THE SPINOthalamic TRACT

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I. INTRODUCTION

Since the discovery of the importance of the anterolateral spinal cord pathways for the rostral transmission of nociceptive information and the finding that a portion of these anterolateral pathways terminates in the thalamus, a great deal of clinical and research attention has been devoted to elucidating the anatomy and physiology of the spinothalamic tract (STT). Because of the perceived importance of this pathway for neural processing resulting in the sensation of pain in man, the STT has been the subject of several recent excellent reviews documenting the anatomy, physiologic characteristics, and importance of this pathway for nociception.1-4 This review focuses on several aspects of the STT, including the heterogeneity of this pathway in terms of cells of origin, functional responses, and thalamic terminations, as well as new anatomic data indicating the need for reevaluation of the current ideas concerning the anatomic localization and functional importance of the component parts of the STT. An initial, brief historical introduction is given followed by a description of the terminations of the STT in the thalamus. The locations and functional characteristics of the cells of origin of the STT are presented and compared with the response characteristics of thalamic neurons in regions of STT terminations. The funicular organization of the STT in the spinal cord together with the clinical implications of this organization are discussed. The final section of the paper deals with the questions concerning the role of the STT in pain perception.

II. HISTORICAL PERSPECTIVE

The concept of anatomic separation of motor and sensory function was elucidated by Bell and Magendie in their separate studies of dorsal and ventral root function (cited in Reference 5). Schiff extended these observations, indicating a separation of spinal pathways transmitting innocuous and noxious information, by demonstrating that animals with spinal cord section sparing the dorsal columns react to innocuous but not to noxious cutaneous stimulation (cited in Reference 5). Brown-Sequard6-8 demonstrated that the effects of section of a single spinal cord ventral quadrant were an apparent increase in sensibility of the ipsilateral hindlimb and a loss or great decrease in sensibility of the contralateral hindlimb, and he described a series of clinical cases that demonstrated loss of nociception contralateral to a hemi-spinal cord lesion.9,10 Although initially skeptical concerning the sensory role of the dorsal columns, he eventually agreed that the dorsal columns were important in transmitting information about innocuous cutaneous stimulation. Brown-Sequard6-8 also noted a bilateral loss of response to noxious stimulation following longitudinal section of the spinal

cord, thus adding confirmatory evidence for the local crossing of fibers transmitting information about noxious stimulation, as previously hypothesized by earlier anatomists (discussed in Reference 5). Several further clinical examples were provided by Gowers,\textsuperscript{11,12} who described a patient suffering from a gunshot wound of a single anterolateral column. He noted that "the sensation of pain was very distinctly diminished on the side opposite the injury." A second case was reported\textsuperscript{12} describing a patient who had suffered a stab wound of the spinal cord resulting in a hemisection of the cord and destruction of the contralateral dorsal column. The effects were bilateral loss of touch sensation and loss of the sensation of pain contralaterally. In 1891, Gowers wrote that "painful sensations are conducted in the lateral column, those of touch in the posterior column."\textsuperscript{12} This opinion was echoed by Sherrington,\textsuperscript{13} who concluded "that the lateral column furnishes the headward path in the spinal cord for nociceptive (algesic) arcs" and "that this is true for these arcs, whether they be traced from skin, muscle or viscus." These case reports underscore the further separation of sensory function with information about noxious stimuli being transmitted through ventral spinal cord pathways and information about innocuous stimuli being transmitted through the dorsal spinal cord.

In 1905, Spiller\textsuperscript{14} described a patient who was analgesic below the level of anterior column lesions caused by tuberculomas, and in 1912, he and Martin\textsuperscript{15} described a case in which bilateral anterolateral spinal cord section was done for intractable pain due to unresectable spinal tumor at a more caudal level. This procedure resulted in clinical pain relief and served to herald modern interest in anterior spinal cord pathway involvement in nociception. Anterolateral cordotomy (originally chordotomy because of the nature of the incision connecting two points on a circle) for pain relief rapidly became a standard clinical treatment for patients with intractable pain, particularly that resulting from malignant disease.\textsuperscript{16}

Since Edinger (see Reference 5) in 1889 and Mott\textsuperscript{17,18} in 1895 provided early evidence for a direct pathway from the spinal cord to the thalamus traveling in the anterolateral quadrants of the spinal cord using developmental and degeneration techniques, respectively, the focus of interest in anterolateral spinal cord pathways has been heavily concentrated on the STT as a major direct nociceptive pathway from the spinal cord to the thalamus. Research has focused on STT anatomic organization and physiologic characteristics as well as on the experimental and clinical behavioral effects of lesions of the STT. The monosynaptic projection of the STT to the thalamus has allowed retrograde tracing and antidromic activation to be used in identifying STT neurons, aiding immensely in defining their characteristics. The theoretical bases that have spurred modern research and synthesis of ideas concerning pain perception in general, and the role of the STT in particular, are twofold. These ideas have allowed the disparate results of many investigators to be placed conceptually in perspective. First is the hypothesis that the direct STT is a neural pathway, capable of signaling tissue damaging events, that assumes greater functional importance when primates are compared with other mammalian branches of the phylogenetic tree.\textsuperscript{19-23} This permits rational comparison of the differences and similarities of the STT cells of origin, funicular trajectories, and thalamic termination sites of varying species. Second is the dualistic approach to pain perception refined by Melzack and Casey.\textsuperscript{24} The essence of this approach is that there are two major attributes of pain perception, one being the sensory-discriminative aspects of noception and the other being the affective, emotionally aversive response to noception. The sensory-discriminative view of noception demands that, for cells to be considered as important in this facet of noception, they must be able to define the details of the nociceptive experience, i.e., localization, intensity determination, threshold determination, sensitization, somatic referral of visceral noxious events, and should receive input from those groups of afferent peripheral nerve fibers known to be associated with behavioral noception.\textsuperscript{25} Furthermore, stimulation of such groups of cells should result in pain, and their ablation or decrease in responsiveness should interfere with noception. These criteria have been ex-
ceptionally useful for developing experimental paradigms that allow identification of groups of neurons, including some of the STT cells and their rostral targets, as candidate nociceptive pathways. Consideration of the emotional, aversive aspects of nociception has not been as productive in identifying pathways involved in this aspect of pain perception because the details of the behavior of cells or tracts involved in this aspect of nociception are not clearly defined. Consequently, most of the assumptions made about neural structures involved in aversive responses to pain have been based on data resulting from ablative treatments in humans, on the basic connectivity to areas of cortex thought involved in emotional responses, or on input from cell groups that respond to noxious peripheral stimulation, but which lack the specificity needed to qualify as discriminative neuronal populations.

III. ANATOMIC ORGANIZATION

A. THALAMIC TERMINATION SITES

The nomenclature of thalamic structures is variable depending on the species being described and the author’s choice of reference atlas. This review generally uses the terminology used by Jones in his work on the thalamus. When appropriate, species-specific names derived from thalamic atlases for cat and monkey are used. The thalamic nuclei are divided into groups depending on developmental and connectivity characteristics. The ventral nuclear group includes the principal sensory nucleus of the thalamus, i.e., the ventral posterior lateral nucleus (VPL), which in rat and cat is commonly referred to as being part of the ventrobasal complex (VB) and which in primate is divided into an oral and caudal section (VPLo and VPLc, VPLc being the homolog of feline VPL); the ventrolateral nucleus (VL); the ventral posterior medial nucleus (VPM), which is the facial homolog of VPL; the nucleus submedius (SM); and other ventrally located nuclei. VPL (VPLc in primate) and VPM are of particular importance, being the primary termination sites of the lemniscal systems from the body and face, respectively, and projecting to the primary sensory cortex. The primate oral portion of the VPL nucleus (VPLo) is equivalent to the VL nucleus of rat and cat based on its subcortical input and its cortical projections, receiving cerebellar input and projecting to the primary motor cortex.

The posterior group of nuclei (PO) include the three divisions of the posterior complex, the medial, lateral, and intermediate portions of the posterior thalamic group (POm, POL, and POi) as well as the suprageniculate (SG) and nucleus limitans (Li) complex. In primate, the oral portion of the pulvinar (PULo) is generally equivalent to POm. Because of anatomic proximity, the magnocellular portion of the medial geniculate nucleus (MGm) is included in this group. POm and MGm receive multiple sensory inputs and project diffusely to retrolenticular and insular cortical areas, respectively.

The intralaminar complex includes, in its anterior division, the centrolateral nucleus (CL), the paracentral nucleus (Pc), and the centromedial nucleus (CeM); and in its posterior division the centre median (CM) and the parafascicular nucleus (PF). The medial division of the thalamic nuclei include the dorsal and ventral medial nuclei (MD and MV). In primate, the MD is divided into a variety of components.

While the functional importance of the lateral thalamic nuclei (VPL, VPLc) as transmitters of precise information about the location, intensity, and type of somatic stimulation is generally accepted, the functional role of the other thalamic groups is less certain. The intralaminar group is thought related to arousal, based on its diffuse cortical projections and multiplicity. The thalamic areas projecting to the medial frontal, orbital frontal, and insular cortices (i.e., MD, SM, POm, MGm, SG) might be related to stimulus recognition or behavioral integration, but their role in sensory processing is unclear at best.

The size of the STT varies with the general phylogenetic level of the species being studied. For instance, there is essentially no direct STT in reptiles, but instead a prominent
input to the intralaminar thalamic nuclei via one or more relays in the reticular formation.\textsuperscript{19,22,23,31} This pathway, originating in the spinal cord and relaying in the nucleus gigantocellularis of the medulla (as well as in other brainstem areas), terminates primarily in CM and is prominent in all species studied including rat,\textsuperscript{32} cat,\textsuperscript{33} and man.\textsuperscript{34} Cooling the nucleus gigantocellularis results in near abolition of the responses of neurons in CM to somatic stimuli.\textsuperscript{35} This multisynaptic pathway is then considered phylogenetically primitive access for afferent information to thalamus (see references in Reference 36) that persists through all mammalian species and upon which the more direct STT is added to a progressively greater extent in mammals, particularly primates. Its termination in CM is consistent with this idea since lesions of this area in humans are able to result in pain relief without major alterations in the sensory discriminative aspects of nociception.\textsuperscript{5,16}

Direct STT terminations in the thalamus were first described by Edinger (cited in Reference 5) and by Mott.\textsuperscript{17,18} Mott’s study\textsuperscript{17} was of particular interest since it was the first study in primate that indicated that the anterolateral quadrant pathway reached as far cephalad as the thalamus. Mott\textsuperscript{17} used the Marchi method to trace degeneration of fibers following spinal cord anterolateral quadrant section and found degenerating terminals in the brainstem reticular formation and a fiber tract ascending to the region of the posterior thalamic junction with the mesencephalon. Using the same technique following a midline myelotomy, he was able to demonstrate anterolateral quadrant fiber ascending degeneration, thereby confirming the fact that the ascending anterolateral quadrant pathways arise, at least in part, from the contralateral spinal cord.

Le Gros Clark,\textsuperscript{37} in 1936, using degeneration techniques in primate, was able to demonstrate the termination of the STT in a variety of thalamic nuclei, including the VPL, Pf, and CL nuclei, of which the latter two are part of the intralaminar thalamic system. STT fibers passed through but did not seem to terminate in the CM. Later studies in a variety of species have confirmed and expanded the basic STT thalamic termination sites originally described by Le Gros Clark\textsuperscript{37} (see also Reference 38). Table 1 tabulates and Figure 1 illustrates the distribution of STT terminations in primate thalamus identified using anterograde transport of horseradish peroxidase (HRP).\textsuperscript{39}

1. The Ventral and Posterior Thalamic Groups:

STT projections have been identified in the rat VB using both degeneration techniques and anterograde transport of HRP conjugated with wheat germ agglutinin (WGA).\textsuperscript{40-42} STT terminations in rat VB visualized using anterograde HRP transport are contralateral to the side of the spinal cord injection and are somatotopically organized,\textsuperscript{41} with the cervical projection terminating in the medial portion of the caudal and lateral VB, while the lumbar injections resulted in visible label in the rostral and more lateral portion of VB. The STT terminations in cat VPL (VB) are not as clear as in the rat and primate (vide infra). Getz\textsuperscript{43} described degenerating boutons in the VPL nucleus in cat following spinal cord hemisection. The degeneration indicated that, as in rat, there is a somatotopic organization with the lumbar terminals being found in the most lateral portion of VPL. Boivie,\textsuperscript{44} in his examination of STT terminations in cat, found conflicting results, reporting that the lateral thalamic terminals were found anterior to VPL in VL and that there was no somatotopic organization. However, studies using anterograde transport techniques\textsuperscript{45,46} demonstrated label in VPL as well as in the anterior VL. The STT terminals in VPL were somatotopically organized and were found primarily in the ventral and lateral borders (shell region) of this nucleus, while they were more diffuse in VL. Similar results are described by Berkley,\textsuperscript{20,21} i.e., in cat VPL, STT terminations are located primarily in a shell-like distribution around the bulk of the VPL nucleus, with a particularly heavy grouping of terminations at the VL-VPL border. Nonhuman primates have extensive STT terminations in VPLc demonstrated by degeneration techniques and by anterograde techniques.\textsuperscript{20,39,47-49} These terminations are scattered through-
### TABLE 1
Primate Spinothalamic Terminations

<table>
<thead>
<tr>
<th>Thalamic nucleus</th>
<th>Density of label</th>
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<tbody>
<tr>
<td>Ventral group</td>
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<td>VA</td>
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<td>VAmc</td>
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<td>VLo</td>
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<td>VPM</td>
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<td>VPMpc</td>
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<td>VIP</td>
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<td>SM</td>
<td>+ +</td>
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<td>LD</td>
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<td>SG (+ MGmc)</td>
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<td>Li</td>
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<td>PULi</td>
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<td>PULo</td>
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<td>Anterior group</td>
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<td>CM</td>
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<td>Border nuclei</td>
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<td>SF</td>
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out the VPLc nucleus, but are most dense in the thalamic regions at the periphery of VPLc\(^{20,48,49}\) in a shell-like fashion. There is clear extension of STT terminal fields beyond the anterior border of VPLc to VPLo\(^{20,21,39,48}\) equivalent to the VPL-VL border in rat and cat (see Figure 1). As in rat and cat, primate VPLc terminations are somatotopically organized,\(^{48}\) with the foot area most rostral and lateral and the forelimb area more medial and caudal. The morphology of the primate STT terminations is unique in VPLc with patchy, "archipelago-like"\(^{47,50}\) terminal clusters (Figure 2), which on three-dimensional reconstruction appear rod-like.\(^{48}\) Terminations of human STT have been studied following anterolateral cordotomy\(^{34,46,47,50}\) and are found present in the VPL nucleus with typical bursts of terminals
FIGURE 1. The distribution of STT terminations in primate thalamus visualized using anterograde transport of WGA-HRP from the lumbar spinal cord. The numbers at the upper left of each thalamic figure represent the anterior-posterior level of the section displayed.

The nomenclature of the thalamic nuclei is from Olszewski. See text for details. (Unpublished observations of Apgarian and Hodge, 1988.)

throughout the nucleus. It is apparent that the number of fibers reaching the thalamus are far fewer than the number of degenerating fibers seen in the anterolateral quadrant of the spinal cord rostral to the lesion, likely a manifestation of the extensive anterolateral cord input to brainstem nuclei. The total number of STT fibers reaching the VB (i.e., VB,
VPL, or VPLc) increases from rat to cat to monkey and man\textsuperscript{19} (see also references in Reference 23).

The PO thalamus is divided into three parts: POM, POI, and POi portions.\textsuperscript{26} These nuclei cap the dorsal and posterior parts of the VPL and VPM nuclei in cat, but in monkey are located more ventrally and medially.\textsuperscript{30} In primates, POM is equivalent to the oral pulvinar (PULO) of Olziewski.\textsuperscript{28} Just ventral and lateral to the posterior portion of the PO group of nuclei is the magnocellular division of MGmc as well as the SG, Li complex.\textsuperscript{26-28} MGmc has been considered part of the POM area by some\textsuperscript{1} but not other workers.\textsuperscript{20,26} There is extensive terminations of the STT in the POM and to a lesser degree to MGmc and adjacent
SG regions in rat,\textsuperscript{40} cat,\textsuperscript{20,44,45,51} and primate\textsuperscript{19,20,39,48} (Figure 1). The usual description of the POM terminals is that they are not somatotopically organized, although Craig and Burton\textsuperscript{51} describe a definite medial-lateral and caudal-ventral difference in the terminals when anterograde transport from lumbar and cervical areas are compared. Mehler\textsuperscript{46} has described STT terminations in MGmc and a POM-like region in human material. While there are clear differences between the characteristics of VPL terminations and those found in the surrounding PO and adjacent nuclei (MGmc and SG), the differences in the functional implications of POM, MGmc, and SG terminations are unclear.

The SM receives STT terminations in rat, cat, and monkey.\textsuperscript{37,39,45,52,53} This area, which projects to the orbital frontal cortex,\textsuperscript{54} receives its primary STT input from cells found in the apex of the medullary and spinal cord dorsal horn,\textsuperscript{52} suggesting an important role for this nucleus in pain processing.\textsuperscript{52} The distribution of fibers in SM is somatotopically organized, with the trigeminal input being located more caudal than the lumbar spinal cord input.

The important aspects then of STT input to the ventral and posterior groups of nuclei of the thalamus are (1) there is a clear somatotopic input to the VPL (VPL\textsubscript{c} in primate) nucleus that has characteristic terminals in the primate thalamus and which in cat is limited to the ventral and lateral border of VPL; (2) there is extensive, diffuse STT input to the areas surrounding the VPL nucleus including VL (VPL\textsubscript{O} in primate), POM (PUL\textsubscript{O} in primates), SG, Li, and MGmc; and (3) there is significant input to SM from dorsal horn apex (lamina 1) cells.

The terminals of STT axons in VPL make direct synapses with thalamic neurons,\textsuperscript{55-57} at times with the presence of intercalated presynaptic dendrites. Although there is overlap in the distribution of STT terminations in VPL with the input of dorsal column nuclei\textsuperscript{20} such that at times both tracts can be identified ending on the same thalamic neuron,\textsuperscript{52} a majority of STT terminals are relatively peripheral to the bulk of the lemniscal input forming a core-shell configuration\textsuperscript{20,21} which is most extreme in the cat, but also prominent in monkey.

2. The Intralaminar Nuclei

In rat, cat, monkey, and man, there is a dense termination of the STT in the posterior part of CL,\textsuperscript{20,37,39,44-46,48,51,53,58} (Figure 1). The remaining nuclei of the anterior intralaminar group (Pc, CeM) also receive STT terminations which are most easily seen with anterograde HRP transport techniques.\textsuperscript{39,51} In the posterior group of intralaminar nuclei, Pf receives a fairly dense STT input, while CM receives only a very modest input, which is rarely seen except when anterograde HRP is used.\textsuperscript{37,39,44,45,51} The intralaminar terminations are not somatotopically organized. Although the terminations of the STT in the CL nuclei have been related to motoric functions of the STT, Greenan and Strick\textsuperscript{58} point out that the STT terminals have no direct overlap with thalamic neurons known to project to the various motor cortical areas, emphasizing the danger of relating all parts of a thalamic nucleus to a single functional group based on architectonics.

3. The Dorsal Thalamic Group

In both cat and monkey, STT terminals have been described in MD.\textsuperscript{39,51} This label occurs in several distinct areas of MD, including its medial border with CL, and its parvocellular (pc) and densocellular (dc) components (see Figure 1).

STT terminations are also apparent in cat and monkey using anterograde techniques in a variety of other nuclei including zona incerta (ZI), the subfascicular nucleus (SF), and some of the midline nuclei of the thalamus. The studies using anterograde HRP transport,\textsuperscript{45,48,51} exemplified by Table 1 and Figure 1, are the only ones showing terminal concentrations outside of VPL, VL, MD, PO complex, and the intralaminar nuclei. Consequently, these results, particularly where termination site label is light, must be viewed with caution given the potential for transynaptic\textsuperscript{39,59} and transneuronal transport.
B. CELLS OF ORIGIN OF THE STT

Given the variety of thalamic nuclei which are the recipients of STT terminations, the existence of a functionally and anatomically heterogeneous population of cells whose axons form the STT would be expected. The initial studies of the origins of the STT were based on retrograde degeneration following anterolateral spinal cord section; however, these studies suffer from the serious flaw of not being able to differentiate cells whose axons reach the thalamus from those with more caudal termination sites such as the brainstem reticular formation. The most reliable data concerning this topic then are from studies that have used either retrograde tracing techniques or antidromic electrical activation, by thalamic stimulation, of cells in the spinal cord with thalamic terminations. These studies have shown some consistent patterns of the locations and functional characteristics of the cells of origin of the STT, although there are clear species variations as well as variations between various rostral caudal divisions of the spinal cord.

Foerster and Gagel\(^{60}\) described the cells that degenerated in man following anterolateral cordotomy. These were found in three distinct groups within the cord, the apical portion of the dorsal horn, i.e., lamina 1 of Rexed,\(^{61}\) the base or neck of the dorsal horn, i.e., probably laminae 5-6, and the ventral horn. These locations were represented bilaterally, with a contralateral predominance. Similar studies by Kurth\(^{62}\) described chromatolytic changes of cells in both apical and deep portions of the dorsal horn in man and were confirmed in cats and monkeys by Morin et al.\(^{63}\) The development of retrograde tracing using HRP alone or conjugated with WGA and the development of criteria for identifying cells whose axons or terminals are stimulated at a distant site have allowed much more precise evaluation of the cells of origin of the STT. Figure 3 illustrates the locations of the cells of origin of the primate STT identified using retrograde transport of WGA-HRP and Figure 4 demonstrates a quantitative estimate of the segmental distribution of the cells of origin of the ipsilateral and contralateral STT in primate.\(^{64}\)

1. Upper Cervical (C1-C2) Spinal Cord

a. Rat

In rat, the upper cervical spinal cord contains a number of groups of STT cells identified using retrograde HRP tracing techniques.\(^{65-67}\) Approximately one half of the total STT in rat is from the upper cervical (C1-C4) segments.\(^{67}\) Contralaterally, STT neurons are found in marginal zone equivalent to lamina 1 of Rexed and in small numbers in substantia gelatinosa. The ventromedial dorsal horn (internal basilar column), equivalent to medial laminae 5-6, has an extremely dense concentration of STT neurons, while only scattered neurons are found in nucleus proprius and in the intermediate gray zone. Bilateral ventral horn projections are dense in the upper cervical segments of rat, although the contralaterally projecting cells are located deeper in the ventral horn than the ipsilaterally projecting neurons according to Granum.\(^{66}\) The upper cervical cord has the densest ipsilateral STT projection of any cord area.

b. Cat

The upper cervical cord contribution to the STT has been studied in cat by Comans and Snow\(^{68}\) and by Carstens and Trevino.\(^{69,70}\) Relatively few lamina 1 cells were identified, and the major contralateral STT contribution was from the base of the dorsal horn (laminae 5-6) and the ventral horn. There is, as in rat, a large contribution from cells ipsilateral to the thalamic injection located primarily in laminae 7-8 of the ventral horn. Contralaterally projecting cells in the medial ventral area of the dorsal horn were labeled after injections into either the VB-VL area laterally or the POm-SG area in the posterior thalamus. The contralateral ventral horn cells were labeled by injections into either the VB-VL area, the intralaminar complex (CL and medial MD), or the Pf. Some ipsilaterally projecting ventral
FIGURE 3. The distribution of cells labeled in primate spinal cord determined using retrograde transport of WGA-HRP injected into the thalamus. (Left) The distribution of STT cells in the third and fourth cervical segments. (Center) The distribution of STT cells in the cervical enlargement. (Right) The distribution of STT cells in the lumbar enlargement.64
IPSILATERAL AND CONTRALATERAL SPINOthalamic TRACT
BY SEGMENTS

FIGURE 4. The segmental distribution of the cells of origin of the primate spinothalamic tract. The inset indicates the relative sizes of the ipsilateral and contralateral spinothalamic tracts. The paired bar graphs indicate the percent of the total ipsilateral (solid bars) or contralateral (crosshatched bars) found in each segmental group. (Unpublished observations of Apkarian and Hodge, 1988.)

horn cells were labeled after injections into any of four major thalamic termination sites, i.e., VB-VL, CL-MD, POm-SG, Pf.68-70

c. Monkey

Only several studies have looked at the upper cervical cord contribution to the STT in primate.64,71-73 The upper cervical STT constitutes approximately 30% of the total primate STT.64 The distributions of STT neurons presented for the upper cervical area by Apkarian and Hodge,64 Trevino,72 and Hayes and Rustioni73 are similar (Figures 3 and 4). There is a prominent contribution of the contralateral marginal layer, while the deeper dorsal horn contains scattered STT cells with a particular concentration in lateral laminae 6-7. There is a relatively diffuse ventral horn contribution in laminae 7 and 8. A striking ipsilateral STT projection is found from the ventral horn in medial lamina 7 as well as a smaller contribution from lateral laminae 6-7. Thalamically projecting neurons have also been identified in the ipsilateral upper cervical spinal cord at the C2 level in laminae 6-8 using antidromic stimulation techniques.70

The upper cervical cord of all species examined then have certain features in common, including a strikingly high concentration of STT cells, particularly in the ipsilateral ventral horn. It is unclear whether this group of cells has a preferential thalamic termination site, although their location and response characteristics suggest (vide infra) a projection more in keeping with the function of the intralaminar and posterior groups of nuclei as opposed
to the VB (VPL, VPLc). Of particular interest is the fact that the upper cervical spinal cord contains between one half and one third of the entire STT cell population, suggesting an important role for this area in nociceptive processing.

2. Cervical Enlargement
   a. Rat

   In rat, the contribution of the cervical enlargement to the total STT is much less than that of the upper cervical cord,\textsuperscript{66,74} this area supplying only 3.62% of the total STT, while the segments C1-C3 supply 49.82% of the STT.\textsuperscript{67} There is almost no ipsilateral projection to the thalamus from the rat cervical enlargement.\textsuperscript{66,67,74} The cell groups of the cervical enlargement that contribute to the STT are found in the apex (lamina 1), the nucleus proprius, and internal basilar column of the dorsal horn and from the ventral horn. The distribution of ventral horn cells contributing to the cervical enlargement STT have been described to be sparse in the dorsomedial region\textsuperscript{66,74} and in the more lateral portion of the ventral horn.\textsuperscript{67}

   b. Cat

   Between about one sixth to one third of cat cervical enlargement cells contributing axons to the contralateral thalamus are found in lamina 1.\textsuperscript{69,75} The other major groups of contralaterally projecting cells are in laminae 4-6 and in the ventral horn laminae 7-8. While Carstens and Trevino\textsuperscript{69} reported approximately equal distribution of cells between the laminae 4-6 and laminae 7-8, Jones et al.\textsuperscript{72} found that 53% of the contralateral STT in the cervical region arise from laminae 4-6 and only 18% from the ventral horn. The reasons for this discrepancy are unclear, although the work by Jones et al.\textsuperscript{72} labeled two to three times as many STT neurons as did the work of Carstens and Trevino.\textsuperscript{69} The lamina 1 group projects primarily to the VB-VL area of the thalamus while the ventral horn STT neurons project primarily to the intralaminar nuclei, and the laminae 4-6 group was labeled to a limited extent following injections into either VB-VL, the intralaminar complex, or into POm.\textsuperscript{69} Compared with the upper cervical spinal cord, the ipsilateral projection from the cervical enlargement is small and limited to a few lamina 1 and a few lamina 5 cells. Using electrical identification of projecting neurons, Albe-Fessard et al.\textsuperscript{76} were not able to identify any lamina 5 STT neurons in the cervical cord of cat, although Ferrington et al.\textsuperscript{77} were able to identify STT neurons in lateral laminae 4 and 5. Most of the successful sites for antidromic activation were in the POm region of the thalamus.\textsuperscript{77}

   c. Monkey

   Using retrograde transport of HRP, Trevino\textsuperscript{72} and Hayes and Rustioni\textsuperscript{73} showed that primate cervical enlargement neurons projecting to the contralateral thalamus were found primarily in lamina 1 and in lateral laminae 4-5. There was a scant ipsilateral STT projection from lateral lamina 5. A quantitative study revealed that 18% of the total STT originates from the cervical enlargement and that laminae 1 and 5 contain the highest concentrations of STT cells (11 to 50% were located in laminae 1-3 and 33 to 79% were located in laminae 4-6).\textsuperscript{64} This study showed relatively scant STT neurons scattered in ventral horn laminae 7-8 and very small ipsilateral ventral horn STT projection. (Figures 3 and 4).

   Thus, the cervical enlargement STT contribution is different from that found in the upper cervical cord in that there is a much higher concentration of contralateral lamina 1 cells, relatively few contralateral laminae 7-8 cells, and nearly no neurons projecting to the ipsilateral thalamus. The differential projections of primate cervical enlargement cells to the various termination areas of the STT within the thalamus has not been studied.

3. Thoracic Spinal Cord
   a. Rat and Cat

   In the rat thoracic spinal cord, relatively few STT neurons are found compared with the upper cervical area,\textsuperscript{66,67,74} with the thoracic STT in rat contributing less than 10% of the
total STT.\textsuperscript{67} The contralaterally projecting STT neurons in these cord segments are found scattered in lamina 1, with denser concentrations of neurons in the nucleus proprius and the intermediate gray zone around the central canal.\textsuperscript{56,67} There is almost no ventral horn or ipsilateral contribution to the rat thoracic STT. There seems little preferential projection of thoracic STT neurons to either medial or lateral thalamus.\textsuperscript{74} The cat, like the rat, has a meager STT originating from the thoracic spinal cord. The cat thoracic STT neurons are found in laminae 1, 5, and 8, with the lamina 8 projection being the most dense.\textsuperscript{69}

b. \textit{Monkey}

The primate thoracic spinal cord has been shown to contribute axons to the contralateral thalamus using both retrograde transport and electrical antidromic activation techniques. The transport studies\textsuperscript{64,72,73} reveal a small thoracic STT from this area compared with the cervical and lumbar STT contributions. The thoracic STT comprises 18\% of the total STT, with most of the STT neurons being found in the upper three thoracic segments.\textsuperscript{64} The cells projecting to the contralateral thalamus are found in lamina 1 and lateral lamina 5,\textsuperscript{72,73} and there is also some input to the contralateral thalamus from the ventral horn.\textsuperscript{64} Of the thoracic STT label, 58 to 65\% is found in laminae 4-6.\textsuperscript{64} Antidromic activation of thalamically projecting thoracic neurons has indicated their laminar locations to be distributed essentially as described by the retrograde transport studies,\textsuperscript{78-80} although these studies have revealed a more prominent distribution of recording sites in lamina 4 than would be suggested on the basis of the tracer sites. This may be a reflection of recording sites on neuronal structures separate from the soma. In one study,\textsuperscript{78} 22 of 62 thoracic STT cells projected only to the VPL thalamus, while 27 projected to only medial thalamus and 13 projected to both medial and lateral thalamus. The medially projecting group contained neurons in laminae 1, 4, 5, and 7, with the greatest number of cells being found in lamina 7. No lamina 1 cells were found to project to the lateral thalamus; the largest projection to this area was from lamina 4. The cells projecting to both medial and lateral thalamus were found predominantly in lamina 5.

The thoracic component of the STT then, although smaller than the cervical or lumbar enlargement (\textit{vida infra}) projection to thalamus, has similar organizational characteristics, with contributions from three groups of neurons, i.e., dorsal horn apex, neck of the dorsal horn, and the ventral horn. The deeper cells are more likely to project to the medial thalamus than the cells located in the dorsal horn.

4. Lumbosacral Spinal Cord

\textit{a. Rat}

The lumbosacral spinal cord STT is the most extensively studied of the spinal cord segments. In rat, between 30 and 35\% of the total STT is from segments T13-L5.\textsuperscript{67} Occasional cells are found in the marginal zone of the lumbosacral spinal cord, however, the greater concentrations are located in the nucleus proprius and in deeper discrete areas of the ventromedial dorsal horn and the dorsomedial ventral horn.\textsuperscript{74} The ventromedial dorsal horn group is particularly dense in the mid and upper lumbar spinal cord.\textsuperscript{67} There is nearly no ipsilateral STT projection from the rat lumbosacral cord. Antidromic activation of rat lumbar STT neurons has confirmed their locations primarily in the ventromedial dorsal horn and in the ventral horn.\textsuperscript{65,81-83} The ventromedial dorsal horn and ventral horn groups project to the medial and lateral thalamus, while the neurons in nucleus proprius project primarily to the lateral thalamus.\textsuperscript{74}

\textit{b. Cat}

In cat, retrograde HRP studies have indicated that the lamina 1 contribution is much denser than that found in rat,\textsuperscript{69} accounting for slightly over 20\% of the lumbar STT.\textsuperscript{75}
Fluorescent retrograde study by Craig et al., however, revealed that 46% of labeled cells were found in lamina 1 and that about half of these cells projected medially to nucleus submedius. Craig et al. hypothesized that there is a population of lamina 1 cell terminations in submedius not labeled by HRP, but which are capable of being labeled by fluorescent dyes. The fluorescent study by Stevens et al. revealed 33% of lumbar STT neurons to be located in lamina 1-3. The same studies reveal a discrepancy in the amount of laminae 4-6 input to the contralateral thalamus, with the paper by Jones et al. revealing about 20% of the STT to arise from this group, while Carstens and Tревino show only a rare laminae 4-6 cell contributing to the lumbar STT. Fluorescent studies show a 13% STT contribution from this group. All retrograde transport studies reveal a large STT (42 to 75% of the lumbar STT) projection originating from medial laminae 7-8. The specificity of the thalamic termination sites of lumbar STT neurons has been evaluated with both retrograde HRP and fluorescent study. Lamina 1 was shown to project preferentially to the lateral (VPL-VL) thalamus when compared with injections in the intralaminar group or PO. However, when the more medial injections included the region of SM, 51% of lamina 1 cells projected laterally and 36% projected medially with 13% projected to both areas. Very few lamina 1 cells projected to the intralaminar complex. The intralaminar group of nuclei receives its STT projection primarily from the ventral horn cells, and these cells project to the intralaminar and more medial thalamic nuclei, with 11% of laminae 7-8 neurons being double labeled following injections into the lateral and intralaminar nuclei. Electrical identification of cat lumbar STT neurons has confirmed the basics of their distributions. Axons in the lumbar cord, ipsilateral to the stimulation site, were most often found following stimulation in the area of CL, CM, medial MD, and ZI. Little antidromic activity was found when VPL was stimulated, providing good correlation with the lack of a dense STT termination in VPL of cat. Presumably, lamina 1 terminals were not found when the VLQ of the cord was searched for antidromic activity (vida infra). In a study of antidromically activated lamina 1 STT cell, Craig and Kniffki found that 47% of these neurons projected to the medial thalamus only, 19% projected solely to the lateral thalamus, and 26% projected to both medial and lateral thalamus.

c. Monkey

The primate lumbar STT is organized somewhat differently than the cat or rat and has been recently summarized by Willis. Of the total STT, 20% is from the spinal cord below the thoracolumbar junction. Retrograde tracing studies using HRP indicate three major lumbar spinal cord groups of cells contributing to the STT projection to the contralateral thalamus (Figures 3 and 4). These include the dorsal horn apex (laminae 1), lamina 5, and the ventral horn laminae 7-8. The density of the lamina 1 contribution to the lumbar STT is much greater than in rat and similar in relative concentration to that found in cat, constituting about one third of this projection, while 28 to 51% of the lumbar STT is from laminae 4-6 and 27 to 56% is from laminae 7 and 8. Of the sparse ipsilateral lumbar STT projection, the vast majority is found in the deep laminae of the ventral horn and only rare cells are identified in ipsilateral laminae 1 or 5. Identification of the locations of STT neurons mapped by antidromic thalamic stimulation in general confirms the locations as described in the retrograde tracer studies, i.e., there are particular concentrations of neurons at the dorsal horn apex, lateral lamina 5 (although there is a fair amount of deviation of these neurons into laminae 4 and 6, possibly a reflection of the extensive arborization of lamina 5 cell dendritic trees, and in the ventral horn. Lamina 1 cells project primarily to VPLc as do deeper dorsal horn STT neurons, while the ventral horn laminae 7-8 neurons project preferentially into the intralaminar nuclei (especially CL). Some cells in all three laminar groupings have been found to project to both medial and lateral thalamus. The contribution of primate lamina 1 STT neurons to terminations in SM remains to be evaluated.
The lumbar enlargement, because of its physiologic accessibility, has been a major area of study for those interested in the STT. Significant species variations are apparent. For instance, the number of cells contributing to the STT from the lumbosacral spinal cord dramatically increases from rat to cat to monkey. As opposed to rat, both cat and monkey have about one third of the lumbar STT made up of lamina 1 cell axons. The cat has a small deep dorsal horn contribution to the STT while the rat deep dorsal horn contribution is located primarily medially and the monkey deep dorsal horn contribution is located primarily laterally. There is a large input from the ventral horn laminae 7-8, which projects primarily to the medial thalamus in both cat and monkey.

Figure 5 summarizes the segmental and laminar distributions of cells of origin of the primate spinothalamic tract. The striking features of the study of the cells of origin of the STT in all species is the large contribution of the upper cervical cord to the STT and the large ipsilateral STT projection found in the upper cervical cord. Furthermore, it is apparent that the various laminar groups of STT neurons represent functional heterogeneity, at least based on their particular thalamic termination sites. For instance, lamina 1 cells project both the the lateral thalamus and have an unique medulal projection to SM, while deep dorsal horn neurons project to both medial and lateral thalamus, and the ventral horn neurons, including those found in the high ipsilateral cervical cord, project primarily to the intralaminar nuclei.

The functional study of STT neurons documented in the next section generally supports the idea that the STT is a heterogeneous group of axons divisible into three basic groups, i.e., lamina 1, deeper dorsal horn, and ventral horn.

IV. FUNCTIONAL ORGANIZATION

A. STT NEURONAL CHARACTERISTICS

Dorsal horn neuronal responses to afferent stimulation are generally classified according to the types of cutaneous afferent stimuli that can activate them. Cells that respond to
either hair movement or gentle cutaneous pressure, and which do not increase their firing rate when more vigorous frankly noxious stimuli are applied, are referred to as low threshold (LT) units. Cells which respond to hair movement or gentle mechanical stimulation and increase their responses when noxious stimuli are applied to the skin such that they respond maximally to noxious cutaneous stimuli are termed wide dynamic range (WDR) neurons. Units that respond only to intense mechanical or thermal cutaneous stimuli are termed high threshold (HT) neurons. Those that respond to manipulation of subcutaneous tissues such as muscles, tendon, or joints are termed deep (D) neurons. Further subdivisions of these groups are needed to define those neurons that receive exclusively or additionally visceral input (visceral specific or somato-visceral units) or that respond to innocuous warming or cooling (thermoreceptive units) of their receptive fields.

1. Dorsal Horn Apex (Lamina 1)

The finding that lamina 1 cells contribute to the STT in all species and in all spinal cord segments is of particular significance since these units receive afferent input from fine myelinated and/or unmyelinated afferent fibers and respond to noxious cutaneous mechanical stimulation.102,103 Those units which receive A-delta input in cat respond to intense mechanical stimulation, while those receiving A-delta and C fiber input respond to intense mechanical stimulation and to noxious heating of the skin; a subdivision of the latter group also responds to innocuous warming or cooling of the receptive field.103 Price and Mayer104 described in monkey the responses of primate lamina 1 cells and found the predominant response type to be HT.

It has been estimated that approximately two thirds of lamina 1 neurons function as segmental interneurons without supraspinal connections while the remaining one third can be shown, at least in cat, to project rostrally.105 Detailed study of the functional properties of lamina 1 cells projecting to the thalamus in monkey shows that they respond predominantly to noxious mechanical stimulation.106,107 Of the 21 cells studied by Willis et al.,106 20 also responded to noxious levels of cutaneous thermal stimulation; however, a more recent study has stressed the presence of WDR-type neurons in primate lamina 1 (12/21 responded to brushing the skin or to innocuous pressure).108 The important point is that essentially all lamina 1 cells in primate respond maximally to noxious cutaneous stimulation. As in primates, the lamina 1 cell population in cat contains a large group of WDR cells; however, unlike primate, those that project to the thalamus are exclusively nociceptive (HT) or thermoreceptive.90,91 The receptive fields of lamina 1 cells are typically small,91,92,104,106,108 comprising a portion of a digit or a small area of distal skin up to several digits. Responses to heat stimuli in both cat and monkey generally had thresholds at or above noxious temperatures (45°C),91,108 with primate HT lamina 1 units having a higher threshold than WDR lamina 1 neurons. Similarly, a number of the lamina 1 cells in both species responded to cooling stimuli applied to the skin. Above noxious threshold, lamina 1 cells are able to code for heat intensity and demonstrate characteristics of sensitization following repeated applications of noxious heat.33,91 Repeat noxious thermal or high-intensity cutaneous stimulation results in a progressive increase in the responses ("windup") of STT neurons located in the superficial dorsal horn.96,97 Convergence of deep muscle input onto some lamina 1 cells has been demonstrated in cat,91 although in the monkey lumbar cord lamina 1 cells seem uniquely unresponsive to noxious muscular input.109 Visceral convergence into lamina 1 neurons has been demonstrated in cat.110,111 Some of these neurons, located primarily in the thoracic and high lumbar areas, project rostrally.111 Similarly, lamina 1 STT cell that have striking viscero-somatic convergence have been identified in the primate thoracic spinal cord.78,79 The responses of lamina 1 cells in both cat and primate receive input from fine myelinated and unmyelinated fibers91,97,108 and mimic the response characteristics of these fibers in many respects.96,97
The mean conduction velocities of lamina 1 STT axons is low (12.7 ± 8.6 m/s in primate; 3.7 m/s in cat), suggesting that their ascending axons are small, finely myelinated fibers. The electrically identified termination sites of lamina 1 cell axons agree with that shown by anatomical studies, i.e., there are both medial and lateral thalamic termination sites. Interestingly, the study by Craig and Kniffki showed that a very high percentage (47%) of lamina 1 cells projected medially while only 19% projected solely to the lateral thalamus and 26% projected to both areas. The lamina 1 neurons that were cold specific projected only to the medial thalamus. There were only several lamina 1 cells in the study by Giesler et al. one projected only to the lateral thalamus and the other projected to both medial (the medial stimulation area in this study was the intralaminar nuclei) and lateral thalamus. Primate lamina 1 cells project preferentially to lateral thalamus (VPLc and VPLo) as opposed to projecting to CL; however, it is not clear if search antidromic stimulation was applied to the area of SM.

The lamina 1 STT characteristics then are (1) small receptive fields implying ability to code for locus of peripheral stimulation, (2) maximal response to noxious or thermal peripheral stimulation, (3) convergent input from deep and visceral structures, (4) sensitization and windup as a result of repeated noxious thermal stimulation, (5) input from A-delta and C peripheral fibers, (6) ability to code threshold and intensity of peripheral thermal stimulation, (7) inhibition by stimulation of areas of the brain associated with behavioral analgesia (see later), and (8) fine myelinated axons terminating in both medial and lateral thalamus.

2. Deep Dorsal Horn (Laminae 4, 5, and 6)

Rat, cat, and monkey have STT neurons located in laminae 4 through 6 as outlined previously. In rat, the cells located in the lumbar ventromedial dorsal horn form a concentrated and unique group studied by Menetrey et al. and Menetrey and Besson. These units all had ongoing spontaneous activity related to ankle position and responded to both joint movement and to innocuous skin stimulation to their small distal cutaneous receptive fields. Noxious skin stimulation resulted in inhibition of ongoing activity. These cells, which are known to project to the intralaminar nuclei (CL) are thought to be involved in motor coordination activities. Other units in the “middle laminae” of rat dorsal horn have either LT- or WDR-type responses. Cat has relatively few lumbar laminae 4-6 STT neurons that can be antidromically activated by thalamic stimulation. However, the density of laminae 4-6 STT neurons in the cervical cord is apparently denser, allowing physiologic study. In the study by Ferrington et al., the area from which most laminae 4-6 STT neurons could be activated was POm. Of 26 of these cells, 22 had background activity averaging 1.4 impulses per second. Most receptive fields were small and located on the distal upper limb. Of these units, 56% were classified as WDR, 13% LT, 13% HT, and 16% D. The WDR and HT units had thresholds at or above behavioral nociceptive levels, were able to code thermal intensity, and demonstrated characteristics of sensitization after repeated noxious thermal trials. Mean conduction velocity of the ascending axon was higher than that found for lamina 1 cells at 38 ± 17 m/s. Primate lumbar laminae 4-6 contain large numbers of STT neurons. Most of the 38% of the lumbar STT neurons that respond to hair movement in primate are found in laminae 4-6. Of 24 of these cells, 23 responded with a maintained discharge to noxious pinch, and more than half of the cells responded to temperature of greater than 45°C. The finding of units responsive to light mechanical stimulation and to noxious pinch or thermal stimulation was common. Another group of neurons responding only to HT stimuli or to deep stimuli were found in laminae 4-6. In a summary of 318 lumbar STT neurons, Willis indicates that 61% of laminae 4-6 cells is WDR type, 10% LT type, and 28.9% HT type. Receptive field sizes for these cells was generally small or medium sized (larger than a foot, but smaller than the entire leg); however, as cells with more proximal receptive fields were encountered, they became larger.
location of cells in lamina 4 was somatotopically organized, with flexor foot surfaces being most medial, while the laminae 5 and 6 cells were not so organized.\textsuperscript{106} Laminae 4-6 cells located more rostrally in the thoracic cord had larger receptive fields, often encompassing part of the chest wall and upper extremity.\textsuperscript{78} There is convergence of noncutaneous input on to laminae 4-6 STT neurons. For instance, Foreman et al.\textsuperscript{109,114} have shown that 35/50 lumbar STT neurons, many of which were located in these laminae, responded to one or more algesic chemicals injected into lower extremity muscle. Ammons\textsuperscript{88} described renal input to cat low thoracic spinale laminae 4-6 STT cells, and Foreman\textsuperscript{79} reviewed the data showing afferent sympathetic input to thoracic STT neurons, many of which were located in the deep dorsal horn. STT neurons in the dorsal horn are able to accurately code innocuous mechanical transient and sustained skin perturbations.\textsuperscript{115} Additionally, lumbar STT neurons respond to noxious thermal stimuli with thresholds over 45°C and code for thermal stimulus intensity.\textsuperscript{97,116,117} Repetitive noxious thermal stimuli result in responses of these units consistent with their activation by A-delta and C fiber input, i.e., the early (A-delta) response decreases with stimulus repetition while the late (C fiber) response increases with stimulus repetition.\textsuperscript{97} Surmeier et al.\textsuperscript{116,117} suggest that the early response of STT cells to noxious heat is due to C fiber activity while the late response is due to A-delta activity, a finding different from what is usually assumed based on timing of responses.\textsuperscript{97} Sensitization to tactile stimulation following damaging heat stimulation has been described.\textsuperscript{118} SST cells located in lamina 4 project only to lateral thalamus in primate, while those in laminae 5-6 can project to either intralaminar (CL) or lateral thalamus.\textsuperscript{92,112} In a study of thalamic projection sites of thoracic STT neurons, most of the units projecting to the lateral thalamus were found in lamina 4, while those projecting to either the medial only or both lateral and medial thalamus were found in laminae 4, 5, and 6.\textsuperscript{78} In the lumbar cord, most units projecting either to the lateral thalamus only or to medial and lateral thalamus were found in laminae 4-6, while medially projecting neurons were found in the ventral horn.\textsuperscript{100} Both groups in laminae 4-6 had similar response characteristics, i.e., WDR-type responses with relatively limited ipsilateral cutaneous receptive fields.

The characteristics then of the group of STT neurons found in laminae 4-6 are (1) WDR-type responses, although some LT and some HT responses are found; (2) ability to accurately code both innocuous and noxious cutaneous stimuli; (3) sensitization following repeated noxious thermal stimulation; (4) convergence of input from deep somatic and visceral structures; (5) generally small- or medium-sized ipsilateral receptive fields; (6) thalamic projections to lateral and medial (intralaminar) (at times both) nuclei in the thalamus; and (7) ability to be inhibited by activation of recognized antinociceptive areas of the brain and spinal cord (see following).

3. Ventral Horn (Laminae 7 and 8)

In rat, cells of laminae 7-8 have been studied electrophysiologically.\textsuperscript{65,83,113} These cells have unusual and, at times, difficult to define receptive fields and response characteristics. For instance, Giesler et al.\textsuperscript{65} described their receptive fields as poorly definable, with the cells often responding to innocuous cutaneous stimulation and to pressure in deep tissues; Menetre and Besson\textsuperscript{83} (see also Reference 113) described these cells as having a high rate of resting discharge, at times related to knee joint position, and widespread nociceptive inhibitory receptive fields, at times spanning three limbs. Consequently, in rat these cells seem likely to participate in processing of proprioceptive information, like the cells located more dorsally in the dorsomedial dorsal horn.

A large proportion of feline antidromically identified STT neurons fall within laminae 7-8.\textsuperscript{87} These units had conduction velocities ranging from 10 to 97 m/s (median = 33 m/s). Most deep cat STT cell were antidromically activated by stimulation of regions in or around the intralaminar nuclei or the magnocellular portion of the MGmc complex in the
The axonal conduction velocities of these axons ranged from 18 to 83 m/s (mean = 42.2 m/s), and 84% of these neurons had ongoing activity. The receptive fields of these neurons were large and complex, with 81% showing excitatory and 54% showing inhibitory responses to both noxious (45.9%), innocuous (78.3%), or deep (24.7%) somatic stimuli. The cells were not somatotopically organized in the dorsal horn and 78.3% had bilateral receptive fields.

Some primate STT neurons are also located in laminae 7-8 and have conduction velocities (26.5 and 22.7 m/s for cells in laminae 7 and 8, respectively) slower than the cells found in laminae 4-6. The cells in laminae 7-8 responded primarily to deep somatic (muscle and joint) stimuli, but at times also responded to innocuous and/or noxious cutaneous stimuli. Most STT units electrically identified as projecting to the medial (CL) thalamus are found in laminae 7-8 and most laminae 7-8 STT cells project to the medial thalamus. Of these cells in the primate ventral horn, as in cat, 71% has complex receptive fields that commonly are large and, at times, bilateral. As the laterally projecting STT laminae 4-6 cells in primate, the cells projecting exclusively to medial thalamus receive input from all (A-beta, A-delta, and C) cutaneous fiber classes and many receive convergent input from deep structures. Of these medially projecting cells, 25% responded as WDR type, 63% were HT, and 12% D. These cells typically have little or no spontaneous activity and can respond to noxious stimuli applied to widespread areas of the body. The widespread excitatory effects on these cells is dependent on supraspinal connections, possibly in the caudal pontine reticular formation, descending in the cord bilaterally. Like the lumbar area, thoracic ventral horn STT neurons project predominantly to the medial thalamus and have receptive fields that are large and complex, at times bilateral, compared with laterally projecting STT neurons.

The majority of thoracic ventral horn cells in primate and cat receive convergent input from visceral afferent fibers. The single published study concerning the physiologic characteristics of the striking ipsilateral high cervical spinal cord STT projection, originating in laminae 7-8, show that these cells are like the lumbar ventral horn neurons in terms of their large complex receptive fields and medial projections. Preliminary studies in our laboratory indicate that cat high cervical contralateral ventral horn neurons possess similar characteristics.

The contributions to the STT from the ventral horn are clearly distinct from those in the apex and laminae 4-6 of the dorsal horn. This group of neurons, including those found in the high cervical area, are characterized by: (1) large, complex, at times bilateral receptive fields (except in rat where these neurons seem to serve a proprioceptive function), (2) convergent input from deep and visceral structures, (3) low spontaneous activity, (4) dependence on descending fibers of supraspinal origin for the full expression of their receptive fields, and (5) projections predominantly to the intralaminar nuclei of the thalamus.

Overall, the STT is composed of a heterogeneous group of cells that can be identified by their laminar locations and that transmit information concerning the full spectrum of sensation from hair movement to frankly damaging peripheral and visceral events.

3. Alteration of Spinothalamic Cell Responsiveness

As noted in Section I of this review, cell groups participating in the chain of transmission leading to the conscious appreciation of pain should have response characteristics that can be altered by maneuvers known to be effective in altering behavioral responses to noxious stimuli. This question has been approached in a variety of studies dealing with the STT. For instance activation of descending inhibitory pathways from nucleus raphe magnus inhibits lamina 1 cell responses to both A-beta and A-delta afferent volleys. Further study of the effects of nucleus raphe magnus stimulation has been provided by Gerhart et al., who demonstrated inhibition by medial medullary stimulation of STT cell responses. This inhibitory effect was more prominent when afferent C fiber (as opposed to A-beta and A-delta)
volleys were used to elicit the control STT cell response. Similarly, periventricular gray stimulation inhibits response of STT cells, including those projecting to either the medial or the lateral thalamus, to visceral and somatic stimulation. Foreman et al. have demonstrated inhibition of STT unit responses by dorsal column stimulation. Haber et al. have demonstrated inhibition of STT cell responses to both noxious and innocuous skin stimulation by stimulation in the region of the medullary nucleus gigantocellularis. This effect was greater when small-diameter, myelinated-fiber activity was used to activate the STT neuron compared with A-beta evoked activity. Stimulation of the ipsilateral or contralateral VPLc results in prolonged inhibition of STT neuronal responses to cutaneous and electrical peripheral nerve stimulation. This inhibition is dependent on descending pathways in the dorsolateral funiculus and in the dorsal portion of the ventrolateral funiculus. This suggests a possible role of activation of lamina I cell terminals (vide infra). The STT, then, has responses that can be altered by activation of a variety of suprasegmental structures. The inhibitory responses described coincide nicely with behavioral and clinical experience using similar or equivalent modalities for pain control.

B. FUNICULAR ORGANIZATION

The assumption that the STT ascend in the ventral quadrant (VQ) of the spinal cord contralateral to its cells of origin and ipsilateral to its thalamic termination site is well founded on clinical and experimental observations. This evidence is based on the identification of degenerating axons within the VQ following anterolateral cordotomy in both monkey and man, as well as the presence of HRP-containing fibers in the VQ following thalamic injections of HRP. Additionally, physiologic study has confirmed the presence of STT fibers in the VQ. Stimulation of the VQ in humans during percutaneous cordotomy can result in sensations of warmth and pain (see also the review by Albe-Fessard et al.2). Further evidence is circularly found in the efficacy of section of the VQ in both human and experimental animals in abolishing sensations thought transmitted by the STT, i.e., pain and temperature appreciation. There is a clear somatotopic organization of spinothalamic fibers as they ascend through the spinal cord. The fibers arising in the sacral spinal cord assume a progressively more posterior and lateral position within the VQ as more rostral cord segments are reached and fibers from more rostral levels are added to the tract in progressively more ventral positions. A number of workers thought that there was a differential location of the fibers conducting pain compared with those conducting temperature sensation and/or touch sensation, with the temperature fibers being located more posteriorly (reviewed by Vierck et al.4) and those conducting pain more ventrally with fibers concerned with innocuous processing lying in the ventral column. There is some direct evidence that, at least in cat, the ascending fibers related to temperature discrimination lie in the mid-portion of the lateral column extending into the most ventral portion of the dorsolateral funiculus (DLF) (assuming that the position of the dentate ligament marks the division between the DLF and the VQ). In rat, differential funicular locations of fibers ascending to medial and lateral thalamus are found, with those projecting to the medial thalamus being located in the ventral funiculus and those destined for the lateral thalamus being located in the ventrolateral funiculus. However, direct recordings from VQ fibers in primates indicate that there is no functional segregation of the axons with the LT (LT fibers in this study also included some WDR-type responses since these neurons were categorized by the most gentle stimulus to which they responded) and HT fibers being interspersed. The exception to this is that the fibers with D characteristics are located more superficially in the VLQ.

The fact that the sensory loss and pain relief following cordotomy can decrease over time in both humans and animals and that the analgesia following cordotomy is not absolute suggests that alternate pain pathways exist outside the VQs, and in fact most
ascending pathways including the spinocervical tract, the postsynaptic dorsal column pathway, and the dorsal column system all have some response characteristics suggesting an ability to code noxious stimuli. For the reasons cited in the preceding paragraph, little attention has been given to the possibility that a significant portion of the STT might be located outside the VQ. This, despite the writing of Kuru,52 who described, based on the study of chromatolytic changes in humans following cordotomy, the existence of a dorsolateral STT (DSTT) arising primarily from lamina 1 cells and ascending in the DLF of the spinal cord. McMahon and Wall133 found that the majority of rat lamina 1 cells ascended in the dorsolateral quadrant of the spinal cord and, because of this, thought these cells contributed to nociceptive functions separate from those involved in direct transfer of information to the thalamus. In cat, Apkarian et al.134 found that essentially all lamina 1 cell axons ascend in the DLF and suggested that any pathway with a lamina 1 cell contribution, including the STT, would have part of the pathway in the DLF. Jones et al.75,135 extended these observations in cat, demonstrating that following HRP injections into cat thalamus, lumbar lamina 1 cells continued to be labeled when the appropriate VQ was sectioned and that when similar injections were combined with a DLF lesion, the deep, but not the lamina 1 component of the STT cells of origin were seen. They concluded then that there are two components of the STT, a DSTT made up of lamina 1 cell axons and a VSTT made up of axons from neurons located in laminae 4-8. Using retrograde transport of fluorescent tracers, Stevens et al.85 confirmed the location of ascending lamina 1 cell axons to the DLF. In monkey, a similar situation exists. Apkarian and Hodge71 have shown that in primate approximately 80% of ascending lamina 1 cell axons travel in the DLF and the remaining 20% ascend in the VQ (Figure 6). Similarly, anterograde transport to the thalamus from the lumbar spinal cord of primates, following thoracic spinal cord anterior quadrant section ipsilateral to the thalamic side being studied, reveals that anterograde transport through the DLF labels multiple thalamic targets, including VPLc, CL, MD, PULo, SM, and the MGmc-SG complex.39 From the details of both the fluorescent studies in cat and the HRP studies in primate, the lamina 1 cell axons appear to be located primarily in the ventral portion of the DLF. Interestingly, the behavioral study of Kennard136 indicated an important role for dorsal spinal pathways in transmitting noxious information in cat, a finding confirmed by a recent study.137 These findings raise significant questions regarding the role of the lamina 1 contribution to the appreciation of noxious peripheral stimuli as painful since anterolateral cordotomy, an effective analgesia-producing procedure, presumably leaves uncut the group of axons with the highest concentration of nocireponsive units.

C. THALAMIC NEURONAL CHARACTERISTICS

Given the extensive terminations of the STT in the thalamus and the documented response characteristics of STT neuronal responses to peripheral stimuli and the assumption that this pathway is important in the recognition of stimuli as painful, it is of great interest to determine if neuronal responses found in areas of the thalamus in which the STT terminates are consistent with nociceptive processing. In brief, thalamic neuronal responses are a reasonable reflection of the input through the portions of the STT which terminate in the particular nucleus being studied.

1. Ventral Posterior Lateral Nucleus

As documented in preceding sections, the STT has terminations in the VPL area of the thalamus (VPLc in primate) that demonstrate some species specificity in that the terminations in cat are relatively sparse and are limited primarily to the ventral and lateral shell region of this nucleus. In cat, rat, and primate, these terminations extend anteriorly to include the VL nucleus (VPLo in primate). As exemplified by the study of Loe et al.138 of primate VPLc, there is a precise somatotopic organization of this nucleus with the caudal body
regions represented laterally and anteriorly, while the more rostral body structures are represented more posteriorly and medially consistent with the somatotopic arrangement of both medial lemniscal and STT input to VPL. Early studies\(^{39-41}\) revealed that there are a relatively few number of neurons in VPL with responses to other than gentle mechanical or proprioceptive stimuli and that these responses are primarily dependent on input through the dorsal part of the spinal cord.\(^{142}\) Mitchell and Hellen\(^{43}\) described the characteristics of neurons located in the lateral part of rat VPL that responded to both pinch and noxious levels of thermal stimuli. The neurons they found had receptive fields limited to all or part of the tail, although they were at times bilateral. All neurons responding to thermal stimuli also responded to pinch. The temperature thresholds were at about 42°C. Some of the neurons displayed only transient responses to increases in temperature stimulus above 42°C; this transient increase in activity was greater as the starting and ending temperatures were increased. At higher temperatures, the transient responses rapidly diminished. Similarly, the static neuronal responses rapidly increased in the temperature range just above threshold, but then decreased dramatically as the stimulus temperature was raised above 50°C. Pes-
anychski et al.\textsuperscript{144} described the responses of rat ventrobasal neurons responding to noxious mechanical and thermal stimuli. The mean threshold for their units was $45.2^\circ\text{C}$ and the units' responses increased monotonically for skin temperatures up to $60^\circ\text{C}$. They were able to demonstrate sensitization by prior heating as well as spatial convergence, i.e., the greater the proportion of the unit's receptive field exposed to the temperature stimulus, the greater the neuronal response. Since the thresholds of the units were spread over a temperature range of about 42 to $47^\circ\text{C}$, it was hypothesized that one of the mechanisms of temperature coding was progressive recruitment of higher threshold neurons as the applied skin temperature was increased. The locations within VPL of neurons responding to nociceptive stimuli in rat seem to have a tendency to cluster around the periphery of the central part of VPL (see Figure 1 in Reference 140). Cells responding only to noxious stimuli were activated by C fiber input only, while those of the WDR type were responsive to both low and high strengths of cutaneous electrical stimuli.\textsuperscript{45,140} A large proportion of the HT- and WDR-type thalamic neurons in rat VPL have bilateral, at times symmetrical, receptive fields, although the cutaneous area of the receptive fields was not particularly large. Cells responding only to innocuous stimuli have purely contralateral receptive fields.\textsuperscript{41,140} The WDR and HT units responded to nociceptive noxious stimuli (intraperitoneal bradykinin) as well. Narcotics depressed responsiveness of HT units to noxious cutaneous stimuli.\textsuperscript{145} Peschanski et al.\textsuperscript{146} have shown that responses in rat VPL to noxious stimuli are dependent on conduction through the anterolateral quadrant of the spinal cord ipsilateral to the thalamic recording site. The participation of ventrobasal neurons in chronically painful conditions is demonstrated in rat by the dramatic change in response properties of VB neurons following induction of arthritis.\textsuperscript{145,147} In these animals, a large number of VB units can be driven by gentle movement of inflamed joints, and long after discharges were commonly observed after mild mechanical skin or joint stimulation. The temperature threshold for these units was paradoxically increased, although sensitization was much more prominent.

Bowsher\textsuperscript{148} described two types of units in the cat VPL following destruction of medial lemniscal and spinocervical input, those with contralateral receptive fields, thought activated by the neospinothalamic input, and those with bilateral receptive fields, thought activated through spinoreticulothalamic input. Whitlock and Perl\textsuperscript{149,150} described somatotopically organized neuronal responses in cat VPL transmitted through the VQ of the spinal cord. Similarly, cortical responses to fine tactile stimulation can be found with only the VQs intact.\textsuperscript{151} Berkley\textsuperscript{141} found cells in cat VB with multimodality characteristics, suggesting anterolateral spinal input; however, the number of these units was relatively small and only a rare VB neuron could be activated by anterolateral spinal cord stimulation. Harris\textsuperscript{152} described feline VPL neurons responding to noxious stimulation, although these were rare (15/437). Neurons with wide receptive fields, involving more than one limb, were typically clustered in the caudal lateral part of the nucleus and were hypothesized to receive input through the STT. In an extensive study of over 1000 VPL units, Honda et al.\textsuperscript{153} found a small group of neurons responsive to noxious stimuli. These units had peripheral electrical thresholds in the A-delta range and were located at the periphery of the VPL, a location consistent with known STT termination areas in cat VPL. Guilbaud et al.\textsuperscript{140} have also emphasized the relative scarcity of units in cat VPL responsive to noxious peripheral stimulation. Kniffki and Mizumura\textsuperscript{154} also found that cat thalamic units responsive to noxious cutaneous and muscle stimulation were located in the dorsal and ventral periphery of VPL and in the VPL-VL border region, i.e., the known termination sites of the STT. Similar findings have been reported by Kniffki and Craig,\textsuperscript{155} who found, at the dorsal border of VPL with PO, only 11/1200 neurons with WDR responses and no HT units and at the ventral border of VPL 7/134 units with HT responses and 16/134 with WDR responses (see also Reference 156). In our studies of cat VB,\textsuperscript{157,158} we found that WDR and HT neurons were difficult to find. Their locations were generally at the periphery of the VPL nucleus and
these units had response thresholds to thermal stimuli between 44 and 48°C. These units were generally able to code for thermal stimulus intensity. An effort was made to determine whether such units depended on ipsilateral, anterolateral, or dorsolateral spinal pathways.\textsuperscript{157,158} One third of the units had the unit responses decreased by interrupting transmission in the ventral pathways and a similar number by interruption of transmission through the dorsolateral pathway. No units were found that had responses to noxious thermal stimuli interrupted by blocking conduction through both pathways. Extensive bilateral spinal cord lesions were necessary to interrupt the responses of many of these units to noxious skin stimulation. All these VPL units had receptive fields that were contralateral and consisted of a limited portion of the hindlimb. The somatotopy of the unit locations followed the somatotopy of the VPL units responding to purelylemniscal input. Unit activity in the primate VPL can be elicited by contralateral cutaneous nerve electrical stimulation after spinal cord lesion sparing only the ventrolateral spinal cord ipsilateral to the recording site.\textsuperscript{159} This activity is somatotopically organized, with the lower extremity input being located more laterally than the upper extremity input. Despite this, initial study of the responses in VPL to natural peripheral stimulation revealed that the vast majority, i.e., 98\%, of VPL neurons in primate had lemniscal properties (this was done in unanesthetized monkeys which made use of intense peripheral stimuli inappropriate).\textsuperscript{159,160} In anesthetized primate, Kenshalo et al.\textsuperscript{161} were able to identify units in VPLc that responded to noxious peripheral mechanical and thermal stimuli. Of these units, 60\% projected to somatosensory cortex. The units were somatotopically organized and had purely contralateral receptive fields, generally limited to a single extremity. There were 48 WDR-type and 6HT-type responses. The thresholds of these units to thermal stimulation ranged from between 43—45 to over 47°C, and they were able to accurately code thermal intensity above threshold levels. Sensitization was demonstrable. Although the authors show that anterolateral cord lesions were necessary to abolish the responses of these units to thermal stimuli, their Figure 6 (see Reference 161) shows a clear decrease in response following a lesion of the dorsolateral spinal cord ipsilateral to the recording site. Primate VPLc nocireponsive units receive input from peripheral fibers of A-alpha-beta size as well as from A-delta and C fibers.\textsuperscript{162} The response characteristics of the units described by Chung et al.\textsuperscript{162} were similar to those described by Kenshalo et al.\textsuperscript{161} As found in cat, both stimulation and lesions of the various spinal cord funiculi suggest activation of VPLc neurons by a variety of pathways including the dorsal columns, the spinocervical tract, and the STT.\textsuperscript{162} VPL units responding preferentially to noxious cutaneous stimuli have also been found in conscious monkeys.\textsuperscript{163} Interestingly, morphine administration had little effect on several VPLc neurons responsive to noxious stimulation in the conscious monkey.\textsuperscript{163}

Poggio and Mountcastle\textsuperscript{164} originally described responses of units in the POm consistent with STT input and suggested a role for this area in processing nociceptive stimuli. This was in contrast to their findings in the previously described study of VPLc.\textsuperscript{139} Whitlock and Perl\textsuperscript{149} described the presence of units in the caudal thalamus (POm and MGCc) that responded nonsomatotopically to bilateral input through the ventrolateral quadrant of spinal cord of cat. Brinkhus et al.\textsuperscript{165} found that 17/24 units in POM in cat responded to noxious stimuli. These units generally had large receptive fields, and when a thermal response was identified, its threshold was between 43 to 45°C. In monkey, Whitlock and Perl\textsuperscript{159} also described nonsomatotopically organized input to the MGC as well as to the intralaminar nuclei (CL and CM) through the ventrolateral quadrant and felt that this was related to the loci of STT terminations in primate. Their\textsuperscript{159} recordings from POM indicated that the likely presence of neurons with responses to noxious stimuli; the receptive fields of these neurons were frequently large and or complex. Similarly, neurons located in CM were described to respond exclusively to noxious stimuli from widespread bilateral areas of the body.\textsuperscript{160} In a study of conscious monkey, Casey and Morrow\textsuperscript{163} described the presence of units in the intralaminar
nuclei and in the MD nucleus that responded preferentially to noxious stimuli. The response properties of these units were dependent in part on the arousal state of the animal. Curry and Gordon evaluated the posterior group of nuclei in cat. They found input to the PO area from the dorsal columns as well as from the VQs of the spinal cord. The ipsilateral VQ, containing the STT that terminated primarily on the side of interest, was more effective than the contralateral VQ. Input to POM was also identified to come from the contralateral DLF (spino-cervical tract) and to a much less extent from the ipsilateral DLF. Despite this input, Curry found that only 3% of POM cells responded to noxious cutaneous stimulation; most POM units responded to innocuous hair movement and auditory stimuli. POM in cat has been found to have a relatively high proportion of the multimodal cell responses when compared with the units in the VPL area. Guillaud et al. described POM and MGmc in cat to contain both WDR- and HT-type units with multiple separate and frequently bilateral receptive fields. Units in POM are able to code thermal skin stimulus intensity above noxious thresholds and have thresholds from about 40 to 48°C. Dong et al. were able to find large numbers of nocire sponsive units in a variety of medial and intralaminar nuclei including CL, PF, and SF. Interestingly, none were found in CM. However, Nyquist and Greenhoot were unable to find many nocire sponsive units in either CM or PF. Large and, at times, bilateral receptive fields were typical of these cells. The units responded to noxious stimuli of both skin and deep structures such as muscle and tendon. Cells found in these areas received input via both A-delta and C peripheral fibers. Lesions of the DLF contralateral (spino-cervical tract) to the recording site slightly decreased the responses of these units, while ipsilateral DLF section (DSTT) had no effect on the responses of the units to peripheral nerve stimulation. Further lesion studies indicated that the VQs were most important for the full expression of the responses properties of these cells. Albe-Fessard et al. described marked increases in activity of the cells of CL associated with experimental paradigms thought related to human chronic pain situations such as denervation and polyarthritis. The SM nucleus, which has been hypothesized to be important in pain processing, has been difficult to study. However, Dostrovsky and Guillaud have shown that, in rat, dorsal SM neurons respond almost exclusively to noxious stimuli or to innocuous stimuli in the presence of prior sensitization. The receptive fields of these neurons usually represent the whole body, and the responses do not code well for intensity above noxious levels of stimulation. These characteristics are what might be predicted for neurons signaling the presence, but not the intensity, of a noxious stimulus and are curiously at variance with the characteristics of lamina 1 neurons.

The responses of thalamic neurons in areas known to contain STT terminations vary according to the area of the thalamus studied and generally reflect the response characteristics of the groups of STT neurons terminating in the area in question. The responses in VPL are well suited to characterize the sensory discriminative aspects of painful experience. The responses of the other thalamic areas, particularly SM, POM, and the intralaminar nuclei, are more difficult to functionally characterize, but presumably are related to the alerting and/or aversive roles ascribed to these areas.

2. Collateralization of STT Axons

The collateralization of STT axons has been reviewed by Kevetter and Willis. While it is not necessary to review their entire line of evidence, this topic has significant implications for understanding the phylogenetic development and the functional implications of the various connections of the STT. The STT is an uniquely mammalian tract that is superimposed on the more primitive indirect pathways from the spinal cord to the reticular formation of the brainstem and thence to the thalamic intralaminar nuclei. All mammals have a "paleospinothalamic" tract which remains relatively constant in size across the phylogenetic spectrum and is characterized by collateral input into the reticular formation and direct
terminations in the intralaminar nuclei. These theoretical collateral pathways have been identified in a variety of species using both anatomic and physiologic techniques (reviewed in Reference 22). As the phylogenetic scale is ascended, the direct neospinothalamic tract becomes larger, as does its primary termination site, the VB (VPL, VPLc). This is well exemplified by the dramatic increase in the numbers of neurons projecting to the lateral thalamus from dorsal horn lamina 1 and more ventral portions of the dorsal horn as one goes from rat to cat to primate. As already detailed in preceding sections, the units projecting to the lateral thalamus have quite different response characteristics from those projecting in the paleospinothalamic pathway to the more medial temperature — the major difference being the relatively small size of the receptive fields compared with medially projecting cells which are fit to signal the occurrence of a noxious stimulus, but are incapable of accurately localizing it.

Other aspects of collateralization that are of particular interest are the collaterals of the lamina 1 cell rostral projection. The lamina 1 cell rostral projection has collaterals to both the periaqueductal gray region and the parabrachial area, both areas with important descending antinociceptive control functions. Based on the connectivity of these neurons, a role for lamina 1 cells in controlling feedback mechanisms and affective responses to nociceptive stimuli has been hypothesized.

V. THE STT AND PAIN PERCEPTION

The preceding summary documents the heterogeneity of the STT in terms of cells of origin, termination sites, response characteristics, and funicular trajectories. The STT can crudely be separated into three separate groups of cells that have a variably intense expression depending on the species and spinal cord segmental level being evaluated. The first consists of laminae 1-3 or dorsal horn apex cells. The vast majority of these are in lamina 1, although some STT neurons have been found in substantia gelatinosa. These units are characterized by small to medium receptive fields ipsilateral to their spinal cord location. They respond best to nociceptive stimuli, although there is significant species variation, with cat lamina 1 STT cells being exclusively HT or thermoceptive while primate STT lamina 1 neurons are both WDR and HT types. These neurons are more common in primates than in rats or cats. The discovery that lamina 1 cells contribute to the STT seemed to answer many of the perplexing problems in dealing with understanding pain mechanisms since this group of neurons contains such a high percentage of HT neurons. Several facts, however, speak against a prominent role of these neurons in conscious pain perception. Most interesting to us is their funicular course, in the dorsolateral quadrant, outside the classical confines of the STT in the VQ of the spinal cord. Whether this location justifies calling this pathway the dorsolateral spinothalamic tract (DSTT) or whether it should be considered only a posteriorly displaced portion of the STT is a moot point, but serves to emphasize its unexpected location and the unique characteristics of its component neurons. On the most superficial level, this provides another non-VQ, alternate pain pathway that may assume increasing importance after anterolateral cordotomy. When the published locations of the human anterolateral quadrant lesions done to relieve pain are examined, it is obvious that at times the dorsolateral quadrant, or at least its most ventral aspect, is included in lesions that are successful in providing pain relief and appropriate sensory loss; in fact, Sweet has published several examples of clinical pain relief when the cordotomy lesion is confined primarily to the dorsolateral quadrant. Nonetheless, examination of clinically successful spinal cord lesions reveals that they do not have to include the DLF in order to relieve pain. Furthermore, animal studies in cat indicate that lesions confined to the DLF rarely result in analgesia, and studies in primate have indicated that the recovery of functional nociception after anterolateral cordotomy is only mildly and transiently reversed.
by added dorsolateral quadrant lesions. The case report of Noordenbos and Wall indicates clearly that nociceptive stimuli can be transmitted rostrally with only the VQ white matter fibers intact. Spinal cord stimulation in humans indicates that the characteristics of the stimulation resulting in pain sensations is likely to depend on deeper dorsal horn neurons with WDR characteristics. One must conclude then that lamina 1 input to rostral structures including the thalamus is neither necessary nor sufficient for noxious peripheral stimuli to result in clinical pain. Although the STT projection to SM has been thought to be related to aversive aspects of nociception, it must be pointed out that the primary projection target of lamina 1 neurons in all species is the VPL nucleus and that, although stimulation of VPL can result in painful sensations in humans, lesions of this area are notoriously ineffective for pain relief. Furthermore, the projection to SM is not very prominent in primates, and response characteristics of SM neurons in rat do not parallel those of the lamina 1 cell input. Other roles for this pathway are suggested by its demonstrated collateralization to both the periaqueductal gray of the mesencephalon and the dorsolateral pons, suggesting an important role in triggering descending inhibitory mechanisms. For all these reasons, the role of the DSTT and lamina 1 cell axons is at best uncertain.

The second group of cells to be considered is the group found in laminae 4-6 of the dorsal horn. This group is more prominent in rat and monkey than it is in cat. Neurons of this group are characterized by responses to a wide variety of peripheral stimuli. Some of the cells have only LT characteristics, some have HT characteristics, but the most common responses are those typical of WDR neurons. The receptive fields of these neurons are ipsilateral to their spinal cord location and are small to medium in size. Their axons ascend in the ventrolateral quadrant of the spinal cord and terminate in VPL and immediately adjacent to nuclei. It is unclear if POm, MGmc, and SG have unique spinal cord inputs. Some laminae 4-6 neurons collateralize to terminate in both the medial and intralaminar thalamus, and a few terminate exclusively in the intralaminar thalamus. These neurons are capable of signaling discriminative information about nociceptive stimuli and are also able to convey information about innocuous mechanical, proprioceptive, and visceral events. Their response characteristics are compatible with the reported ability of a single VQ to transmit information about innocuous and noxious stimuli. The human stimulation studies of Mayer et al. suggested that this group of cells is responsible for the feelings of warmth and pain that can result from human anterolateral quadrant spinal cord stimulation. These cells are ideally suited to transmit information about the sensory discriminative aspects of a nociceptive experience to the lateral thalamus and also have access to the intralaminar nuclei as well as the shell nuclei around VPL (i.e., POm, VL, MGmc, and SG), suggesting a potential role in both the discriminative and aversive aspects of pain perception. An important question about human pain and its relief by cordotomy is what exactly is being relieved. There can be little question that successful cordotomies result in the disruption of most if not all of the ascending axons of the laminae 4-6 group of neurons. Should this be taken as evidence that these neurons cause the pain? No. Since a variety of other axons are also cut during ventrolateral cordotomy, most notably spinoreticular fibers, it is impossible to use spinal cord section data alone to implicate a pathway in pain perception. For instance, if this group of neurons is crucial for transmission of nociceptive messages, then destruction of its termination site, i.e., VPL and VL (VPLc and VPLo) should result in alleviation of pain. This is not the case. We hypothesize that, while the lateral thalamic termination portion of this part of the STT is undoubtedly related to definition of some of the discriminative aspects of pain perception such as localization and intensity estimation, these parameters are of little importance in the clinical setting of intractable pain. The suffering patient does not care if his pain is localized to one spot as opposed to another many centimeters away. What he generally cares about is the noxious quality of his pain, which is generally poorly localized and rarely characterized by precise definitions of intensity and location. The abolition of
these latter pain characteristics is what made cordotomy such an effective treatment for pain. Perhaps the more medial, intralaminar projection of these neurons is what is more important to the patient with uncontrolled pain due to peripheral destructive processes.

The third group of STT neurons to consider is the group found within the ventral horn laminae 7 and 8. These cells are distinctly different from the first two groups. These ventral horn cells generally have large and commonly bilateral receptive fields. The receptive fields are often poorly definable and complex, extending over many diverse body areas. The predominant response pattern is not as easily characterized as the preceding two groups. Cells in this area respond at times in a WDR mode and at times in a HT mode or only to sudden brusk stimuli such as tap. They commonly, however, develop a maximal response to noxious cutaneous, deep, or visceral stimulation. The unique characteristic of these neurons is their projection to the intralaminar and dorsal thalamic nuclei, i.e., CL, PF, and parts of MD. Neurons in CL and other intralaminar areas are particularly active in paradigms mimicking chronic pain.\textsuperscript{171} The axons of these neurons are also interrupted by anterolateral cordotomy. It is uncertain whether VQ stimulation activates axons of these neurons, although it would seem reasonable to assume that their axonal electrical characteristics are similar to the WDR laminae 4-6 cells studied by Mayer et al.\textsuperscript{127} It seems reasonable to hypothesize that this group of neurons, together with the multisynaptic spinoreticulothalamic pathway, are the transmitters of nociceptive information to areas of the thalamus that are associated with the suffering related to clinically intractable pain. Further definition of the characteristics of these neurons, including their precise thalamic terminations, would be useful. For instance, are the cells of origin of terminals in POm, MGmc, and SG similar to those with terminals in VPL or similar to those with terminals in the intralaminar group? A real necessity for further definition of the role of medially projecting STT cells in pain processing is a theoretical basis for predicting activity of neurons that participate in the aversive aspects of nociception.

An important subset of this group of neurons is made up of the ipsilaterally projecting ventral horn STT neurons found in the upper cervical cord. These, together with the contralaterally projecting ventral horn neurons of the cervical cord, are the most prominent part of the STT and yet have been minimally studied. Some hint of the importance of this group can be gleaned from the ability of central high cervical cord lesions to diminish nociception over the entire body.\textsuperscript{182-185} One can presume, based on analogy with lumbar ventral horn cells and the few reports dealing with this group of neurons, that they have large receptive fields, respond maximally to noxious stimuli, and terminate in thalamic areas such as CL, Pf, MD, etc. This group clearly warrants further study.

It is perhaps a fruitless effort to attempt to identify any single group of ascending STT neurons as "the pain pathway" since there must be a complex thalamic and cortical interaction between the effects of the coactivation of these various groups of neurons. It seems likely that anything that can alter the sum of the total information transmitted cephalad about peripheral nociceptive events has the potential for providing clinical pain relief, but that, given the anatomic and physiologic diversity of the components of ascending nociceptive systems, such pain relief from alteration of only one or several of these pathways is unlikely to abolish permanently the potential for the recognition of and response to noxious peripheral stimuli.

In summary, the STT is a complex and heterogeneous pathway in terms of cells of origin, funicular trajectories, response characteristics, and thalamic termination sites. Despite extensive knowledge about its component parts, treatment of human chronic pain is still at a rudimentary level for the most part. Current treatments seem to fall into Lewis Thomas\textsuperscript{186} first two levels of treatment, i.e., level one which is basically handholding because nothing works, or at level two, the use of highly technological, expensive, and at times dangerous treatments based on a partial understanding of the phenomena associated with a disease. True understanding of a clinical problem, such as pain, can result in his level-three treatment, exemplified by the use of immunization which is both effective and simple in delivery.
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SUBJECT INDEX — VOLUME 5

Critical Reviews in Neurobiology

Page Numbers for Issues:

Issue 1, 1—91; Issue 2, 93—219; Issue 3, 221—311; Issue 4, 313—397

Cellular and Molecular Aspects of the Pathomechanism and Therapy of Murine
Experimental Allergic Encephalomyelitis, Tabira, T., .............................................. 113
Control of Aromatic Amino Acid Catabolism and its Relationship to Neurotransmitter
Ganglioside Reduction of CNS Ischemic Injury, Karpiak, S. E., Mahadik, S. P., and
Wakade, C. G., ................................................................. 221
Microenvironment of the Peripheral Nervous System under Normal and Pathological
Conditions, Olsson, Y., .................................................................................................. 265
Myelin-Associated Glycoprotein in Demyelinating Disorders, Quarles, R. H., .......... 1
Neurochemical, Neurophysiological, and Neuropathological Studies in
Vitamin E Deficiency, Muller, D. P. R. and Goss-Sampson, M. A., ......................... 239
Neuropathology of AIDS, Kanzer, M. D., ................................................................. 313
Pathogenesis of Diabetic Neuropathy: Role of Altered Phosphoinositide Metabolism,
Greene, D. A., Lattimer-Greene, S., and Sima, A. A. F., ......................................... 143
Proteolipid Proteins: Structure and Genetic Expression in Normal and Myelin-
Deficient Mutant Mice, Nave, K.-A. and Milner, R. J., ............................................ 65
Radiation Treatment of Brain Tumors: Concepts and Strategies, Marks, J. E., ........ 93
Spinothalamic Tract, The, Hodge, C. J., Jr. and Apkarian, A. V., ......................... 363