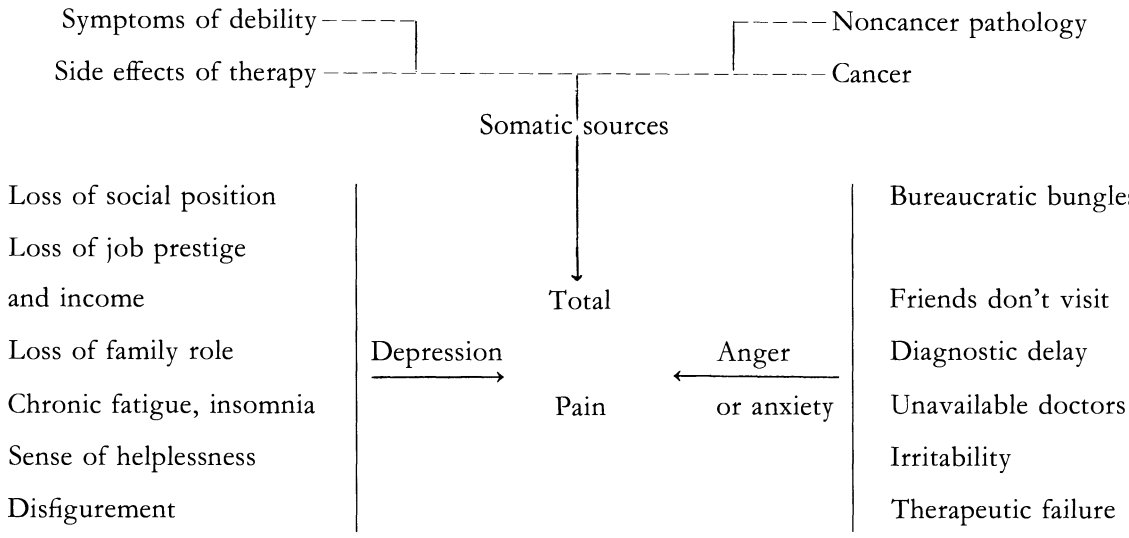
Chronic Pain and Concomitant Depression

Chronic pain may lead to depression via several routes. One avenue is the "pain-prone" individuals of Blumer and Heilbrun. These individuals present a significant subtype of patients who may respond to antidepressants. Blumer's data suggest a particular premorbid personality and a family history with a high incidence of unipolar depression and alcoholism.

When it is clinically clear that *both* chronic depression and chronic pain coexist, [12–13], the treating physician should use maximum doses of tricyclics. Blood level assessments must be considered when approaching the highest levels to monitor toxicity and avoid

Influences modifying a patient's perception of pain

(Twycross and Lock, 1983)



Other Affective Disorders with Chronic Pain:

Anxiety

(Named or unnamed fears with physiological responses)

Fear of hospital ←----------→ Fear of pain

Worry about family ←----------→ Financial fears

Fear of death ←----------→ Loss of dignity, body control

Religious concerns ←----------→ Fears of future

Analgesic Medications

(that may relieve associated fears of pain)

Category	*Parent drug*	*Alternative*
Nonopioid (NSAID)	Aspirin	Paracetanol
Opioids		
Weak opioid	Codeine	Dextropropoxyphene (Darvon)
Strong opioid	Morphine	Methadone (Dolophine)
		Levorphanol (Levo-Dromoran)
		Hydromorphone (Dilaudid)
		Meperidine (Demerol)

TABLE 13-2. General classes of adjuvants to analgesic medications

	Primary Drug	Alternative
Antidepressants	Amitriptyline (tricyclic type)	Imipramine
	Phenelzine (monoamine type)	Tranylcypromine
Anxiolytic	Diazepam	Oxazepam
Tranquilizers	Chlorpromazine	Haloperidol
Stimulant	d-amphetamine	Methylphenidate

complications. The following diagram gives a picture of the variety of factors influencing pain perception in the largest sense.

It is important to understand that narcotics have a powerful *mood*-altering effect on the patient's reaction to pain. They do not invariably eliminate the perception of pain, but in adequate regular dose do diminish fear and also alter affective responses. The action of the drugs then is both at the spinal cord level as well as the higher cortical levels, including the limbic system.

Chronic pain may lead to depression via drug abuse of minor tranquilizers with analgesics and/or narcotics.

Relatively little has been written about the influence of anxiety on chronic pain. An assumption has been made that fear and anxiety are predominantly experienced with acute pain. However, it is intuitively and clinically apparent that many patients with chronic pain may have coexistent anxiety that is unassuaged by the mere passage of time (Table 3). The benzodiazepines have generally been shunned because of fear on the physician's part of inducing addiction, dependency, or depression. In fact, there appears to be a group of chronic pain amplifiers who respond well to these drugs when given in moderate doses for a limited period of 3–6 months in conjunction with a form of cognitive therapy. The group of pain amplifiers are often raised in a home where fears of cancer or the presence of a cancer victim became a lifetime household specter. Other chronic illness such as angina, diabetes, or Crohn's disease may induce in unaffected members an emotional tendency to amplify their own painful concerns about identification with the "victim" in the developmental home. Goal-directed psychotherapy may help to clarify or relieve the tendency to express emotional conflict via the "painful" or "victim" route.

TABLE 13-3. Specific medications for anxiety

Branch name	Generic name	Average dose
Ativan	Lorazepam	2–4 mg/day
Serax	Oxazepam	15–30 mg b.i.d.
Valium	Diazepam	10–20 mg/day
Librium	Chlordiazepoxide	75 mg/day
Xanax	Alprazalam	.75–1.5 mg/day

Summary

Acupuncture, operant conditioning, and transcutaneous nerve stimulation are other nonpharmacologic methods for pain relief. The psychological or psychiatric milieu in which all pain treatments are carried out influences success rates reported. In the last analysis, the physician aims to help the individual sufferer to live with less pain or function at a level in spite of the discomfort [14]. Perhaps there is a learned stoicism, which permits an individual to find a different kind of existence when a secure dependence on a physician is well defined and maintained.

References

1. Carette S, McCain GA, Bell DA, Fam AG: Evaluation of amitriptyline in primary fibro-

sitis. A double-blind, placebo-controlled study. *Arthritis Rheum* 29:655–659, 1986.
2. Macfarlane JG, Jalali S, Grace EM: Trimipramine in rheumatoid arthritis: A randomized double-blind trial in relieving pain and joint tenderness. *Curr Med Res Opin* 10:89–93, 1986.
3. Stimmel GL, Escobar JI: Antidepressants in chronic pain: A review of efficacy. *Pharmacotherapy* 6:262–267, 1986.
4. Ward NG: Tricyclic antidepressants for chronic low-back pain. Mechanisms of action and predictors of response. *Spine* 11:661–665, 1986.
5. Kocher R: Use of psychotropic drugs for the treatment of chronic severe pain. In: Advances in Pain Research and Therapy, Vol 1: Bonica JJ, Albefessard D, eds. Raven Press, New York, 1976.
6. Kuipers RKW: Imipramine in the treatment of rheumatoid patients. *Acta Rheumatol Scand* 8:45, 1962.
7. Lee R, Spencer PSJ: Antidepressants and pain: A review of the tricyclics in chronic pain. *J Int Med Res* 5: (Suppl 1) 146, 1977.
8. Merskey H, Hester RA: The treatment of chronic pain with psychotropic drugs. Postgrad Med J 48:594, 1972.
9. Pilowsky I, Hakket EC, Basset DL, Thomas PG, Penhall RK: A controlled study of amitriptyline in the treatment of chronic pain. *Pain* 14:169, 1982.
10. Alcoff J, Jones E, Rust P, Newman R: Controlled trial of imipramine for chronic low back pain. J Fam Pract 14:841–846, 1982.
11. Couch JR, Hassanein, RS: Amitriptyline in migraine prophylaxis. Arch Neurol 36:695–699, 1979.
12. Ward NG, Bloom VL, Dworkin S, et al.: Psychobiological markers in coexisting pain and depression: Toward a unified theory. J Clin Psychiatry 43:32–39, 1982.
13. Ward NG, Bokan JA, Phillips M, et al.: Antidepressants in concomitant chronic back pain and depression: Doxepin and desipramine compared. J Clin Psychiatry 45:54–57, 1984.
14. Ford CV: *The Somatizing Disorders*. Elsevier, New York, 1983.

14. PHYSIATRIC MANAGEMENT OF CHRONIC BENIGN PAIN

Stanley J. Myers, M.D.

All of us have experienced pain. We have at one time or another been pricked by a needle or pin, burned, banged our shin, or perhaps strained our back or suffered from bursitis or even a fractured bone. The underlying pathophysiology of an acute pain syndrome is usually not difficult to understand, and once the precipitating factor is removed or treated the pain will often promptly subside. Unfortunately, in our clinical practices we are not infrequently called upon to see patients suffering from more severe, perhaps intractable, pain, and we must (sometimes reluctantly) accept the challenge of being responsible for the management of such patients. When dealing with patients with chronic pain, there are a number of considerations that must be taken into account in order to devise an effective treatment plan. Can the etiology of the pain be determined and is it possible to directly treat the causative elements? Thus the history, including social and psychological factors, physical examination, and laboratory and radiological evaluations, is essential. The diagnosis cannot be taken for granted, but one must make sure that all appropriate diagnostic measures have been carried out and that the diagnosis is correct.

Appropriate medication is an integral part of managing patients with chronic pain. There are various classes of analgesics to be considered. Certainly in chronic benign pain the long-term use of narcotic agents as well as short-acting benzodiazepines is to be avoided. There is often a role for salicylates, nonsteroidal antiinflammatory drugs, muscle relaxants, tricyclic antidepressants, antianxiety agents, and, in some instances, sympatholytic medicines. The chronic-pain patient has taken a whole host of medications and could still be on an inappropriate drug regimen. A careful evaluation of all medicines and a planned approach is essential.

Very often the pain-precipitating factor may have been long removed but the pain still persists. What is the best means of managing this? A useful axiom in dealing with patients with chronic pain is that one single treatment modality alone is rarely sufficient. Providing pain is not aggravated, the treatment plan should be carried out for a long enough period of time to assess its effectiveness. Patients with pain like to see instant results, as do physicians, and there is a tendency to jump from one treatment modality to another before any specific treatment is given a true trial. Most patients will indicate that they have received many medications and treatments without obtaining relief of pain and it is of value to review previous treatment plans, including time given and possible benefits, adverse effects, or lack of change.

The use of the physical modalities is often effective in treating musculoskeletal pain syndromes. In addition, exercises to restore range of motion, strength, and activities of daily living can be effective in reducing pain. This will be the main focus of the present chapter,

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and a more detailed discussion will follow. Psychological and emotional support, counseling, and sometimes specific long-term psychiatric management may be another adjunct to overall treatment. Injection therapy, including but not limited to trigger points, facet joints, nerve blocks, intrathecal and epidural catheters and pumps, are therapeutic options; however, one usually starts with the most benign treatments first and then proceeds to the riskier ones as indicated. Surgery that is destructive and aimed at treating the pain alone without attacking the cause (if not known) becomes a last resort for obvious reasons.

The above topics, with the exception of the physical modalities, are discussed by other authors in this volume and will not be dwelt on here other than to reinforce the concepts of multimodality progressive therapy and to try not to make the treatment worse than the condition. This chapter cannot be a definitive text on the physical medicine and rehabilitation approach to all pain syndromes and will not directly discuss management of specific disease entities or syndromes, but rather will attempt to present general principles concerning various physical modalities and treatments often utilized in an attempt to provide a rationale and understanding of the use for such therapies in specific situations. There are a number of useful and comprehensive texts available that the reader can refer to if he or she so chooses [1–5].

When dealing with chronic-pain patients, the physiatrist will not only use physical modalities and order exercises, but will also utilize appropriate diagnostic testing and drug therapy, and will work together with other physicians and nonphysician colleagues in an attempt to offer optimal management. While there may be some overlap in the armamentarium of the various specialists, each can still play a crucial role in the treatment of the long-term complex patient.

Heat

As noted by Lehmann and de Lateur [6], heat is often used as a therapeutic modality in order to obtain the following physiologic responses:

Increase in the extensibility of collagen tissue
Decreased joint stiffness
Analgesia
Relief of muscle spasm
Increased blood flow
Assist in resolution of inflammation
An adjunct in cancer therapy

The effects of heat may be local or more distant. Heat can have a direct effect on tissue, altering cellular function and metabolism. The physical properties of fibrous tissue are changed so that it becomes more flexible and can be more readily stretched. Blood flow increases both by direct and indirect mechanisms. Heating one part of the body surface will cause an increase in blood flow in other parts of the skin distant to the area heated. Superficial heat can cause relaxation of smooth and skeletal muscle. Heat can have a psychological sedative effect as well as a direct effect on raising the pain threshold in the area heated. Heat can have an antispasmodic effect by decreasing gamma fiber activity in the muscle spindle.

There are, however, adverse effects from heat, and certain general precaution should be followed. The use of heat should be avoided, if possible, over areas that are anesthetic, have sensory deficits, or in an obtunded patient. If there is vascular insufficiency, such as in patients who have diabetes mellitus, heat that normally would be non-harmful and removed by the circulation will, in the presence of poor circulation, accumulate and can cause burns. The vascular responses are inadequate to cope with the metabolic increases, with resultant ischemic tissue necrosis. Tumor growth may increase with moderate heating not sufficient to treat malignant cells. Bleeding tendencies can also be aggravated with heat. In general

one must also try to avoid heating the gonads or a gravid uterus.

VIGOROUS VERSUS MILD HEATING

There is a minimal and a maximal duration for application of heat in order to obtain a desired biological reaction. For example, when using ultrasound to produce hyperemia, a minimal effective duration of 5 minutes was required, whereas maximal reactions were obtained after 30 minutes [7]. There is a therapeutic temperature range that is relatively narrow (approximately 40°C to 45.5°C or 104°F to 114°F), with limited responses noted in the lower range and more vigorous effects in the upper. The safety range may be small. The rate of temperature increase also influences response, with rapidly rising temperatures producing a more pronounced effect. In general, the larger the area treated, the greater the reflex effects and the more likely the effect on core body temperature. Vigorous heating produces a high temperature at the site of the pathological lesion. Heating is rapid and close to tolerance levels in regard to both actual temperature and time delivered. In general, vigorous heating is used in more chronic conditions such as for treating contractures. It should not be used in acute inflammatory situations, as symptoms and side effects can be aggravated. In acute radiculopathy with foraminal impingement, vigorous heating with temperature elevation at the site of the lesion can increase the inflammatory response, and therefore the heating applied is usually mild and superficial for relief of the associated muscle spasm. Mild heating results in a relatively small temperature rise in tissues at the site of the pathological lesion, with the greatest rise in temperature being superficial to and distant from the lesion. The rate of temperature increase is slow, with the tissue temperature maintained for a relatively short time. Although superficial heating is a form of mild heating, this does result in the highest temperature rise in the most superficial tissues, especially the skin. If the acute pathology is in the skin of small body parts (e.g., hands) then this may produce a physiological response there equivalent to vigorous heating and this must be kept in mind. Heat alone is rarely effective in treating most pain situations but must be combined with other modalities.

SUPERFICIAL HEATING

In *conductive heating* heat is transferred from a warmer to a cooler surface, with the rate of heat transfer dependent upon the temperature gradient. Conductive heating is most commonly a superficial and mild heating modality. Hot water bottles are frequently used, but these lose heat very rapidly and caution is necessary not to start with them too hot. Moist heat is often most effective for treating musculoskeletal, joint, and tendon pain. Moist wet packs can retain heat up to 30 minutes and are quite effective. A terry cover or several layers of towels are necessary in order to avoid burning the patient, as the temperature of the packs are usually 71°C–79°C (160°F–175°F). Electric heating pads produce constant levels of heat, but patients should avoid falling asleep when using them and should also not lie on the heating pad, but rather place the pad over the area to be treated as pressure from body weight will compromise local circulation. This reduces heat removal and what appears to be a relatively low temperature can actually result in serious burns.

Radiant heating (a form of heat conversion) utilizes an infrared heating lamp, with treatment time usually approximately 30 minutes. Intensity levels are controlled by the wattage and the distance of the lamp from the body. It is simple to use but can be dangerous if not used correctly and if there is no protection from a shattering bulb. Radiant heating can be used over an open wound and with an extremity elevated to decrease edema formation.

In *convective heating* there is usually heat exchange between a liquid or gas moving past the surface of a solid (the patient). This will be discussed later under hydrotherapy.

DEEP HEATING

With *conversive heating*, other forms of energy are converted into thermal energy. Most conversive heating can penetrate deeper into the body. The three major types of conversive heating convert electrical (short-wave diathermy), sound (ultrasound), or electromagnetic (microwave) energy into heat.

In *short-wave diathermy*, a high-frequency oscillating current is applied to the patient, who actually becomes part of the circuit. The frequencies of the oscillating circuit allowed are controlled by the Federal Communications Commission and are short wave. Heating is greatest in the subcutaneous tissues and superficial muscles [6]. Short-wave diathermy cannot be used if there are metallic surgical implants such as joint prostheses or pacemakers, as the metal can concentrate the current and heat selectively, resulting in deep burns. Metallic jewelry, obviously, should also not be worn. The patient should be treated on a wooden table, and a terry cloth is used to prevent sweat beads. Short-wave diathermy should not be applied close to the fetus in pregnant women. It also should not be used over insensate areas. It is difficult to accurately determine the dose, with the patient usually feeling a sensation of warmth at therapeutic levels. Treatment is applied for approximately 20–30 minutes over the involved area and is then followed by other exercise modalities.

With *ultrasound*, high-frequency current is converted to mechanical acoustic vibrations at frequencies that are too high to hear. The sound waves are selectively and variably absorbed and converted into heat. Ultrasound causes relatively little temperature elevation in the superficial tissues and can penetrate quite deeply into the body, including the hip joint. The depth of penetration is controllable. Ultrasound can be used in the presence of metallic implants without selective heating of the metal [8]. When ultrasound is followed by stretching and range of motion, an enhanced effect on collagen tissue stretching is obtained. Ultrasound is applied via a sound head (applicator), which is rhythmically moved over the part to be heated, either under water or with an oil interface, for 5–10 minutes. If held stationary, too rapid heating or cavitation can occur. Ultrasound should not be used over the eye or gravid uterus. Caution should also be observed in treating over an exposed spinal cord (e.g., post-laminectomy). Methylmethacrylate and other materials used in joint replacements may absorb more sound energy and, therefore, even though the metal implant will not overheat, the cement can possibly weaken so that use of ultrasound directly over cemented joint replacements should also be avoided. Caution should also be exercised in use over malignant tumors unless the tumor is being specifically treated with a controlled dose.

With *microwave diathermy*, electromagnetic waves are converted into heat. Microwaves are reflected at the body surfaces and selectively absorbed in tissues with high water content, such as subcutaneous fat and bursae. Bone is not a good absorber. Microwave diathermy is not as effective as ultrasound in penetrating deeper joint tissues, although potentially it could be at other frequencies that are presently not allowed. Microwave is relatively easy to apply. Caution should be taken when used around the eyes, which should be protected because of the effects of microwaves on cataract production. Caution should also be observed when used around the testicles.

All deep-heat modalities should be used only upon proper prescription and indications, and applied only by trained personnel familiar with the use of the equipment, techniques, and precautions to be taken.

Cold

The physiological responses to cold stimulation are opposite from those of heat, however, the clinical effects are often the same. Both heat and cold can elevate the threshold of free nerve fibers, and cold therapy is therefore used for pain relief. Cold will reduce acute inflammation, slow local metabolism, decrease edema, and reduce spasms. Cold results in vasoconstriction and reduction in regional blood flow. Prolonged cold, however, can result in secondary vasodilatation — the Hunting reaction [9]. At times, prolonged cold can cause local tissue damage if this vasodilatation does not occur. Cold is usually applied by means of ice packs and vapocoolant sprays. There are patients with painful muscle spasms who do not respond to heat and will do better with cold and, again, vice versa. The use of cold is contraindicated in Raynaud's phenomenon, ischemia, vasculitis, and labile hypertension. Both heat and cold can have a counterirritant effect.

Massage

Massage is used to relax muscles, reduce pain, free bound down scar tissue, reduce swelling, and decrease hypersensitivity. There are several basic types of massage.

EFFLEURAGE (STROKING)

In this type of massage the hand is run lightly over the skin surface, with force going distally to proximally. This is usually quite relaxing. The pain threshold may be decreased with associated vasodilatation.

PETRESSAGE (COMPRESSION)

This is used to mobilize tissue fluids and to stretch adhesions. This type of massage consists of squeezing, kneading, and friction movements.

TAPOTMENT (PERCUSSION)

This consists of tapping, cupping, pounding, etc. in order to produce stimulation and is most commonly used in association with pulmonary postural drainage. Vigorous massage over sensitive areas may aggravate pain.

Massage should be done by trained personnel. Usually an oil, cream, or powder is applied over the body parts being massaged in order to prevent skin irritation. Massage is contraindicated over areas of damaged skin tissue, infection, malignancies, and thrombophlebitis. Massage does not result in weight loss and is not considered exercise, except for the therapist doing the massaging.

Hydrotherapy

Hydrotherapy is the use of water for therapeutic purposes. It can combine the effects of heat (cold) together with massage if used with an agitator (whirlpool). Aside from its use in muscle reeducation and strengthening utilizing the buoyant or weightless effect of water, hydrotherapy is also good for decreasing spasm, debriding wounds, improving range of motion, and relaxation. The tank should be kept clean, and there are health standards that must be met. If most of the patient's body surface is to be under water in a hot or cold tank, core body temperature may be raised or lowered accordingly, causing increasing stress on the cardiovascular and nervous system. The temperature of the water for total immersion should be less than 105°F (40.6°C) and is usually about 100°F. Caution should also be used in patients with multiple sclerosis, as elevation in body temperature can exacerbate this condition. The use of hydrotherapy can take up considerable aide or therapist time (and if a large Hubbard type tank is used, much water as well), thereby taking away time from other treatments, so that judgment is necessary in ordering this. Hydrotherapy

should be used under appropriate prescription and guidance.

Traction

The use of manual or mechanical force in order to stretch tissues and separate articular surfaces can be helpful in reducing pain and increasing mobility, although controlled studies have not definitely established its efficacy [10]. Traction can be applied continuously for short or long periods of time or intermittently. Cervical traction is usually given intermittently as part of a formal therapeutic regimen since greater forces can be tolerated for the shorter periods of traction time involved. Usually about 25–35 lbs is the maximum weight reached, although greater weights can be used. The position of the traction is important. The cervical interspace distances are increased and traction can cause opening of the intervertebral foramina, but this is most effective with the head in 15°–20° of flexion [11]. Pressure from cervical traction can aggravate sensitive occipital areas and can also cause temporomandibular joint pain. Lower weights are necessary if continuous traction is used. Patients can be taught home traction, but there should be good instruction by qualified people. Traction should not be used if pain is aggravated or if paresthesias, weakness, or spasticity is increased. Severe cervical spondylosis with upper motor neuron signs in the extremities (cervical myelopathy) is considered a contraindication for cervical traction, but at times traction may be used if carefully and professionally monitored. Traction should not be used if there are bone metastases. Manual traction is applied by the therapist for relatively short periods of time and is usually given in combination with gentle manipulation. This is most often done for management of an acute situation. Pelvic traction requires forces much larger than those used in cervical traction and requires special equipment and knowledge of proper application techniques, including positioning, which can reduce the force required. Pelvic traction is most commonly applied continuously while the patient is a hospital inpatient. Both cervical and pelvic continuous traction are mainly used to immobilize patients (preferably in a comfortable position), as the forces that can be tolerated for prolonged periods are not sufficient for significant distraction.

Traction relieves pain and muscle spasm, and is used in conjunction with other physical modalities such as heat, range of motion, etc.

Therapeutic Exercise

Exercise is used for specific goals. Patients with pain will benefit from therapeutic exercise if there is a rationale for the particular type of exercise used and it is carried out as part of the overall rehabilitation program by therapists aware of individual indications and contraindications. Later on the patient can be taught a home or self-program of exercises.

RANGE OF MOTION

This type of exercise is used to restore or maintain motion through a joint. When the patient is unable to move his or her own joint, passive range of motion carefully performed by the therapist is used to prevent contractures. This should be done with care, especially if the patient has decreased sensation, as tissue damage can occur, ultimately resulting in increased pain and further limitation of motion. With active assistive exercises (AAE), the therapist helps the patient to complete the range of motion. This is done to the point of pain and usually not forced beyond this. Active range of motion exercises are done by the patient, although initially under supervision. Effectiveness of range of motion exercises can be judged by increased mobility, with less pain for that range of joint motion and greater function and endurance. In general the

involved joints should be exercised through the functional range twice daily at least 3 times a session. Caution should be observed if there is inflammation or spasm, as pain can be aggravated. The involved joint is also usually treated before the exercise with some type of heat modality depending on the specific problem and location. The exercise regimen may progress from passive to an active program.

STRENGTH AND ENDURANCE

Patients who have been immobilized because of illness associated with pain often may be weak and have poor endurance. This can be localized, such as the stiffness of the knee and ankle after coming out of a long leg cast post-lower-extremity fracture, or more generalized following bedrest for prolonged periods. After or in conjunction with the restoration of the range of motion, the exercises are then tailored to improve muscle strength (high resistance with few repetitions) and endurance (less resistance with frequent repetitions). Newer techniques may utilize resistive therapy during joint range of motion at specific velocities, at times with the motion passively provided by the equipment. There is some transfer of training between strengthening and endurance exercises if fatigue is the end point, although in patients with pain, fatigue as an end point may not be initially feasible. The ultimate goal is that of increasing mobility, strength, endurance, and, ultimately, function, while decreasing pain for each level of achievement reached. A more detailed discussion and review of exercise physiology and therapeutic applications is provided by Kotke [12] and de Lateur [13].

Splinting and Orthotics

When used in patients with pain, orthotic devices are usually nondynamic (static) and the primary function is that of immobilization. These devices should not be used for prolonged periods of time and, therefore, in general, have relatively little use in the treatment of patients with chronic pain, as there can be further limitations of joint motion with secondary increased weakness, decreased endurance, and ultimately pain. Osteoporosis and sympathetic nervous system pain may compound the picture following prolonged immobilization.

The cervical collar protects the neck and reduces pain, but if worn continuously for long periods neck mobility is decreased. The muscles become weak and there is increased fatigability with more neck pain when the collar is not worn. The lumbosacral corset increases intra-abdominal pressure, thereby supporting back muscles and reducing back discomfort, but allows the abdominal muscles to become even more flabby so that pain can increase when not worn, making the patient dependent on the corset. By providing some immobilization of the spine, spinal orthotic devices may help reduce pain in metastatic disease or spinal fractures and often permit increased activity. Total immobilization of the spine is rarely feasible by orthotic devices. The rationale is, therefore, to gradually taper the use of the orthosis as the treatment progresses, working on range of motion, strengthening, and endurance for the specific muscle groups that the support was used to protect. Some orthotic devices can be utilized on a more regular basis to protect weak painful structures, as with shoe orthotics. Dynamic and corrective splinting can be used to improve joint range of motion in the extremities, helping to reduce pain within the limits of the functional range. At times this is combined with nerve blocks or surgical release procedures. Any orthotic device must be properly fitted in order to achieve proper function and avoid skin pressure changes. The device should not press over painful sensitive areas, as this can have a result opposite to that desired.

Electrical Stimulation and Biofeedback

There are a number of accepted uses for electrical stimulation for the treatment of patients with pain. *Transcutaneous electrical neurostimulation* (TENS) has become a major therapeutic tool. Electrical stimulation has been shown to selectively fatigue the A-delta and C fibers [14, 15], but this alone cannot account for the long-term lasting effects. Furthermore, TENS as used is not painful in itself. It is also not likely that the gate control theory, as originally described by Melzak and Wall [16], applies here, as it has been shown that selective large-fiber stimulation does not affect C fiber pain [17]. TENS, however, may result in the production of endorphins, with the analgesic effect blocked by administration of naloxone.

Iontophoresis [18] is occasionally used to anesthetize large areas of skin surface and is the process of transferring ions into the body by an electromotive force. Histamine, vasodilating drugs, and local anesthetics are positively charged and can be introduced into the skin at the anode. Iontophoresis can concentrate a relatively large amount of medication in local areas of the skin without penetrating deeper structures; however, ultimately ions transferred through the skin will be taken up by the circulation. The technique must be administered by trained personnel. It is difficult to quantify the dosage of the drug that will be taken up both locally and systemically, and allergic reactions can be severe.

NERVE AND MUSCLE STIMULATION

Faradic stimulation of motor nerves or galvanic stimulation of muscle can help to decrease muscle spasm, prevent atrophy, reduce pain, and aid in muscle reeducation. As with other modalities, these methods should be used with caution, as pain can be aggravated if there is active inflammation or if the muscles are particularly sensitive.

BIOFEEDBACK

This approach utilizes instrumentation whereby the patient is able to monitor his or her own body processes and responses. As used in patients with chronic pain, the patient often monitors specific muscle signals (EMG) and with the feedback tries to decrease muscle activity and spasm — promoting relaxation and analgesia. Biofeedback has probably been most effectively used in treating tension headaches and migraine. Other biologic systems can be monitored as well, such as galvanic skin response, sweating, and skin temperature. Patients must be highly motivated and a large number of sessions are often necessary with a trained therapist before the patient can do these procedures without the aid of a therapist. Biofeedback therapy is often used as part of a relaxation training program.

Injection Therapy

In rehabilitation medicine, trigger-point injections, nerve blocks, and local analgesic infiltration are often used as treatment modalities. These techniques have been described elsewhere in this volume [19]. As noted, injection therapy alone is usually not sufficient to abolish most chronic pain and should be part of a comprehensive treatment program. An in-depth presentation into the pathophysiology and treatment of myofascial pain syndromes with emphasis on trigger points is provided by Travell and Simons [20].

Illustrative Case Presentation

A representative case presentation may be of benefit as an example of the practical application and utilization of the techniques discussed. The patient is a 56-year-old male who developed the onset of low back pain following a business trip in which he had to carry heavy luggage. The pain began gradually as an ache in the mid-lower back and progressed to the

point where he was unable to function and remained in bed. He was seen by his local physician, who prescribed rest, a heating pad, and nonsteroidal antiinflammatory medications. There was some relief but the patient could not tolerate any activity and the pain began to radiate down the posterolateral aspect of the right lower extremity to the foot. There was some dragging of the left foot with prolonged walking. He was seen by a number of physicians and given other medication including Percodan and placed on a physical therapy program of heat, electrical stimulation, and exercises, which made him worse. He was then seen by a neurologist where testing confirmed the clinical impression of L5 radiculopathy with a herniated nucleus pulpolsus at L5–S1. The patient underwent laminectomy and foraminotomy on the right side. There was a good post-operative recovery but the pain gradually recurred, now in both buttocks. Rest helped decrease the pain, but the patient had intolerance for any activity, with prolonged sitting, standing, or walking aggravating the pain. He was again seen by many physicians over a course of 1 year and many modalities were tried for short periods, including chiropractic manipulation, acupuncture, various nonsteroidal antiinflammatory drugs, and Diazepam, none of which provided lasting benefit. Further diagnostic workup showed nonspecific changes, bulging at L4–5, and the patient then underwent a second laminectomy and fusion of L4–sacrum. There was no significant benefit following this second surgery and the patient had continued intolerance for any activities. The medications that he was on made him ill so that he voluntarily discontinued most of them. When finally seen in our program he had been unable to work for over 1 year. The patient was a mechanical engineer designing factory equipment, doing much standing, stair climbing, and driving, together with some lifting. He was depressed. The patient had been seen by a psychiatrist who reported no psychosis. He was worried about finances, as the insurance companies were now reviewing his case and threatening not to pay for any further medical care, and he was under considerable emotional tension and stress with his family at home. Physical examination was negative except for the neuromuscular system. The patient was overweight at 185 lbs, 5′9″. He walked with a stiff antalgic gait guarding with trunk tilted. There was decreased forward trunk flexion at 45° with hands two feet from the floor. There was discomfort present on trunk tilt and twist. Straight leg raising was possible to 50° bilaterally with tight hamstrings and some buttock pain on the side tested. There was good rotation of the hips. The patient was unable to fully place his knees onto his chest. Hip flexors were also tight, lacking approximately 15° to neutral. The patient was guarding on testing muscle strength, but this appeared to be grossly normal except for some questionable weakness of toe extensors on the right side. Deep tendon reflexes were symmetrical, plantar responses were downward, and sensation was normal. The patient was consistent in his responses to examination in that there was evidence of tight hamstrings when testing with routine straight-leg raising, patient supine, as well as when testing quadriceps strength with the patient sitting. The patient was not tender over the old surgical scar areas, but was tender over the lumbosacral and gluteal areas bilaterally, with many specific point areas of hypersensitivity.

At this time one must review the diagnosis and course before a rationale plan for therapy can be made. On review, although the first operation did appear to be indicated, the second surgery may not have been necessary and may have further contributed to the patient's pain syndrome. Any further diagnostic testing would be to rule out a condition that requires more immediate medical or surgical intervention and permit a safe plan of

therapy. It is not the purpose here to definitively review all tests that can be done, but CBC; ESR; HLA B27; x-rays of the spine, hips, and pelvis; CT scan; and MRI have probably already been done and can be reviewed and either repeated or ordered if indicated. Myelography, of course, should also be reviewed, although repeat myelogram would probably not be done unless one is considering surgery. Bone scan, EMG, and nerve conduction studies should also be reviewed or considered as appropriate. For purposes of discussion here, laboratory tests were noncontributory.

At this time, bed rest alone is not likely to be effective. This decreases the patient's pain, but the pain comes on again with activity, and by now it is obvious that additional therapy is necessary in order to get the patient mobilized and functional. He will be advised to limit activities and not provoke pain production, but the ultimate aim will be to increase activities as tolerated. It is best to place the patient on one analgesic antiinflammatory medication on a regular basis rather than PRN. A nonsteroidal antiinflammatory drug is a good choice if there are no medical contraindications. A drug that the patient has not been on before can be tried or, if he has been on all of them, the one that has been most effecive should be considered. It can be pointed out to the patient that, although he did not respond in the past, his condition may now have changed so that he will be more responsive to this medication. The patient should not be on narcotic medications. If there is significant muscle spasm and guarding then a nontranquilizing muscle relaxant can also be used. Tricyclic antidepressant medication may be of benefit in low doses, e.g., amitriptyline 25–50 mg given h.s. This may not only help the patient to sleep but have an effect on decreasing pain. The patient should be placed on a weight-reduction program. A physical therapy regimen should be ordered tailored to the patient's specific needs — in this situation the reduction of pain, improving mechanical body limitations, and then increasing endurance and function. The prescribing physician should discuss the detailed program with the therapist including goals and contraindications. Just as a competent physician would not think of ordering "heart medicine," so a physician should not order "physical therapy," and if the physician is not sure as to the specific prescription required or how to prescribe the therapy, a consultation is in order, as physical therapy is best ordered by a physician who is aware of the medical situation, indications, contraindications, and complications of therapy. This is most commonly a physiatrist. There are a number of prescriptions that might be considered appropriate for this patient. If inpatient admission is felt not to be necessary, then one might start with an outpatient physical therapy program 3 times a week for 3–4 weeks, with the program then reviewed. This would consist of moist heat to the lumbosacral and gluteal areas, and massage, and deep heat — such as ultrasound — could also be part of the therapeutic program, with wattage and duration specified and possibly combined with electrical stimulation. The mechanical aspects of a patient's limitations can be treated with a gentle progressive exercise regimen emphasizing pelvic tilt, lumbar flexion (extensor stretching), hamstring stretching, hip flexor stretching, and, later, abdominal strengthening. At the same time, a home program can also be taught to the patient. The program should be tapered or discontinued if pain is aggravated and if this lasts for a prolonged period of time. There are many different ways to perform the same basic exercises such as hamstring stretching (thus the large number of books written about back pain management), but most are variations on a theme. There may be indications for back extension exercises, but for the time being — as hyperextension aggravates this patient's pain — this will not be ordered. The exercises should be gradually increased in frequency

and, for most of them, the pelvis should be stabilized (usually with one or both knees bent). Exact techniques will not be discussed here. As the pain decreases, the patient is allowed to increase his activities as tolerated. He should increase walking distance and rate but jogging should be avoided. He can begin swimming (caution: crawl and hyperextension of the back may aggravate pain). A lumbosacral corset might be tried, but, as noted, this should be discontinued as pain lessens. If there is a large component of stress and tension, then biofeedback and relaxation training can be ordered. If there is no significant relief or if the patient is progressing too slowly and the tender spots are more localized, then trigger-point injections can be added to the regimen. (Some would begin injecting trigger points even at the start of the program.) The use of TENS would also be considered as an adjunct for the management of this patient, again decreasing use as pain improves. The attitude of the treating physician and the therapist is important — providing encouragement; advice; realistic expectations; not dwelling on the patient's complaints, but not disregarding them either; and encouraging success. The physician and therapist must provide emotional support and counseling. The patient should gradually become the therapist himself, doing more and more of a home program. The formal program should be of long enough duration to provide a reasonable chance for success but not so long that it continues after it is obvious that treatment is not effective and time is being wasted or that the patient becomes overly dependent upon the therapist. The program should be tapered or discontinued if pain is aggravated and the treatment should then be reviewed. Some pain may be necessary in treating chronic long-term patients in order for them to improve their mobility and function, and while pain may stay the same, this can be acceptable if function and mobility improve. Hopefully, with time, for that same degree of activity the pain will diminish. If all is to no avail, then one must consider other techniques of therapy mentioned in this volume including a pain clinic, epidural and intrathecal medication, more in-depth psychiatric involvement, and the neurosurgical approach, but it should be kept in mind that the mechanical back limitations will still have to be treated if the patient is to return to a reasonable level of function.

In summary, the role of physical medicine and rehabilitation in the management of chronic benign pain has been presented. Various physical modalities have been described and a clinical example presented to illustrate some of the applications. Often, however, when dealing with patients with chronic pain, many specialties are involved, and although there is some overlap, a combined approach is most effective. Hopefully this will be grasped by the reader of this volume.

References

1. Kotke FJ, Stillwell GK, Lehmann JF: Krusen's Handbook of Physical Medicine and Rehabilitation, 3rd ed. WB Saunders Philadelphia, 1982.
2. Lehmann JF: Therapeutic Heat and Cold, 3rd ed. Williams and Wilkins, Baltimore, 1982.
3. Rogoff JB: Manipulation, Traction and Massage, 2nd ed. Williams and Wilkins, Baltimore, 1980.
4. Basmajian JV: Therapeutic Exercise, 3rd ed. Williams and Wilkins, Baltimore, 1978.
5. Redford JB: Orthotics Etcetera, 2nd ed. Williams and Wilkins, Baltimore, 1980.
6. Lehman JF, de Lateur BJ: Diathermy and superficial heat and cold therapy, In: Handbook of Physical Medicine and Rehabilitation, 3rd ed., WB Saunders, Philadelphia, 1982, 275 pp.
7. Lehman JF: The biophysical basis of biologic ultrasonic reactions with special reference to ultrasonic therapy. Arch Phys Med Rehabil 34:139–152, 1953.
8. Lehman JF, Love CE, Bell JW, Brunner GD: Influence of surgical metal implants on the distribution of the intensity of the ultrasonic field. Arch Phys Med Rehabil 39:756–760, 1958.

9. Clarke RSJ, Hellon RF, Lind AR: Vascular reactions of the human forearm to cold. Clin Sci 17:165–179, 1958.
10. Hinterbuchner, C. Traction, In: Manipulation, Traction and Massage, 2nd edition, Rogoff JB, ed. Williams and Wilkins, Baltimore, 1980, pp 184–216.
11. Colachis SC Jr, Strohm BR: A study of tractive forces and angle of pull on vertebral interspaces in the cervical spine. Arch Phys Med Rehabil 46:820–830, 1965.
12. Kotke FJ: Therapeutic exercise to maintain mobility, In: Handbook of Physical Medicine and Rehabilitation, 3rd ed. Saunders, Philadelphia, 1982, pp 389–402.
13. de Lateur BJ: Therapeutic exercise to develop strength and endurance, In: Handbook of Physical Medicine and Rehabilitation, 3rd ed. Saunders, Philadelphia, 1982, pp 427–464.
14. Campbell JN Taub A: Local analgesia from percutaneous electrical stimulation. Arch Neurol 28:347–350, 1973.
15. Torebjork HE, Hallin RG: Responses in human A and C fibers to repeated electrical introdermal stimulation. J Neurol Neurosurg Psychiat 37:653–664, 1974.
16. Melzack R, Wall PD: Pain mechanism: A new theory. Science 150:971–979, 1965.
17. Nathan PW, Rudge P: Testing the gate-control theory of pain in man. J Neurol Neurosurg Psychiat 37:1366–1372, 1974.
18. Stillwell GK: Electrotherapy, In: Handbook of Physical Medicine and Rehabilitation, 3rd ed. Saunders, Philadelphia, 1982, pp 369–370.
19. Rosner H: Anesthiologic Management of chronic benign pain, In: Neurosurgical and Medical Management of Pain, Brisman, R, ed. Kluwer Academic Publishers, Boston, 1989.
20. Travell JG, Simons DG: Myofascial Pain and Dysfunction: The Trigger Point Manual, Williams and Wilkins, Baltimore, 1983.

15. NEUROSURGICAL ASPECTS OF CHRONIC PAIN

Ronald Brisman, M.D.

Most patients with chronic pain do not need neurosurgical pain-relieving procedures. Most of these patients do not require any surgery. A few will benefit from direct surgical decompression of nerve roots, and some can be helped by neurosurgical pain-relieving operations.

The first approach to the patient with chronic pain requires a careful history, physical examination, and appropriate laboratory and imaging tests. Patients with chronic pain sometimes develop new illnesses that may require acute or subacute intervention. The patient who had several unsuccessful operations for a left fifth lumbar radiculopathy may develop a real herniated disc at a new level or on the other side that may be relieved by direct surgical decompression. Previously unrecognized bony compression by stenosis or spondylosis may be improved by surgical decompression. Spinal instability, which may develop after previous back surgeries, may require fusion. Disc-space infection requires immobilization and antibiotics.

When direct medical and surgical treatments are ineffective or inappropriate and the patient has much pain, other medical disciplines such as physical medicine, anesthesiology, and psychiatry are consulted; behavioral modification may also be attempted. Patients who persist with intractable, agonizing, chronic (at least 6 months) pain, who have an organic cause for their pain, and have a consistent pattern of pain usually in one location, may be considered possible candidates for neurosurgical pain-relieving surgery.

These patients should realize that the neurosurgical procedure is unlikely to cure them totally of their pain, and that it is unlikely to cause them to alter pain behavior; rarely these benefits do result from the procedure and sometimes they occur independent of it. In approximately half the patients, no benefit results at all from the neurosurgical intervention. The other half do feel that they are subjectively improved, although the improvement is usually 25%–75%.

Implanted spinal cord stimulation is the most important neurosurgical procedure for most patients with chronic intractable noncancer pain because of its safety and broad applicability. It is helpful in providing some pain relief in approximately half of those patients who are otherwise resistant to other forms of treatment.

For those who are not helped by spinal stimulation and who continue with agonizing pain, I used to offer deep-brain stimulation (between 1980 and 1984), but since then have cautiously suggested intraspinal morphine if they had a positive response to a subarachnoid injection of morphine. The development of CT-guided stereotaxic procedures and futher reports of long-term effectiveness of deep-brain stimulation have encouraged me to continue to offer this for selected patients.

Multiple rhizotomies may be offered to those with high cervical or thoracic pain

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where section of three or more dorsal roots does not cause any disability. Causalgic pain is treated by sympathectomy. Dorsal root entry zone lesions may be made in patients with nerve root avulsion injuries, herpes zoster neuralgia, or paraplegic pain.

Neurosurgical results can be improved by selecting the most appropriate procedure for a particular problem. Sometimes more than one kind of procedure is necessary.

16. SPINAL CORD STIMULATION FOR RELIEF OF CHRONIC PAIN

Ronald Brisman, M.D.

Introduction

Spinal cord stimulation was used in the early 1970s for treatment of chronic pain [1–3]. The procedure was done under general anesthesia, and a laminectomy was performed. The electrodes were placed in either the epidural, endodural, or subdural spaces. Initial reports were enthusiastic, but as longer followups became available, it became apparent that many patients were not helped by the procedure [4, 5]. There were many technical problems, and complications developed that sometimes were serious [3].

In the mid 1970s, a percutaneous technique was developed that eliminated the need for general anesthesia and allowed for neurophysiologic testing in an awake patient [6]. This increased the chance for proper placement of the electrodes so that electrical stimulation could be felt in the area of pain, a situation more likely to result in pain relief. A trial period could be established without internalizing the receiver, because the wires connected to the leads could be externalized. Only those patients who benefited from trial stimulation would then have the receiver internalized.

I started using spinal cord stimulation for treatment of intractable noncancer pain in 1980. Initially I used a percutaneous technique but later modified the approach so that the lead was introduced via a small hemilaminectomy that was performed under local anesthesia; the receiver was inserted during the same procedure. Better results with fewer complications have resulted.

Clinical Material (Table 16-1)

Between 1980 and 1987, 58 patients with chronic pain were treated with spinal cord stimulation. In two of these, leads that had been inserted at other institutions but were still working were attached to new receivers. Leads were inserted percutaneously in 24 patients between April 1980 and July 1983 and were placed during a partial hemilaminectomy in 32 patients between September 1983 and October 1986; followup of at least 6 months was available on 31 of these patients who were considered evaluable. These two groups of patients (percutaneous and laminectomy) have been compared as to age of patients, duration of preoperative symptoms, number of prestimulation procedures, cause of pain, and location of pain. No significant differences could be detected between the two groups (Table 16-1). Only one patient had cancer pain. Discogenic disease that had not responded to conventional back surgeries (failed back) was the most common cause of pain (Tables 16-2).

Medtronic equipment was used in all patients except two who had Neuromed receivers and leads. Bipolar stimulation was used in most patients. Since February 1985, the totally implanted Itrel device has been im-

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TABLE 16-1. Patient characteristics

	Percutaneous	Laminectomy
Total evaluable	24	31
Age average (range)	51.6 (24–82)	46 (29–72)
Female (percent)	58	55
Months of pain (average)*	117	105
Prestimulator ORs (average)	2.6	2.5

* Prior to first spine stimulator placed by this author.

planted in all patients, usually with a quad lead.

Operative Technique

PERCUTANEOUS

Local anesthesia (0.5% xylocaine and epinephrine) and intravenous analgesia and sedation are used. After position is identified with fluoroscopy, an incision is made a few segments below the desired level of stimulation. For patients with back and leg pain, the incision is usually betwen T12 and L1, and the final position of the electrodes is between T10 and T11. The midline incision is carried down to the deep fascia, and a Tuohy needle is inserted into the epidural space. The epidural space may be identified by placing sterile solution in the needle and observing it disappear as the epidural space is entered.

A lead blank is inserted through the Tuohy needle, and after it threads properly into the epidural space, it is removed and the lead is manipulated into place. Stimulation is carried out, and the response of the awake patient is recorded. The quad lead is recommended because it contains four different electrodes, each a centimeter apart. Various bipolar configurations are tried until the patient feels stimulation in the area of pain. Placement as close to the midline as possible is attempted.

TABLE 16-2. Cause of pain

	Percutaneous	Laminectomy
Failed back	15 (62.5%)	19 (61%)
Other		
Sympathetic dystrophy	1	2
Cancer (thoracic pain)	0	1
Herpes zoster	0	1
Paraplegia, traumatic	1	0
Amputation	1	0
Neuropathy	3	2
Osteochondroma, scapula	0	1
Urolithiasis, chronic	0	1
Vertebral fracture	0	1
Uncertain		
Thoracic radiculopathy	1	0
Perineal pain	1	0
Groin pain	1	0
Lumbar radiculopathy	0	2
Lumbar pain	0	1

When proper placement is completed, the lead is secured to the deep fascia with an anchoring device. The stylet is removed from the lead, and the lead is connected to a percutaneous extension that is brought out through the skin, several centimeters away from the original incision. The exiting extension is fixed to the skin with tape, and a sterile dressing is applied.

During the next several days, the system is tested at the patient's bedside. If pain relief is obtained, the patient is returned to the operating room for internalization of the stimulator. Another incision is made either over the abdomen (which is usually preferred) or on the patient's side where the receiver is inserted. The percutaneous extension is removed, and the lead is connected to the receiver extension, which is tunneled subcutaneously.

The receiver may be unipolar or bipolar. A multiprogrammable receiver may allow the patient to change combinations and polarity of electrodes. An antenna is taped to the skin and connected to a small battery-powered box that controls the rate, pulse width, and amplitude of the stimulation. Some units also have a time cycle that can be automatically set.

A totally internalized stimulator (Itrel) does not require the patient to wear any device on the skin. The system is easily programmed by holding an external unit near the receiver. Once it is programmed, the receiver is turned on or off when a small magnet is held near it for two seconds. The battery is inside the receiver and must be changed approximately every 2 years, or more frequently if high-amplitude stimulation is carried out for many hours each day. Changing the receiver is a minor surgical procedure that requires opening only the incision over the receiver.

LAMINECTOMY

Under local anesthesia, a partial hemilaminectomy is done, usually at T12-L1, or a few segments below where the lead is to be. Once the epidural space is encountered, the lead is inserted rostrally to the desired location. Occasionally, in order to avoid previously operated areas, the incision must be placed higher than the desired place of stimulation. The lead can then be easily inserted caudally to its final destination. The lead can be brought percutaneously for later testing, or may be internalized at the same sitting after initial testing confirms proper placement.

Results (Tables 16-3 and 16-4)

Patients who continued to use the stimulator for 6 months or more and found that it reduced their pain by at least 25% were considered good results. Good results occurred in 16.6% of the total percutaneous group, 30.7% of the internalized percutaneous group, and 48% of the laminectomy group; there was no significant difference between the Itrel and non-Itrel laminectomy groups. Very good results (pain relief greater than 50%) occurred in 6 of 31 (19%) of the laminectomy patients. The results were not influenced by the type of pains; similar results were obtained whether or not the pain was from "failed back," other known causes, or uncertain cause (Table 16-3). In the laminectomy group, men were more likely than women to have a good result (Table 16-4 $p < .001$).

TABLE 16-3. Results according to cause of pain

Cause of pain	Percutaneous		Laminectomy	
	Good	Fail	Good	Fail
Failed back	2	13	8	11
Other	2	4	4	5
Uncertain	0	3	3	0

TABLE 16-4. Factors associated with good result from spinal stimulation

	Good/Total		p
Laminectomy vs. (percutaneous) group	15/31	(4/24)	$<.05$
Male vs. (female) laminectomy group	12/14	(3/17)	$<.001$
Male vs. (female) total group	13/24	(6/31)	$<.01$

* Probability was determined by the chi-square test with Yates' correction.

Revisions (Table 16-5)

Excluding removal or internalization (in the percutaneous group), revisions were required in 25% of the internalized percutaneous group and 19% of the laminectomy group; some of these patients had more than one revision.

Complications

One patient in the percutaneous group developed an epidural bacterial infection on the fifth

TABLE 16-5. Revisions

	Percutaneous	Laminectomy	
		No Itrel	Itrel
Patients evaluable	24	17	14
Remove[1]	12	3	2
Revise lead (patients)	2 (2)	0	3 (3)[2]
connector (patients)		1 (1)	2 (2)[2]
receiver (patients)	1 (1)	2 (2)	1 (1)[2]

[1] Remove at a separate operation.
[2] These six revisions were done on a total of three patients.

day of percutaneous testing. The entire device was removed, antibiotics given, and the patient made a full recovery without residual deficit. There were no other complications.

Discussion

PATIENT SELECTION

Patients with chronic intractable organic pain are possible candidates for spinal cord stimulation. Spinal stimulation has been shown to relieve many different kinds of pain. These include epidural arachnoiditis [7], peripheral nerve lesions [7], myelopathy [7], amputation [8], peripheral vascular ischemia [9], causalgia [10], and angina pectoris [11]. Cancer pain [3, 7, 12], post-traumatic paraplegia [3, 7], and herpetic neuralgia [3, 12] respond less well than other forms of pain, but these opinions are based on few observations.

Pain should be focal rather than diffuse. An organic cause should be present, although persistent focal pains without a clearly determined etiology may also benefit from spinal stimulation (Table 16-3).

Some reports suggest that functional pain assessment is useful as a part of preimplantation screening and emphasize the importance of psychological factors in the outcome of implanted spinal cord stimulation treatment for chronic pain [13, 14]. Other investigators find that rigid selection criteria, such as detoxification prior to surgery and exclusion of anyone with obvious emotional disturbances or secondary gain, make no difference in the final outcome [5]. I do not offer spinal stimulation to patients with the kind of florid psychosis that is easily detected by a nonpsychiatric physician during a routine history and physical examination but find formal psychological tesing of no value in selecting patients who are more likley to benefit from such surgery.

SURGICAL TECHNIQUE

There were two main problems with the original technique of inserting spinal-cord stimulating devices through a laminectomy with the patient under general anesthesia. First, the placement was not always proper, and this could not be detected until after the surgery, when the awake patient could be tested; optimal stimulation-induced analgesia requires that the patient feel the stimulation in the area of pain. Second, major injury to the spinal cord sometimes occurred; the devices were relatively large and caused a mass lesion with spinal cord compression, and because of the general anesthesia it was not possible to detect compromise of the spinal cord until after the surgery [3].

The percutaneous placement had the advantage of being done under local anesthesia with an awake, cooperating patient on whom stimulation could be done to improve the accuracy of electrode placement; the catheter-type electrodes were safer because they exerted less

TABLE 16-6. Results of spinal stimulation

		Laminectomy	
	Percutaneous	No Itrel	Itel
Patients treated	24	18	14
Receiver implanted	13	18	14
Patients evaluable[1]	24	17	14
Good Results (%)			
25%–50% improved	3 (12.5)	4 (23.5)	5 (35.7)
>50% improved	1 (4.3)	4 (23.5)	2 (14.3)
Total	4 (16.5)	8 (47)	7 (50)
Followup (mos)[2]			
Average	44.7	23	11.9
Range	18–78	7–41	6.0–24

[1] One patient with implanted receiver was lost to followup after discharge from the hospital.
[2] Patients with good results.

of a mass effect on the spinal cord and any possible compression could be detected immediately. In addition, the patient could be tested for several days to see whether or not the stimulation was effective before the receiver was internalized.

However, there were disadvantages with the percutaneous procedure. The patient was committed to a minimum of two operations: one to insert the electrodes and a second to either remove them or internalize the receiver. Initial placement was not always easy or even possible, and maneuvering the electrode to the exact location desired was often difficult. Sometimes, inadvertent subarachnoid placement occurred, which further complicated the operation. The percutaneous extension of the lead wires through the skin for several days added to the risk of infection. The longer period of several weeks required by some patients for trial stimulation further increased the risk of infection or displacement of the leads.

Placing the leads under local anesthesia via a partial hemilaminectomy has the advantages of facilitating lead manipulation and making it more likely that the electrodes will be positioned in the proper place. Internalization at the same operation lessens the risk of infection and gives the patient a longer period to use the stimulator in the environment of his home or work after the discomfort of the procedure has disappeared. Although it may seem that because of the laminectomy the procedure takes longer, this is often not the case, because once the epidural space is encountered, placement of the electrode is usually quickly accomplished. Results with this technique have been better than with the percutaneous method (Table 16-6).

The totally implantable device (Itrel) is preferred by most patients, who usually do not like to apply the antenna to the skin and to walk around with a stimulating box. Occasionally a patient will prefer the added flexibility of changing electrodes that is provided by a multiprogrammable device, such as the SE4, even though an antenna and an external stimulator are necessary. A few who stimulate at high amplitudes for prolonged periods may not like to have frequent replacements of an internalized transmitter and may choose to have an external one.

Results Including Method for Evaluation

The apparent results of spinal cord stimulation are influenced by the definition of a good response, duration of followup, the method of

TABLE 16-7. Results of spinal stimulation

	Patients		Immediate		Longer Followup		
	(Lam)[4] No.	Perc No.	Pts %	Relief %	Pts %	Relief %	mos
Young [4]	37	11	47%	100%	8%	100%	36
Long/Erickson [2]	69				33.3%	100%	5–28
					16%	50–75%	5–28
Erickson/Long [5]	70				3%	100%	> 84
Lazorthes/Verdie [7]	17	76			66%[3]	>50%[1]	12–120
Sweet/Wepsic [3]	68				25%	Success[2]	> 6
Urban/Nashold [6]		20			10%	25%–49%	5–24
					20%	75%–99%	5–24

[1] Equal to or greater than 50%.
[2] Relief that permits patient to maintain full productivity without narcotics.
[3] Since only 36% of percutaneously tested patients were internalized, 24% of the total group (rather than 66%) were good results.
[4] All laminectomies (except for some reported by Sweet/Wepsic, where patients were awakened in the middle of the operation for testing) were done under general anesthesia.

calculating percentage of good responders, and the types of pain treated.

If a good result is defined as total relief of pain, then the results will appear worse than if patients with partial relief are included (Table 16-7). If in addition to relief of pain one requires a favorable alteration of life style, such as discontinuation of narcotics and return to work, as necessary before considering a result good, then the results will appear worse (15%) than if only subjective relief of pain is considered (50%) [5].

Patients followed for a long period are less likely to report a good response to stimulation than those followed for a shorter time [4, 5]. Sometimes the loss of stimulation effectiveness after a longer followup occurs because of technical failures, although these can usually be corrected surgically. Occasionally a patient improves to the point where he or she no longer finds the stimulator necessary; this does not necessarily imply that the stimulator failed. Some patients can use the stimulator for years and continue to obtain stimulation-induced analgesia.

The method of calculating the percentage of good responders will also affect the apparent results. This is especially the case with the percutaneous technique. If all patients tested percutaneously are considered to be the total group, and therefore at risk for possible stimulator failure, the percentage of good responders will be much less than if only those selected for internalization because they respond well to the percutaneous trial are designated as the total group.

Because certain types of patients, such as those with "failed back," respond better to spinal stimulation than those with cancer or profound denervation, the relative numbers of these different categories will influence the total results in any series.

Summary and Conclusions

Spinal-cord epidural stimulation is the neurosurgical procedure of choice for most patients with chronic non-cancer pain that remains intractable and agonizing in spite of conservative forms of treatment.

A technique in which the leads are inserted via a partial hemilaminectomy in an awake and cooperating patient and internalized during the same procedure, usually with a totally

implantable unit, provides better results than a percutaneous two-staged procedure.

In 31 patients who underwent laminectomy and internalization at the same operation, 50% reported stimulation-induced analgesia of at least 25% that persisted during an average followup of 11.9 months. There were nine revisions but no other complications.

References

1. Shealy CN, Mortimer JT, Hagfors NR: Dorsal column electroanalgesia. J Neurosurg 32: 560–564, 1970.
2. Long DM, Erickson DE: Stimulation of the posterior columns of the spinal cord for relief of intractable pain. Surg Neurol 4:134–141, 1975.
3. Sweet WH, Wepsic JG: Stimulation of the posterior columns of the spinal cord for pain control: Indications, technique, and results. Clinical Neuro 21:278–310, 1974.
4. Young RF: Evaluation of dorsal column stimulation in the treatment of chronic pain. Neurosurgery 3:373–79, 1978.
5. Erickson DL, Long DM: Ten-year follow-up of dorsal column stimulation. In: Advances in Pain Research and Therapy, Vol 5, Bonica J, et al., eds. Raven Press, New York, 1983, pp 583–589.
6. Urban BJ, Nashold BS Jr: Percutaneous epidural stimulation of the spinal cord for relief of pain. Long-term results. J Neurosurg 48:323–328, 1978.
7. Lazorthes Y, Verdie J: Technical evolution and long-term results of chronic spinal cord stimulation. In: Neurostimulation: An Overview. Lazorthes Y, Upton ARM, eds. Futura Publishing, Mt. Kisco, New York, 1985, pp 67–86.
8. Krainick J, Thoden U, Riechert T: Pain reduction in amputees by long-term spinal cord stimulation. Long-term follow-up study over 5 years. J Neurosurg 52:346–350, 1980.
9. Groth KE: Spinal cord stimulation for the treatment of peripheral vascular disease. In: Advances in Pain Research and Therapy, Vol 9, Fields HL, et al., eds. Raven Press, New York, 1985, pp 861–869.
10. Broseta J, Roldan P, Gonzalez-Darder J, Bordes V, Barcia-Salorio JL: Chronic epidural dorsal column stimulation in the treatment of causalgic pain. Appl Neurophysiol 45:190–194, 1982.
11. Murphy DF, Giles KE: Clinical note. Dorsal column stimulation for pain relief from intractable angina pectoris. Pain 28:365–368, 1987.
12. Vogel HP, Heppner B, Humbs N, Schramm J, Wagner C: Long-term effects of spinal cord stimulation in chronic pain syndromes J Neurol 233, 16–18, 1986.
13. Daniel MS, Long C, Hutcherson WL, Hunter S: Psychological factors and outcome of electrode implantation for chronic pain. Neurosurgery 17:773–777, 1985.
14. Nielson KD, Adams JE, Hosobuchi Y: Experience with dorsal column stimulation for relief of chronic intractable pain: 1968–1973. Surg Neurol 4:148–152, 1975.

17. INTRASPINAL MORPHINE FOR TREATMENT OF CHRONIC NONCANCER PAIN

Ronald Brisman, M.D.
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Intraspinal morphine may provide analgesia by binding to opiate receptors in the dorsal horn of the spinal cord [1]. The intraspinal administration of morphine, either epidural or intrathecal, provides a very high concentration of morphine to the spinal cord. When the catheter is placed near that part of the spinal cord that mediates pain for a particular part of the body, a much higher level of morphine can be delivered to that part of the spinal cord than to other parts of the nervous system [2].

An implanted pump (Infusaid Model 400, Shiley Infusaid, Inc., Norwood, Massachusetts) continuously infuses a small dose of morphine [3]. The pump is filled percutaneously at 2-week intervals and provides a convenient method outside the hospital for long-term management of patients.

Intraspinal morphine has been most effective in cancer patients [4–11], and initial reports of patients with chronic noncancer pain have been disappointing [4, 12]. In those reports of chronic noncancer pain, there were only a few patients, and epidural rather than subarachnoid morphine was given. More recent data suggest that patients with chronic intractable noncancer pain may benefit from continuous infusion of morphine, and the subarachnoid route is preferable [10].

Our experience with continuous subarachnoid morphine via the Infusaid pump in patients with chronic noncancer pain has been moderately encouraging, especially in three patients with reflex sympathetic dystrophy, one patient with flexor spasms, and one patient with discogenic disease.

Clinical Material

Between 1984 and 1987, we have implanted subarachnoid silastic catheters connected to Infusaid pumps for continuous administration of intraspinal morphine in 13 patients, 9 of whom had chronic intractable noncancer pain (Table 17-1).

Spinal stimulators had been implanted in three patients and had not provided significant pain relief (Table 17-1); one of these patients had then been treated with a deep-brain stimulator, also without benefit.

All patients were tested with a lumbar subarachnoid injection of 1 mg to 1.5 mg morphine (in preservative-free solution) and had obtained some temporary analgesia prior to insertion of the Infusaid pump. One additional patient with post-herpes-zoster-induced thoracic radiculopathy did not show any improvement with the subarachnoid injection and so did not have a permanent system established.

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TABLE 17-1. Results of continuous morphine infusion

Age	Sex	Cause of pain	Location	Mos	Followup relief[1]	Daily max	MS mg final
32	F	Degenerative[2]	Back (lumbar)	35	Excellent	7.5	.05
33	F	Trauma (RSD)[3]	L leg	13	Moderate	10.0	10.0
34	F	Trauma (RSD)	R leg	24	Moderate	5	2
38[4]	M	Discogenic	Back, R leg	18	Mild	7.5	5.0
31[4]	F	Neurofibroma (RSD)	Feet	14	Mild	9.0	9.0
57	F	Failed back	Back, legs L > R	12	Minimal	25.0	25.0
70[5]	M	Traumatic paraplegia	Back, hips	30	Minimal	2.5	0
60[6]	F	Failed back	Perineum	32	None	10.0	0

[1] Excellent relief is > 90% pain relief; moderate relief is 25%–50%; mild relief is 15%–25%; minimal relief is < 15%.
[2] Spinocerebellar degenerative myelopathy, paraparesis, and flexor spasms
[3] RSD = Reflex sympathetic dystrophy.
[4] Previous spinal stimulator.
[5] Morphine stopped because of toxicity (coma, pinpoint pupils, hypercapnia).
[6] Previous deep brain (thalamic) stimulator.

The catheter was inserted via a small laminectomy at T10 and directed downward so that the tip was at T12-L1. The procedure was done under general anesthesia.

RESULTS (Table 17-1)

Eight patients continued to use the Infusaid pump for more than 6 months. Five of these had definite improvement on nonescalating (or slightly increasing) doses of morphine. Mild improvement (15%–25%) was noted in two patients, and two others had moderate improvement (25%–50%). Three of these patients who showed some improvement had reflex sympathetic dystrophy involving a lower extremity.

An excellent effect was noted in one patient with spinocerebellar degeneration, pain, and flexor spasms in whom severe spasms and intractable pain were totally relieved for the duration of followup, which is now 35 months. Efforts to decrease gradually the dose of morphine revealed that the pain and spasms could be abolished by a very small dose of intraspinal morphine (0.05 mg per 24 hours). Several attempts to reduce the dose below this were unsuccessful, even when clonidine was given orally to block symptoms of narcotic withdrawal.

COMPLICATIONS

One patient developed a hematoma in the subcutaneous abdominal pocket where the pump was placed. Fluid leaked out of an incision, and infection (meningitis) developed several days following the initial surgery. The entire apparatus was removed, antibiotics were given, and the patient made a full recovery without sequelae.

Two other patients developed spinal fluid collections around the pump. These were drained percutaneously and disappeared after a few weeks.

One patient, a traumatic paraplegic, developed unresponsiveness, pinpoint pupils, and hypercapnia 3 years after subarachnoid morphine had begun. Throughout this time, he had remained on 2.5 mg morphine per 24 hours. The morphine toxicity was reversed with naloxone, but returned when the morphine was resumed. The intraspinal morphine had to be discontinued, and the possibility of resuming it at a smaller dose was being considered.

Discussion

SURGICAL TECHNIQUE

The subarachnoid catheter can be inserted via a Tuohy needle, thus eliminating the need for a laminectomy. However, the catheter may subsequently pull out of the subarachnoid space [8]. If there is much pathology in the lumbar subarachnoid space, it may be difficult to position a catheter percutaneously.

I place the catheter directly inside the dura after doing a small laminectomy. A nonabsorbable, purse-string suture in the dura is used to secure the catheter in the subarachnoid space. Two additional sutures, one at each end of the dural opening, are tied to minimize any opening around the catheter; this is done to lessen the chance of a spinal fluid collection tracking around the catheter. A thickened bead of the silastic catheter that is a couple of centimeters from the tip is inserted under the dura prior to tightening the sutures. This prevents the catheter from pulling out. Direct placement through the dura in the lower thoracic area avoids pathology, which is frequently present in the lumbar spine. Individualization of the exact location of catheter placement is appropriate, and placement should depend upon the location of the patient's pain and spinal pathology.

I have usually reserved the use of intraspinal morphine for patients with pain in the lower half of the body in order to allow for the highest concentration of morphine to be placed near the spinal cord segment subserving the pain and far away from the high cervical and medullary levels of the brain stem. It was hoped that this would minimize the chance of respiratory failure and other unpleasant consequences of morphine, such as nausea or mental impairment.

TECHNIQUE OF FILLING THE PUMP

The patient is positioned supine, thus placing the pump in a horizontal position. Under sterile conditions, the center of the pump is punctured with a Huber needle. This kind of needle is less likely to damage the soft septum. A plastic template placed over the pump helps identify the small central opening that is to be punctured, although the template is not always necessary.

The new fluid must be injected into the pump and not the subcutaneous tissues, because the subcutaneous injection of large doses of morphine can cause respiratory arrest. Prior to refilling the pump, one should be certain that there is return of the remaining fluid in the pump into the syringe from which the barrel has been removed. If the pump is empty, a small volume of sterile water or saline should be injected, and return of the fluid back into the syringe will confirm that the pump has been punctured successfully.

DISTRIBUTION OF SPINAL MORPHINE

Subarachnoid injection of morphine is preferred over epidural injection because the subarachnoid route ensures maximum concentration of morphine at the spinal cord opiate receptors. There is rostral diffusion but the concentration of morphine at the cisterna magna is approximately one seventh of the lumbar CSF when the catheter is placed in the lumbar location [2].

Epidural morphine is distributed partially into the blood stream through the epidural venous system, and this morphine acts similarly to any parenteral injection [13]. Some epidural morphine does pass through the dura into the spinal fluid and then into the spinal cord, but this transdural movement is variable and may diminish with time if epidural fibrosis develops.

Continuous infusion by the Infusaid pump provides a constant level of intraspinal morphine and is safer than the bolus method, which may cause initially elevated levels of morphine; such an abruptly elevated level may be more likely to cause respiratory impairment, nausea, or vomiting. Infection is also

less likely when a totally implanted device is used rather than a percutaneous catheter.

A programmable pump has been described [8] that allows the physician to control the rate, flow, or duration of the bolus. Frequent pump failures were noted [8]. The Infusaid pump works more reliably but has a fixed flow rate; the dose can be changed only by emptying the pump and refilling it with a new solution that has a different concentration of morphine.

The Infusaid pump is divided into two chambers by a cylindrical metal bellows. The outer chamber is a sealed reservoir containing a fluorocarbon propellant; the drug (morphine) is located within the inner chamber. At body temperature, the fluorocarbon exerts a continuous pressure upon the bellows diaphragm and thus the drug chamber. The compressed fluid exits through a filter into a flow restrictor tube. The flow rate may vary up to 15% under changes in body temperature and barometric pressure. As body temperature increases, the flow through the pump may increase [3, 5].

A disadvantage of the Infusaid pump is its high cost. A less expensive system, which allows the patient to vary the dose by manually pumping a tube, has been described [7]. The advantage of allowing the patient to vary the dose of morphine in response to individual need has to be balanced against the possibility that the patient may overdose, perphaps fatally. The tendency of these patients to willfully overdose is very great, and I prefer not to allow them the opportunity.

TYPES OF NONCANCER PAIN THAT MAY BENEFIT FROM INTRASPINAL MORPHINE

Acute pain of women in labor, multiple trauma, surgery, or acute radiculitis may benefit from extradural spinal morphine [14].

Chronic pain associated with advanced peripheral vascular disease and low-back-pain syndrome have also been reported as being helped [14] when percutaneous catheter techniques were used.

Patients with thoracic postherpetic neuralgia have not obtained much benefit from epidural morphine [12]. Two of five patients had sufficient pain relief during a temporary trial to warrant implantation of an Infusaid pump for continuous infusion [12]. These two patients were followed for 10 and 12 months and have obtained pain relief that was only marginally superior to that achieved with more conventional medications [12]. Our experience with one patient with postherpetic thoracic neuralgia was similarly disappointing; the patient did not have any benefit from the subarachnoid injection of 1 mg morphine.

Our most dramatic improvement from the continuous subarachnoid morphine infusion occurred in a patient with painful flexor spasms, paraplegia, and spinocerebellar degeneration. Extremely low doses of morphine (0.05 mg per 24 hours) have relieved her spasms and pain; tolerance has not developed.

Control of pain and spasticity has been reported in a few patients who also did not develop tolerance when the primary problem was spasticity [15]. Since morphine affects the multisynaptic reflexes associated with A-delta or C-fiber stimulation, it has been suggested that the reflex arc contributing to spasticity might also be inhibited by intrathecal morphine [15].

Three of our patients with lower extremity reflex sympathetic dystrophy, characterized by swelling and burning pain worsened by light touch, were improved to varying degrees by continous morphine infusion. These patients were atypical as far as reflex sympathetic dystrophy is concerned because their pain was not relieved by sympathetic blockade. Since morphine does not affect the sympathetic nervous system [14], there must be another mechanism involved in the analgesia provided to these patients.

COMPLICATIONS

Respiratory failure is the most severe complication of intraspinal morphine. Most of the reported cases have occurred following bolus injection in postoperative patients. Intrathecal injections are more likely than epidural ones to cause this problem [16]. The respiratory problem may be delayed for several hours after the injection. Maintaining the patient in an elevated position (head-up tilt of 30° to 40°) and using a hyperbaric solution (dextrose 15%) may help to prevent rostral distribution of the morphine and thus may prevent respiratory impairment [17]. Naloxone will reverse the respiratory problem, but sometimes more than one injection of naloxone is necessary. Systemic sedatives or narcotics should be given with great caution because these may precipitate respiratory failure in patients who have recently received intraspinal morphine. Respiratory difficulties have not been a problem in patients receiving continuous infusion of intraspinal morphine.

Pruritis, urinary retention, nausea, or vomiting may also occur with intraspinal morphine [18]. These effects are usually mild and temporary.

Tolerance to intraspinal morphine develops frequently, but not always. The dose often has to be increased. After a while, it may be necessary to decrease the dose and manage the withdrawal symptoms with clonidine. Nonopiate spinal anesthetics can relieve the pain temporarily until the spinal morphine can be resumed at a lower dose.

MULTIPLE SPINAL ANALGESIC RECEPTORS

Although morphine has been the most frequently used agent for spinal analgesia, there are other drugs that can produce analgesia by selectively activating adrenergic, opiate, and baclofenergic receptor systems in the spinal cord [1]. Baclofen causes a dose-dependent decrease in muscle strength, while morphine does not [1]. There is more than one opiate receptor, and while morphine acts mainly on the mu receptors, DADL (D-Ala2-D-Leu5-enkephalin) affects primarily the delta receptors. Preliminary attempts have been made to use some of these agents to control pain while the patient is being withdrawn from morphine [19, 20].

Summary and Conclusions

There are opiate receptors in the spinal cord, and direct placement of morphine on the spinal cord can result in analgesia. Long-term continuous infusion of morphine into the subarachnoid space can be maintained by a totally implanted pump system.

Although patients with intractable cancer pain are the best candidates for this treatment, a few highly selected patients with noncancer pain may also benefit. Patients with pain and spasms and those with reflex sympathetic dystrophy unresponsive to sympathectomy may be some of the better candidates. The role of intraspinal morphine in noncancer patients has not been fully determined and it should be offered cautiously. Spinal stimulation is less dangerous and should be considered first, especially for patients with failed back syndrome.

References

1. Yaksh TL, Reddy SVR: Studies in the primate on the analgesic effects associated with intrathecal actions of opiates. A-adrenergic agonists and baclofen. Anesthesiology 54:451–467, 1981.
2. Moulin DE, Inturrisi CE, Foley KM: Epidural and intrathecal opioids: Cerebrospinal fluid and plasma pharmacokinetics in cancer pain patients. In: Advances in Pain Research and Therapy, Vol 8. Raven Press, New York, 1986, pp 369–383.
3. Harbaugh RE, Coombs DW, Saunders RL, Gaylor M, Pageau M: Implanted continuous epidural morphine infusion system. Prelimi-

nary report. J Neurosurg 56:803–806, 1982.
4. Coombs DW, Saunders RL, Gaylor MS, Block AR, Colton T, Harbaugh R, Pageau MG, Mroz W: Relief of continuous chronic pain by intraspinal narcotics infusion via an implanted reservoir. JAMA 250:2336–2339, 1983.
5. Coombs DW, Saunders RL: Intraspinal infusion of narcotic drugs. In: Neurosurgery, Wilkins RH, Rengachary SS, eds. McGraw-Hill, New York, 1985, pp 2390–2397.
6. Onofrio BM, Yaksh TL, Arnold PG: Continuous low-dose intrathecal morphine administration in the treatment of chronic pain of malignant origin. Mayo Clin Proc 56:516–520, 1981.
7. Poletti CE, Cohen AM, Todd DP, Ojemann RG, Sweet WH, Zervas NT: Cancer pain relieved by long-term epidural morphine with permanent indwelling systems for self-administration. J Neurosurg 55:581–584, 1981.
8. Penn RD, Paice JA, Gottschalk W, Ivankovich AD: Cancer pain relief using chronic morphine infusion. Early experience with a programmable implanted drug pump. J Neurosurg 61:302–306, 1984.
9. Wang JK, Nauss LA, Thomas JE: Pain relief by intrathecally applied morphine in man. Anesthesiology 50:149–151, 1979.
10. Penn RD, Paice JA: Chronic intrathecal morphine for intractable pain. J Neurosurg 67:182–186, 1987.
11. Brazenor GA: Long-term intrathecal administration of morphine: A comparison of bolus injection via reservoir with continuous infusion by implanted pump. Neurosurgery 21:484–491, 1987.
12. Hadley MN, Shetter AG: Intrathecal opiate administration for analgesia. Contemp Neurosurg 8:1–5, 1986.
13. Jorgensen BC, Andersen HB, Engquist A: CSF and plasma morphine after epidural and intrathecal application. Anesthesiology 55: 714–715, 1981.
14. Magora F, Olshwang D, Eimerl D, Shorr J, Katzenelson R, Cotev S, Davidson JT: Observations on extradural morphine analgesia in various pain conditions. Br J Anaesth 52:247–252, 1980.
15. Erickson DL, Blacklock JB, Michaelson M, Sperling KB, Lo JN: Control of spasticity by inplantable continuous flow morphine pump. Neurosurgery 16:215–217, 1985.
16. Gustafsson LL, Schildt B, Jacobsen K: Adverse effects of extradural and intrathecal opiates: Report of a nationwide survey in Sweden. Br J Anaesth 54:479–486, 1982.
17. Samii K, Feret J, Hakari A, Viars P: Selective spinal analgesia. Lancet 1142, 1979.
18. Yaksh TL: Spinal opiate analgesia: Characteristics and principles of action. Pain 11: 293–346, 1981.
19. Krames ES, Wilkie DJ, Gershow J: Intrathecal D-Ala2-D-Leu5-enkephalin (DADL) restores analgesia in a patient analgesically tolerant to intrathecal morphine sulfate. Pain 24:205–209, 1986.
20. Stein C, Brechner T: Epidural morphine tolerance: Use of norepinephrine. Clin J Pain 2:267–269, 1987.

18. DEEP BRAIN STIMULATION FOR RELIEF OF CHRONIC PAIN

Ronald Brisman, M.D.

Electrical stimulation of two parts of the brain may produce pain relief. These are the periventricular gray (PVG) and the somatosensory area of the thalamus (SST).

Between 1980 and 1984, I offered brain stimulation to some patients with intractable chronic pain, especially those who failed to improve with spinal cord stimulation or those with face pain, and to cancer patients with upper extremity pain. At that time, I was not treating patients with morphine infusion.

Surgical Technique

General anesthesia is used with endotracheal intubation. Trephination is made just anterior to the coronal suture 3 cm from the midline. The dura is cauterized then opened with a cruciate incision. An acrylic ring is inserted in the burr hole and is used for securing the leads at the end of the procedure.

The ventricles are not cannulated. Preoperative CT scanning is done to determine the width of the third ventricle. The medial (PVG) thalamic electrode is placed approximately 1 mm lateral to the posterior aspect of the third ventricle. In the operating room, anteroposterior and lateral x-rays are used. The midline marker is the pineal when it is calcified, or one half the distance between the outer tables near the level where the pineal would be.

The lateral target is 8 mm deep to the point 1 mm anterior to the habenula commissure on a trajectory from the coronal suture. The preoperative CT scan futher helps identify the habenula calcification if it is present on skull x-rays. If it cannot be seen on skull x-rays, then a point 3.4 cm from the tip of the dorsum sella in a plane perpendicular to the clivus is used.

X-rays are taken in the operating room with the radioopaque brain probe just inside the pial membrane. Lines are drawn on the x-ray, and when it is apparent that the trajectory is on target, the probe is advanced into the brain. Usually only one or two minor adjustments are necessary prior to advancing the probe into the brain. Postoperative CT scans are done to identify the location of the electrodes.

The Medtronic quad lead is used; there are four closely placed platinum electrodes. Frequently PVG and SST electrodes are positioned. Postoperatively, various bipolar combinations are tested. If pain relief is obtained during several days of stimulation, the leads are internalized and a receiver is positioned subcutaneously in the infraclavicular area.

Final target position was correct in 11 of 14 patients, as determined by postoperative CT and response to stimulation. In one patient, the lead was a little too anterior and the patient had some movement of his upper extremity when he stimulated. He still had satisfactory pain relief (50%) and so the lead was not revised. In another patient with leg pain, stimulation of SST resulted in sensations felt only in the upper extremity, so the lead was

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TABLE 18-1. Deep brain stimulation: Results for failed back

Age	Sex	Location	Cause	Lead	Result[1]	FUP
29	F	Leg	Arachnoiditis	VPL & PAG	Fails	Not internalized
60	F	Perineum	Arachnoiditis	VPL & PAG	Fails	Never helped
50	F	Back/leg	Arachnoiditis	VPL	Fails	Never helped
35	F	Back/leg	Arachnoiditis	VPL	Fails	Never helped
25	F	Back/leg	Discogenic	VPL & PAG	Mild	Tc[2] fail 24 mos
45	F	Leg	Discogenic	VPL & PAG	Mild	Pa[3] fail 4 mos
38	F	Back/legs	Discogenic	VPL & PAG	Good	50 mos

[1] Mild = 25%–50% pain relief; good = > 50% pain relief.
[2] Tc = technical, equipment failure.
[3] Pa = fails to relieve pain but technically working.

revised to a deeper and more lateral position where a proper stimulation response was obtained. In a third patient with face pain, stimulation was felt more in the arm than the face; the patient had mild initial pain relief, so the lead was not repositioned.

Complications

There were no infections. One patient developed mildly bothersome hypoalgesia and dysesthesias in the hand (without stimulation) immediately following insertion of the leads. This has persisted for 2 years. Another patient became hypoalgesic in the entire one half of the body contralateral to the SST stimulator 3 years after it was inserted.

Equipment failures were noted in three patients: one with a multiprogrammable (SE4) Medtronic system never was able to feel stimulation placed in the SST. Later failures developed in two other patients, at 3 and 9 months postoperatively, who suddenly lost the ability to feel electrical stimulation. Those two patients had the regular Medtronic equipment that was not multiprogrammable.

Results (Tables 18-1 through 18-3)

Six of the seven patients in the failed-back group had initial pain relief from stimulation, and the electrodes were internalized (Table 18-1). Two of these patients had mild relief (25%–50%) for 4 and 24 months, when they failed to obtain further relief because of intractable pain in one and equipment failure in the other. One patient had excellent relief, which has persisted for 50 months, as long as the stimulator was on for several hours each day. The patient benefits from both SST and PVG stimulation; the PVG stimulation is used for 15 minutes 2 or 3 times a day. This patient failed to obtain any analgesia from technically satisfactory spinal cord stimulation.

In the miscellaneous category (Table 18-2), two of the three patients had mild pain relief from stimulation. One of them suddenly lost the ability to feel any sensations when she used the stimulator and also lost any analgesic effect. The other patient had face pain and anesthesia dolorosa; she felt the stimulation more in the arm than the face and had only a mild temporary stimulation-induced analgesia. The third patient, the first one done in this series, had unbearable intractable tinnitus. He was initially being evaluated for a cingulotomy, but it was decided to try deep brain stimulation instead; it never helped him, and such a patient would not be considered a candidate for deep brain stimulation today.

All four patients with cancer pain had tumors in the lung apex with brachial plexus

TABLE 18-2. Deep brain stimulation: Results (miscellaneous)

Age	Sex	Location	Cause	Lead	Result[1]	Followup
43	F	Back/leg	Paraplegia	VPL & PVG	Mild	Tc[2] fails 3 mos
41	F	Face	Anesth dolorosa	VPL	Mild	Pa[3] 9 mos
72	M	Head	Tinnitus	PVG	Fails	Never helped

[1] mild = 25%–50% pain relief.
[2] Stimulation felt in arm more than face.
[3] Lose stimulation.

TABLE 18-3. Deep brain stimulation: Results (cancer)

Age	Sex	Location	Cause	Lead	Result	Followup
65	M	Arm	Lung cancer	VPL	Good	Died ca. 3 weeks
57	M	Arm	Lung cancer	VPL	Good	5 mos
55	M	Arm	Lung cancer	VPL	Mild	Arm moves, 3 mos[1]
62	F	Arm	Metastatic cancer	VPL	Fails	Technical[2]

[1] Arm movement with stimulation.
[2] No stimulation felt; multiprogrammable device.

involvement and upper extremity pain (Table 18-3). All three who had technically satisfactory stimulators had pain relief that was noted immediately after the insertion of the electrodes and before they began stimulation; when pain returned a few weeks later, analgesia could be regained with stimulation in the SST.

Discussion

SURGICAL TECHNIQUE

A standard technique for inserting leads into the PVG has been described [1]. The patient's head was placed in a Trent Wells stereotaxic unit and a trephination was made just behind the coronal suture on the side contralateral to the more severe pain. After Conray ventriculography, a Medtronic four-contact electrode was inserted so that its tip lay 2 mm to 3 mm lateral to the ventricular wall, just anterior to the posterior commissure.

For implantation in the somatosensory region, the target point is in the ventral posterior medialis (VPM) for patients with face pain, and it is in the ventral posterior lateralis (VPL) for those with arm, leg, or trunk pain [2, 3].

CT-guided stereotaxis provides a safe, quick, and accurate method for inserting deep-brain stimulating electrodes and is now our method of choice. It eliminates the more invasive technique of cannulating the ventricles, which are usually small, and of injecting contrast materials. There are certain limitations inherent in the imaging and localization possibilities of CT, although these can be minimized by very thin sections. Extremely precise placement is also not usually necessary because of the multiple electrodes in the quad lead and the wide areas of stimulation that can be reached by varying the bipolar combinations. Magnetic resonance imaging, with its excellent sagittal image, may provide further improvements in lead placement.

Improvements in stimulator technology, such as reliable totally implantable devices, are already available. With this equipment, the patient does not have to apply an antenna to the skin or carry a stimulating box, and is more likely to be pleased with the stimulator.

TABLE 18-4. Results of deep brain stimulation (PVG/PAG): Other authors

Source	Pts No.	Place	Type of pain	% of Pts analgesic	Degree of analgesia	Followup mos
[8]	19	PVG	Nociceptive	None		
[8]	67	PAG	Nociceptive[1]	22%[2] (12%–38%)	Significant	
[9]	28	PVG	Nociceptive[4]	75%	> 49%	14[3]
[7]	75	PVG		20%–45% 60%–90%	Still[6] use it	1973–77 1978–80
[6]	26	PVG/PAG		58% 23%	Excellent Partial	20[5]
[6]	16	PVG + SST		6% 69%	Excellent Partial	
[2]	65	PAG	Peripheral	77%	Successful	
[11]	57[7]	PAG/PVG	Nociceptive	56% 32%	(Use it with pain relief)	Initial 80[5]

[1] 95% of significant pain relief was in patients with nociceptive pain; 5% had deafferentation.
[2] Electrodes 1 mm–3 mm from midline: 12% analgesia; electrodes 4 mm–6 mm from midline: 38% analgesia.
[3] Median
[4] Mostly failed back and cancer.
[5] Mean for entire group.
[6] Continued to use stimulator as of 1981.
[7] 51 had low back and skeletal pain; 6 had cancer pain; a small number in each group had SST electrodes.

PAG/PVG STIMULATION

Periaqueductal gray (PAG) was an early location for electrode placement that produced stimulation-induced analgesia in animals [4] and humans [1, 5]. It was found that there were unpleasant side effects including nystagmus, nausea, and vertigo in addition to analgesia. Stimulation-induced analgesia could be maintained without these side effects when the leads were placed in the PVG just lateral to the posterior third ventricle along the medial aspect of the nucleus parafascicularis [5]. PVG stimulation frequently does not produce dysesthesias, and bilateral analgesia may be produced from unilateral stimulation [5], although patients with bilateral or midline pain are usually treated with bilateral electrodes [6].

A PAG location has been recommended (3 mm from the midline at the iter of the aqueduct), but a more ventral and rostral location should be avoided because stimulation here often induces a reaction of anxiety or fear [2]. PAG electrodes were positioned bilaterally to maximize analgesic effect, implying the surgeon's feeling that PAG stimulation is more effective on the side contralateral to stimulation [2].

PAG/PVG stimulation has usually been recommended for peripheral pain [2] or pain where there is noxious input [7] (Table 18-4). Some of the best results have been in patients with failed back [2, 6, 9]. Occasionally unpredictable results may occur such as the relief of deafferentation pain in postherpetic neuralgia from PVG stimulation [6]. Other investigators have reported no analgesic effect from PVG stimulation [8, 10].

Initial success from deep brain stimulation (mainly PVG/PAG) for nociceptive pain was much better than long-term relief (32%, Table 18-4) [11].

Mazars found that results of PAG stimulation were better when the electrodes were 4 mm–6 mm from the midline rather than 1 mm–3 mm. He thinks that stimulation of the spinothalamic tracts explains the improved results from the more lateral placement [8].

Improved results may occur when patients with psychogenic pain and major personality defects are screened out [7].

It used to be thought that the main mechanism of action of PAG/PVG stimulation was release of beta endorphin [11]. More recent evidence indicates that this is not the case [13, 14] that PAG/PVG-stimulation-induced analgesia is not blocked by naloxone, and that patients who are tolerant to morphine may experience pain relief from PAG/PVG stimulation [14]. It has been suggested that serotonin, dopamine, and norepinephrine may play important roles in analgesia produced by PAG/PVG stimulation [14–16], which may activate a descending inhibitory system.

Tolerance, with progressively less effective pain relief, may develop to PAG/PVG stimulation. PAG/PVG stimulation should be limited to 10 to 15 minutes for 3 or 4 times a day to prevent the development of tolerance. Disulfiram, which inhibits noradrenalin synthesis, may prevent tolerance [12]. It has been suggested that oral supplement of L-tryptophan, a serotonin precursor, will prevent the tolerance to PAG stimulation [12]. Four and a half grams of L-tryptophan daily will reverse the tolerant state [12]. Abstinence from PAG stimulation will also reverse tolerance.

SOMATOSENSORY THALAMIC STIMULATION (SST)

SST stimulation is produced from electodes placed in either the VPL or VPM of the thalamus or the posterior limb of the internal capsule. Coordinates for the posterior limb of the internal capsule are posterior commissure in the parasagittal plane and 23 mm lateral from the midline [17]. Coordinates for the VPL (arm and leg portion) are: 2 mm–3 mm anterior to posterior commissure on the intercommissural line and 13 mm–15 mm lateral [17]; the leg area is often slightly more lateral and deeper. Coordinates for the face portion of this nucleus (VPM) are 2 mm–3 mm anterior to the posterior commissure, 3 mm–5 mm superior to the intercommissural line, and 8 mm lateral [17].

Patients with deafferentation, such as brachial plexus lesions or postherpetic pain, have responded well to this kind of stimulation if they had hyperpathia without large areas of anesthesia [18] (Table 18-5). Many with arachnoiditis also are relieved by this stimulation [19], and dysesthetic leg pain may respond better than back pain [2].

Paraplegic pain and anesthesia dolorosa respond poorly to deep brain stimulation (mainly SST) [11]. Initial success from deep brain stimulation (mainly SST) for various deafferentation pains was 61%, but fell to 30% after longer followup (mean 80 months, Table 18-5). [11]

Although many patients with SST stimulation will not develop tolerance [2], a loss of effectiveness after prolonged stimulation occasionally develops. L-dopa could prevent tolerance [21] or restore pain relief (1 g daily of L-dopa) to those who lost it [2] after prolonged SST stimulation. In one study, tolerance to SST stimulation developed as often as to PVG-PAG stimulation [14]. SST stimulation analgesia is not mediated by endogenous opiates but may be explained by activation of the monoaminergic descending fibers to synapses receiving noxious inputs [21].

A small thalamotomy occurs as a result of passing the brain probe and electrode for SST stimulation. This may cause initial temporary pain relief, which occurred in three of my patients with upper arm pain and lung cancer. Occasionally following placement of SST electrodes, patients are aware of altered sensation, which is sometimes unpleasant. It has been suggested that placement of the electrode in the posterior limb of the internal capsule is less likely to be associated with this complication [7].

SST stimulation is similar to spinal stimulation in that the patient feels an electriclike sensation when the stimulation is turned on;

TABLE 18-5. Results of posterior thalamic stimulation (SST): Other authors

Source	Pts No.	Place	Type of Pain	% of Pts Analgesic	Degree of Analgesia	Followup mos
[8]	93	SST	Deafferentation	89%	Significant	
[8]	22	SST	Nociceptive[1]	None		
[18]	17	SST	Hyperpathia	88%	Relief	
[18]	13	SST	Anesth dolorosa	8	Relief	
[19]	18	SST	Neuropathic[2]	44% 28%	Complete Partial	
[6]	6	SST		0% 33%	Excellent Partial	
[20]	67	SST	Deafferentation	50%–80%		9–56
[2]	76	SST	Deafferentation	58%	Successful	
[11]	84	SST[3]	Deafferentation	61% 30%	(Use it with pain relief)	Initial 80 mean

[1] Mostly cancer pain and root compression.
[2] Most good results were in lumbar arachnoiditis.
[3] A small number had PVG/PAG electrodes.

the parameters of stimulation (amplitude, rate, and pulse width) are adjusted until the sensation is comfortable. Unlike spinal stimulation, SST results in a constant stimulation that is not altered by position (sitting or standing) or the arterial pulsation. This constant stimulation is usually more comfortable for the patient. Some patients find SST more effective in relieving their pain than spinal stimulation. However, there is a greater risk asociated with deep brain stimulation, which may cause a hemorrhage, infection, or encephalomalacia of the brain.

Summary and Conclusions

Deep brain stimulation should not be the initial neurosurgical pain-relieving procedure for most patients with intractable pain because of the small but real risk of a serious complication. Lesser complications such as sensory impairment, which may be bothersome, also occur though infrequently. Spinal stimulation is safer and should be offered first to most patients with noncancer pain below the neck.

Recent improvement in deep brain stimulation such as CT-guided stereotaxis, totally internalized stimulators, and good long-term results in some patients, indicate that deep brain stimulation may be offered to highly selected patients with intractable pain, especially if they have failed to respond to simpler procedures. Patients with large areas of anesthesia without hyperpathia are unlikely to be helped by deep brain stimulation and should not be offered it.

The two main areas where stimulation-induced analgesia has been detected are the periventricular gray or periaqueductal gray (PVG/PAG) and somatosensory thalamus (SST). SST and PVG/PAG stimulation analgesia is not mediated by endorphins, contrary to the earlier reports of investigators about PVG/PAG stimulation.

SST stimulation is more likely to relieve deafferentation pain than is PVG/PAG stimulation. Back pain may respond better to PVG/PAG stimulation, and dysesthetic leg pain may respond better to SST stimulation.

Because of adverse effects (nausea, eye movements, or anxiety) that often occur with PAG stimulation, it is preferable to implant PVG rather than PAG electrodes.

Although I suspect that SST is probably more effective in most patients than PVG stimulation, the data are not conclusive, and enough uncertainty and unpredictability exists so that it is often best to implant both PVG and SST electrodes and test the awake patient to see which work best. Sometimes both are effective and then both can be internalized.

References

1. Richardson DE, Akil H: Pain reduction by electrical brain stimulation in man. Part 2: Chronic self-administration in the periventricular gray matter. J Neurosurg 47:184–194, 1977.
2. Hosobuchi Y: Subcortical electrical stimulation for control of intractable pain in humans. J Neurosurg 64:543–553, 1986.
3. Schaltenbrand G, Bailey P: Introduction to Stereotaxis with an Altas of the Human Brain. Grune & Stratton, New York, 1959, Vol 2, plates 38–47.
4. Reynolds DV: Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science 164:444–445, 1969.
5. Richardson DE, Akil H: Pain reduction by electrical brain stimulation in man. Part 1: Acute administration in periaqueductal and periventricular sites. J Neurosurg 47:178–183, 1977.
6. Young RF, Kroening R, Fulton W, Feldman RA, Chambi I: Electrical stimulation of the brain in the treatment of chronic pain. J Neurosurg 62:389–396, 1985.
7. Richardson DE: Deep brain stimulation for pain relief. In: Neurosurgery, Wilkins RH, Rengachary SS eds. McGraw-Hill, New York, 1985, pp 2421–2426.
8. Mazars GJ, Merienne L, Cioloca C: Comparative study of electrical stimulation of posterior thalamic nuclei, periaqueductal gray, and other midline mesencephalic structures in man. In: Advances in Pain Research and Therapy, Vol 3. Bonica JJ, et al., eds. Raven Press, New York 1979, pp 541–546.
9. Ray CD, Burton CV: Deep brain stimulation for severe, chronic pain. Acta Neurochirurg, Suppl 30:289–293, 1980.
10. Greenberg RP, Hoffert MJ, Gracely RH, Wolskee PJ, Dionne RA, Dubner R: Symposium, — NIDR Medical College of Virginia Collaborative Study on Chronic Pain and the Effects of Peri-ventricular Grey Stimulation. Presented at the American Pain Society, Oct. 1982.
11. Levy RM, Lamb S, Adams JE: Treatment of chronic pain by deep brain stimulation: Long-term follow-up and review of the literature. Neurosurgery 6:885–893, 1987.
12. Hosobuchi Y: The current status of analgesic brain stimulation. Acta Neurochirurg, Suppl 30, 219–227, 1980.
13. Dionne RA, Mueller GP, Young RF, Greenberg RP, Hargreaves KM, Gracely R, Dubner R: Contrast medium causes the apparent increase in B-endorphin levels in human cerebrospinal fluid following brain stimulation. Pain 20:313–321, 1984.
14. Young RF, Chambi I: Pain relief by electrical stimulation of the periaqueductal and periventricular gray matter. Evidence for a non-opioid mechanism. J Neurosurg 66:364–371, 1987.
15. Akil H, Liebeskind JC: Monoaminergic mechanisms of stimulation-produced analgesia. Brain Res 94:279–296, 1975.
16. Jensen TS, Yaksh TL: Glutamate-induced analgesia: Effects of spinal serotonin, norepinephrine, and opioid antagonists. In: Advances in Pain Research and Therapy, Vol 9, ed. Raven Press, New York, 1985, pp 513–518.
17. Ojemann GA, Loeser JD: Brain stimulators for pain. Contemp Neurosurg 2:1–5, 1980.
18. Mazars GJ, Choppy JM: Reevaluation of the deafferentation pain syndrome. Advances in Pain Research and Therapy, Vol 5. Bonica JJ, ed. Raven Press, New York, 1983, pp 769–773.
19. Turnbull IM, Shulman R, Woodhurst WB: Thalamic stimulation for neuropathic pain. J Neurosurg 52:486–493, 1980.
20. Siegfried J: Long-term results of intermittent stimulation of the sensory thalamic nuclei in 67 cases of deafferentation pain. In: Neurostimulation: An overview, Lazorthes Y, Upton ARM, eds. Futura Publishing, Mt. Kisco, New York, 1985, pp 129–143.
21. Tsubokawa T, Yamamoto T, Katayama Y, Hirayama T, Sibuya H: Thalamic relay nucleus stimulation for relief of intractable pain. Clinical results and B-endorphin immunoreactivity in the cerebrospinal fluid. Pain 18:115–126, 1984.

19. NONCANCER PAIN, OTHER OPERATIONS: SYMPATHECTOMY, DORSAL ROOT ENTRY ZONE LESIONS, DORSAL RHIZOTOMY, FACET DENERVATION

Ronald Brisman, M.D.

In addition to neuroaugmentation (the main neurosurgical approach) and morphine infusion (of limited value in most noncancer situations), there are other neurosurgical procedures used for treatment of intractable noncancer pain. Some, such as sympathectomy, have limited but specific indications. Others, dorsal root entry zone (DREZ) lesions, dorsal rhizotomy, and facet denervation have less well-defined use, although occasionally may be beneficial.

Sympathectomy for Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD) is a condition of pain, hyperesthesia, and vasomotor changes that usually responds to sympathetic denervation [1]. The pain is often burning, although other kinds of pain may occur [2]. Various types of RSD have been described depending on certain clinical features and precipitating injuries [1]. When peripheral nerve injury has occurred, the condition has been called *causalgia* [3]; the median and posterior tibial nerves are frequently involved, and the injury is usually partial. In major causalgia, which may follow peripheral nerve injury, pain is provoked by the slightest movement or even psychological events. RSD that occurs after soft-tissue trauma with bony atrophy as a predominant finding is called *Sudek's atrophy of bone* [1].

Physical therapy that encourages movement of the involved limb to which moisture is applied and sympathetic denervation are appropriate treatment. Early treatment is recommended to prevent the immobilization that can further aggravate the condition.

Sympathetic denervation may be accomplished with oral medication. Phenoxybenzamine is a postsynaptic α_1-blocker and presynaptic α_2-blocking agent that is given in gradually increasing increments until a maximum daily dose of 40 mg to 120 mg is reached [4]. Duration of treatment in one study was usually 6 to 8 weeks, with total resolution of pain achieved in all 40 cases [4].

Sympathetic blocks may be diagnostic and therapeutic [1]. A series of blocks are often necessary. Sometimes a continuous infusion of local anesthetic into the sympathetic ganglion (stellate) [5] may be used for upper extremity causalgia. Epidural blocks may be done for

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lower extremity involvement. Good long-term results from sympathetic blocks are frequently obtained with patients who have mild or moderate pain [2, 6] but are much less likely in those with severe pain, unless a sympathectomy is done.

Regional sympathetic blockade can be performed by injecting guanethidine intravenously and inflating a tourniquet proximally [7, 8]. Guanethidine displaces norepinephrine in presynaptic vesicles and prevents its reuptake.

Paravertebral sympathectomy is reserved for those with severe causalgia and those who do not respond to less invasive maneuvers. Better results occur when the sympathectomy is more complete [2]. Preganglionic denervation of the upper extremity may be preferable to postganglionic denervation because of the lesser likelihood of a Horner's syndrome from the preganglionic procedure [2]. Some surgeons recommend a T2 or T2 and T3 ganglionectomy, which has a low incidence of complications [9, 10].

Sympathetic denervation of the lower extremity can usually be accomplished by resection of the second and third lumbar sympathetic ganglia [9]. Excision of the L1 ganglion is sometimes necessary. Bilateral denervation of the L1 ganglia must be avoided in males to prevent permanent sexual dysfunction [9].

DREZ Lesions

DREZ lesions are used to treat deafferentation pain, especially that associated with brachial plexus avulsion, paraplegia, herpes zoster, and phantom limb pain [11–16].

SURGICAL TECHNIQUE

A laminectomy is done to include the involved nerve roots and two or three nerve roots rostrally, especially in cases of thoracic lesions or paraplegia [14]. The electrode is introduced 2 mm into the cord at an angle of approximately 25° on a vertical plane through the intermediolateral sulcus [11, 12, 14]. Sequential lesions 1 mm to 2 mm apart are made by heating 60 mA–75 mA for 15 seconds [11, 16], 30 mA–40 mA for 10 to 15 seconds [12], or 75°C for 15–30 seconds [14].

PERSONAL EXPERIENCE

Because of concern that DREZ lesions might increase the neurological deficit, I did my first three procedures on paraplegic patients with pain. Two of three patients with paraplegic pain showed 25% relief. In one, there was some added weakness in the proximal leg and added analgesia contralateral to the DREZ lesions, reflecting an extensive radiofrequency lesion in the spinal cord. A subsequent patient with thoracic postherpetic pain was treated with smaller DREZ lesions and noted improvement in superficial pain but persistence of agonizing deep pain; there was no postoperative leg weakness.

INDICATIONS

There aren't many neurosurgical options available for treatment of intractable deafferentation pain. Deep brain stimulation (somatosensory thalamic) and DREZ lesions are two of the major choices. Deep brain stimulation is not effective if there is a large area of analgesia without hyperpathia [17]. It is not certain whether or not this influences the outcome of the DREZ operation. In the series of postherpetic pain patients treated with DREZ lesions, hyperesthesia extended over two to three dermatomes [13], suggesting that these patients, who responded well to DREZ lesions, may have been similar to those patients who were helped by deep brain stimulation [17]. However, Nashold describes patients with totally deafferented limbs with brachial plexus avulsion [14] who benefit from the DREZ procedure, suggesting that DREZ lesions may work in some patients who would not respond to deep brain stimulation.

COMPLICATIONS

With the DREZ operation, a lesion is made in the spinal cord, and it is not always possible to confine the lesion precisely to the dorsal root entry zone. Damage to the corticospinal tracts may occur, which can cause ipsilateral leg weakness. Also, there may be added hypoalgesia when lesions are made above the area of previous nerve root injury. Patients are sometimes bothered by discomforts associated with the new surgical incision, especially if it is for a thoracic laminectomy.

A smaller lesion in the cord is less likely to cause unwanted cord damage. Such a smaller lesion is recommended for patients who have preserved corticospinal tract function prior to surgery.

Other complications that may occur following laminectomy and intradural exploration, such as spinal fluid leak or hematoma, can be minimized by careful surgical technique.

RESULTS OF DREZ LESIONS

The best reported long-term relief (5 years) has been in patients with brachial plexus avulsion, 66% of whom have 75% or more reduction of their pain [14].

Fifty percent of patients with spinal cord injury pain had good pain relief. Those with pain extending caudally from the level of the injury and patients with unilateral pain were most likely to be helped; diffuse pain and predominant sacral pain did not respond so well [16].

Eight of 12 patients with postherpetic neuralgia reported good pain relief with followup periods ranging from 6 to 21 months [13].

Although most patients with postamputation pain did not do well following DREZ, good results were obtained in six (67%) of nine with phantom pain alone and in five of six with traumatic amputations and root avulsion. Poor results occurred in patients with both phantom and stump pain, or stump pain alone [14].

Dorsal Rhizotomy

Varying and uncertain pain relief occurs following dorsal rhizotomy, and its role is presently very limited in the treatment of noncancer pain.

Probably safer and possibly providing longer lasting relief than cordotomy, dorsal rhizotomy was looked upon with modest enthusiasm by some surgeons for trunk and limb pain where satisfactory relief of pain was noted in 50% to 60% of patients [18, 19]; this was prior to the age of neuroaugmentation. Others were less enthusiastic with dorsal rhizotomy [20, 21] and found few patients with good pain relief, especially when they were followed for a long time.

Problems with the procedure relate to the dermatomal overlap of sensory root innervation below the face. Usually at least three nerve roots need to be divided to provide analgesia to a small area of skin. Multiple root denervations may produce proprioceptive problems and significant functional impairment in the upper or lower extremities, although cutting two important roots of the brachial (C6 and 7) or lumbar plexus (L5 and S1) does not usually cause much deficit [18]. Section of L5 and S1 may be more effective than cutting only one root [22], but there is a greater risk of ankle weakness when the two roots are cut.

Care must be taken to protect radicular vessels that travel along the dorsal nerve roots to supply the spinal cord. The operating microscope is very helpful in this regard.

A percutaneous technique for electrothermocoagulation of spinal nerve trunk, ganglion, and rootlets has been described [23, 24], but it is unlikely to be more effective than open procedures. The percutaneous technique is less precise and more likely to damage

motor nerves and blood vessels. This method produces an incomplete rhizotomy. The advantages are that the procedure is done under local anesthesia, does not require a formal laminectomy, and can be easily repeated.

A selective technique of radicular surgery involves section of the small nociceptive fibers in the ventrolateral region of the posterior spinal cord-rootlet junction [25], but data are not adequate to determine whether this is superior to the standard dorsal rhizotomy.

Some reports have suggested that denervation of the dorsal root ganglion may be more effective than cutting just the dorsal root because of ventral root afferents [26, 27]. Ganglionectomy may remove all afferents for a particular segment, including those that run in the dorsal and ventral roots. Trans-spinal ganglionectomy, which involves a rhizotomy and isolation of the spinal ganglion from autonomic and somatic central pathways, has been reported to be effective for post-thoracotomy and thoracic postherpetic neuralgia in which a burning pain and hypersensitivity to light touch exist [28]. These pains have responded poorly to standard dorsal rhizotomy [21].

Cordotomy

Anterolateral cordotomy is not recommended for noncancer pain because of the high rate of recurrence and complications.

Facet Denervation [29–33]

Percutaneous radiofrequency facet denervation is a controversial procedure that may provide temporary and sometimes prolonged relief for some patients with intractable back pain from zygapophyseal joint arthritis but is very unlikely to help those who have had previous back surgery, especially spine fusion. x-ray evidence of joint arthritis and a beneficial response to a small amount of local anesthetic may help the physician select patients who are more likely to respond to radiofrequency facet denervation.

Summary

Sympathetic denervation and active physical therapy are effective for treating reflex sympathetic dystrophy (RSD). Sympathetic blockade with oral phenoxybenzamine, local anesthetic blocks, or regional intravenous guanethedine will often be sufficient for mild or moderately severe cases. For those with persistent severe pain in spite of these treatments, paravertebral sympathectomy is indicated.

Dorsal root entry zone (DREZ) lesions is a relatively new procedure that may be helpful for patients with deafferentation pain, especially those with nerve root avulsion, postherpetic neuropathy, and paraplegia. The procedure involves a destructive lesion in the spinal cord and may add to the patient's neurological deficit, especially ipsilateral analgesia at the level of the lesions and ipsilateral leg weakness.

Dorsal rhizotomy has not provided consistent relief for noncancer pain. Multiple nerve roots must be cut for best results. When extremities are involved, this risks functional disability, especially if three or more roots are sectioned. Perhaps results can be improved if ventral afferents are also removed by ganglionectomy and if sympathetic denervation is combined with rhizotomy in those cases where there is also a causalgic (or reflex sympathetic dystrophy) component.

References

1. Schwartzman RJ, McLellan TL: Reflex sympathetic dystrophy. A review. Arch Neurol 44:555–561, 1987.
2. Sweet WH: Causalgia; Sympathetic dystrophy (Sudeck's atrophy). In: Neurosurgery, Wilkins RH, Rengachary SS, eds, McGraw-Hill, New York, 1985, pp 1886–1893.

3. Mitchell SW: Injuries of Nerves and their Consequences, JB Lippincott, New York, 1972.
4. Ghostine SY, Comair YG, Turner DM, Kassell NF, Azar CG: Phenoxybenzamine in the treatment of causalgia. Report of 40 cases. J Neurosurg 60:1263–1268, 1984.
5. Leipzig TJ, Mullan SF: Causalgic pain relieved by prolonged procaine amide sympathetic blockade. Case report. J Neurosurg 60:1095–1096, 1984.
6. Rasmussen TB, Freedman H: Treatment of causalgia: An analysis of 100 cases. J Neurosurg 3:165–173, 1946.
7. Hannington-Kiff JG: Relief of Sudeck's atrophy by regional intravenous guanethidine. Lancet 1:1132–1133, 1977.
8. Hannington-Kiff JG: Relief of causalgia in limbs by regional intravenous guanethidine. Br Med J 2:367–368, 1979.
9. Bay JW, Dohn DF: Surgical sympathectomy. In: Neurosurgery, Wilkins RH, Rengachary SS, eds, McGraw-Hill, New York, 1985, pp 1912–1917.
10. Hardy RW Jr: Surgery of the sympathetic nervous system. In: Operative Neurosurgical Techniques, Vol 2, Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1045–1061.
11. Nashold BS Jr, Ostdahl RH: Dorsal root entry zone lesions for pain relief. J Neurosurg 51:57–69, 1979.
12. Nashold BS Jr, Ostdahl RH, Bullitt E, Friedman A, Brophy B: Dorsal root entry zone lesions: A new neurosurgical therapy for deafferentation pain. In: Advances in Pain Research and Therapy, Vol 5, Bonica JJ, et al. eds. Raven Press, New York, 1983, pp 739–749.
13. Friedman AH, Nashold BS Jr, Ovelmen-Levitt J: Dorsal root entry zone lesions for the treatment of post-herpetic neuralgia. J Neurosurg 60:1258–1262, 1984.
14. Nashold BS Jr, Higgins AC, Bllumenkopf B: Dorsal root entry zone lesions for pain relief. In: Neurosurgery, Wilkins RH, Rengachary SS, eds, McGraw-Hill, New York, 1985, pp 2433–2437.
15. Saris SC, Iacono RP, Nashold BS Jr: Dorsal root entry zone lesions for post-amputation pain. J Neurosurg 62:72–76, 1985.
16. Friedman AH, Nashold BS Jr: DREZ lesions for relief of pain related to spinal cord injury. J Neurosurg 65:465–469, 1986.
17. Mazars GJ, Choppy JM: Reevaluation of the deafferentation pain syndrome. In: Advances in Pain Research and Therapy, Vol 5, Bonica JJ, ed. Raven Press, New York, 1983, pp 769–773.
18. White JC: Posterior rhizotomy: A possible substitute for cordotomy in otherwise intractable neuralgias of the trunk and extremities of nonmalignant origin. Clin Neurosurg 13:20–41, 1966.
19. Echols DH: Sensory rhizotomy following operation for ruptured intervertebral disc. A review of 62 cases. J Neurosurg 31:355–338, 1969.
20. Loeser JD: Dorsal rhizotomy for the relief of chronic pain. J Neurosurg 36:745–750, 1972.
21. Onofrio BM, Campa HK: Evaluation of rhizotomy. Review of 12 years' experience. J Neurosurg 36:751–755, 1972.
22. Strait TA, Hunter SE: Intraspinal extradural sensory rhizotomy in patients with failure of lumbar disc surgery. J Neurosurg 54:193–196, 1981.
23. Uematsu S, Udvarhelyi GB, Benson DW, Siebens AA: Percutaneous radiofrequency rhizotomy. Surg Neurol 2:319–325, 1974.
24. Uematsu S: Percutaneous electrothermocoagulation of spinal nerve trunk, ganglion, and rootlets. In: Operative Neurosurgical Techniques, Vol 2, Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1177–1198.
25. Sindou M, Fischer G, Mansuy L: Posterior spinal rhizotomy and selective posterior rhizidiotomy. Prog Neurol Surg 7:201–250, 1976.
26. Coggeshall RE: Afferent fibers in the ventral root. Neurosurgery 4:443–448, 1979.
27. Taub A: Relief of chronic intractable sciatica by dorsal root ganglionectomy. Am Neurol Assoc Trans 105:340–343, 1980.
28. Smith FP: Trans-spinal ganglionectomy for relief of intercostal pain. J Neurosurg 32:574–577, 1970.
29. Shealy CN: Percutaneous radiofrequency denervation of spinal facets. J Neurosurg 43:448–451, 1975.
30. Fox JL, Rizzoli HV: Identification of radiologic coordinates for the posterior articular nerve of Luschka in the lumbar spine. Surg Neurol 1:343–346, 1973.
31. Bogduk N, Long DM: Percutaneous lumbar medial branch neurotomy: A modification of facet denervation. Spine 5:193–200, 1980.
32. Kennemore DE: Percutaneous radio-

frequency denervation of spinal facets. In: Neurosurgery, Wilkins RH, Rengachary SS, eds, McGraw-Hill, New York, 1985, pp 2427–2429.

33. Bogduk N, Macintosh J, Marsland A: Technical limitations to the efficacy of radiofrequency neurotomy for spinal pain. Neurosurgery 20:529–525, 1987.

IV. CANCER PAIN

20. CANCER PAIN: NATURAL HISTORY AND PHARMACOLOGICAL TREATMENT

Richard Payne, M.D.

Introduction, Definitions, and Epidemiology of Cancer Pain

EPIDEMIOLOGY, PHYSIOLOGY, AND TYPES OF CANCER PAIN

Many epidemiological studies report that about one third of adult patients receiving therapy for cancer and up to 60% of patients with advanced cancer experience moderate to severe pain sufficient to reduce their activity or to require the use of analgesic drugs [1]. Surveys of inpatient pediatric cancer centers report that one half of all children may have pain [1]. Estimates from the World Health Organization (WHO) suggest that up to 25% of cancer patients worldwide may die without relief from severe pain [2].

Pain in cancer has many possible causes (see Table 20-1). The pathophysiology of cancer pain is complex, but in general three basic categories can be recognized (See Table 20-2 and reference 3). Activation of specific sensory receptors (nociceptors) in somatic and visceral organs by tumor infiltration or tissue injury secondary to surgery, chemotherapy, or radiation therapy may produce *somatic* or *visceral* pain. Somatic pain is usually well localized, often has a familiar aching or sharp quality, and may respond to a variety of pain therapies, including local treatments such as ice, heat and massage, analgesic drugs, local anesthetic infiltration, and cordotomy.

Visceral pain often has a deep aching or gnawing quality, is usually poorly localized and often referred to cutaneous sites (e.g., pancreatic cancer producing back pain or liver metastasis with diaphragmatic irritation producing shoulder pain). Visceral pain may respond to analgesic drugs, anesthetic infiltration, and cordotomy, but it is usually more difficult to manage than pain emanating from somatic structures. For pain complicating pancreatic carcinoma, anesthetic blockade of the celiac axis may be the treatment of choice, particularly if done before the tumor invades the posterior abdominal wall and other structures that are innervated by somatic nerves.

Somatic and visceral pain occur as a consequence of nociceptive activity in normal neural pathways. *Deafferentation* pain, on the other hand, occurs as a consequence of either peripheral or central nervous system injury, and often has a dysesthetic, burning, squeezing quality — unlike the more familiar sensations experienced with somatic and visceral involvement. Deafferentation pain syndromes

Table 20-3 and 20-4 were written in collaboration with Drs. Charles E. Inturrisi and Mitchell Max. I thank Diane Longest for assistance in preparation of this manuscript.

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TABLE 20-1. Specific pain syndromes in patients with cancer

Pain Syndromes Associated with Direct Tumor Infiltration
Tumor infiltration of bone
Base of skull syndromes
Jugular foramen metastases
Clivus metastases
Sphenoid sinus metastases
Vertebral body syndromes
C2 metastases
C7, T1 metastases
L1 metastases
Sacral syndrome
Tumor infiltration of nerve
Peripheral nerve
Peripheral neuropathy
Plexus
Brachial plexopathy
Lumbar plexopathy
Sacral plexopathy
Root
Leptomeningeal metastases
Spinal cord
Epidural spinal cord compression
Pain Syndromes Associated with Cancer Therapy
Postsurgery syndromes
Post-thoracotomy syndrome
Post-mastectomy syndrome
Post-radical neck syndrome
Phantom-limb syndrome
Postchemotherapy syndromes
Mucositis and pharyngitis*
Peripheral neuropathy
Aseptic necrosis of the femoral head
Steroid pseudorheumatism
Postherpetic neuralgia
Postradiation syndromes
Pharyngitis and esophagitis*
Radiation fibrosis of brachial and lumbar plexus
Radiation myelopathy
Radiation-induced second primary tumors
Radiation necrosis of bone
Pain Syndromes Not Associated with Cancer or Cancer Therapy
Osteoporosis
Cervical and lumbar osteoarthritis
Thoracic and abdominal aneurysms
Diabetic neuropathy

* Usual self-limited.
Adapted from Payne R and Foley KM: Recent advances in cancer pain management. Cancer Treatment Reports; 68:173–183, 1984.

are quite common in the cancer patient and include postherpetic neuralgia, painful cisplatinum or vincristine neuropathies, postmastectomy pain, epidural spinal cord compression, and metastatic or radiation-induced lumbar and brachial plexopathies. These pain syndromes may be very difficult to treat by conventional analgesic or surgical therapies since the basic pathophysiology involves injury to the nervous system, which may not heal even if the underlying cause can be reversed. The use of adjuvant "analgesic" agents such as carbamazepine, amitriptyline, and steroids are often added to opioids and, indeed, may be more useful than opioids in the management of deafferentation pain. Anesthetic blockade of somatic and autonomic nerves may also be useful, especially if deafferentation pain is complicated by reflex sympathetic dystrophy [4].

Often patients with bone metastasis, pathological fractures, and metastatic plexopathies can maintain comfort in a stationary sitting or lying position. However, any movement may precipitate acute bouts of severe pain. This is termed *incident* pain and may be difficult to manage with conventional analgesic or anesthetic approaches without limiting side effects. Theoretically, strategies for management of incident pain may include therapies that are quick acting and can be given in anticipation of movement, such as intermittent nitrous oxide administration or intravenous or subcutaneous bolus administration of opioids in patient-controlled analgesia (PCA) system. However, none of these therapies are in common usage and there are no controlled studies demonstrating their efficacy in incident pain. If drug therapy fails, cordotomy or neurolytic blocks may be required [5].

The sympathetic nervous system may be involved in the pathogenesis of cancer-related pain, particularly acute visceral and deafferentation pain. Although the exact role of the sympathetic nervous system in these pain states is unclear, anesthetic blockade of

TABLE 20-2. Types of cancer-related pain

	Somatic	Visceral	Deafferentation
Characteristics of pain	Constant, aching, gnawing; well localized	Constant; aching, poorly localized; often referred to cutaneous sites	Paroxysms of pain "shooting or shock-like" on background of burning, aching sensations
Putative mechanisms	Activation of nociceptors	Activation of nociceptors	Spontaneous and paroxysmal discharges in the PNS and CNS
Examples	Bone metastasis	Pancreatic cancer liver/lung mets with shoulder pain	Metastatic brachial and lumbosacral plexopathies
Management of pain	Treat tumor; analgesics; nerve blocks; cordotomy	Treat tumor; analgesics; nerve blocks; cordotomy (?)	Analgesics (esp. adjuvants); sympathetic blocks; treat tumor (?); TENS (?)

From Payne R: Anatomy, physiology and neuropharmacology of cancer. In: Payne R, Foley KM, eds. *Medical Clinics of North America*, Vol 71, No 2. WB Saunders, Philadelphia, 1987, pp 154.

sympathetic ganglion may produce dramatic pain relief in pancreatic carcinoma and reflex sympathetic dystrophy complicating metastatic brachial and lumbosacral plexopathy.

CLINICAL ASSESSMENT OF CANCER PAIN AND THE RECOGNITION OF SPECIFIC PAIN SYNDROMES

Details concerning the assessment of the cancer patient with pain is beyond the scope of this chapter [1, 6]. However, as in any other medical evaluation, taking a careful history of the pain complaint, doing a detailed physical and neurological examination, and assessment of the psychosocial factors unique to the individual patient are crucial in defining a cause and treatment for pain.

There are specific pain syndromes that occur commonly in the cancer patient and indeed may even herald the diagnosis of cancer. The physician must be familiar with the more common syndromes, so the definitive diagnostic workup can be completed quickly. This often involves ordering (*and personally reviewing*) all appropriate laboratory tests, especially CT and magnetic resonance (MRI) scans to view specific bone and soft-tissue areas not well seen by conventional radiographs. For example, the onset of pain radiating into the occiput or vertex of the skull associated with paralysis of the tongue often complicates metastasis to the clivus [7]. This is best confirmed by CT scan of the brain with specific views and bone definition of the base of the skull, as this metastasis is often missed by routine skull x-rays. The more common cancer pain syndromes are listed in Table 20-1 and detailed below. As implied from the above, CT scans, MRI scans, and tomography are often more helpful than plain x-rays and bone scans in imaging bone and soft-tissue lesions in the cancer patient, especially in defining pathology responsible for painful neurological complications of metastatic cancer. This is true because severe pain may precede readily definable tumors in many cases, and tumor metastasis from myeloma or small-cell lung cancer may occur in bone (especially previously radiated bone) in the presence of a negative bone scan [8]. Detailed reviews of

specific painful complications of cancer may be found elsewhere [9]; the following summarizes the more common syndromes.

Specific Pain Syndromes in Patients with Cancer

TUMOR INFILTRATION OF BONE

Pain from tumor invasion of bone is the most common cause of pain in patients with cancer. Several important pain syndromes involving bone metastasis and neurological complications are often misdiagnosed because (non-neurological) physicians are unfamiliar with the characteristic signs and symptoms. This often leads to delays in instituting appropriate therapy for pain and may adversely affect preservation of neurological function. Some of these syndromes are considered below.

Metastases to the Base of Skull [7] . These patients characteristically present to neurologists because of severe head pain, which may in fact precede neurological signs and symptoms by several weeks to months. Documentation of bone metastasis at the base of the skull with plain x-rays is difficult; CT scans with thin sections ("bone windows") through the base of the skull or plain tomography of the skull are the diagnostic procedures of choice. The more common syndromes include: *jugular foramen syndrome*, characterized by occipital pain referred to the vertex and ipsilateral shoulder and arm. In addition to headache, other signs and symptoms include hoarseness, dysarthria, dysphagia, neck and shoulder weakness, (IX, X, XI cranial nerve palsies); *clivus metastases*, characterized by vertex headache, exacerbated by neck flexion, lower (unilateral and bilateral) cranial nerve dysfunction, especially dysarthria and dysphagia secondary to hypoglossal nerve (XII) palsy; *sphenoid-sinus metastases*, characterized by severe bifrontal headache, radiating to temporal area, intermittent retroorbital pain, nasal stuffiness or fullness and diplopia with unilateral or bilateral seventh nerve palsies.

Direct antitumor treatment, i.e., radiation therapy (usually with the concomitant administration of corticosteroids) directed to the base of the skull is the preferred method for managing the pain and neurological dysfunction in these syndromes. It is often helpful to administer nonsteroidal anti-inflammatory analgesics and narcotics as well.

Metastases to the Vertebral Bodies. Pain is an early symptom that, if not accurately diagnosed, may lead to an irreversible neurological deficit, e.g., paraplegia or quadraplegia, secondary to spinal cord compression resulting from tumor extension or bony subluxation into the epidural space. These vertebral body syndromes can be grouped into five common types [1, 8].

SUBLUXATION OF THE ATLAS. Metastatic disease involving the odontoid process of the axis (C–1 vertebral body) may result in a pathologic fracture, with secondary subluxation resulting in spinal cord and/or brainstem compression. The symptoms are usually severe neck pain radiating over the posterior aspect of the skull to the vertex, exacerbated by movement. The neck should be moved only with great caution; early neurosurgical consultation and external support of the neck should be considered, especially during the neurological evaluation. Plain x-rays may be negative; tomography may be necessary.

C-7/T-1 METASTASIS. Pain localized to the adjacent paraspinal area and interscapular areas may be characterized by a constant dull aching pain radiating bilaterally to both shoulders with tenderness to percussion over the spinous process. Radicular pain in the C7, C8, or T1 distribution occurs most commonly in a unilateral fashion, radiating into the posterior arm, elbow, and ulnar aspect of the hand. Paresthesias and numbness in the fourth and fifth fingers, and progressive hand and triceps weakness are the neurological signs.

An associated Horner's syndrome (ipsilateral pupillary meiosis ptosis) suggests paraspinal involvement. Plain x-rays are often negative since they visualize this area poorly; plain tomography and CT scan are necessary to define metastatic disease. Myelography is often necessary to rule out associated epidural spinal cord compression, particularly in patients with an associated Horner's syndrome.

L-1 METASTASIS. Dull and aching mid-back pain exacerbated by lying or sitting and relieved by standing is the usual presenting complaint. Radicular pain radiating anteriorly to both paraspinal lumbosacral areas or referred pain to the sacroiliac joint or superior iliac crest may occur and cause diagnostic confusion for the inexperienced physician. Plain x-rays including anteroposterior, lateral, oblique projections of the lumbar spine are indicated. Bone scan and tomography may also be helpful. If metastasis is documented, myelography and/or perhaps MRI may be necessary to define the presence of epidural disease [20, 21].

SACRAL METASTASES. Aching pain in the low back or coccygeal region exacerbated by lying or sitting (in particular) and relieved by walking is the common complaint. (These characteristics readily distinguish this entity from nonmalignant or discogenic) pain. Associated symptoms include perianal sensory loss, bowel or bladder dysfunction, and impotence. Tomography of the sacrum, and more commonly CT scans of the pelvis, usually define the extent of bony metastasis. Myelography (and/or MRI) is often needed to exclude coexistent cauda equina metastasis and allows appropriate definition of the radiation therapy ports.

TUMOR INFILTRATION OF PERIPHERAL NERVE, PLEXUS, ROOT, OR SPINAL CORD

Peripheral Nerve Infiltration. Large peripheral nerve trunks such as the brachial and lumbar plexus may be compressed by solid tumor metastasis in the paravertebral or extraperitoneal area. Less commonly, infiltration of smaller peripheral nerves by leukemia or lymphoma may produce pain. Pain is often of a constant burning nature, usually with hyperesthesias and dysesthesias in an area of sensory loss. CT and MRI scans are useful to define associated soft-tissue masses and paraspinal disease. Rarely, biopsy of peripheral nerve is required to diagnose tumor infiltration by lymphoma or leukemia.

Brachial Plexopathy [10]. Brachial plexopathy in patients with cancer may occur in one of several ways: 1) metastatic spread of tumor to the plexus; 2) radiation injury resulting from previous radiation therapy (RT portal that has included the plexus; 3) involvement of the plexus by radiation-induced tumor such as malignant schwannoma or fibrosarcoma; or 4) trauma to the plexus during surgery and anesthesia.

Tumor infiltration and radiation injury are the most common. A recent review of 100 cases suggests that there are reliable clinical signs and symptoms to distinguish metastatic plexopathy from radiation injury [10]. The characteristics of the pain and other associated signs are quite useful in distinguishing tumor infiltration from radiation injury [10]. For example, metastasis to the brachial plexus most commonly involves the lower cords of the brachial plexus, giving pain, sensory loss, and weakness in the elbow, medial aspect of the arms, and fourth and fifth digits of the hand in the distribution of the C8, T1 roots. On the other hand, radiation plexopathy most commonly involves the upper cords of the plexus (which lie more superficially than the lower trunk), predominantly in the distribution of the C5, C6, and C7 roots. Pain, lymphedema, sensory loss, and weakness in the shoulder, the lateral aspect of the forearm and arm, and first, second, and third digits are common signs and symptoms. Severe pain is most commonly associated with metastatic plexopathy. Horner's syndrome was more commonly associated with metastatic plex-

opathy than radiation plexopathy and suggests paraspinal tumor metastasis. In fact, in one series, 32% of patients with metastatic plexopathy showed epidural extension of disease [10]. In summary, factors associated with brachial plexopathy that increase the likelihood of coexistent epidural cord compression are: 1) primary tumor of the lung, 2) the presence of Horner's syndrome, and 3) involvement of the whole plexus.

CT scans are positive in 96% of cases with metastatic brachial plexopathy, usually showing a mass infiltrating the neurovascular bundle encompassing the plexus [11]. Rarely exploration and biopsy of the brachial plexus is indicated, however, neither a negative surgical biopsy nor observation for several years for other metastases rules out recurrence of tumor in the plexus [12].

Tumor infiltration of the brachial plexus is an early sign and part of the clinical diagnosis of Pancoast syndrome [13]. Pain is also the most reliable sign to follow, as it closely reflects progression of disease and may be the only sign of epidural cord compression. Plain x-rays and bone scans are not reliable diagnostic tests in assessing this disorder and CT scans of the chest and brachial plexus, and myelograms yield the most important diagnostic information — as many as 50% of patients develop epidural cord compression with pain the earliest and most consistent clinical symptom.

Lumbosacral Plexus Tumor Infiltration [14]. This painful disorder is most commonly a complication of genitourinary, gynecologic, and colonic cancers. Pain varies with the site of plexus involvement. Upper lumbar plexopathy is associated with radicular pain in an L1, 2, 3 distribution — pain and sensory loss in the anterior thigh and groin, with weakness in the proximal lower extremity. Lower lumbar plexopathy produces pain radiating down the posterior aspect of the leg to the heel (in an L5, S1 distribution). In some instances, there may only be referred pain without local pain over the plexus. Common referred points are the anterior thigh, knee, and lateral aspect of the calf. These areas may be tender and cause diagnostic confusion as to the origin of the pain in the plexus. Also, pain may precede by weeks other neurological signs or symptoms such as paresthesias, numbness, dysesthesias, motor or sensory loss, and may occur when all diagnostic tests, such as CT scan, are negative [14]. EMGs are helpful in defining the extent of lumbosacral plexus involvement and may be particularly helpful in distinguishing tumor involvement versus radiation injury to the plexus particularly when myokymia is present [14]. Serial CT scans are helpful in following patients, even if the initial scan is negative. Myelography may be necessary to rule out epidural extension, particularly when there is severe pain and bilateral lumbar or sacral radicular symptoms or signs [14].

Leptomeningeal Metastases. This complication may be increasing in frequency [15]. Pain occurs in 40% of patients and is of two types: 1) headache with or without neck stiffness and back pain localized to the low back and buttock regions [16]. Solid tumors such as breast, lung, and melanoma are commonly associated with leptomeningeal metastasis, and as many as 4% of patients with non-Hodgkin's lymphoma (as high as 25%–30% in diffuse histiocytic lymphoma) [17].

Epidural Spinal Cord Compression [18]. Several reviews have been published recently on this important neurological complication of cancer [19–21]. Severe neck and back pain is the hallmark of this entity. Pain was the initial symptom in 96% patients and in 10% was the only symptom [18]. Pain is of two types: 1) local pain over the involved vertebral body and 2) radicular pain, which may be unilateral with cervical or lumbosacral compression or bilateral in patients with thoracic cord compression. Myelography is still the

gold standard, although MR scanning may replace it for many patients. The treatment of ESCC consists of analgesics, corticosteroids, and radiation therapy [18]. Less commonly, surgery is indicated 1) to establish a tissue diagnosis of cancer, 2) to stabilize the spine and decompress the cord when there is bony subluxation and compression, and 3) to prevent progressive neurological deterioration in patients who have radioresistent tumors (i.e., melanoma) or have relapsed in a site of prior radiation therapy [19]. Since most cases of ESCC occur when vertebral body tumor metastasis grows to compress the spinal cord anteriorly, surgical resection of the vertebral body with spinal stabilization has been advocated as a treatment approach and shows some promise, particularly as a means to manage intractable pain [22, 23].

PAIN SYNDROMES ASSOCIATED WITH CANCER THERAPY

Pain in the cancer patient may occur as a result of chemotherapy, radiation therapy, or surgery; and pain related to cancer therapy comprised about 20% of patients in one survey [24]. Some of the therapy-related pain syndromes, such as stomatitis or peripheral neuropathy, although severe, may be self-limited if therapy is discontinued. This section will detail the more intractable therapy-related pain syndromes and discuss diagnostic issues and treatment approaches.

Postsurgical Pain Syndromes.

POST-THORACOTOMY PAIN [13, 25]. In this entity, pain may occur in the distribution of an intercostal nerve, which may be injured by the thoracotomy incision or by retraction of the chest wall during surgery. This usually produces pain in the immediate postoperative period. The pain is characteristically constant and corresponds to an area of sensory loss with dysesthesia in the scar area and hypesthesia in surrounding zones. Movement often exacerbates the pain, and patients commonly develop musculoskeletal complications such as a frozen shoulder because of this. Physical therapy is thus a helpful adjunct to treatment. The return of chest wall pain several months post-operatively is strongly suggestive of recurrent tumor [13, 25].

Postmastectomy Pain. This complication may occur in as many as 5% of women undergoing simple or radical mastectomy or even lumpectomy [26]. The pain is located in the posterior arm, axilla, and anterior chest wall and follows interruption of the intercostobrachial nerve, a cutaneous branch of the T2 nerve root [27]. Pain usually occurs within 2 months following surgery and is characterized as a tight, constricting, burning sensation without associated lymphedema. Pain is exacerbated by movement and patients often posture the arm in a flexed position close to the chest wall, predisposing to secondary myofascial pain such as a frozen shoulder. Treatment includes reassurance to the patient that the pain does not represent recurrent breast cancer, physical therapy to avoid a frozen shoulder, and drug therapy, usually including amitriptyline.

Post-Radical Neck Dissection Pain. Pain following radical neck dissection results from surgical injury or interruption of upper cervical or lower cranial nerves (spinal accessory nerve). Pain is characterized by a constant, burning sensation in the area of sensory loss. Dysesthesias and intermittent shocklike pain may also be present [9]. Management options include narcotic and non-narcotic analgesics, carbamazepine (when the shocklike pain predominates), amitriptyline, and perhaps transcutaneous electrical nerve stimulation (TENS).

Phantom-Limb Pain. This topic has been recently reviewed [28]. Pain following surgical amputation of a limb is of two types: stump pain and phantom-limb pain. These painful

clinical entities are separate from phantom-limb sensation, which occurs in all patients following limb amputation. By contrast, true phantom pain may occur in from 1%–50% of patients following amputation [28]. Stump pain often results from local nerve injury with neuroma formation — trigger points are common.

Postchemotherapy Pain.

PERIPHERAL NEUROPATHY. Painful dysesthesias may follow treatment with a variety of chemotherapeutic agents, especially vinca alkaloid drugs (e.g., vincristine) and cis-platinum, and may occur in the setting of a symmetrical polyneuropathy [29]. Pain is usually localized to the hands and feet, characterized as burning and prickling; there may be accompanying hyperpathia. The peripheral neuropathy is usually self-limited, resolving on discontinuation of the offending agent.

STEROID PSEUDORHEUMATISM. This interesting syndrome is characterized by diffuse myalgias and arthralgias with associated muscle and joint tenderness on palpation [30]. It follows both rapid and slow withdrawal of steroid medication in patients taking these drugs for variable periods of time. The signs and symptoms revert with reinstitution of the steroid medication. This complication of steroid withdrawal may cause diagnostic confusion if unrecognized.

ASEPTIC NECROSIS OF BONE. Aseptic necrosis of the humeral and, more commonly, femoral head are known complications of chronic steroid therapy [31]. Pain in the shoulder and knee or leg are the common presenting complaints, with x-ray changes occurring several weeks to months after the onset of pain. Therefore, bone and CT scans are the most useful diagnostic procedures, particularly early in the course of pain.

POSTHERPETIC NEURALGIA. This complication of acute herpes zoster is more common in the elderly. Several recent reviews have discussed theories of pathogenesis and summarized management options [32–35]. Pain in postherpetic neuralgia has three components: 1) continuous burning pain in the area of sensory loss sometimes associated with hyperpathia 2) painful dysesthesias, and 3) intermittent shocklike pain. A variety of treatment approaches have been advocated; almost none have been studied in a controlled fashion. Standard therapies include amitriptyline [33], carbamazepine (when shocklike pain predominates), and perhaps somatic and autonomic nerve blocks, especially in thoracic zoster.

Post-Radiation Therapy Pain. Fortunately, these syndromes are rare, although they are becoming more frequent as there are more long-term survivors of cancer. They produce progressive neurological dysfunction and pain resulting from irreversible injury to bone and neural tissue.

RADIATION FIBROSIS OF THE BRACHIAL AND LUMBAR PLEXUS. (see above discussions on brachial and lumbar plexopathy and references 9, 36)

RADIATION MYELOPATHY. Pain is an early symptom in 15% of patients with this entity [37]. Pain may be localized to the area of spinal cord damage or may be referred with dysesthesias below the level of injury. The neurologic symptoms and signs are that of a Brown-Sequard syndrome — unilateral corticospinal tract and posterior column dysfunction with contralateral spinothalamic tract dysfunction (pain, dysesthesia) and early bowel and bladder dysfunction. This contrasts with ESCC in which *bilateral* motor signs occur early, bowel and bladder dysfunction occur late, and pain is usually more severe [19].

RADIATION-INDUCED PERIPHERAL NERVE TUMORS [38, 39]. These tumors may be highly malignant fibrosarcomas and may directly contribute to the death of the patient. A painful enlarging mass in an area of previous irradiation suggests this entity. In one study, seven of nine patients who developed radiation-

induced nerve tumors presented with pain and progressive neurological deficit with a palpable mass involving the brachial or lumbar plexus [38]. Patients may develop this complication years following RT and may be cured of their original tumor [38, 39]. Pain is difficult to manage; treatment approaches include resection of tumor, narcotic analgesics, neuroablative surgery, and neurolytic anesthetic procedures (when appropriate).

It is usually necessary to treat pain with narcotic analgesics so that adequate diagnostic procedures can be performed and the patient can remain functional to participate in therapy. This is particularly true when invasive radiological procedures such as myelography or angiography are required. The lack of adequate pain control is *never* an acceptable reason for inadequate diagnostic evaluation. The following section discusses principles and guidelines for the appropriate use of analgesics in acute and chronic cancer pain.

Management of Cancer Pain With Analgesics

Drug therapy is the mainstay of treatment for the management of acute and chronic cancer pain [1, 40, 41, 79]. Three classes of analgesic drugs are used: 1) aspirin and nonsteroidal antiinflammatory drugs (NSAIDs), which act on peripheral nerve endings at the site of injury, and produce analgesia by altering the prostaglandin system; 2) adjuvant analgesics, which act centrally to produce analgesia in certain pain states; and 3) narcotic analgesics, which act by binding to opiate receptors and activating endogenous pain suppression in systems in the CNS. The choice of the specific drug approach is based on the type of pain, the acute or chronic nature of the pain, and an understanding of the clinical pharmacology of analgesics. Several recent reviews have discussed guidelines and principles for the use of analgesic drugs [1, 9, 40, 41]. The following summary emphasizes the guidelines and practical aspects of the use of analgesic drugs in the management of cancer pain.

NON-NARCOTIC ANALGESICS
(see Table 20-3)

These agents are considered "general purpose" analgesics and are often used early in the management of mild to moderate cancer pain, especially if related to bone metastasis and musculoskeletal inflammation. These drugs include aspirin, choline magnesium trisalicylate, fenoprofen, ibuprofen, diflunisal, and naproxen. They have four major pharmacologic properties: analgesic, antipyretic, antiplatelet, and anti-inflammatory actions [42]. However, there is a ceiling effect to analgesia (i.e., increasing the dose of aspirin beyond 975-mg to 1300-mg dose will produce no increase in peak effect but may increase the duration of analgesia).

In addition to the analgesic ceiling effect, these agents differ from morphinelike analgesics in that: 1) they do not produce tolerance, physical or psychological dependence (i.e., "addiction"), and 2) their presumed mechanism of action is inhibition of the enzyme prostaglandin synthetase, preventing the formation of prostaglandin E2 (PGE2) [42]. This prostaglandin is known to sensitize nociceptors on peripheral nerves to the pain producing effects of substances such as bradykinin. Thus, NSAIDs can influence pain at the level of the peripheral nervous system and may act synergistically with narcotic analgesics, which modulate pain in the central nervous system. Each of the NSAIDs are approved for use as analgesics for mild to moderate pain, and all have been shown to be equal to or more effective than aspirin in controlled clinical trials. They differ from each other in their pharmacokinetics and duration of analgesia and perhaps in side effects. For example, ibuprofen and fenoprofen have short half-lives and the same duration of action as aspirin; diflunisal and naproxen have longer half-lives and are longer acting than aspirin.

TABLE 20-3. Analgesics commonly used orally for mild to moderate pain

Name	Equianalgesic Dose* (mg)	Oral dose range (mg)	Duration of analgesia (hours)	Plasma half-life (hours)	Comments
A. NON-NARCOTICS					
Aspirin	650	650 QID	4–6	3–5	Standard of comparison for non-narcotics; often used in combination with narcotic-type analgesics; papillary necrosis and interstitial nephritis with chronic use; avoid during pregnancy, in hemostatic disorders, and in combination with steroids
Acetaminophen	650	650 QID	4–6	1–4	Like aspirin (but no antiinflammatory or antiplatelet effects)
Ibuprofen (Motrin®)	—	200–400 QID	4–6	2	Higher analgesic potential than aspirin
Fenoprofen (Nalfon®)	—	200–400 QID	4–6	3	Like ibuprofen
Diflunisal (Dolobid®)	—	500–1000 BID	8–12	8–12	Longer duration of action than ibuprofen; higher analgesic potential than aspirin
Naproxen (Naprosyn®)	—	250–500 QID	8–12	14	Like diflunisal
Choline magnesium salicylate (Trilisate®)	—	500–750 BID, TID	8–12	9–17	Antiinflammatory potency similar to aspirin; few antiplatelet or G.I. effects

B. NARCOTICS					
Codeine	32–65	32–65 q4h	4–6	3	"Weak" morphine; often used in combination with non-narcotic analgesics; bio-transformed, in part, to morphine; nausea and sedation common with dose escalation.
Oxycodone	5	5–10 q3h	3–5	—	Short acting; also formulated in combination with non-narcotic analgesics (Percodan®, Percocet®), which limits dose escalation.
Meperidine	50	50–100 q3h	3–5	3–4	Short acting; biotransformed to normeperidine, a toxic metabolite; normeperidine ($t_{1/2}$ = 12–16 h) accumulates with repetitive dosing, causing CNS excitation; not for patients with impaired renal function receiving monoamine oxidase inhibitors
Propoxyphene HCl (Darvon®) Propoxyphene napsylate (Darvon-N®)	65–130	65–130 q4h	4–6	12	"Weak" narcotic; often used in combination with non-narcotic analgesics;.long half-life, biotransformed to potentially toxic metabolite (norpropoxyphene); propoxyphene and metabolites accumulate with repetitive dosing; overdose complications by convulsions.
Pentazocine (Talwin®)	50	50–100 q4h	4–6	2–3	In combination with non-narcotics; in combination with naloxone to discourage parenteral abuse; may cause psychotomimetic effects; mixed agonist-antagonist and, therefore, may precipitate withdrawal in narcotic-dependent patients.

* These doses are recommended starting doses from which the optimal dose for each patient is determined by titration and the maximal dose is limited by adverse effects. For non-narcotic analgesics, relative potency was compared to aspirin. For narcotic analgesics, relative potency was compared to 10 mg i.m. morphine.
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Prolongation of the bleeding time may occur due to inhibition of platelet cyclooxygenase and reduced formation of thromboxane A. Gastric irritation also occurs commonly with this class of drugs.

Acetaminophen is also grouped in this class. It is roughly equipotent to aspirin in its analgesic and antipyretic potency, but has no antiinflammatory or antiplatelet effects [43]. Side effects include hepato-toxicity at doses greater than 10–15 g/day. Choline magnesium trisalicylate is also an effective analgesic, lacks antiplatelet effects, and has fewer gastrointestinal side effects than aspirin [41].

Nonsteroidal antiinflammatory analgesics may have a unique role in the management of bone pain secondary to tumor metastasis [1, 9]. However, the use of NSAIDs in oncology is limited because of their antipyretic effects, which may mask infection and because their effects on platelet function may risk hemorrhage in patients with coagulopathy.

NARCOTIC ANALGESICS

(See Tables 20-3 and 20-4)

Narcotic analgesics are used to manage moderate to severe acute and chronic cancer-related pain. The typical oral and parenteral starting doses and relative potencies of opioids with respect to morphine are listed in Tables 20-3 and 20-4. The following principles provide a basis for their rational use in cancer patients [40, 41].

1. *Individual dosage.* The optimal analgesic dose varies widely among patients. The typical starting dose for morphine ranges from 5 mg–15 mg s.c. or i.m. or 30 mg–60 mg p.o. q 3–4 hours.

   Give each analgesic an adequate trial by dose titration (i.e., increasing the dose up to the appearance of limiting side effects) before switching to another drug.

   Use the oral route whenever possible, but gear route of administration to the patient's needs. The oral route is convenient and probably associated with a slower rate of tolerance as compared to parenteral routes of administration. However, the onset of action is generally slower after oral administration and drugs are subject to a "first-pass" effect, (i.e., metabolism in the gut wall and liver), thereby reducing their potency. Other routes of administration include: sublingual, continuous subcutaneous and intravenous infusion, spinal epidural and intrathecal injections, infusions, and intraventricular and perhaps transdermal. (See the section novel routes of opioid administration for discussion of indications, drug doses, and possible complications for each of these routes of administration).
2. *Administer analgesic regularly (not prn)* — continuous pain requires continuous analgesics. However, this should be done after establishing the optimal dose by titration (especially when using a long half-life drug such as levorphanol or methadone). Once the dose requirements for a 24-hour period have been established, the analgesics can be administered on an around-the-clock basis. This will allow smoother pain control, a reduction in the daily amount of drug required, and perhaps fewer side effects.
3. *Recognize and treat side effects appropriately.* Among the more important are: sedation, constipation, nausea, vomiting, and respiratory depression. Sedation is sometimes associated with high peak concentrations of drug in brain, especially during acute parenteral narcotic administration, and is best treated by reducing the dose and increasing the frequency of administration. Dextroamphetamine (5 mg–15 mg/day, p.o.) may be added to increase alertness if sedation limits the patient's function and pain control is otherwise adequate. All patients taking narcotic analgesics acutely or chronically will be constipated and should be given stool softeners and laxatives. A useful laxative regimen includes dioctyl sodium sulfosuccinate (Colace) 100 mg–300 mg/day and Senokot tablets or suppositories that stimulate colonic motility. Bulk-forming laxatives such as Metamucil should be avoided. Nausea and

TABLE 20-4. Narcotic-type analgesics commonly used for severe pain

Name	Equianalgesic i.m. dose (mg)*	I.M./P.O. Potency ratio	Starting oral dose range (mg)	Plasma half-life (hours)	Comments
A. MORPHINELIKE AGONISTS					
Morphine	10	6	30–60	2–3	Standard of comparison for narcotic-type analgesics lower doses for aged patients with impaired ventilation; bronchial asthma; increased intracranial pressure; liver failure
Hydromorphone (Dilaudid®)	1.5	5	4–8	2–3	Slightly shorter acting than morphine; high-potency i.m. dosage form for tolerant patients
Methadone (Dolophine®)	10	2	5–20	24–36	Good oral potency: long plasma half-life; may accumulate with repetitive dosing, causing excessive sedation (on days 2–5)
Levorphanol (Levo-Dromoran®)	2	2	2–4	12–16	Like methadone, may accumulate on days 2–3; delirium and hallucinations may occur
Oxymorphone (Numorphan®)	1	—	—	—	Not available orally; like i.m. morphine
Heroin	5	6–10	not	0.5	Slightly shorter acting than morphine; biotransformed to active metabolites (e.g., morphine); not available in the U.S.
Meperidine (Demerol®)	75	4	not	3–4	Slightly shorter acting than morphine; used orally for less severe pain (see Table 20-2); toxic metabolite, normeperidine, accumulates with repetitive dosing, causing CNS excitation; not for patients with impaired renal function or receiving monoamine oxidase inhibitors

TABLE 20-4. (Continued)

B. MIXED AGONIST-ANTAGONISTS					
Pentazocine (Talwin®)	60	3	50–100	2–3	Used orally for less severe pain; less abuse liability than morphine (?); included in Schedule IV of Controlled Substances Act; may cause psychotomimetic effects; may precipitate withdrawal in narcotic-dependent patients; not for myocardial infarction
Nalbuphine (Nubain®)	10	—	—	5	Not available orally; like i.m. pentazocine but not scheduled; incidence of psychotomimetic effects lower with pentazocine
Butorphanol (Stadol®)	2	—	—	2–4	Not available orally; like nalbuphine
C. PARTIAL AGONISTS					
Buprenorphine (Temgesic®)	0.4	—	—	—	Not available orally; sublingual preparation not yet in U.S.; less abuse liability than morphine; does not produce psychotomimetic effects; may precipitate withdrawal in narcotic-dependent patients

For these equianalgesic i.m. doses, the time of peak analgesia in nontolerant patients ranges from $\frac{1}{2}$ in 1 hour and the duration from 4–6 hours. The peak analgesic effect is delayed and the duration prolonged after oral administration.

* These doses are recommended starting i.m. doses from which the optimal dose for each patient is determined by titration and the maximal dose limited by adverse effects. Equianalgesic doses are based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish relative potency.

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vomiting may be treated by administering hydroxyzine or a phenothiazine, or by switching to another opiate.

4. *Watch for the development of tolerance and treat appropriately*, especially using drug combinations that will enhance analgesia (see section on adjuvant analgesics). Also be aware of the development of physical dependence and prevent withdrawal, and do not confuse the concepts of tolerance, physical dependence, and psychological dependence (or addiction). These phenomena may be distinguished on clinical grounds [44]. In addition, recent experimental evidence in animals suggests that respiratory depression, physical dependence, and analgesia are mediated by different opiate receptor subtypes [45, 46].

Tolerance is an operational term which indicates that a larger dose of narcotic analgesic is required to maintain the original effect. Tolerance may develop in all patients taking narcotic analgesics chronically. Tolerance usually occurs in association with physical dependence but does not imply psychological dependence. The first sign of the development of tolerance is a decrease in the duration of effective analgesia. However, in patients with cancer, increasing requirements for analgesics is usually also associated with progression of disease. The following may be done to delay the development of tolerance and to provide effective analgesia in the tolerant patient: 1) combine narcotics and non-narcotics; 2) switch to an alternative narcotic and select one half of the predicted equianalgesic dose given in Tables 20-2 and 20-3 as the stating dose, since cross tolerance among narcotics is not complete; 3) use the oral route in preference to parenteral routes since tolerance is a function of the dose and frequency of administration — intravenous and spinal infusion of narcotics may produce rapid tolerance [41, 47–49].

Physical dependence is revealed in patients taking chronic opioids (usually longer than 2 weeks) when the abrupt discontinuation of a narcotic or the administration of a narcotic antagonist produces an abstinence syndrome. This syndrome is characterized by anxiety, nervousness, irritability, chills alternating with hot flashes, salivation, lacrimation, rhinorrhea, diaphoresis, piloerection, nausea, vomiting, abdominal cramps, insomnia, and, rarely, multifocal myoclonus [50]. The time course of this abstinence syndrome is a function of the half life of the narcotic. With short half-life drugs such as morphine or hydromorphone, the symptoms may appear in 6–12 hours and peak at 24–72 hours; for methadone and levorphanol (long half-life drugs), the symptoms may be delayed for several days and are typically milder. The abstinence syndrome can be avoided by slowly withdrawing chronically used narcotics — about 25% of the previous daily dose is required to prevent withdrawal [50].

Patients receiving chronic opioids are often tolerant to the respiratory depressant effects of these agents. In patients who have received a relative overdose of a short half-life opioid drug, physical stimulation may be enough to prevent significant hypoventilation. No patient has succumbed to respiratory depression while awake. However, if an opiate antagonist is required to reverse respiratory depression or coma in a patient who has been using narcotics chronically, a dilute solution of naloxone should be used (0.4 mg in 10 cc saline, administered as 0.5 cc by i.v. push every 2 minutes) since these patients are usually extraordinarily sensitive to opioid antagonists. The dose of naloxone should be titrated to avoid precipitation of profound withdrawal, seizures, and severe pain. Prior to naloxone administration in comatose patients, an endotracheal tube should be placed to prevent pulmonary aspiration. In patients receiving meperidine chronically, naloxone is contraindicated, as it may precipitate seizures by lowering the seizure threshold, allowing the convulsant activity of the active metabolite normeperidine to become evident [51].

Psychological dependence (addiction) is defined as a pattern of compulsive drug use characterized by a continued craving for a narcotic and the need to use the narcotic for effects other than pain relief [52]. The patient has drug-seeking and drug-abuse behavior, leading to overwhelming involvement with the use and procurement of the drugs. These behaviors might include forgery and theft of prescriptions, obtaining the same prescription from multiple doctors under false pretenses, and diversion of drugs for illegal use. Although most patients with psychological dependence are also physically dependent, the reverse is rarely the case in patients using narcotics for management of pain. The available data suggest that the risk of iatrogenic addiction is very small [44, 53–55] and the fear of narcotic addiction should not be a primary concern to the physician in cancer patients. Drug use alone is not the major factor in the development of psychological dependence; other medical, social, and economic factors appear to play a more important role [56].

REASONS FOR CHOOSING A NARCOTIC ANALGESIC IN PREFERENCE TO MORPHINE

All narcotics provide similar qualities of analgesia, and have similar qualities and frequency of side effects as well. However, there may be differences in individual responses to specific narcotics. Reasons for selecting a narcotic analgesic in preference to morphine (which is the standard against which all others are compared) include [41]:

1. A favorable prior experience with another drug.
2. A different time-action for analgesia is required. For example, methadone and levorphanol have much longer elimination half-lives (18–24 hours and 24–36 hours, respectively) than morphine (2–3 hours), and may provide a slightly longer duration of analgesia than morphine, especially in the opioid-naive patient. Methadone and/or levorphanol should be given every 4–6 hours to obtain constant pain relief, since the analgesic duration of action is shorter than the plasma half-life.
3. Avoiding a limiting adverse effect of morphine. For example, nausea may be associated with any of the narcotics, but some patients may be more sensitive to the emetic effects of morphine than other narcotics or vice versa.
4. To take advantage of incomplete cross tolerance among the morphinelike drugs by switching to another drug at an equianalgesic dose (see Tables 20-3 and 20-4).
5. The availability of a more desirable dosage form: *Sustained-release morphine preparations*: MS-Contin, Roxinol-SR. These morphine formulations are available in the USA as 30-mg tablets and have a duration of action of 8–12 hours (in Canada, MS CONTIN is available in 15-mg, 30-mg, 60-mg, and 100-mg tablets). The major indication for their use is to provide a longer duration of pain relief, especially at night. Their use may increase patient compliance (since fewer doses need to be taken during the day), and they often allow patients to sleep through the night without having to awake to take pain medications. To start a patient on a sustained-release morphine preparation, the 24-hour dose of an "immediate-release" opioid preparation should be calculated (in morphine equivalents using the relative potency estimates given in Tables 20-3 and 20-4), and one third or one half of this dose should be given q 8–12 hours, respectively, in the sustained-release morphine preparation. If the patient has breakthrough pain and "rescue doses" of narcotics are required before the scheduled 8–12 hours, these should be given as required with a standard morphine preparation.
   Rectal suppositories: hydromorphone (4 mg), numorphan (5 mg), and morphine (5 mg, 10 mg, 20 mg). These may be used in patients who cannot take oral drugs because of sedation, confusion, gastroin-

testinal obstruction, or when s.c. or i.v. administration is impractical.
High-potency preparation: hydromorphone-HP (10 mg/ml) is particularly useful for parenteral administration in an emaciated patient in whom administration of a potent analgesic in limited volume is desirable.

6. When more rapid onset of action is desired. Lipophilic drugs such as methadone, meperidine, or fentanyl may be desirable when premedicating a patient for a radiologic or surgical procedure. These drugs have more rapid entry into the brain than morphine and have a faster onset of action.

NOVEL ROUTES OF OPIOID ADMINISTRATION

Administration of opioids by other than oral ingestion or intermittent subcutaneous or intravenous injection may be necessary: 1) when these routes are impractical, 2) to minimize side effects, 3) to provide a longer duration of action, or 4) to facilitate nursing care and provide smoother pain control [57]. Guidelines have been published recently for the use of subcutaneous and intravenous infusions of opioids [47, 58, 59], and there is now more than a 10-year experience with spinal opioid administration [67]. Although the safety of these routes of administration have been demonstrated recently, their use requires sound knowledge of the clinical pharmacology of opioid analgesics and should only be undertaken if patients can be monitored carefully, particularly when used outside of the hospital. In addition, careful clinical studies documenting the efficacy of these routes have been sparse. Therefore, these routes of administration should not be used as first-line treatment for most cancer-related pain and should still be considered experimental. A review of novel routes of opioid administration has been published recently [57].

Sublingual administration of opioids may be desirable in patients with bowel obstructions who cannot absorb oral drugs and also avoids the first-pass metabolism effect when narcotics are absorbed through the bowel wall. Currently, there are no formulations of narcotic analgesics approved for sublingual administration in this country, although buprenorphine, a partial opioid agonist, is available in Europe [60, 61]. Other potential limitations in the use of sublingual opioids include poor bioavailability and unpalatable taste.

Intravenous infusion of opioids is indicated when 1) patients require injections more frequently than every 3 hours, 2) patients experience prominent "bolus effects" such as sedation and a rapid return of pain following single injections, or 3) rapid titration of drug is required to produce rapid pain relief.

Recently a series of guidelines have been suggested for use of i.v. infusions in the management of cancer pain [47]. Subcutaneous infusion obviates the need for intravenous access and allows long-term parenteral administration of opioids outside of the hospital. The indications for its use are similar to intravenous infusion, and this route is particularly effective in emaciated patients in whom loss of subcutaneous and muscle bulk makes repetitive injections painful [58, 59]. Any opioid may be infused by the subcutaneous or intravenous routes, but it is perhaps best to use short half-life drugs (such as morphine or hydromorphone) since drug accumulation over time is less dramatic than with long half-life drugs. Infusions of meperidine should be avoided since this may be associated with the accumulation of normeperidine with resultant tremors, multifocal myoclonus, and seizures.

Patient-controlled analgesia involves the intermittent bolus administration of opioids, the frequency of administration being determined by the patient [62]. This is usually accomplished with a drug delivery device in which the physician can program the dose or infusion rate and maximum frequency of drug injection available to the patient. By pushing a button, the patient can decide on the timing of a preselected dose, volume, and/or concentra-

tion of drug to be delivered by the intravenous, subcutaneous, or epidural route of administration. Patient-controlled analgesia has been studied most extensively by the intravenous route in the management of postoperative pain [62, 63]. Current data suggest that patients will titrate the frequency of administration to maintain a minimally effective plasma concentration with minimum side effects without overdosing themselves and, when offered a choice, prefer this method to more conventional methods of postoperative pain management. PCA may also have a role in the management of incident pain since the patient can administer a dose of medication in anticipation of movement, although its role in this condition is only speculative. Four PCA pumps are now approved by the FDA [64].

Spinal epidural or subarachnoid (intrathecal) administration may be accomplished by intermittent injection through reservoir devices or by continuous infusion through implantable and external pumps [67]. Spinal opioids have the potential advantage of affording long durations of pain relief (18 hours or longer) after administration of small doses (5 mg–10 mg morphine) in comparison to intravenous or subcutaneous administration. The indications for spinal opiate administration are still being defined, but this route may be particularly useful in patients with bilateral or midline pain below the umbilicus in whom adequate pain relief cannot be obtained with systemic opioids because of dose-limiting side effects. Epidural or intrathecal morphine administration is associated with significant levels of drug in the plasma, however, and blood-borne drug delivery to the brain, coupled with rostral CSF redistribution of drug, may produce nausea and vomiting, sedation, and respiratory depression. In the author's opinion, all patients should undergo myelography prior to initiation of spinal opiate therapy since obstruction of the epidural or subarachnoid space by tumor metastasis is frequent in cancer patients and is a major contraindication to the use of this technique [65]. Spinal opiate administration shows cross tolerance with systemically administered opiates and may be associated with the need for rapid dose escalation with chronic use. The rapid development of tolerance that may occur with spinal opiate administration has been a major limiting feature [48, 49, 66, 67].

Intraventricular (icv) morphine administration has been used to manage diffuse pain caused by advanced metastatic cancer, and, although long-lasting analgesia with rapid (15–20 minutes) onset may be achieved with smaller doses of drug than would be required with systemic administration, its advantage over more conventional routes is still unclarified. For example, sedation, nausea, vomiting, and pruritus occur commonly after intraventricular morphine administration, [57, 68]; these side effects may limit the use of icv morphine in individual patients, just as with systemic administration.

POTENTIALLY HAZARDOUS NARCOTICS

Pentazocine is the only mixed agonist-antagonist narcotic analgesic available in an oral formulation (Table 20-3). The mixed agonist-antagonist drugs bind to opioid receptors to produce analgesia (and are, therefore, opioid agonists) but also have antagonist properties — they reverse opioid analgesia and can precipitate withdrawal when given to patients who are taking morphinelike agonists — usually as a result of their activity at a different receptor [69]. Pentazocine may cause confusion and hallucinations and is not effective against severe pain. For these reasons the routine use of pentazocine cannot be recommended for management of chronic cancer pain. Nalbuphine, butorphanol, and buprenorphine (in the USA) are available for parenteral use, but these opioids frequently cannot be used in managing acute cancer pain because they antagonize the effects of classic opioid

analgesics and have a ceiling effect to their analgesic efficacy [61].

Meperidine is a synthetic, short-acting narcotic (3–4 hours) with poor oral potency (300 mg p.o. is roughly equivalent to 10 mg of i.m. morphine in single-dose analgesic studies). Normeperidine, a metabolite of meperidine, is a central nervous system stimulant and will produce anxiety, tremors, myoclonus, and generalized seizures if it accumulates with repetitive dosing of meperidine [51, 70]. This is more likely to occur in patients who are given naloxone, and in fact the administration of naloxone to patients receiving meperidine chronically may exacerbate the toxicity. For these reasons, meperidine should not be used chronically.

ADJUVANT "ANALGESICS" (Table 20-5)

These agents may be useful when combined with narcotic or non-narcotic analgesics [41, 71]. In some deafferentation pain syndromes they are the drug of choice. The classes of drug that are used as adjuvant analgesics are:

Anticonvulsants (phenytoin, carbamazepine). These are particularly useful for the management of pain in chronic neuralgias such as trigeminal neuralgia, postherpetic neuralgia, glossopharyngeal neuralgia, and post-traumatic neuralgias. Carbamazepine (400 mg–800 mg/day or higher) is the drug of choice for management of pain in trigeminal neuralgia, and any painful peripheral neuropathy in which there is a paroxysmal, shooting, electric shocklike quality to the pain. It is generally less useful in managing the burning and aching sensations associated with neuropathic pain.

Phenothiazines (methotrimeprazine, fluphenazine). Methotrimeprazine (Levoprome 20 mg/cc; available in parenteral formulation only) produces pain relief by non-opioid mechanisms [1, 9]. It may be useful for the treatment of opioid-tolerant patients and to avoid the constipating and respiratory-depressant effects of narcotics, but sedation and orthostatic hypotension are limiting side effects. Fluphenazine is also a useful adjuvant analgesic, particularly when used in combination with a tricyclic antidepressant (i.e., imipramine or amitriptyline). All phenothiazines are useful to combat narcotic-induced emesis. They are not used routinely in combination with narcotics because they may exacerbate the sedative effects of narcotics.

Tricyclic antidepressants (amitriptyline, imipramine, doxepin, others). These agents provide direct analgesic effects, possibly through their action of blocking the re-uptake of serotonin and norepinephrine at CNS synapses and are useful as primary and adjuvant analgesic drugs in pain of malignant and nonmalignant origin [41, 72, 73]. Amitriptyline has the best-documented analgesic actions but is also the least well tolerated because of its potent anti-cholinergic effects (dry mouth, urinary retention, delirium). Sedation and orthostatic hypotension may also be limiting side effects in the use of tricyclic compounds. The analgesic effects are seen at lower doses (typically 25 mg–150 mg/day for amitriptyline) than are their antidepressant effects. These drugs may ameliorate insomnia and may be given at bedtime for this additional beneficial effect. Their use is recommended for a wide variety of pain syndromes, in particular, pain due to nerve injury such as diabetic neuropathy, postherpetic neuralgia, vincristine- and cisplatin-induced neuropathy, and post-thoracotomy or postlaparotomy incisional pain.

Dextroamphetamine. Dextroamphetamine may produce additive analgesia when combined with narcotics in the postoperative period [74]. An additional indication for its use is the reduction of sedative effects of

TABLE 20-5. Adjuvant analgesic drugs useful in cancer pain management

Drug	Usual dose and rate of administration	Indications for use	Comment
Amitriptyline (Elavil®, others)	10–125 mg p.o./day	Deafferentation pain	Start treatment at 10 mg HS for elderly (25 mg HS for others) and slowly escalate to 125 mg as tolerated over 1–2 weeks *Side effects*: sedation, dry mouth, urinary retention (esp. in elderly males)
Fluphenazine (Prolixin®, others)	1–3 mg p.o./day	Deafferentation pain	Usually used in combination with amitriptyline (50–100 mg) or imipramine (50–100 mg) *Side effects*: sedation, orthostatic hypotension, extrapyramidal effects, including tardive dyskinesia
Methotrimeprazine (Levoprome®)	10–15 mg i.m.; then 10–20 mg i.m. q6–8h	Opioid-tolerant patients; to avoid severe opioid-induced constipation or respiratory depression	Not available orally. Should give 10–15 mg i.m. test dose. Analgesic effects are independent of opioid effects. 15 mg i.m. equipotent to 15 mg i.m. morphine *Side effects*: orthostatic hypotension, sedation, extrapyramidal effects, including tardive dyskinesia
Haloperidol (Haldol®)	0.5–1.0 mg p.o. BID or TID	Coanalgesic (with opioids) in acutely agitated or psychotic patients	May potentiate morphine analgesia and allow reduction in dose. Antipsychotic dose is higher (10 mg BID or TID) *Side effects*: sedation, hypotension, extrapyramidal effects, including tardive dyskinesia
Dextroamphetamine (Dexedrine®)	5–10 mg p.o. BID	Reduce sedative effects of narcotics	Avoid giving last dose in evening to minimize insomnia. May be co-analgesic with morphine in post-operative pain management *Side effects*: tachycardia, agitation, insomnia
Dexamethasone (Decadron®)	4–8 mg p.o. QID	Refractory bone and deafferentation pain. Epidural spinal cord compression (ESCC)	May have specific oncolytic effects. Dose and route of administration vary depending on clinical situation (may give up to 100 mg i.v. bolus for acute ESCC). Usually give over 1–2 week period. May give equivalent in prednisone *Side effects* (with acute use): weight gain, G.I. hemorrhaging, myopathy, psychosis (rare). Avoid concomitant NSAID use.
Carbamazepine (Tegretol®)	200 mg/day (start) 800–1200 mg/day	Deafferentation pain (esp. with lancinating or shooting qualities)	Should check blood counts at regular intervals. *Side effects*: nausea, dizziness, ataxia
Hydroxyzine (Vistaril®, others)	25–50 mg p.o./i.m. q6h	Coanalgesic in anxious, nauseated patient	Synergistic analgesic effect with narcotics. *Side effect*: drowsiness

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narcotics in cancer patients who are not able to function despite adequate pain relief because of sedation.

Steroids. Steroids have specific and nonspecific effects in managing acute and chronic cancer pain [41, 71]. They are oncolytic in some tumors (e.g., lymphoma) and ameliorate painful nerve or spinal cord compression by reducing edema in tumor and nervous tissue. Their use is standard emergency practice in the treatment of suspected malignant spinal cord compression (dexamethasone 16 mg–96 mg/day or its equivalent). One to two weeks of prednisone, 60 mg–80 mg, (or its equivalent in dexamethasone) treatment may be useful in the management of pain caused by malignant lesions of the brachial or lumbosacral plexus in patients in whom large doses of opioids are ineffective. In the moribund patient, steroids may provide euphoria and increase the appetite as well as relieve tumor-related pain; chronic side effects are not to be feared in this situation. Chronic use produces weight gain, Cushing's syndrome, proximal myopathy, psychosis (rarely), and increases the risk of G.I. bleeding (especially when used in combination with NSAIDs). In addition, rapid withdrawal of steroids may exacerbate pain independent of progression of systemic cancer ("pseudo-rheumatoid syndrome," see reference 30).

Antihistamines. Hydroxyzine has analgesic and anti-emetic activity in addition to its antihistamine effects. The usual dose is 25 mg–30 mg p.o./i.m. q 6 hours prn. It may produce additive analgesia when combined with narcotics, with only slightly more sedation, so that it is a useful adjuvant for the anxious, nauseated patient.

Common Misconceptions Regarding Drug Therapy in Cancer Pain

PAIN IN CHILDREN

Children may have acute or chronic pain, but inadequate verbal skills and/or misconceptions about the etiology or consequences of pain may alter the symptoms and signs. Children may not report pain because they fear it will lead to painful diagnostic evaluations. Behavioral changes such as an abnormal gait or persistent crying may be the only clue to the existence of pain.

There is no evidence that preadolescent and adolescent children are at higher risk for addiction than the general population when narcotics are prescribed for the management of pain. Like adults, they will develop tolerance during chronic narcotic treatment and may require larger doses to adequately control their pain, especially children with advanced cancer.

Young children may refuse to take oral medication or intermittent injections. Therefore, the intravenous route is used in the majority of children who cannot, or will not, take oral medications [75]. Narcotic infusions are being used increasingly frequently in the management of pediatric cancer pain [76].

In choosing the starting dose of narcotic analgesics for children for management of postoperative or cancer pain, the age, weight, and prior narcotic experience of the child should be considered. It is generally recommended that children 12 years of age or older require full adult doses (using 10 mg morphine i.m. as the standard dose, as depicted in Tables 20-3 and 20-4). Children 7–12 years old generally require 50% of the starting adult dose and children 2–6 years of age require 20%–25% of the starting adult dose. For infants under 2 years of age, the starting morphine dose is generally 0.1 mg/kg. It must be emphasized that these are starting doses, and, as in the adult patient, dose titration up or down is always necessary to obtain analgesia with a minimum of side effects.

HEROIN AND CANCER PAIN

Heroin does not offer any unique pharmacokinetic or pharmacodynamic advantages over morphine or other currently available narcotics for the management of pain of malignant

origin [77, 78]. Although oral heroin may provide analgesia in cancer patients [80], its effects are due to its in vivo biotransformation to morphine and 6-acetylmorphine, and it is a relatively inefficient way to deliver morphine [77].

Summary of Clinical Approach to Management of Cancer Pain with Analgesics

The following is a stepwise clinical approach to drug treatment of patients with acute pain or chronic cancer-related pain [41].

1. Start with non-narcotic analgesic (e.g., aspirin 650 mg or its equivalent every 4–6 hours). These agents may be effective without producing tolerance or physical dependence. The use of all aspirin-like drugs except choline magnesium salicylate and acetaminophen may be limited in the thrombocytopenic or surgical patient due to their antiplatelet effects and G.I. toxicity. The non-narcotic analgesics have a ceiling effect; for aspirin this is roughly 1000 mg/day. Increasing the dose beyond this amount may increase the duration of analgesia but will not increase the peak effect.
2. If additional analgesia is required, add a "weak" narcotic agonist such as oxycodone or codeine (see Tables 20-2 and 20-3 for typical starting doses). Oxycodone and codeine have no ceiling effect, but dose escalation is frequently limited by side effects such as nausea and mental clouding.
3. If more analgesia is required, then switch to a stronger narcotic (methadone, levorphanol, morphine, hydromorphone; see Tables 20-2 and 20-3 for typical starting doses). Although they are strong narcotics, morphine and hydromorphone have short durations of effect (3–4 hours). Levorphanol and methadone will accumulate with repetitive dosing, reaching steady state after 5–6 half-lives (2–3 days for levorphanol; 5–6 days for methadone).
4. Beware that in switching from a short half-life drug to a long half-life drug, a reduction in dose may by needed after 24 hours; the long half-life drug progressively accumulates over the first 3–5 days of therapy. Conversely, in switching from a long to short half-life drug, increased doses may be needed as early as 12 hours, as the former drug is eliminated from the body over 3–5 days.
5. Respect individual differences among patients and expect to titrate the dose of analgesics to maximum effect. Ask the patient if pain relief is adequate so that you can rapidly adjust the dose if necessary. Otherwise, patients may "put up" with suboptimal doses of analgesics.

References

1. Foley KM: The treatment of cancer pain. N Engl J Med 313:84–95, 1985.
2. Stjernsward J: Cancer pain relief: An important global public health issue. In: *Advances in Pain Research Therapy*, Vol 9. Fields HL, Dubner F, Servero, et al., eds. Raven Press, New York, 1985, pp 555–558.
3. Payne R: Anatomy, physiology and neuropharmacology of cancer pain. In: *Medical Clinics of North America*, Vol 71, No 2, Payne R, Foley KM, eds WB Saunders, Philadelphia, 1987, pp 153–168.
4. Payne R: Neuropathic pain syndromes with special reference to causalgia and reflex sympathetic dystrophy. Clin J Pain 2:59–73, 1986.
5. Sundaresan N, DiGiacinto GV: Antitumor and antinociceptive approaches to control cancer pain. In: *Medical Clinics of North America*, Vol 71, No 2, Payne R, Foley KM, eds. WB Saunders, Philadelphia, 1987, pp 329–348.
6. Foley KM: Clinical assessment of cancer pain. Acta Anaesth Scand (Suppl) 74:91–96, 1982.
7. Greenburg JS, Deck MDF, Vikram B, et al.: Metastasis to the base of the skull: Clinical findings in 43 patients. Neurology 31:530–537, 1981.
8. Foley KM, Sundaresan N: Management of cancer pain. In: *Cancer: Principles and Practice of Oncology*. Devita VT, Hellman S, Rosenberg SA, eds. J B Lippincott, Philadelphia, 1984, pp 1941–1961.
9. Foley KM: Pain syndromes in patients with cancer. In: Medical Clinics of North America,

Vol 71, No 2, Payne R, Foley KM, eds. Saunders, Philadelphia, 1987, pp 169–184.
10. Kori S, Foley KM, Posner JB: Brachial plexus lesions in patients with cancer: Clinical findings in 100 cases. Neurology 31:45–50, 1981.
11. Cascino TL, Kori S, Krol G, et al: CT scanning of the brachial plexus in patients with cancer. Neurology 33:1553–1557, 1983.
12. Payne R, Foley KM: Evaluation of the brachial plexus in patients with cancer. Neurology 76 (Suppl 1):329, 1986.
13. Kanner RM, Martini N, Foley KM: Incidence of pain and other clinical manifestations of superior pulmonary sulcus tumors (Pancoast tumors). In: *Advances in Pain Research and Therapy*, Vol 4, Bonica JJ, Ventafridda CA, Pagni, eds. Raven Press, New York, 1982, pp 27–38.
14. Jaeckle KA, Young DF, Foley KM: The natural history of lumbosacral plexopathy in cancer. Neurology 35:8–15, 1985.
15. Posner JB: Secondary neoplastic disease. In: *Diseases of the Nervous System: Clinical Neurobiology*. Asbury A, McKhan G, McDonald WI, eds. Saunders, Philadelphia, 1986, pp 1155–1168.
16. Wasserstrom WR. Glass JP, Posner JB: Diagnosis and treatment of leptomeningeal metastasis from solid tumors: Experience with 90 patients. Cancer 49:759–779, 1987.
17. Cairncross J, Posner JB: Neurological complications of malignant lymphoma. In: *Handbook of Neurology*, Vol 39,Vinken PJ, Broyen AW, eds. North Holland Publishing, Amsterdam, 1982, pp 27–62.
18. Gilbert RW, Kim JH, Posner JB: Epidural spinal cord compression from metastatic tumor: Diagnosis and treatment. Ann Neurol 3:183, 1978.
19. Posner JB: Back pain and epidural spinal cord compression. In: *Medical Clinics of North America*, Vol 71, Payne R, Foley KM, eds. Saunders, Philadelphia, 1987, pp 185–205.
20. Portenoy R, Lipton RB, Foley KM: Back pain in the cancer patient: An algorithm for evaluation and management. Neurology 37: 134–138, 1987.
21. Rodichok LD, Ruckdeschel JC, Harper GR, et al.: Early detection and treatment of spinal epidural metastasis: The role of myelography. Ann Neurol 20:696–702, 1986.
22. Siegal T, Siegal T: Vertebral body resection for epidural compression by malignant tumors. J Bone J Surg 67A:375–382, 1985.
23. Sundaresen N, Galicich JH, Lane JM, et al.: The treatment of neoplastic epidural cord compression by vertebral body resection and stabilization. J Neurosurg 63:676–684, 1985.
24. Foley KM: Pain syndromes in patients with cancer. In: *Advances in Pain Research Therapy*, Vol 21, Bonica JJ, Ventafridda V, eds. Raven Press, New York, 1979, pp 59–75.
25. Kanner RM, Martini N, Foley KM: Nature and incidence of postthoracotomy pain. Am Soc Clin Oncol 1:152, 1982.
26. Granek I, Achikari R, Foley KM: Postmastectomy pain syndrome: Clinical and anatomic correlates. Proc Assoc 3:122, 1983.
27. Assa J: The intercostobrachial nerve in radical mastectomy. J Surg Oncol 6:123–126, 1974.
28. Sherman RA, Sherman CJ, Gall NG: A survey of current phantom limb pain treatment in the United States. Pain 8:85–99, 1980.
29. Young DF, Posner JB: Nervous system toxicity of chemotherapeutic agents. In: *Handbook of Clinical Neurology*, Viaken PJ, Broyn CTW, eds. North-Holland Publishing, Amsterdam, 1980, pp 91–129.
30. Rotstein J, Good RA: Steroid pseudorheumatism. Arch Intern Med 99:545–555, 1957.
31. Ihde DC, Devita VT: Osteonecrosis of the femoral head in patients with lymphoma treated with intermittent combination chemotherapy (including corticosteroids). Cancer 36:1585–1588, 1975.
32. Portenoy RK, Duma C, Foley KM: Acute herpetic and postherpetic neuralgia: Clinical review and current management. Ann Neurol 20:651–664, 1986.
33. Watson CP, Evans RJ, Reed K, et al.: Amitriptyline versus placebo in postherpetic neuralgia. Neurology 32:671–673, 1982.
34. Watson PN, Evans RJ: Postherpetic neuralgia: A review. Arch Neurol 43:836–840, 1986.
35. Loeser JD: Herpes zoster and postherpetic neuralgia. Pain 25:149–164, 1986.
36. Thomas JE, Cascino TL, Earle JD: Differential diagnosis between radiation and tumor plexopathy of the pelvis. Neurology 35:1–7, 1985.
37. Jellinger K, Sturm KW: Delayed radiation myelopathy in man. J Neurol Sci 14:389–408, 1971.
38. Foley KM, Woodruff J, Ellis F, et al.: Radiation induced malignant and atypical peripheral nerve sheath tumors. Ann Neurol 7:311–318, 1980.
39. Ducatman BS, Scheithauer BW: Postirradia-

tion neurofibrosarcoma. Cancer 51:1028–1033, 1983.
40. Inturrisi CE, Foley KM: Narcotic analgesics in the management of pain. In: Analgesics: *Neurochemical, Behavioral and Clinical Perspectives*. Kuhar M, Pasternak G, eds. Raven Press, New York, 1984, pp 257–288.
41. Payne R, Max M, Inturrisi CE, et al.: Principles of analgesic use in the treatment of acute pain and chronic cancer pain: A concise guide to medical practice. American Pain Society, Washington, D.C., 1987.
42. Kantor TG: The control of pain by nonsteroidal anti-inflammatory drugs. Med Clin North Am 66:1053–1059, 1982.
43. Amcer B, Greenblatt DJ: Acetaminophen. Ann Intern Med 87:202–209, 1977.
44. Kanner RM, Foley KM: Patterns of narcotic drug use in a cancer pain clinic. Ann New York Acad Sci 362:161–172, 1981.
45. Ling GSF, Spiegal K, Lockhart SH, Pasternak GW: Separation of opioid analgesia from respiratory depression: Evidence for different receptor mechanisms. J Pharm Exp Ther 232:149–155, 1985.
46. Ling GSF, Macleod JM, Lee S, et al.: Separation of morphine analgesia from physical dependence. Science 226:462–464, 1984.
47. Portenoy RK, Moulin DE, Rogers AL: IV infusion of opioids for cancer pain: Clinical review and questions for use. Cancer Treat Rep 70:575–581, 1981.
48. Greenberg HS, Taven J, Ensminger W, et al.: Benefit from and tolerance to continuous intrathecal infusion of morphine for intractable cancer pain. J Neurosurg 57:360–364, 1982.
49. Max M, Inturrisi CE, Kaiko R, et al.: Epidural and intrathecal opiates: Cerebrospinal fluid and plasma profiles in patients with chronic cancer pain. Clin Pharmacol Ther 38:631–641, 1985.
50. Kolb L, Himmelsbach CK: Clinical studies of drug addiction III: A critical review of withdrawal treatments with methods of evaluating abstinence syndromes. Am J Psychiat 94: 759–797, 1938.
51. Kaiko RF, Foley KM, Grabinski PY, et al.: Central nervous system excitatory effects of meperidine in cancer patients. Ann Neurol 13:180–185, 1983.
52. Jaffee JH: Drug addiction and drug abuse. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th edition, Gillman AG, Goodman LS, Gilman A, eds Macmillan, New York, 1980, pp 535–584.
53. Perry S, Heidrisch G: Management of pain during debridement: A survey of U.S. burn units. Pain 13:267–280, 1982.
54. Porter J, Jick H: Addiction, rare in patients treated with narcotics. N Engl J Med 302:123, 1980.
55. Medina JL, Diamond S: Drug dependency in patients with chronic headache. Headache 17:12–14, 1977.
56. Newman RG: The need to redefine 'addiction.' Engl J Med 308:1096–1098, 1983.
57. Payne R: Novel routes of opioid administration. Oncol Suppl 1:10–18, 1987.
58. Coyle N, Manskop A, Maggard J, et al.: Continuous subcutaneous infusions of opiates in cancer patients with pain. Onc Nucs Forum 13:53–57, 1986.
59. Ventafridda V, Spoldi E, Ceraceni A, et al.: The importance of continuous morphine administration for cancer pain control. The Pain Clinic 1:47–55, 1986.
60. Wallenstein SL, Kaiko RF, Rodgers AG, et al.: Clinical analgesic assay of sublingual buprenorphine and intramuscular morphine. In: MDA Research Monograph, Vol 41, *Problems of Drug Dependence*, Cooper AR, Altman F, Brown BS, et al., eds USDHHS, Rockville, 1981, pp 288–293.
61. Houde RW: Analgesic effectiveness of narcotic agonist-antagonists. Br J Clin Pharmacol 7:297S–380S, 1979.
62. Graves DA, Foster JS, Batenhorst RL, et al.: Patient-controlled analgesia. Ann Intern Med 99:360–366, 1983.
63. Bennett RL, Batenhorst RL, Bivins BA, et al.: Patient-controlled analgesia: A new concept in post-operative pain relief. Ann Surg 195: 700–705, 1982.
64. Wall RT: Patient-controlled analgesia. In: *Mediguide to Pain*, Vol 7, Armoff Am, ed. DellaCorte Publications, New York, 1986, pp 1–4.
65. Cherry DA, Gourlay GK, Cousins MJ: Epidural mass associated with lack of efficacy of epidural morphine and undetectable CSF morphine concentration. Pain 25:69–73, 1986.
66. Coombs DW, Saunders RL: Intrathecal morphine tolerance: Use of intrathecal clonidine, DADLE and intraventricular morphine. Anesthesiology 62:358–363, 1985.
67. Payne R: Role of epidural and intrathecal narcotics in the management of cancer pain. In: *Medical Clinics of North America*, Vol 71,

Payne R, Foley K eds. Saunders, Philadelphia, 1987, pp 313–328.
68. Lobato RD, Madrid JL, Fatela LV: Analgesia elicited by low-dose intraventricular morphine in terminal cancer patients. In: *Advances in Pain Research Therapy*, Vol 9, Fields HL, et al., eds. Raven Press, New York, 1985, pp 673–681.
69. Martin WR: Pharmacology of opioids. Pharmacol Rev 35:283–323, 1984.
70. Szeto HH, Inturrisi CE, Houde R, et al.: Accumulation of normeperidine, an active metabolite of meperidine in patients with renal failure or cancer. Ann Int Med 86:738–741, 1977.
71. Foley KM: Adjuvant analgesic drugs in cancer pain management. In: *Evaluation and Treatment of Chronic Pain,* Aronoff GM, ed. Urban and Schwarzenberg, Baltimore, Munich, 1985, pp 425–434.
72. Getto CJ, Sorkness CA, Howell T: Antidepressants and chronic non-malignant pain: A review. J Pain Symptom Manag 2:9–18, 1987.
73. Feinmann C: Pain relief by antidepressants: Possible modes of action. Pain 23:1–8, 1985.
74. Forrest WH, et al.: Dextroamphetamine with morphine for the treatment of post-operative pain. N Engl J Med 296:712–715, 1977.
75. Schechter NL: Pain and pain control in children. Current problems in pediatrics. Year Book Medical Publishers, 1985, pp 3–67.
76. Miser AW, Miser JS, Clark BS: Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. J Pediat 96:930–932, 1980.
77. Inturrisi CE, Max MB, Foley KM, et al.: The pharmacokinetics of heroin in patients with chronic pain. N Engl J Med 210:1213–1217, 1984.
78. Kaiko RF, Wallenstein SL, Rogers AG, et al.: Analgesic and mood effects of heroin and morphine in cancer patients with post-operative pain. N Engl J Med 304:1501–1505, 1981.
79. Twycross RG, Lack SA: Symptom Control in Far Advanced Cancer Pain Relief. Pitman, London, 1984.
80. Twycross RG: Clinical experience with diamorphine in advanced malignant disease. Int J Clin Pharmacol 7:184–198, 1974.

21. INTRODUCTION TO NEUROSURGICAL TREATMENT OF CANCER PAIN

Ronald Brisman, M.D.

Most patients with pain from cancer do not require neurosurgical procedures. After a thorough diagnostic evaluation and treatment with appropriate surgery, radiotherapy, or chemotherapy, patients who continue to have pain are managed with medication. If milder analgesics are not adequate, narcotics are given and increased in dose and frequency according to pharmacokinetic principles outlined in Chapter 20. For patients who continue to have incapacitating pain, neurosurgical intervention may be beneficial. This is offered to patients who cannot be managed with oral narcotics because of inadequate analgesia, unacceptable mental impairment, nausea, or vomiting.

Anterolateral cordotomy used to be the major neurosurgical procedure for intractable cancer pain. This has been superseded by the insertion of an intrathecal catheter connected to an internalized pump that continuously infuses morphine. Other neurosurgical techniques that occasionally may be useful, especially when intraspinal morphine is not effective or not applicable, are intraventricular morphine, deep brain stimulation, anterolateral cordotomy, rhizotomies, and commissural myelotomy.

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22. ANTEROLATERAL SPINAL CORDOTOMY FOR CANCER PAIN

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Anterolateral spinal cordotomy can relieve certain kinds of pain, but its usefulness is severely limited by difficulty in performing the procedure, unreliability in relieving pain, and complications, which may be fatal. Because of these, which include postcordotomy dysesthesias, the procedure is limited to patients with terminal cancer. Even here, however, cordotomy should be reserved for those with intractable cancer pain that does not respond to intrathecal morphine or deep brain stimulation.

Anterolateral cordotomy can provide pain relief contralateral and two or more segments below the level of the lesion. It is most effective for somatic or nociceptive pain, which may be lancinating or toothachelike [1], and much less helpful for dysesthetic [2] deafferentation pain, which may be burning, prickling, pressure, or crawling [1].

Open Cordotomy

Open cordotomy is done at either the high cervical region (C1-2) or C3 because the pyramidal fibers may not be fully crossed and into the posterior aspect of the cord until the caudal half of C2 [3]. It may also be done at the upper thoracic area. Bilateral high cervical cordotomy should not be done because of the high risk of sleep apnea. If bilateral cordotomy needs to be performed, it can be done at the upper thoracic location; one side is done at T1-2 and the other side at T2-3. If the pain is located higher, the side of the higher pain can be treated with a contralateral high cervical cordotomy and the other side can be treated with an upper thoracic cordotomy.

Bilateral cordotomy is often necessary. Patients with midline cancer may have predominantly unilateral pain, but after a contralateral cordotomy that relieves their initial pain they may then become aware of pain on the opposite side.

The open cordotomy was the first kind of cordotomy to be available. It is a major surgical procedure, and patients who are very debilitated and terminally ill may not tolerate it very well. In addition, it is usually done under general anesthesia, and it is possible to damage the corticospinal tracts with resulting ipsilateral weakness. Impairment of urinary control may also result and is much more likely to occur when bilateral cordotomy is done. The paraplegic cancer patient with impaired urinary function and bilateral pain who is not terminal is one of the best candidates for a bilateral open upper thoracic cordotomy.

Most patients treated with open cordotomy have good relief of their pain (Table 22-1). There was one postoperative death from urinary sepsis in the seven patients treated this way. Since most of these patients were paraplegic, it is difficult to assess the added risk of corticospinal tract damage in these patients. Similar data are reported by others [4], includ-

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TABLE 22-1. Open cordotomy

Pts	OR	Cancer[1]	Type OR[2]	Pain relief	Death
7	8	6/7	3 high cervical	2	1
			6 high thoracic	5	0

[1] One patient with traumatic paraplegia did not get relief.
[2] Four operations were bilateral cordotomies.

ing the occasional complication of hypotension that may occur following bilateral high thoracic or cervical cordotomy.

Percutaneous High Cervical (C1-2) Cordotomy

Because of the frequent complications associated with open cordotomy and the difficulty in doing such a procedure in very debilitated patients, a percutaneous technique was devised [5, 6]. This procedure could often be accomplished on very ill patients and had the additional advantage of being done on an awake and cooperating patient. Small incremental lesions [5] and stimulation to detect the precise location of the electrode before lesioning [6, 7] were additional advantages.

The patient is positioned supine in the x-ray suite. The head rests on the Rosomoff head holder [5]. C-arm fluoroscopy and standard PA (with mouth open so the odontoid can be visualized) and lateral x-rays are taken. The electrode is presized prior to the procedure so that 2 mm of bare electrode and 2 mm of insulated sheath will protrude from the spinal needle when the electrode is fully inserted. The C1-2 interpace is identified with lateral x-ray and the thin-walled, short-beveled, 18-gauge spinal needle is directed slightly anterior to the midpoint of the spinal canal until spinal fluid is obtained. An emulsification of 3 ml of spinal fluid, 3 ml of Pantopaque and air is prepared, and 2 ml of this solution and 8 ml of air are injected; PA and lateral x-rays are taken. The anterior border of the spinal cord is seen below the air and the Pantopaque helps identify the dentate ligament. The needle is positioned lateral to the spinal cord, usually between the lateral border of the odontoid and the lateral border of the spinal canal. The tip of the needle is directed to the anterior quadrant of the spinal cord, 1 mm anterior to the dentate ligament or 4 mm posterior to the anterior border of the spinal cord for sacral or lumbar pain, or 2 mm below the anterior border of the spinal cord for arm pain.

The electrode is now inserted fully into the spinal needle and the impedance is monitored [7]. The impedance rises from an average of 190 ohms when the electrode is in the spinal fluid, to 290 ohms when it touches the pia, to 600 ohms when it is in the spinal cord.

Electrical stimulation is now carried out. At 50 Hz–60Hz, contralateral sensations are obtained when the lateral spinothalamic tract is stimulated, with the upper extremity being anterior to the lower extremity. Sometimes bilateral sensations in the hands may be elicited when the more anterior aspect of the anterolateral quadrant is stimulated.

Radiofrequency electrocoagulations are made at 80 mA for 15 to 30 seconds until the desired level of analgesia is produced. In between each lesion, the patient is tested for possible weakness and the needle repositioned or the procedure terminated if any weakness develops.

Problems with High Cervical Percutaneous Cordotomy

The most serious problem, which is not too uncommon, is respiratory impairment; it is often fatal. This occurred in 4 of 24 procedures in 21 patients (Table 22-2). Three of these patients died suddenly with little apparent warning. Respiratory failure is presumed to be the cause. The risk of this occurring is much

TABLE 22-2. Percutaneous C1–2 Cordotomy

Pts	OR	Cancer[1]	Lower Body	Pain Relief	C1–2 Unilat	Death
21	24	20	19	19/24	22	4[2]

[1] One patient had herpes zoster thoracic radiculopathy.
[2] Includes one patient with bilateral C1–2 cordotomy who died.

higher in cases of bilateral than unilateral high cervical cordotomy. Because of this, bilateral high cervical cordotomy is sometimes staged with a delay of at least 1–2 weeks between the procedures. Even with staging, bilateral high cervical cordotomy is too dangerous and should not be done.

Respiratory difficulties may develop even when unilateral cordotomy is attempted at the high cervical level. Patients who have pulmonary function impairment on one side (frequently the side of the cancer and the pain), may not tolerate a unilateral high cervical cordotomy well because it may interfere with respiratory function on the side of the cordotomy, which is contralateral to the side of the pain. Even patients with normal preoperative pulmonary function may develop significant respiratory problems after what was thought to be a unilateral cordotomy, because the needle and electrode may traverse both sides of the spinal cord and may cause damage to both anterior quadrants. The lateral percutaneous C1–2 cordotomy involves final placement that is often across the midline of the spinal canal because the cord moves away from the needle. A definite resistance has to be overcome, both to penetrate the dura and to enter the cord. In doing this, the needle may damage both sides of the cord.

Respiratory pathways in the high cervical cord include an involuntary descending pathway in the ventrolateral white matter, a descending pathway in the corticospinal tract for voluntary respiration, and an ascending respiratory pathway in the lateral columns of the cord constituting part of the spinoreticular system [8]. The anterior aspect of the anterolateral quadrant carries the fibers responsible for involuntary breathing. The cervical part of the spinothalamic tract is nearby and just lateral.

Sleep apnea may develop when the autonomic neural control of breathing is interrupted, especially if the defect is bilateral. Apnea monitoring is an important precaution to take for any patient with high cervical cordotomy in order to detect and manage such a complication. However, apnea monitoring will not guarantee the prevention of a fatal outcome.

Another complication is the development of post-cordotomy dysesthesias, a discomforting consequence of deafferentation that is more likely to develop 1 or 2 years after cordotomy.

Impairment of bladder and bowel control and sexual function may also occur, especially after bilateral cordotomy. Permanent major bladder dysfunction requiring catheter or condom occurred in 3.7% of unilateral cordotomies and 22% of bilateral cordotomies [2]. Ipsilateral weakness may develop from corticospinal tract damage and was major in 0.5% [2]; slight paresis was noted at discharge in 21% of unilateral cordotomies and was present at postdischarge followup in 8.8% [2].

Failure to obtain a satisfactory level occasionally occurs. Some patients may be in too much pain to lie supine and cooperate during the procedure. Anatomic variations exist in the spinal cord so that the spinothalamic tracts and the corticospinal tracts are not always where they are expected to be [9]. The dentate ligament does not always demonstrate the equator of the spinal cord; it may be dorsally displaced, and the anterior border of the cord is a more reliable landmark [9].

Recurrent pain over a period of time develops in many patients. In one series, 90% were free of pain immediately following unilateral and bilateral cordotomy, 60% had good

relief after 1 year, and only 40% after 2 years [1].

Anterior Approach for Low Cervical Percutaneous Cordotomy

An anterior approach through the disc at either C4–5 or C5–6 has been described for percutaneous radiofrequency cordotomy [10]. This has the advantage of avoiding respiratory impairment but is more difficult to do (Table 22-3). There is a small risk of damage to the ipsilateral ventral roots to the upper extremity. It is not possible to get as high a level of analgesia as in the higher cordotomy. Bilateral anterior cordotomy can be done without respiratory problems [10].

TABLE 22-3. Percutaneous anterior cordotomy (Below C1–2)

Pts	OR	Location C34	45	56	Cancer	Pain relief	Death	Arm weakness
9	9	1	5	3	8	3	0	1 mild

Summary

Anterolateral cordotomy may relieve contralateral somatic pain two or more segments below the level of the cordotomy.

Open techniques exist for high cervical and high thoracic cordotomies. These are major neurosurgical procedures that are often effective but inappropriate for most patients who are debilitated and terminally ill.

High cervical percutaneous radiofrequency cordotomy can provide pain relief for many patients and can be done in very ill patients. The risks of respiratory impairment are significant, especially when the procedure is done bilaterally or unilaterally on a patient with already impaired pulmonary function on the side contralateral to the needle.

An anterior approach through the disc space is possible for low cervical percutaneous radiofrequency cordotomy. Respiratory impairment is much less likely than with the high cervical cordotomy, but the low cervical technique is more difficult to do and less likely to result in pain relief.

Other problems associated with cordotomy are the development of pain contralateral to the side made analgesic by the cordotomy, dysesthesias, weakness ipsilateral to the cordotomy, difficulty in obtaining the desired level of analgesia, and impairment of bladder, bowel, or sexual function, which is more likely when the procedure is bilateral.

Cordotomy is too dangerous and too ineffective in the long term to be recommended for noncancer pain. Even for patients with cancer and a limited life expectancy, cordotomy should be a last resort.

References

1. Rosomoff HL: Percutaneous spinothalamic cordotomy. In: Neurosurgery, Wilkins RH, Rengachary SS, eds, McGraw-Hill, New York, 1985, pp 2446–2451.
2. Tasker RR: Percutaneous cordotomy — the lateral high cervical technique. In: Operative Neurosurgical Techniques, Vol 2, Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1137–1153.
3. Poletti CE: Open cordotomy — new techniques. In: Operative Neurosurgical Techniques, Vol 2 Schmidek HH, Sweet WH, eds. Grune & Stratton, New York, 1982, pp 1119–1136.
4. Ehni BL, Ehni G: Open surgical cordotomy. In: Neurosurgery, Wilkins RH, Rengachary SS, eds. McGraw-Hill, New York, 1985, pp 2439–2445.
5. Rosomoff HL, Carroll F, Brown J, Sheptak P: Percutaneous radiofrequency cervical cordotomy: Technique. J Neurosurg 23:639–644, 1965.
6. Mullan S: Percutaneous cordotomy. J Neurosurg 35:360–366, 1971.
7. Taren JA, Davis R, Crosby EC: Target physiologic corroboration in stereotaxic cervical cordotomy. J Neurosurg 30:569–584, 1969.
8. Lema JA, Hitchcock E: Respiratory changes

after stereotactic high cervical cord lesions for pain. Appl Neurophysiol 49:62–68, 1986.
9. Sweet WH: Recent observations pertinent to improving anterolateral cordotomy. Clin Neurosurg 23:80–95, 1976.
10. Lin PM, Gildenberg PL, Polakoff PP: An anterior approach to percutaneous lower cervical cordotomy. J Neurosurg 25:553–560, 1966.

23. NEUROSURGICAL TREATMENT (OTHER THAN CORDOTOMY) FOR CANCER PAIN

Ronald Brisman, M.D.

Morphine Infusion

Intraspinal morphine infusion [1–5] (see Chapter 17) is one of the most important neurosurgical treatments for intractable cancer pain that remains severe in spite of oral analgesics. For patients who respond to a test dose of intraspinal morphine, a catheter is placed in the subarachnoid space and connected to an implanted pump (Infusaid) for continuous infusion of morphine.

Intraspinal morphine infusion has some notable advantages over anterolateral cordotomy. Morphine infusion is much safer and is much less likely to cause a neurological deficit and morphine infusion can relieve bilateral pain as easily as unilateral pain.

Patients with pain in the lower half of the body are the best candidates for morphine infusion, because the catheter can be placed at the lower part of the spinal cord, and a much higher concentration of morphine can be delivered here than at the upper cervical cord or brainstem. A potent analgesic effect can be achieved for the lower part of the body with relatively less morphine to interfere with respiration as mediated by cervical and brainstem centers. In addition, there is less supratentorial than spinal morphine and less somnolence or mental impairment.

Intraspinal morphine may not be as satisfactory for pain in the upper part of the body. Although the lumbar intraspinal route can provide such a high level of morphine in all parts of the nervous system that it might still be effective for relief of pain in the upper part of the body, less differential can be achieved between the concentration of morphine at the spinal segment mediating the pain and the cervical cord that controls respiration or the brain.

Imaging of the spine with either nuclear magnetic resonance or myelography should be considered if there is a possibility of an intraspinal lesion. The location of such pathology may influence the placement of the catheter.

Patients with pain in the face have been treated with intraventricular morphine [6, 7], which has usually been injected into an Ommaya (or other kind of) reservoir that is connected to an intraventricular catheter. The analgesic effect of the morphine may last for 12 to 24 hours. Patients with pain in the lower half of the body may also respond to intraventricular morphine, even after they no longer benefit from intrathecal morphine, suggesting an important supraspinal analgesic mechanism [7, 8]. Although intraventricular administration of morphine is more cumbersome and hazardous than intraspinal injection, the intra-

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ventricular route may be indicated for some patients who are not be helped by the intraspinal method.

Deep Brain Stimulation (see Chapter 18)

Electrical stimulation of the internal capsule or somatosensory thalamus (SST) [9] and periventricular gray (PVG) [10–13] have been reported to relieve cancer pain. Unilateral PVG stimulation is more likely to help bilateral pain, and SST stimulation is better for deafferentation pain [9, 11].

Some doubts as to the effectiveness of PVG stimulation have been expressed [9, 14]. In one study of 17 patients, one investigator found no significant analgesia nor any relief in cases of nociceptive (mostly cancer and nerve root compression) pain [9].

SST stimulation has the added advantage of creating a small thalamotomy effect, which may cause temporary pain relief by itself, even without stimulation. When pain returns, the analgesia may be restored by electrical stimulation. SST stimulation is particularly helpful for patients with unilateral deafferentation pain in the upper part of the body, such as those with lung cancer and brachial plexopathy. High cervical cordotomy is dangerous in these patients because of the risk of respiratory impairment, and morphine infusion is less satisfactory than in patients with lower body pain.

Commissural Myelotomy

Midline, longitudinal commissural myelotomy may relieve pain, especially midline and bilateral pain caused by cancer in the lower part of the body [15–19].

A laminectomy is done bilaterally starting two spinal cord segments above the highest pain level and is extended caudally approximately 40 mm, usually through S1. The operating microscope is used to indentify the midline septum of the dorsal cord. Longitudinal section is carried through the posterior commissure, central canal, and anterior commissure [15–17, 19, 20]. The procedure may be done with carbon dioxide laser [21], but it is uncertain whether this minimizes complications.

The postoperative pain relief does not correspond to the level of analgesia and may result from an imbalance created between the anterolateral and dorsomedial pain-mediating systems [18].

Many patients develop postoperative dysesthesias, which usually subside within a few weeks. It is said that impairment of bladder and bowel function does not occur following the procedure, but this is difficult to assess because many of these patients already have abnormalities in these areas.

Commissural myelotomy is less likely to interfere with walking than bilateral anterolateral cordotomy and may be less likely to cause bladder or bowel impairment. It is preferable to cordotomy for cancer patients with midline or bilateral lower half of the body pain, preserved strength in the legs, and normal bladder and bowel function. Commissural myelotomy is a major neurosurgical procedure that has the drawback of inducing postoperative dysesthesias, dorsal column malfunction, and possible corticospinal tract injury. Morphine infusion should be considered before doing commissural myelotomy.

Because pain is likely to recur within 2 to 5 years of commissural myelotomy [17], and a neurological deficit may be caused by this procedure, it is not indicated for noncancer pain.

Hypophysectomy [22–32]

Pain relief in patients with metastatic cancer has been reported following hypophysectomy. The hypophysectomy has been done by open craniotomy, transsphenoidal, radiofrequency,

cryo, or chemical (alcohol) injection techniques. The results appear similar regardless of the method of hypophysectomy.

Although most patients treated with hypophysectomy have had breast or prostate cancer, some patients with other kinds of cancer and hormone-resistant tumors have also had pain relief. The analgesic effect of hypophysectomy seems unrelated to reduced levels of pituitary hormones and is more likely a result of a hypothalamic effect.

Pain from bone metastases has been reported to respond particularly well to hypophysectomy, although other kinds of pain have also been relieved.

Rhizotomy

Sacrococcygeal rhizotomy may relieve intractable perineal pain caused by malignancy in 53% [33] to 71% [34] of patients. A technique has been described for dorsal rhizotomies using electrical stimulation to distinguish ventral roots [33]. In another procedure, total ligation and section of all motor and sensory elements at the L5, S1 level is done in patients who have had a previous colostomy; if the bladder is functioning normally prior to surgery, the S2 root is preserved on the less painful side [34]. Even though S1 was cut on the painful side, two poor results occurred in patients with carcinoma of the cervix that had spread to the lumbosacral plexus, causing sciatic pain [34].

Stereotaxic Mesencephalotomy

Stereotaxic rostral mesencephalotomy may relieve pain in the face, arm, and entire body contralateral to the lesion [9, 35–37]. The lesion is made in the spinothalamic tract, 5.5 mm posterior, 4.5 mm inferior, and 8–9 mm lateral to the middle point of the anterior aspect of the posterior commissure [35].

The advantage over cordotomy, especially in arm pain from Pancoast syndrome, is that the mesencephalic lesion does not cause respiratory impairment. Disadvantages of the procedure are ocular motor palsies (immediately present in 18% and permanent in 8% of the original group) and dysesthesias (immediately present in 28.7% and permanent anesthesia dolorosa in 8% of the original group) [36].

Pain contralateral to the analgesic side sometimes develops after the procedure; contralateral mesencephalotomy may relieve this pain without respiratory impairment, but bilateral mesencephalotomy may occasionally cause mental impairment with deficient arousal mechanisms and apathy [35].

Mesencephalotomy and other ablative procedures should be restricted to patients with metastatic cancer because of the probability of eventual recurrence of pain and the possibility of complications.

Supratentorial Ablations

Ablative lesions have been made in many different supratentorial locations with relief of chronic pain (frequently cancer pain) without producing somatic sensory loss [38]. Most of these lesions are in the limbic system and may ease the emotional suffering associated with pain. Bilateral and extensive lesions in the frontal lobe white matter or dorsomedial thalamus may cause significant loss of spontaneity and impairment in normal emotional responsiveness [38].

Cingulotomy [39–42]

Smaller, controlled radiofrequency lesions such as bilateral cingulotomy may relieve pain without causing severe adverse effects or any lasting neurological abnormality [42]. Lesions are made 7 mm from the midline, 2 cm to 4 cm posterior to the anterior tips of the lateral ventricles, and 2 cm vertical from a point about 1 mm above the ventricle [42]. Radio-

frequency lesions about 1 cm in diameter are made by heating the ends of the needle electrodes to 85°C for 75 seconds [42]. There was a progressive loss of pain relief with time in patients with cancer [41]. Fourteen of 18 patients followed for 1 to 3 months had some relief (marked in eight, slight to moderate in six. In those followed for more than 3 months, only five of nine patients had some relief (marked in one and mild to moderate in four).

Small radiofrequency heat lesions may also be made in the inferior posteromedial part of the frontal lobes or just behind this in the subcaudate region to relieve the spontaneous complaint of focal pain from cancer and ease the psychological distress associated with the illness [38].

Thalamotomy

Lesions of the posteromedial thalamus in the area of the intralaminar, centrum medianum, and parafascicularis nuclei may relieve cancer pain without producing deficits in perception of pin prick, temperature, touch, or position [38]. Fibers of the nonspecific paleospinothalamic system terminate in these nuclei.

The target is centered 18 mm posterior to the foramen of Monro, 6–10 mm lateral from the midline, and 1 mm below the plane connecting the foramen of Monro and the posterior commissure [43]. In one series, the best results were obtained by placing small serial lesions, about 6–8 mm in diameter, in the centrum medianum-parafascicularis, usually bilaterally, over a period of weeks or months [43].

Many investigators have made lesions in this location with good results [38]. Longer periods of pain relief occurred if the lesions extended a little upward into the dorsomedial nucleus or backward into the pulvinar [38].

Summary

Intraspinal morphine infusion is one of the most effective neurosurgical treatments for intractable cancer pain. An implanted pump connected to a subarachnoid catheter is an effective method for delivering a continuous infusion. Pain in the lower half of the body that responds to a test dose is the best indication for this treatment. The risks of the procedure are small, and tolerance, which often develops, can usually be managed by increasing the dose.

Deep brain stimulation, especially in the somatosensory thalamic area, is helpful in treating deafferentation pain, which may be seen in metastatic carcinoma. Deafferentation pain of the upper extremity from cancer or radiation–induced scar of the brachial plexus is managed successfully by this method.

Stereotaxic mesencephalotomy may relieve pain in the face or arm, but it is often associated with impairment of eye movements and dysesthesias.

Stereotaxic cingulotomy may help ease the emotional aspects of suffering associated with cancer pain, and small lesions are unlikely to cause unpleasant behavioral sequelae.

Stereotaxic radiofrequency lesions of the intralaminar, centrum medianum, and parafascicularis nuclei of the thalamus may relieve cancer pain without producing deficits in perception of pin prick, temperature, touch, or position sense.

CT-guided stereotaxy may facilitate the ease, safety, and acceptability of some of these pain-relieving neurosurgical procedures.

References

1. Cobb CA, French BN, Smith KA: Intrathecal morphine for pelvic and sacral pain caused by cancer. Surg Neurol 22:63–68, 1984.
2. Harbaugh RE, Coombs DW, Saunders RL, Gaylor M, Pageau M: Implanted continuous epidural morphine infusion system. Preliminary report. J Neurosurg 56:803–806, 1982.
3. Penn RD, Paice JA, Gottschalk W, Ivankovich AD: Cancer pain relief using chronic morphine infusion. Early experience with a programmable implanted drug pump. J Neurosurg 61:302–306, 1984.

4. Poletti CE, Cohen AM, Todd DP, Ojemann RG, Sweet WH, Zervas NT: Cancer pain relieved by long-term epidural morphine with permanent indwelling systems for self-administration. J Neurosurg 55:581–584, 1981.
5. Shetter AG, Hadley MN, Wilkinson E: Administration of intraspinal morphine sulfate for the treatment of intractable cancer pain. Neurosurgery 18:740–747, 1986.
6. Lenzi A, Galli G, Gandolfini M, Marini G: Intraventricular morphine in paraneoplastic painful syndrome of the cervicofacial region: Experience in thirty-eight cases. Neurosurgery 17:6–11, 1985.
7. Roquefeuil B, Benezech J, Blanchet P, Batier C, Frerebeau P, Gros C: Intraventricular administration of morphine in patients with neoplastic intractable pain. Surg Neurol 21:115–118, 1984.
8. Obbens EAMT, Hill CS, Leavens ME, Ruthenbeck SS, Otis F: Intraventricular morphine administration for control of chronic cancer pain. Pain 28:61–68, 1987.
9. Mazars GJ, Merienne L, Cioloa C: Comparative study of electrical stimulation of posterior thalamic nuclei, periaqueductal gray, and other midline mesencephalic structures in man. In: Advances in Pain Research and Therapy, Vol 3, Bonica JJ, et al., Raven Press, New York, 1979, pp 541–546.
10. Young RF, Kroening R, Fulton W, Feldman RA, Chambi I: Electrical stimulation of the brain in the treatment of chronic pain. J Neurosurg 62:389–396, 1985.
11. Hosobuchi Y: Subcortical electrical stimulation for control of intractable pain in humans. J Neurosurg 64:543–553, 1986.
12. Meyerson BA, Boethius J, Carlsson AM: Percutaneous central gray stimulation for cancer pain. Appl Neurophysiol 41:57–65, 1978.
13. Richardson DE, Akil H: Pain reduction by electrical brain stimulation in man. Part 2: Chronic self-administration in the periventricular gray matter. J Neurosurg 47:184–194, 1977.
14. Greenberg RP, Hoffert MJ, Gracely RH, Wolskee PJ, Dionne RA, Dubner R: Symposium — NIDR Medical College of Virginia Collaborative Study on Chronic Pain and the Effects of Peri-ventricular Grey Stimulation. Presented at the American Pain Society, Oct., 1982.
15. Adams JE, Lippert R, Hosobuchi Y: Commissural myelotomy. In: Operative Neurosurgical Techniques. Schmidek HH, Sweet WH, ends, Vol 2, Grune & Stratton, New York, 1982, pp 1155–1161.
16. King RB: Anterior commissurotomy for intractable pain. J Neurosurg 47:7–11, 1977.
17. Cook AW, Kawakami Y: Commissural myelotomy. J Neurosurg 47:1–6, 1977.
18. Sourek K: Commissural myelotomy. J Neurosurg 31:524–527, 1969.
19. Broager B: Commissural myelotomy. Surg Neurol 2:71–74, 1974.
20. King RB: Commissural myelotomy for pain relief. In: Neurosurgery, Wilkins RH, Rengachary SS, ends, McGraw-Hill, New York, 1985, pp 2438–2439.
21. Fink RA: Neurosurgical treatment of nonmalignant intractable rectal pain: Microsurgical commissural myelotomy with the carbon dioxide laser. Neurosurgery 14:64–65, 1984.
22. Conway LW, Collins WF: Results of transsphenoidal cryohypophysectomy for carcinoma of the breast. N Engl J Med 281:1–7, 1969.
23. Hardy J: Transsphenoidal hypophysectomy. J Neurosurg 34:582–594, 1971.
24. Levin AB, Katz J, Benson RC, Jones AG: Treatment of pain of diffuse metastatic cancer by stereotactic chemical hypophysectomy: Long term results and observations on mechanism of action. Neurosurgery 6:258–262, 1980.
25. Maddy JA, Winternitz WW, Norrell H: Cryohypophysectomy in the management of advanced prostatic cancer. Cancer 28:322–328, 1971.
26. Ramirez LF, Levin AB: Pain relief after hypophysectomy. Neurosurgery 14:499–504, 1984.
27. Tindall GT, Ambrose SS, Christy JH, Patton JM: Hypophysectomy in the treatment of disseminated carcinoma of the breast and prostate gland. South Med J 69:579–583, 1976.
28. Tindall GT, Payne NS, Nixon DW: Transsphenoidal hypophysectomy for disseminated carcinoma of the prostate gland. J Neurosurg 50:275–282, 1979.
29. Zervas NT: Stereotaxic radiofrequency surgery of the normal and the abnormal pituitary gland. N Engl J Med 280:429–437, 1969.
30. Lipton S, Miles J, Williams N, Bark-Jones N: Pituitary injection of alcohol for widespread cancer pain. Pain 5:73–82, 1978.
31. Moricca G: Neuroadenolysis (chemical hypophysectomy) for diffuse unbearable cancer pain. In: Advances in Pain Research and Therapy, Vol 1, Bonica J, Albe-Fessard, eds,

Raven Press, New York, 1976, pp 863–866.
32. Gros Cl, Frerebeau Ph, Privat JM, Benezeca J: Place of hypophysectomy in the neurosurgical treatment of pain. A comparative study of hypophysectomy and radioisotope implants. Report of 124 cases. In: Advances in Neurosurgery, Vol 3, Penzholz M, et al., eds. Springer-Verlag, Heldelberg, 1975, pp 264–272.
33. Saris SC, Silver JM, Vieira JFS, Nashold BS Jr: Sacrococcygeal rhizotomy for perineal pain. Neurosurgery 5:789–793, 1986.
34. Felsoory A, Crue BL: Results of 19 years experience with sacral rhizotomy for perineal and perianal cancer pain. Pain 2:431–433, 1976.
35. Frank F, Tognetti F, Gaist G, Frank G, Galassi E, Sturiale C: Stereotaxic rostral mesencephalotomy in treatment of malignant faciothoracobrachial pain syndromes. J Neurosurg 56:807–811, 1982.
36. Frank F, Sturiale C, Gaist G, Fabrizi AP, Frank-Ricci R: Stereotactic mesencephalic tractotomy in the treatment of Pancoast Syndrome. Appl Neurophysiol 48:274–276, 1985.
37. Amano K, Iseki H, Notani M, Kawabatake H, Tanikawa T, Kawamura H, Kitamura K: Rostral mesencephalic reticulotomy for pain relief: Report of 15 cases. Acta Neurochir (Wien) (Suppl) 30:391–393, 1980.
38. Sweet WH: Central mechanisms of chronic pain (neuralgias and certain other neurogenic pain). Pain. Bonica JJ, ed, Raven Press, New York, 1980, pp 287–303.
39. Folz EL, White LE Jr: Pain 'relief' by frontal cingulumotomy. J Neurosurg 19:89–100, 1962.
40. Foltz EL, White LE Jr: Affective disorders involving pain. In: Neurological Surgery, Youmans JR, ed. WB Saunders, Philadelphia, 1973, pp 1772–1782.
41. Hurt RW, Ballantine HT Jr: Stereotactic anterior cingulate lesions for persistent pain: A report on 68 cases. Clin Neurosurg 21: 334–351, 1974.
42. Ballantine HT Jr: Neurosurgery for behavioral disorders. In: Neurosurgery, Wilkins RH, Rengachary SS, eds, McGraw-Hill, New York, 1985, pp 2527–2537.
43. Young RF, Modesti LM: Stereotactic ablative procedures for pain relief. In: Neurosurgery, Wilkins RH, Rengachary SS, eds, McGraw-Hill, New York, 1985, pp 2454–2457.

V. APPENDIX

24. TRIGEMINAL NEURALGIA QUESTIONNAIRE

Ronald Brisman, M.D.

A score of 0 means no problem or no interference with normal function. A score of 10 means a very severe problem. Please give a numerical score for each of the following items based on your present situation.

DATE THAT YOU ARE FILLING OUT QUESTIONNAIRE (Today's Date)

NAME_____

Type of last surgical procedure (or injection into the face) for relief of face pain

DATE OF ABOVE PROCEDURE_____

1. HOW SEVERE IS FACE PAIN OR DISCOMFORT (0–10)?

No pain or discomfort	Very mild, almost no bother	Mild but bothersome	Moderately severe	Excruciating
0	1–2	3–5	6–8	9–10

2. HOW FREQUENT IS FACE PAIN OR DISCOMFORT (0–10)?

Never	Rare less than once a month	Infrequent: more than once a month but less than once a week	Frequent: more than once a week but not every day	Most of the time (everyday)	Always
0	1–2	3–4	5–7	8–9	10

3. HOW OFTEN DO YOU HAVE FACE PAIN OR DISCOMFORT? TRY TO ESTIMATE AS A PERCENT OF TOTAL TIME

4. IS THE PAIN TRIGGERED BY LIGHT TOUCH ABOUT THE FACE OR MOUTH?

Never	Infrequently less than 50% of the time	Sometimes approx. 50% of the time	Most of the time	Always
0	1–4	5	6–9	10

Brisman, R., (ed.), *Neurosurgical and Medical Management of Pain: Trigeminal Neuralgia, Chronic Pain, and Cancer Pain.*

5. HOW MUCH MEDICATION DO YOU TAKE TO RELIEVE OR PREVENT FACE PAIN AND/OR DISCOMFORT?

None	Some medicine, but it is no bother and there are no side effects.	Some medication — bothersome to take it but no side effects.
0	1–2	3–4

OR MEDICATION WITH TOXIC SIDE EFFECTS THAT ARE:

Mildly bothersome	Moderately bothersome	Severely bothersome
5–6	7–8	9–10

DESCRIBE THE TOXIC SIDE EFFECTS:_____

_____

_____

_____

WHAT ARE THESE MEDICINES? HOW MUCH AND HOW OFTEN ARE THEY TAKEN?

_____

_____

_____

6. DO YOU DROOL SALIVA OR FOOD OUT OF THE SIDE OF YOUR MOUTH (on operated side)?

No	Infrequently, little bother	Often, but little bother	Often and bothersome	All the time, very disturbing
0	1–3	4–6	7–9	10

7. ARE YOU AWARE OF ANY NUMBNESS OR OTHER ABNORMAL FEELING IN YOUR FACE; SUCH AS TIGHTNESS, CRAWLING, OR ITCHING (Circle one if appropriate)?

No	Yes, but mild and not bother-some	Yes, moderate and of some bother	Yes, marked and quite bothersome	Yes, very severe discomforting, constantly, and very bothersome
0	1–3	4–6	7–9	10

8. HOW MUCH IS HEARING ON THE OPERATED SIDE INTERFERED WITH (COMPARE WITH THE WAY IT WAS BEFORE THE SURGERY)?

Normal	Mildly worse	Moderately worse	Severely worse	Completely deaf
0	1–3	4–6	7–9	10

9. HOW MUCH PROBLEM DO YOU HAVE WITH THE EYE ON THE OPERATED SIDE? (COMPARED WITH THE WAY IT WAS BEFORE THE SURGERY?)

Normal	Normal vision, but must use drops and take eye precautions	Mild, blurry vision	Moderate or severe visual impairment	Can't see at all
0	1–3	4–6	7–9	10

10. HOW DO YOU COMPARE YOURSELF NOW (REGARDING TOTAL FACE PAIN OR DISCOMFORT) WITH THE WAY YOU WERE BEFORE YOUR LAST SURGICAL PROCEDURE (TO RELIEVE FACE PAIN)?

All better	Much better	A little better	Unchanged	A little worse	Much worse
0	1–2	3–4	5	6–8	9–10

Not sure

11. WOULD YOU HAVE GONE THROUGH THE LAST OPERATION IF YOU KNEW THEN HOW YOU WOULD BE FEELING NOW?

Yes	Not sure, but probably yes	Not sure at all	Not sure, but probably no	No
0	1–3	4–6	7–9	10

PLEASE CHECK ONE ANSWER:

12. HAVE YOU EVER HAD SMALL BLISTERS ON YOUR UPPER OR LOWER LIP, FOREHEAD, OR INSIDE THE MOUTH OR OTHER PART OF THE FACE?

No	Yes, very slight	Yes, a little bothersome	Yes, moderately bothersome	Yes, extremely bothersome
0	1–3	4–6	7–9	10

WHEN DID IT OCCUR? _____

HOW LONG DID IT LAST? _____

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