

The Tract of Lissauer in Relation to Sensory Transmission in the Dorsal Horn of Spinal Cord in the Macaque Monkey

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ABSTRACT The classical method for study of the area of innervation of skin by one nerve root, isolated by section of three neighboring roots on either side, was used to study the contribution of neighboring segments of spinal cord to transmission at the first sensory synapse. The area from which response to pin-scratch could be obtained in the conscious monkey was greatly increased if the spinal cord was sectioned just below the test segment, or hemisectioned above it, particularly if vascular infarction was avoided. The enlarged area was hypersensitive. The maximal area of skin innervated by any one nerve root was approximately twice as large as had been found by previous investigators. Each sensory point in the ventral parts of dermatomes must be innervated by at least five nerve roots. Work previously reported had shown that the area of test dermatome was reduced by sectioning neighboring roots medial to their ganglia after previous distal section of the same roots, or by section of more than three neighboring roots. These restrictions of area could be reversed by a subconvulsive dose of strychnine. The facilitatory and suppressive effects from neighboring nerve roots and spinal segments respectively were traced to the mechanism of Lissauer's tract, of which the medial division exerts a facilitatory effect and the lateral division a suppressor effect on transmission through the first synapse of the test root.

These excitatory and inhibitory effects, thought to be derived from collaterals of nerve fibers of like and unlike function of all sizes entering the substantia gelatinosa of neighboring segments, must be transmitted by small cells with axons in the tract of Lissauer. The reversal of the inhibition by strychnine indicates a post-synaptic mechanism at the first synapse. The prolongation of either tonic excitatory or tonic inhibitory influence for as long as five days after section of the corresponding input pathway represents a unique feature of the mass polysynaptic effects of the small interneurons making up the substantia gelatinosa, rather than the presence of a long-lasting transmitter substance. There was evidence that both dorsal root ganglion cells and substantia gelatinosa continue to contribute to fringe effects after isolation from the periphery. The mechanism of the substantia gelatinosa could provide correlation for the type of sequential directional information such as is necessary for the spinal scratch reflex.

The classical method for the study of innervation of the skin by a sensory nerve root is to divide three roots on either side of the test root (Sherrington, 1893, 1898). It has commonly been observed that the threshold of sensation within a dermatome isolated in this way is least in its center and rises as its cephalic or caudal borders are approached. The density of remaining innervation must be greater at

the center of the area and progressively less towards the edges, for the same gradients are found in the electrically recorded response of each individual rootlet

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making up the isolated root (Kuhn, '53). Though the *intensity* of response is greatly variable in the conscious animal, two of the present authors (Kirk and Denny-Brown, '70) have found that the stabilized *area* from which either general or reflex reactions are obtained varied by not more than one or two millimeters from day to day, or week to week. Over many months the area of dermatome response increased slightly (2 or 3 mm). Yet the area of the isolated dermatome was greatly lessened if additional roots were sectioned above or below the three roots that were severed in the original procedure of isolation. The area of the isolated dermatome was also found to be less when the neighboring roots were divided medial to their ganglia, rather than distal to their ganglia.

The restrictions observed were not due to the loss of transmitting pathways for they could be temporarily reversed by the action of strychnine. We concluded that the size of an isolated dermatome resulted from a threshold established at the points of convergence of sensory input from the test root with that of neighboring roots and ganglia, and that the presence of neighboring root ganglia isolated from the periphery facilitated the function of the test root. The maximal area of distribution of any one nerve root was found to be approximately twice as great as that determined by intradural section by the classical method. We now report investigation of the spinal mechanisms involved in the convergence of these sensory effects on the first synapse of the sensory pathway.

METHOD

The experiments reported here are an extension of our previous studies in monkeys (*Macaca mulatta*). The procedures have already been outlined in a previous paper (Kirk and Denny-Brown, '70). As in these earlier studies the animal sat in a wooden chair, with limbs free to explore and push the stimulus away, but with vision excluded by a board at neck level. The essential observation was again extent of the loss of responses to cutaneous stimulation (usually pin-scratch). The sensory borders were marked by pigments,

and when stabilized, by tattoo. The intensity of reaction was greatly variable, and was not usually recorded unless striking hyperesthesia was present. Only with hyperesthesia were responses to light contact, heat or cold regularly obtained. The border of area of loss of reflex response usually lay within 1–3 mm of the border for general reaction, and in most instances the two were identical. Exact measurements were made from landmarks such as costal margin, umbilicus and iliac crest. Each observation was photographed and the borders transferred to standard charts.

Complete transections of the spinal cord (including pia-arachnoid) were made with a number 11 Bard Parker scalpel blade: transections of the spinal cord within the pia-arachnoid ("subpial transection") were made with the blunt end of a needle sharpened along one side, inserted through a small opening in the pia mater and pressed firmly against dura as it was worked round. Lesions in the tract of Lissauer and in the dorsal and lateral columns of the spinal cord were produced with a von Graefe knife or with a small sliver of razor blade held in a hemostat. These lesions and all of the transections were made after opening the dura, and in most instances their position was marked by a small piece of silk threaded through the arachnoid. In most operations half the lamina over the root to be examined was left intact to prevent damage to spinal cord by encroachment of sutured muscle into the spinal canal. All small lesions were made by direct vision through a loupe at $\times 5$ magnification. Where possible a root which was accompanied by a large blood vessel (commonly L1 in the monkey) was chosen as the test root. As before, as a standard procedure, the three neighboring dorsal spinal nerve roots cranial and caudal to the nerve root under study were sectioned and the accuracy and completeness of all of the rhizotomies was checked at autopsy. Unless specifically noted the roots were divided proximal to the ganglia after opening the dura. All the spinal cord lesions and root sections were verified histologically, the most critical feature being examination of the root entry zone

in serial section after myelin stain (luxol fast blue).

RESULTS

(a) Complete spinal transection

In two monkeys (DAF 4, 6) the spinal cord was transected, together with the pia-arachnoid, caudal to the dorsal root entry zone of the ninth thoracic spinal nerve in one, and the seventh pair in the other. From the first day after surgery each animal showed a bilaterally symmetrical 3–4 cm band of increased reactivity and augmented local cutaneous reflexes immediately above the level of the transection (fig. 1). The caudal border of this hyperesthetic zone was sharply demarcated from the caudal insensitive skin: its position closely approximated to that of the caudal border of the dermatome field of the dorsal root immediately above the transection, as isolated by intradural section of neighboring roots in other monkeys. When pricked or scratched lightly with a pin in this band each monkey immediately scratched with moderate intensity at the site. The responses were similar to those obtained from a dermatome isolated by intradural section of adjacent dorsal roots.

By the third or fourth day the hyperesthetic area was only slightly more reactive than the more cranial skin, and while its caudal border had not shifted its cephalic border could no longer be clearly distinguished. The monkeys had ceased to scratch themselves; they did however, occasionally rub briefly at the stimulation site with a semi-closed hand. When pricked with a pin they would often frown and either grope slowly for the pin or merely wave a hand in its general direction. If already vocalising in the quiet manner typical of a monkey apparently at ease and enjoying human attention, the animal did not alter this vocalising when stimulated; and struggle responses, when they occurred, were no more intense than those when followed stimulation of more cranial skin. No definite responses to ice were obtained. The hypersensitivity continued to diminish, and after the first week was no longer discernible, even along the caudal border. However the cutaneous costal reflexes elicited from the caudal border remained brisk. Both monkeys developed, in the second week, a distinctive ipsilateral corrugation of the skin over the dorsal thorax in response to pin scratch in this region: this panniculus response together

ZONES OF HYPERESTHESIA FOLLOWING TRANSECTION OF SPINAL CORD

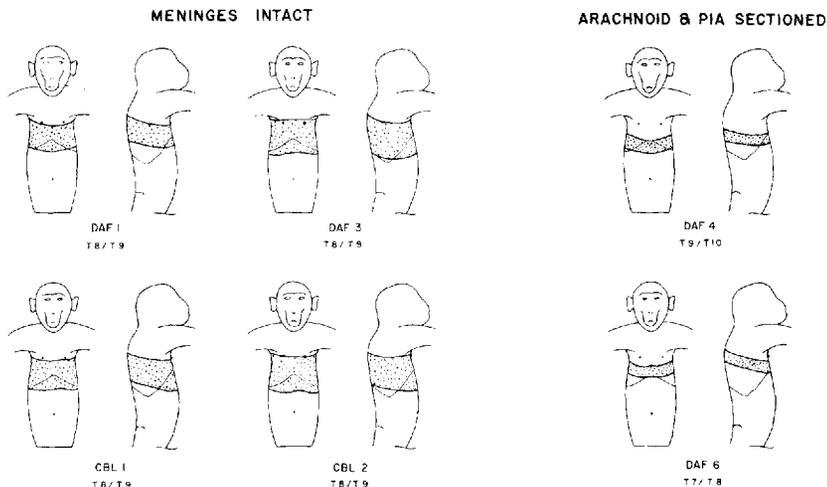


Fig. 1 The contrast in the extent of the zone of hyper-reaction (stippled) immediately above the level of sensory loss in four animals with section of the cord within the pia-arachnoid (left), with that in two animals with total section of pia and cord, right.

with an augmented costal reflex from more ventral areas, persisted throughout the following two and five weeks respectively, for which the animals were observed.

In seven monkeys the spinal cord was transected *within the pia-arachnoid* ("subpial transection"), using a needle blunted at the end and sharpened along one side. Such lesions were not associated with any bleeding, yet were confirmed by subsequent histology to be absolutely complete in these animals. In the first of these animals (DAF-16) with section at T10-11 level the reflexes in the lower limbs and abdominal wall were already extremely active on the first day. Above the border of loss of sensation there was already a wide band of hypersensitivity, in the lower half of which a brisk costal reflex was obtained (a twitch of cutaneous and lower intercostal muscles). By the fourteenth postoperative day there was a band 1.5-2.0 cm wide from which a hyper-reactive general response, costal reflex and abdominal reflex could be obtained (fig. 2). This overlap of responses from above and below the level of the lesion persisted until a root isolation, to be described in the next section, was performed on the eighteenth day.

In four monkeys the spinal cord was transected within the pia-arachnoid immediately caudal to the eighth thoracic

spinal nerves. The bilateral areas of hyper-sensitivity then charted in each animal were approximately twice the width of those seen after complete spinal transections. (fig. 1, left charts, DAF 1, 3, and CBL 1, 2). The caudal border of the hyper-reactive zone lay approximately 1.0 cm (or more) further caudad; the cranial border lay above the level of the nipples. From the first day the costal and local upper abdominal reflex responses were very large and brisk, and the area from which these could be obtained extended 3-4 mm beyond the posterior margin of the hypersensitive zone. In contrast to the reactions of monkeys after complete spinal transection of pia-arachnoid and cord the responses to test stimuli in the hyper-esthetic area were immediate, intense and difficult to fatigue. The monkeys became increasingly restless with continued stimulations and scratched vigorously—but not always at the stimulated site. The monkeys were observed for 12 to 35 days. After the first week very brisk abdominal reflexes could be obtained from a very wide zone extending headwards as much as 25 mm above the most caudal level of general response. In one animal (CBL1) subsequent extirpation of T9-12 segments of spinal cord at the thirty-fifth day abolished this overlapping abdominal reflex without affecting the hyper-reactive zone.

In two further individuals (DAF 8, 11) with subpial spinal transection caudal to the fourth lumbar spinal nerves, the sensory boundary in each leg at first crossed the dorsum of the thigh midway between the groin and the knee, but extended in the following two weeks to include the skin over the knee. Both animals became increasingly restless with continued testing, and were particularly reactive to stimuli along the sensory borders on both the medial and the lateral aspects of the thighs for the 38 and 41 days, respectively, of observation. Pin scratch on the thighs produced a much greater protest than pin prick, and the animals frequently scratched themselves above the sensory borders, and often on the contralateral leg. While sitting in the examination chair both animals were often observed to scratch their thighs spontaneously. The limb reflexes were en-

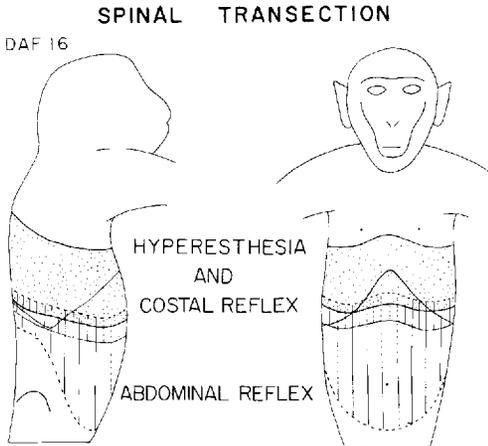


Fig. 2 The overlap of the zone of hyper-esthesia and costal reflex (stippled), with the reflexogenous zone for abdominal reflex (vertical lines) following intrapial section of spinal cord, T8-9.

hanced from the first day. Strong flexion and adduction responses followed pin scratch or prick on the lateral thigh. After the first week extension and external rotation of the ipsilateral leg often followed these stimuli. Pin scratches further proximally caused an extension of both limbs.

In the animal DAF 11 subsequent section of the pia-arachnoid at the original site of intrapial transection produced a transient 3–4 mm contraction of the sensory areas, but after the second day the sensory border returned to its original level, and the brisk reflex responses from the distal portions of the limbs remained apparently unchanged.

It was concluded that intrapial section of the spinal cord secured a more rapid and complete recovery from spinal shock by avoiding the severe disturbance of circulation associated with divisions of all pial vessels. The segments immediately adjacent to the transection, both above and below then exhibited sustained release effects, most evident as hypersensitivity in the cephalad dermatomes. In a preliminary communication of these findings (Denny-Brown and Kirk, '68) we noted their relevance to the frequency of hyperesthesia with intramedullary lesions such as myelitis or multiple sclerosis in man. In order to understand the mechanism of such hypersensitivity it was necessary to examine the sensory function of an isolated root next such a transection.

(b) *Effect of subpial spinal transection below an isolated root*

In two monkeys (DAF 15, 12) in which the eighth thoracic dermatome had been isolated unilaterally by intradural section of the adjacent dorsal roots 35 and 57 days earlier, the spinal cord was transected within the pia approximately 2 mm caudal to the root entry zones of the eighth thoracic nerves. From the first day after cord section the dermatome had expanded cranially (fig. 3), but the upper border of the newly expanded areas was not clearly defined; rather there was a progressive decrease in reactivity within a zone 1.0–1.5 cm wide. The lower border of the dermatome did not change. In the 6 and

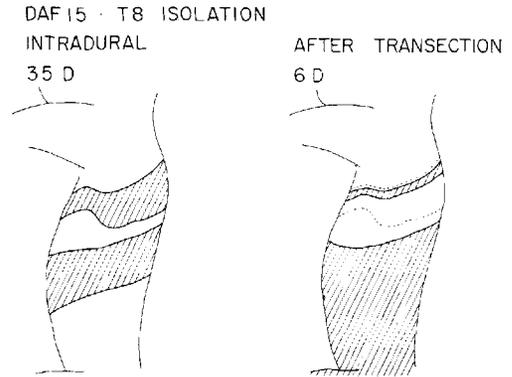


Fig. 3 The residual dermatome (sensitive areas remaining unshaded) after isolation of T8 dorsal root for 35 days (left), and the expansion of the same dermatome, six days after subsequent intrapial section of spinal cord at T9 level (right).

15 days, respectively, for which the monkeys were observed, the dermatome area continued to expand cranially. In the second animal the area stabilized at the end of the first week, but the upper border remained indefinite. The reaction of the animal to stimuli in the initial isolated dermatome areas has been recorded in our earlier paper (Kirk and Denny-Brown, '70). There was only transient mild hyperesthesia. Following the spinal transection sensitivity increased. Pin prick and pin scratch in the isolated area caused the animals to turn their heads abruptly, grasp strongly and accurately for the pin, struggle vigorously and occasionally exhibit prolonged scratching. The costal reflexes were increased in briskness and magnitude, and were readily elicited by pin pricks. In the upper parts of the expanded dermatome the ipsilateral costal reflex responses although augmented, were easily fatigued, and the sensory responses were less than those of the opposite side.

In two further animals, one of which (DAF 16) has already been described, the spinal cord was transected below the ninth and tenth thoracic spinal nerves, respectively, at an initial operation: a wide band of hyper-reactivity then extended almost from the nipples to the umbilicus. At 28 and 18 days respectively, the dorsal root on one side (left) immediately above the transection was isolated by intradural

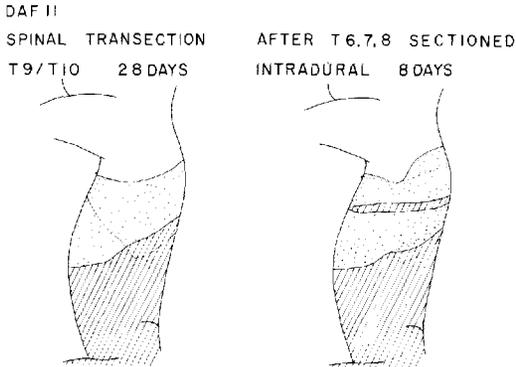


Fig. 4 The zone of hyperesthesia (stippled) immediately above the sensory loss (oblique lines) following intrapial section of spinal cord at T9-10 level 28 days earlier (left). On the right is the change following additional intradural section of T6, 7 and 8 dorsal roots.

section of the next three dorsal roots cranially. The dermatome areas thus isolated were very wide (fig. 4); the caudal border of the dermatome coincided with the previous lower border of the hyper-reactive area and the abdominal reflex from caudal to the posterior border was unchanged. Cranially, there was a gradual transition into the narrow upper insensitive band. The isolated dermatome area became hyper-reactive in its caudal part, with the ipsilateral segmental reflexes enhanced. The upper insensitive band was very narrow (0.5-1.0 cm), and gradually shrank as the isolated dermatome expanded in the first ten days. In the first animal occasional sensory reactions appeared within the upper insensitive zone at the fifth day: three days later the zone had disappeared.

(c) *Isolated root responses caudal to a transverse lesion, or a hemisection*

We have described above the remarkable release of cutaneous sensory function in the segments immediately cephalad from a transection of spinal cord. If the blood vessels in the pia arachnoid were not severed the reflex function in the segments immediately below the transverse lesion were also precociously active. The cutaneous abdominal reflex, and the related costal cutaneous reflex which twitches the

pannicular and intercostal muscles of the stimulated side, could be obtained in very brisk form from a blunt stimulus, or even a camel hair brush stroke applied to the skin for as much as a centimeter cephalad to the "sensory level" at lower T8 (as judged by general protest of the animal to pinscratch) as well as from the upper abdomen. Thus, the same overlapping skin innervation gave reactions from both above and below the lesion. That the sensory field of any nerve root below the level of transection is then greatly enlarged can be then readily observed by isolating one of the roots below the level of transection. The isolated segments of spinal cord do not tolerate a second operation of this type very well, the reflex response being less brisk than without the root isolation, though the reflexogenous area is enlarged. We therefore proceeded to examine the effect of hemisection of spinal cord rostral to the three segments above an isolated root. In two animals (DAF 68, 69) this procedure gave a very clearcut and identical result.

In DAF 68 the left L1 dorsal root was isolated by intradural section of T10-12 and L2-4 roots resulting in a classical L1 dermatome area, shown hatched in the upper diagram in figure 5. The reaction of general protest and scratching the area with the left hand after pinscratch was almost exactly coterminous with the elicitation of the left abdominal reflex. All responses were brisker from the center of the L1 root zone. After the responses had stabilized for ten weeks the effect of a subconvulsive dose of strychnine (0.25 mg/kg) was a remarkable expansion of the L1 dermatome area, beginning in the seventh minute, and almost complete in 15 minutes, reducing in 30 minutes the areas of sensory loss to those shown in black in the upper half of figure 5. The area from which the abdominal reflex could be obtained was then only 2 or 3 mm less extensive than that for general reaction. The lower zone of sensory loss had broken into two islands. The dermatome had again contracted by the following day.

Five days later the upper dorsal spinal cord was exposed for three segments at midthoracic level, and the left side of

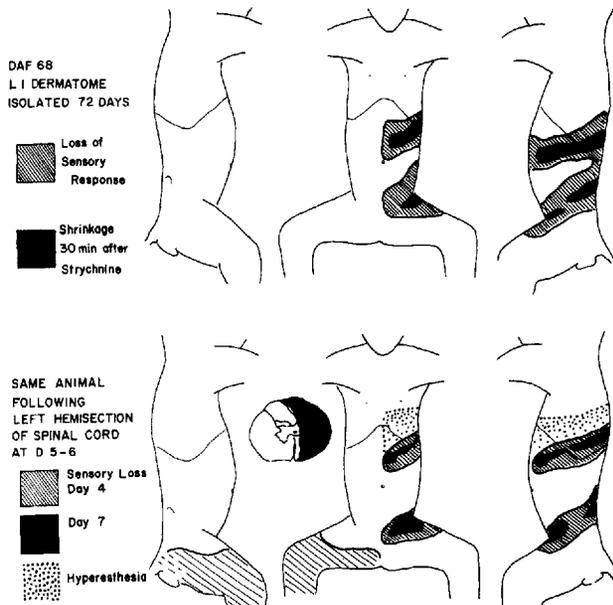


Fig. 5 The upper figures show the sensory loss (oblique lines) 72 days following intradural section of the left T10, 11, 12, L2, 3, 4 dorsal roots, and in black the temporary shrinkage of sensory loss (black) following a subcutaneous injection of strychnine sulfate 0.25 mg/kg. The lower diagrams show the sensory loss (oblique lines) and zone of hyperesthesia (stippled) four days following additional hemisection of spinal cord at T5-6 level. The left sensory loss receded to the areas shown in black by the seventh day, following which it remained stationary. The insert shows the extent of hemisection as verified by later histology.

spinal cord was transected by a needle introduced within the pia at T7-8 level. Subsequent histology of the section showed sparing of a strip 0.25 mm wide next the ventral fissure, as shown in the inset diagram in figure 5. Otherwise the hemisection was complete, and the pia-arachnoid intact. On the first day after operation the animal dragged the left lower limb and gave no response to pinscratch on the left side below D7 level, except a few jerks of contraction of abdomen and extension of spine from a series of points in the center of the left L1 area and flexion of left toes and left hip from stimulation of the left foot. The abdominal and other reflexes were active on the right side but there was no general response to pinscratch below the middle of the right thigh. On the second and third days a brisk but easily fatigued abdominal reflex appeared in the original L1 area together with a very active general protest from stimulation in this area and from any part below the middle third of the left thigh. The flexion reflex of the left lower limb was rapidly

recovering. On the fourth day a band of hypersensitivity had appeared between a level below the nipple and previous upper level of sensory loss (shown stippled in the lower chart in fig. 5) and the areas of loss of sensation had shrunk to those shown shaded in that diagram. The left abdominal reflex had become very brisk, shock-like, and at times followed by one or two myoclonic twitches. Reactions on the right side were normal down to L3 level below which no general protest to pin scratch was obtained (shown in coarse shading in fig. 5). On the seventh day after cord hemisection the areas of loss of reaction to pin scratch (shown in black in lower fig. 5) had shrunk to equal those previously remaining after strychnine. These areas and the very facile left abdominal reflex, with myoclonus remained for over five weeks before the animal was sacrificed. Good use of the left limb in walking and occasionally climbing was recovered. The loss of general reaction of the animal to pin scratch below the mid thigh on the right side persisted, though local flexion re-

flex reaction to the stimulus still occurred, except in the sacral segments where the animal directed the hands in protest equally to right or left stimulus.

The second animal with hemisection at T9-10 level after L1 isolation showed the same changes persisting for over three months after verified hemisection, though the expansion of L1 dermatome was slightly less.

The changes caudal to a hemisection of spinal cord must include the effects of loss of both ascending and descending pathways. The pattern of sensory change shown in figure 5 reveals that a pathway for the elicitation of general reaction to stimulation of the test dermatome must cross the cord. Conversely the pathway for elicitation of response from the six dermatomes below the level of the lesion on the right (opposite) side must remain ipsilateral. We have elsewhere (Denny-Brown, '66) shown how this bilateral survival of responses below a cord hemisection in the monkey is related to the mechanism of ipsilateral avoiding reactions and crossed contact magnet reactions, both determined by non-specific sensory stimuli such as contact, pinch and pinprick which must therefore normally be bilaterally transmitted for many segments. In the experiments reported here the only complete sensory loss attributable to the hemisection was that six to eight segments lower on the right side. The increased reactivity at the level of the cord lesion on the left side appeared identical to that we have found associated with release from inhibitory effects, as after total transection. The enlargement of the test dermatome six segments lower is evidence of a similar but less degree of release of dorsal horn transmission from suprasegmental restraint.

(d) *Lesions in lateral and dorsal columns*

The effect of spinal transection implied that segments of cord below the test root had had a suppressive effect on conduction through the test root. It was therefore of interest to examine the effect of differential partial lesions of spinal cord. The first lumbar dermatome was isolated bilaterally in two monkeys (DAF 22, 28) and the second lumbar field similarly isolated in a

third (DAF 21). The sensory and reflex responses on each side in each animal were typical of intradural isolations. After 14, 27 and 28 days, respectively, a partial lesion was made in the lateral funiculus on one side of the spinal cord, 2-3 mm caudal to the test root. Subsequent histology showed one lesion to be immediately ventral to Lissauer's tract and the subjacent neck of the dorsal horn; the second to include a large part of the lateral column, and the third to extend from the dorsal parts of the lateral column across the ven-

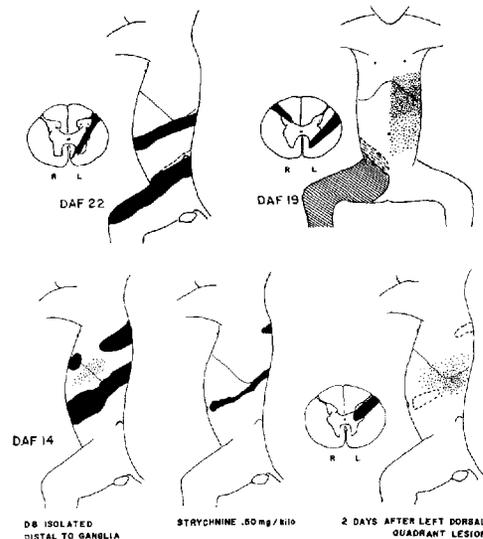


Fig. 6 The upper charts show, left, (DAF 22) the very small expansion (below dotted line) at the caudal limit of an isolated L1 dermatome following an additional lesion (black in inset) of the lateral fasciculus proprius of the grey matter, 13 days later, just caudal to L1 roots. The upper right chart (DAF 19) shows a zone of hyperesthesia (stippled) and sensory loss (oblique lines) below L1 level on the right, with a wide zone of hyperesthesia (stippled) on the left, following two stab lesions at T11-12 level, one interrupting the medial part of the right Lissauer tract and related dorsal column (without effect), the left sectioning the dorsolateral funiculus and anterior horn. The lower three figures (DAF 14) show, from left to right, the areas of sensory loss (black) and of hyperesthesia (stippled) following section of T5-7 and T9-11 roots on the left side distal to their ganglia; the temporary shrinkage of the sensory loss in the same animal 15-30 minutes following a sub-convulsive dose of strychnine (0.50 mg/kg), and on the right the absence of any area of complete loss of sensation from the second day following a small stab lesion of the lateral two thirds of the tract of Lissauer and dorsal horn at T9 level.

tral horn to the ventromedial white matter of the opposite side. Each of these monkeys showed a moderate bilateral increase in the intensity of sensory and reflex responses from the test area for two to three days after surgery; together with an ipsilateral 3–4 mm extension of both upper and lower sensory borders. The sensory borders returned to their initial levels during the third week. This small transient change in the animal DAF 22 is shown in figure 6. It will be noted that the small lesion caudal to the entering test root severed the whole fasciculus proprius of the dorsal horn at that level, leaving, both Lissauer's tract and the long ascending tracts of the lateral column intact. There was no loss of sensation in the opposite lower limb. Lesion of the fasciculus proprius (including the spinocervical tract of Morin) in the monkey produces no clinically observable effect unless the *f. gracilis* is also interrupted, for each pathway can compensate for the other (Gilman and Denny-Brown, '66).

In another animal (DAF 19) in which no roots had been sectioned a more lateral lesion in the lateral column at T11–12 on the left side produced a corresponding loss of general protest to stimuli in the contralateral lower limb, although local reflexes at this lower level were preserved. Hyperesthesia was present on the ipsilateral side and extended both above and below the level of lesion and ipsilateral to it (upper right chart, fig. 6). From a zone just cranial to the loss of sensation on the right side (shown in interrupted hatching in fig. 6) stimulation of the right abdomen led to scratching of the corresponding level of left abdomen. This response, which we have observed also in animals with hemisection of cord, indicates some confusion both of threshold and localization at levels of partial decussation of spinothalamic tract, though segmental sensory loss does not occur with such lesions.

In one animal, not illustrated here, the twelfth thoracic dermatome on each side was isolated intradurally, and at the same operation the dorsal columns on each side were transected 2–3 mm caudal to the twelfth thoracic dorsal root entry zones. The bilaterally-symmetrical root areas were

similar in size to those found in our other intradural isolations, their sensitivity diminished consistently towards their boundaries and they showed hyperesthesia only for the first day. There was no significant change in the abdominal reflexes. Fifteen days later the dorsal columns were transected again, this time caudal to the eleventh thoracic dorsal root entry zones. All four sensory borders on each side (i.e., uppermost and lowermost included) had expanded 3–5 mm when charted the following day. However, they returned to their initial (tattooed) levels on the second day and then showed no further change in the fifteen days the animal was kept under observation. There was some slight diminution in the intensity of the ipsilateral responses after the second operation.

These and other experiments indicated that the most dorsal part of the lateral column and the most lateral part of the dorsal column were the most critical areas for alteration of test dermatome by partial section of spinal funiculi. The changes resulting from damage to these zones were transient, but were consistent with the observations of Vierck et al. ('71) who reported less pain reactivity in the monkey after dorsal column lesion and greater after lateral column lesion.

(e) *Ablations of pre- and post-central cortex*

Since primary afferent depolarization (PAD) can be evoked from the sensorimotor cortex (Carpenter, Lundberg and Norsell, '63) and impulses descending from suprasegmental structures can modify dorsal root potentials (DRP) (Hagbarth and Kerr, '54) we proceeded to examine the effect of cortical ablations on dermatome area.

In each of two animals in which a lumbar dermatome (L4, L6) had been isolated on the left side by intradural section of the neighboring dorsal roots, the right pre- and post-central cortex was ablated 57 and 40 days later respectively. In the 29 and 66 subsequent days for which they were then observed, neither animal showed any alteration in the positions of the sensory borders. There was no

hyperesthesia: on the contrary, the general reactivity of the left side was greatly diminished.

Subpial transection of the thoracic spinal cord in another animal 110 days after a left hemispherectomy produced a wide band of hyperesthesia above the level of the transection. Ablation of Broadman's Area 6 on the right side 22 days later did not produce any detectable change in the extent of the hyperesthetic area on either side or any alteration in the intensity of the sensory responses.

In DAF 18, the eighth thoracic dermatomes were isolated bilaterally, and appeared typical and symmetrical. The left post-central gyrus was ablated on the eighth day and the right pre-central area ablated on the seventy-sixth day. Inattention and facile avoiding characterized responses on the right side after the first operation, but neither operation produced any change in the position of the borders of the isolated root areas. The monkey was destroyed on the one hundred and thirty-third day: in this time the only change seen was a 1.0 cm caudalward extension of the uppermost (i.e., lower fourth thoracic) borders, a change that occurred in other animals without cerebral lesion.

We concluded that the significance of the observed changes in primary afferent depolarization evoked from stimulation of

cerebral cortex is not revealed by ablation experiments.

(f) *The tract of Lissauer*

We then turned our attention to lesions of the tract of Lissauer. The tract is quite small, and our first experiments tended to damage neighboring funiculi, or to lead to infarction of the substantia or lateral column through damage to the dorsolateral artery. It is most superficial and therefore more accessible at the lumbosacral level of spinal cord (fig. 7). The tightly packed fibers of the tract are closely applied to the substantia gelatinosa, and run not more than three segments rostral and caudal to any one level. Earl ('52) found that 75% of the fibers are derived from small cells of substantia gelatinosa, the remainder from dorsal roots. The full extent of Lissauer's tract in transverse section can only be seen after degeneration of all long cord tracts by transection of spinal cord both above and below one or two segments. The T13 and L1 segment of a dog, isolated in this way and stained by a Cajal pyridine silver method by one of us (Denny-Brown) were particularly instructive. An enlargement of a drawing of a dorsal quadrant at L1 level (the corresponding L1 dorsal root having been sectioned) is shown here in figure 8 (enlarged from the drawing of a complete section used by Denny-Brown, '66, for his

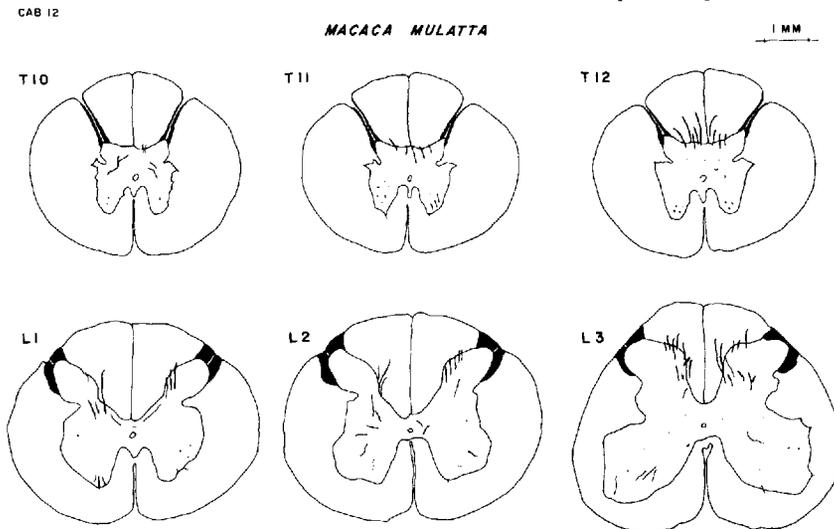


Fig. 7 The tract of Lissauer, outlined in black, in camera lucida drawings to scale, in T10 to L3 segments of a macaque monkey.

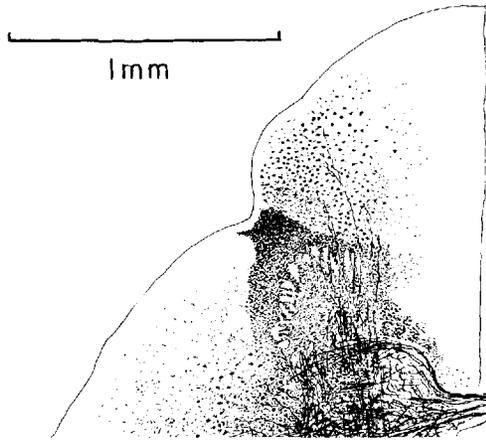


Fig. 8 Camera lucida drawing to exact scale of the right dorsal quadrant of first lumbar segment of a dog, following complete transection of the spinal cord and pia between twelfth and thirteenth thoracic segment ten months earlier, and a further transection between first and second lumbar segment, with division of right first lumbar dorsal root 15 days earlier. Stained by Ranson's modification of Cajal method for axis cylinders. This is an enlargement of the complete section shown in figure 1 of Denny-Brown ('66). Note merging of Lissauer's tract with the propriospinal tracts of the dorsal horn, also the large number of nonmedullated fibers as well as large fibers in the dorsal column derived from the remaining intact D13 root. The large axons of the spinocervical and descending propriospinal tracts are also seen in the lateral funiculus.

fig. 1). The total envelopment of the dorsal horn by fine propriospinal fibers is particularly evident. It will also be noted that many fine non-medullated fibers from the remaining T13 root travel in the dorsal column for short distances, as well as the small medullated fibers that are important for reception of noxious stimuli in the monkey (Perl, '68). To some degree at all levels, but particularly in the lumbar region the tract is divided into medial and lateral divisions by a small septum which comes to the surface of the cord just lateral to the root entry zone at L1-3 levels (fig. 7). The position of this septum can often though not invariably be seen on the surface of the cord with $\times 5$ magnification. It lies just medial to the small dorso-lateral longitudinal artery. Since the septum is often lateral to the line of root entry, the medial and lateral divisions do not exactly correspond to those mentioned

by Szentágothai ('64), or to the medial and lateral "Randzone" of Lissauer (1886).

(g) *Discrete lesion of Lissauer tract*

In a female macaque (DAF 24) a very small discrete lesion in Lissauer's tract was made with a von Graefe knife on the left side. Subsequent histology showed the lesion to be limited to the lateral division of the tract, just caudal to the lowest L1 rootlet. The following day no defect in sensory response was found and the abdominal and costal reflexes were equally brisk on both sides. Between the third and seventh day there appeared a wide zone of increased reflex response covering a maximal L1 dermatome area on the left side (fig. 9). There was no apparent difference in general protest reaction to pin scratch on the two sides. In the following two weeks the area for increased reflex response shrank a little. On the twenty-third day the wound was reopened and dorsal roots T10, T11, T12 and L2, L3 and 4 were sectioned on the left side. The following day a narrow L1 root area could be readily defined by both reflex and general reaction. This root zone gradually enlarged after the second day until it had reached more than twice the extent of a normal L1 dermatome by the fifteenth day (fig. 9). Thereafter its area remained constant for eight weeks of further survival. Throughout all this period stimulation in any part of the left L1 dermatome induced an extremely lively clonic abdominal reflex, twice as active as the right side, with marked corrugation of the skin (contraction of panniculus), accompanied by a marked general response of the animal. In the first two days the monkey showed persistent scratching after stimulation of the lower part of L1 zone on the left.

In four other animals discrete lesions of the whole Lissauer tract at the L3, L4 and/or L5 levels gave a similar result. In one of these (DAF 74) two discrete lesions each damaging chiefly the more lateral part of Lissauer's tract, one just above and one just below the rootlets of L4 gave a remarkable and persistent response. The first day after operation both general reactions and reflex response from any of the lumbar segments on the left side was depressed requiring repeated and stronger

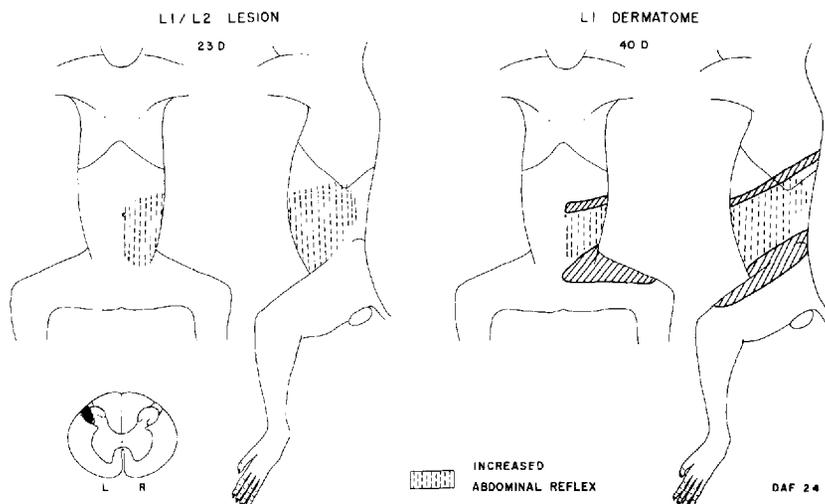


Fig. 9 Charts to show the zone of increased abdominal reflex with mild hyper-reaction (broken vertical lines) following a single stab lesion (black in inset) limited to the lateral part of Lissauer's tract, and related substantia gelatinosa at L1-2 level 23 days earlier, and right the zones of sensory loss following additional intradural section of T10, 11, and 12, and L2, 3 and roots on the fortieth day.

stimuli than on the right. On the second day the abdominal reflexes on the left were brisker than on the right, and from an area extending from left groin to the left patella any pin scratch elicited a strong protest followed by prolonged scratching of the point stimulated. Between the second and seventh day this zone enlarged to extend over a large area of the lower abdomen and front of thigh to below the knee in an area twice the extent of L4 dermatome, though no root sections were made. Pin scratch or pin prick in any part of this area induced both brisk abdominal reflex and general response.

In one further animal without isolation of test root a small discrete lesion of the medial segment of Lissauer's tract was made at T10-11 level contralateral to a lesion of lateral column (DAF 19, fig. 6). No change in skin sensation corresponding to this isolated medial Lissauer lesion could be demonstrated.

(h) *Section of Lissauer's tract after isolation of the test dermatome*

In order to define better the change underlying the hyper-reaction following lesions of Lissauer's tract we began a type of experiment where a lesion of the tract

was made on one side below an isolated test root. In the first such experiment (DAF 14, fig. 6) the Lissauer lesion was made on the left side just below the T8 root isolated previously by section of T5-7 and T9-11 roots on that side distal to their ganglia. The initial isolation had produced a very large dermatome. Strychnine almost completely abolished the bordering areas of sensory loss for some hours. Two days after the Lissauer lesion the bands of sensory loss shown in the lower left diagram in figure 6 had disappeared leaving a wide zone of hyperesthesia (fig. 6, right lower chart). A small zone of lessened reflex response was all that remained of the sensory loss.

In other animals the test roots were isolated bilaterally by section medial to the ganglion, and lumbar nerve roots were chosen because Lissauer's tract is there nearer the surface of the cord. In one animal (DAF 26) the last thoracic dermatome was isolated bilaterally at an initial operation. The isolated root area on each side (identified as T13 at autopsy) appeared symmetrically as a typical standard dermatome produced by "intradural" root section. It stabilized within seven days by which time the increased local reflex reactions of the first few days had subsided

leaving dermatome borders which varied by only a millimeter or two from day to day. As usual the borders were less reactive than the central portions of the dermatome. On the forty-fourth day a unilateral lesion was placed in the Lissauer tract on the left side just below the isolated root. The next day the anterior border of the left dermatome had extended cranially to lie along the center of the previous upper insensitive zone (fig. 10). The caudal border had shifted more caudally by 4–5 mm; and the local reflex responses were now of increased briskness. On the contralateral (control) side there was no change in the positions of the sensory borders, or in the degree of reactivity within each sensory area. The extension of the ipsilateral dermatome increased progressively until at the tenth day both the upper and the lower insensitive zones had disappeared. On the twelfth day responses were again unobtainable from narrow bands above and below the dermatome. After the second week the upper dermatome boundary moved down and finally lay only a few millimeters above the tattooed initial (pre-Lissauer lesion) level. During the period of great extension the monkey gave typical "hyperesthetic" responses, with persistent false reference — scratching itself in the lower "insensitive"

zone when the upper zone was stimulated, and vice versa. The histological confirmation of the Lissauer lesion showed a discrete total lesion of the tract.

In two other monkeys a similar lesion was placed in the lateral division on one (the left) side immediately below the twelfth thoracic (DAF 30) and first lumbar (DAF 31) roots, respectively, at the same operation in which these roots were isolated bilaterally (fig. 10). In each animal a progressive expansion of the dermatome area on the side of the lesion was charted in the first five days; this expansion then persisting for the 21 days each animal was observed. The first of these two monkeys was extremely reactive to touch during the period of expansion and, although he struggled vigorously when ice was applied during the period of expansion, it could not be established that the response was to cold alone. The ipsilateral area continued to expand for ten to twelve days; it then receded until at fourteen days the sensory borders were back at the levels charted on the fourth day. Hyperesthetic reactions were then no longer seen, and the bilaterally equal abdominal reflexes were of only moderate intensity. There was little change in the dimensions or reactivity of the contralateral areas during this time. Subsequent histology revealed a wedge shaped lesion that sectioned the tract of Lissauer completely. In one animal the lesion extended into the outer third of the dorsal column. In the second (DAF 31) the lesion was limited to the tract of Lissauer but also severely damaged the underlying substantia gelatinosa. Nevertheless there was increased intensity of response in the enlarged dermatome with prolonged scratching.

At the initial operation to isolate the first lumbar dermatome in a fourth animal (DAF 33) two very small lesions were also made in Lissauer's tract on the left side aimed for the lateral division of the tract, one just caudal to the first lumbar rootlets, the other just cephalad. On the first day the L1 field on the left side was one-third again as wide as that on the right side. This difference increased until the left field was twice the size of the right field on the eighth day (fig. 10). This remained constant until the twenty-sixth

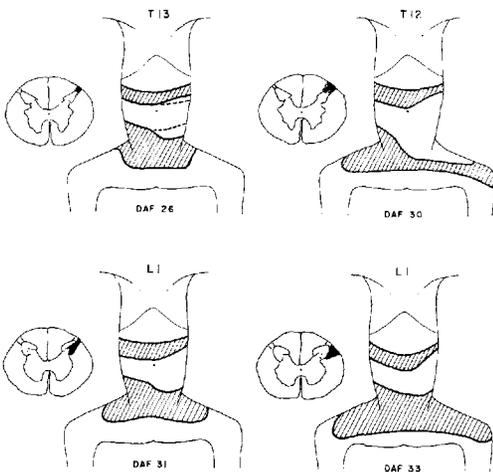


Fig. 10 Showing the effect of an isolated lesion of Lissauer's tract on the left side (as shown in black in inset in each instance) on the extent of a dermatome previously isolated bilaterally as described in text.

day when the animal was sacrificed. On the seventeenth day the animal was given graduated doses of morphine, as described in our earlier report (Kirk and Denny-Brown, '70) without any change in the area of the isolated dermatomes. The histology of these lesions (fig. 10, DAF 33) showed that in each case the lesion lay in the most dorsal part of the lateral column, just missing the tract of Lissauer, though damaging the most lateral part of substantia gelatinosa. This was one of many experiments that showed that the root entry line, as seen clearly at operation, was only an approximate indicator of the position of Lissauer's tract.

(i) *Lesions restricted to the lateral division of Lissauer's tract*

The last two of the experiments just described had indicated that a lesion related to the lateral part of the Lissauer system could alone result in facilitation of transmission from the test root. In subsequent experiments we eventually succeeded in making in each of three animals two very discrete small lesions limited to the lateral division of Lissauer's tract on the left side, one cranial and one caudal to the entry of the test root (fig. 11). In the animal DAF 37 with discrete and well placed lesions of the lateral tract of Lissauer the

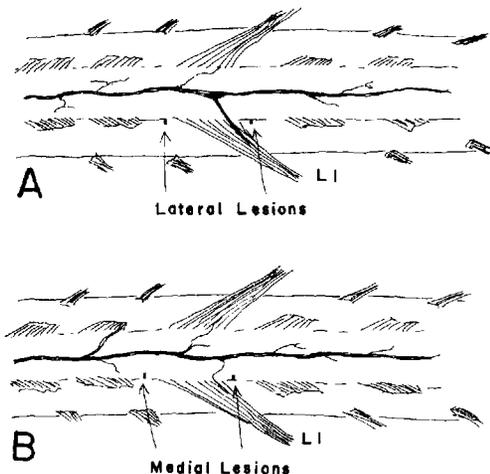


Fig. 11 To show the placing of Lissauer tract lesions at operation. The L1 nerve root was usually chosen for isolation because it has larger vessels than its neighbors.

isolated L1 dermatome on the left side on the day after operation was a little less responsive but of the same extent as that on the right. On the third post-operative day the dermatome on the left was a little larger and perhaps a little more responsive. On the fourth day the left dermatome was considerably enlarged (4.5 cm wide band left, 2.5 cm right) with prolonged and accurate scratching after stimulation on the left side. The left L1 dermatome slowly enlarged further during the second week after operation (fig. 12 upper charts) and more slowly during the third week following which the borders of sensation remained constant for over three months. Abdominal and costal reflexes associated with protest by the animal who pushed the stimulus away, were elicited from any part of the dermatome on the left side by even a light stroke with a few hairs of a camel hair brush. Occasionally there was prolonged scratching after a single stimulus. It will be noted that in the latter part of the period both bands of sensory loss, above and below the test segment, had shrunk as the test dermatome enlarged. The areas of sensory loss on the right side also lessened with the passage of time, but to a less degree. The test segment measured 7.0 cm in its lateral part, 5.0 cm anteriorly. The corresponding measurements on the right were 3.5 cm and 3.0 cm.

In two other animals (DAF 42, 43) the response was almost exactly the same (fig. 13) though the post-operative survival was more brief. The lesions in all three animals (fig. 14) were associated with considerable atrophy of the corresponding lateral division of substantia gelatinosa. In all cases the damage was extremely limited, sections 250 μ from the maximum lesion showing only some reduction in fibers in the lateral part of the tract of Lissauer in myelin stains. Beyond this point the tract appeared the same as the control side with luxol fast blue stain.

(j) *Section of medial division of Lissauer's tract*

Operative section restricted to the medial part of the tract, without damage to the dorsal column, proved to be even more difficult to attain than that of the lateral

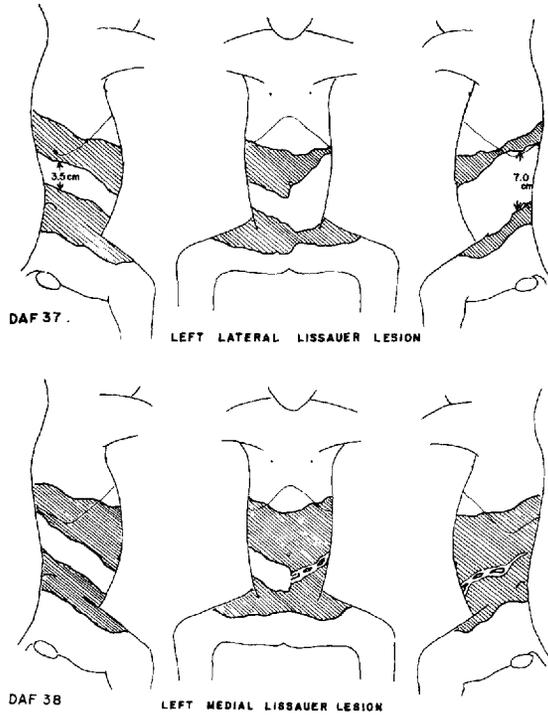


Fig. 12 Charts of two animals with bilateral isolation of L1 dermatome. DAF 37 had, in addition, lesions of the lateral part of Lissauer's tract on the left side above and below the isolated root. DAF 38 had, in addition, lesions of the medial half of Lissauer's tract. In DAF 38 the left dermatome was represented only by a narrow strip on the third post-operative day, and only three very small islands after the fifth day.

division. After many disappointments three pairs of reasonably restricted lesions, each less than half a millimeter wide were obtained DAF 38, 40, 41 (fig. 15). Each lesion damaged a few fibers in the most

lateral part of the dorsal column but in view of the findings of Szentágothai ('64) that the medial part of Lissauer's tract is mingled with dorsal column fibers, a complete distinction by this type of section does not seem possible. In all cases there was some atrophy of the medial portion of substantia gelatinosa at the level of the lesion. This atrophy appeared to result from retrograde degeneration of nerve cells, and was quite distinct from infarction of the dorsal horn due to damage to the dorsolateral artery, seen in the caudal lesion of DAF 40 in figure 15.

In animal DAF 38, with very small lesions above and below the entering rootlets of the left first lumbar root, the first lumbar dermatomes were approximately of equal extent on the first day after operation though responses on the left were irregular. On the second day the left L1 dermatome had become very narrow (1.5 cm in its lateral part, 1.0 cm an-

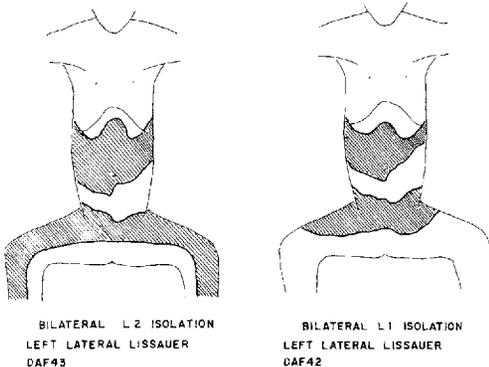


Fig. 13 Charts of two additional animals with bilateral isolation of a lumbar root, and on the left additional lateral lesions of the tract of Lissauer above and below the isolated root. The lesions are shown in figure 14.

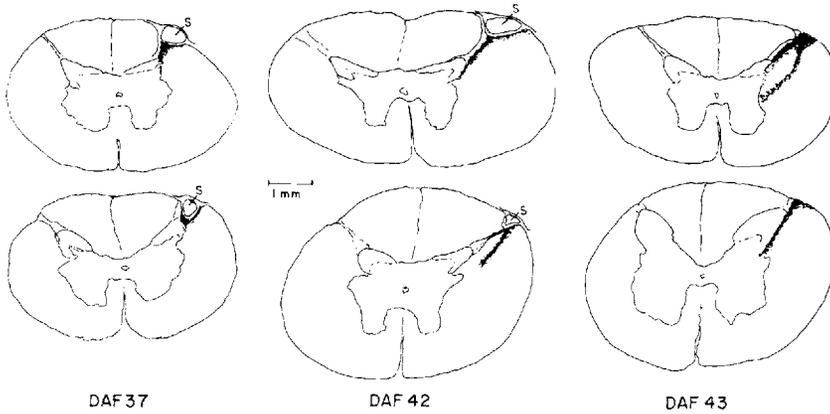


Fig. 14 Camera lucida drawings (to scale) to show above and below the maximum extent of the verified upper and lower lesions of DAF 37, DAF 42 and DAF 43. The maximum extent of destroyed tissue is outlined in black. The structure S is the section of a small piece of black silk, used as marker. From serial sections stained with luxol fast blue.

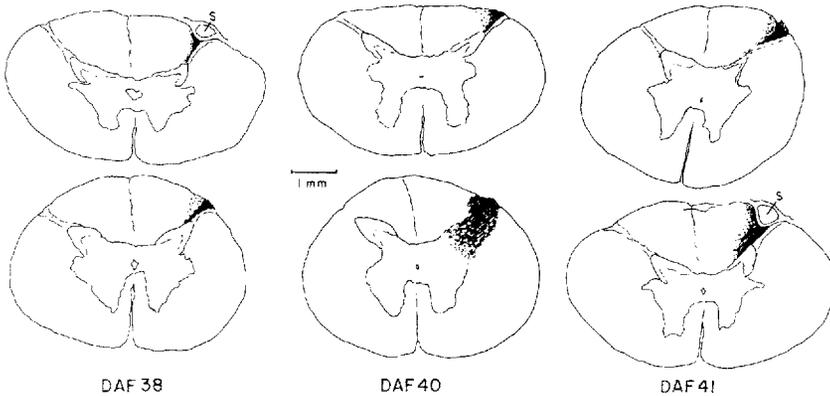


Fig. 15 Camera lucida drawings to scale to show the location and extent of the lesions (each outlined in black) of medial tract of Lissauer in animals DAF 38, DAF 40, DAF 41. The caudal lesion in DAF 40 has an associated small infarct of dorsal horn.

teriorly, compared with 2.5 cm right), and only one weak abdominal reflex was obtained. Between the fourth and sixth days the left dermatome shrank to three small islands, 3–5 mm in width, from which a weak reflex and general response could be obtained only by heavy pin-scratch, and easily fatigued compared with very brisk responses on the right. These small islands remained constant for over three months (fig. 12, lower charts). On the eighty-eighth day the animal was given strychnine sulfate in dosage 0.25 mg/kg subcutaneously. Between seven and ten minutes later responses were obtained from a narrow strip connecting the enlarged islands on the left, and between 13–18 minutes the

area of both general and reflex response had enlarged until it almost equaled that on the right (which had also enlarged a little) (fig. 16). After 30 minutes the left lumbar dermatome had contracted again to a narrow band. The following day only the original small islands remained responsive on the left. On the ninety-third day the effect of strychnine was again explored, with identical results except that the L1 dermatome on the two sides became completely equal in width (3.0 cm) with equal abdominal reflex and scratching response. This time the residual islands remained slightly enlarged for a further six days following the subconvulsive dose of strychnine.

Two further animals (DAF 40, 41) showed an even more remarkable response to medial lesion. In DAF 40 the lower lesion (fig. 15) destroyed the whole dorsal horn over a cranio-caudal extent of 1.5 mm in the characteristic pattern of an infarct,

due to damage to the dorsolateral artery. One day following the operation responses were obtained only from four small islands on the left (the largest 2 mm in diameter) with normal dermatome on the right. The same islands were present up to the seventh day, then no such islands were found on the left side until three days after a strychnine experiment on the fifteenth day. On the eighth, and twelfth days the animal was given strychnine sulfate (0.25 mg/kg) subcutaneously. Between seven and ten minutes following injection responses appeared in a narrow L1 dermatome, which enlarged progressively to equal those of the right side 20 minutes after injection (fig. 17). It will be noted that the uppermost and lowermost borders of sensory loss (T10 and L4 segments) had shrunk on the left side also. By 55 minutes the dermatome had shrunk to the seven minute level, and an hour later there was again no response from any part of the dermatome. In a third experiment on the fifteenth day we gave the animal a dosage of 0.50 mg/kg with again full enlargement of the first lumbar dermatomes, with residual

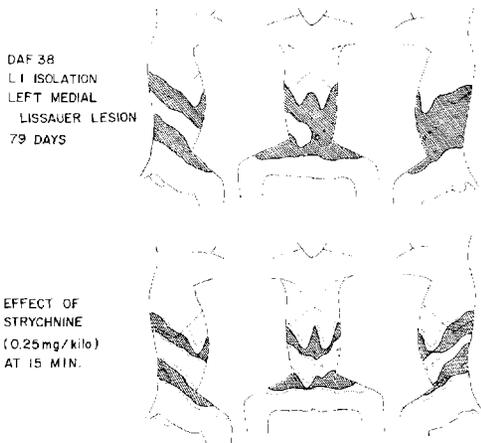


Fig. 16 Charts of the complete sensory loss in the animal DAF 38 at 79 days after operation (above), and below at 15-30 minutes following subcutaneous injection of a subconvulsive dose of strychnine sulfate (0.25 mg/kg).

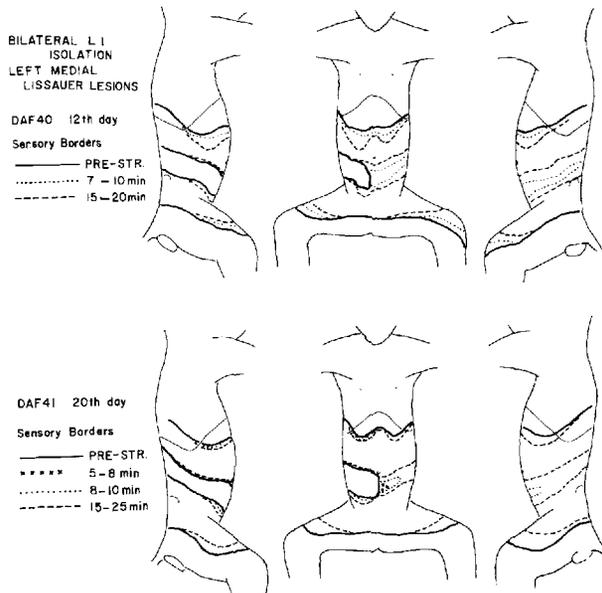


Fig. 17 Charts of animals DAF 40 and DAF 41 at twelfth and twentieth day following bilateral L1 isolation and left medial lesions of Lissauer's tract, showing sensory loss (solid lines), with complete absence of the left dermatome. There was complete restitution of the left dermatome in each animal 15-25 minutes after a subconvulsive dose of strychnine (broken lines).

islands of response the next day, and one residual island nine days later.

In another animal (DAF 41) there was a small island of response on the fourth day, but otherwise no response whatever from the first lumbar dermatome until strychnine was administered on the twentieth day (fig. 17). Again the dermatome was restored, beginning in the fifth minute and equalling the control side at the twenty-fifth minute, and then disappearing again except for a small island which remained for the next two weeks. A second strychnine experiment again yielded full expansion of the left dermatome, with three small islands residual for the following 15 days.

DISCUSSION

In our earlier paper (Kirk and Denny-Brown, '70), we concluded that the integrity of neighboring dorsal roots and ganglia contributed to the efficiency of transmission of sensation from any test root. If the section of neighboring roots was made distal to their ganglia and then at a second operation the same roots were sectioned again proximal to their ganglia, the shrinkage of dermatome area was delayed in appearance, becoming gradually manifest between the second and fifth day after section. This delay, and the reversibility of the change by strychnine implied that the change was functional, and not due to loss of some of the transmitting pathway. It suggested the slow exhaustion of some contribution from the neurons of neighboring ganglia.

In the present communication we have described experiments that showed an effect of neighboring spinal segments contrary to that of neighboring nerve roots. Interruption of connections with either the next caudal or of a cephalad segment resulted in great expansion of the dermatome of the test segment. The critical region, section of which demonstrated this release, was found to be the ipsilateral dorsolateral sector of spinal cord. Section of dorsal columns just below or just above the test segment, or both above and below, had no lasting effect on the area of the dermatome, provided that the proprio-

dorsal horn were not sectioned. Section of the most dorsal part of the lateral column resulted in a temporary enlargement of the test dermatome.

Section of the remainder of the lateral column had no effect on the area of an isolated dermatome, though resulting in the usual remote contralateral sensory loss associated with spinothalamic tract lesion. In the macaque monkey there are evidently both crossed and uncrossed pathways for the information necessary for a general protest reaction, as well as the alternate pathways in dorsal column and spino-cervical tract for tactile placing reactions (Gilman and Denny-Brown, '66). By exclusion therefore it was possible to demonstrate that it was the lateral part of the tract of Lissauer that conveyed the suppressor effect from neighboring segments. Conversely, the medial part of the tract of Lissauer was found to convey the facilitatory effects, which were less, though still present, after neighboring roots were sectioned. Section of the medial part resulted in overactivity of the suppressor effect, even if the most lateral part of the dorsal column remained intact. The full effect of section of either lateral or medial segment of the tract developed slowly over a period of three to ten days, again indicating the presence of some slowly cumulative effect that is also slowly dispersed. The restriction resulting from medial lesion could be temporarily restored at any time by strychnine, indicating a reversal of overacting tonic inhibition. Section of the whole Lissauer tract at any one level had a prolonged release effect on the next headward dermatome.

These Lissauer effects must therefore be independent of the primary sensory pathway, for transmission could be fully restored by strychnine after medial section, and efficiency of conduction was increased, not lessened, by lateral section. Facilitation of conduction by lateral lesion resulted not only in enlargement of the dermatome but also increased and prolonged response if enough neighboring roots remained intact. It may therefore be assumed that the excitatory element was, at least in part, derived from these neighboring roots. It is necessary to emphasise that such hyper-reaction in our animals

would be consistent with increase and prolongation of the effects of *all* the elements of sensation (paraesthesias). At no time and in no instance was there observed immobilization, guarding or apprehension of the effects of stimulation such as may be observed when natural stimulation in man arouses the sensation of pain.

*Excitatory and inhibitory
subliminal fringes*

These findings would be consistent with the presence of an equilibrium of membrane potential at the first sensory synapse of the test root, or of transmitter substances at that site, such as to allow extremely persistent, yet readily reversible states of raised or lowered threshold.

That afferent impulses in dorsal root fibers should depolarize the terminals of neighboring afferent fibers had been apparent since the work of Barron and Matthews ('38). The associated negative field potential over the root entry zone and neighboring roots was shown by Wall ('62) to be generated in the substantia gelatinosa of the three or four segments on either side of the test rootlet, and to depend on the integrity of the tract of Lissauer. It was assumed to be mediated by the small cells of substantia gelatinosa and their collaterals (Wall, '62). This effect has clearly much in common with the inhibitory effects we have found in the lateral Lissauer tract. Long lasting depolarization and hyperpolarization of afferent terminals in the dorsal horn of spinal cord have indeed been demonstrated by Mendell and Wall ('64). The prolonged hyperpolarization appeared to result from stimulation of small nerve fibers. It was assumed by Mendell and Wall that the excitatory effect was due to suppression of a tonic depolarizing system. Their findings led to an hypothesis of mutual interaction between small and large cutaneous afferents in the dorsal horn (Melzak and Wall, '65) such that collaterals of entering large and small fibers respectively facilitate or suppress the small neurons in the substantia gelatinosa whose tonic activity exerted a presynaptic depolarizing blocking of the main terminal arborization of the afferent fibers. Thus a "gate" was predicated by which the impulses in small

fibers could open a pathway for transmission of pain.

The information provided by electrophysiological studies of the dorsal horn has provided further evidence regarding this mechanism. The slow development of the peak of the negative dorsal cord potential and its persistence for more than 200 ms following one afferent impulse led to the postulate of a polysynaptic inhibitory pathway with presynaptic endings on the terminal arbors of dorsal root fibers (Wall, '62; Mendell and Wall, '64; Wall, '64). The electrotonic extension of such potentials to neighboring passive root fibers and neighboring deafferented segments (Wall, '62) certainly favors such a view. Direct recording from the small cells of substantia gelatinosa has not yet been possible owing to its dense structure, but Eccles et al. ('62) found interneurons ("D cells") in the dorsal horn sensitive to cutaneous nerve stimulation with a pattern of firing in prolonged bursts which would fill the requirements of such a prolonged inhibitor. Such cells closely resemble the Renshaw cells of the ventral horn, also involved in prolonged recurrent inhibitions. The presynaptic inhibitions found by Eccles et al. ('62) were, however, at a depth of 1.2–1.6 mm from the surface of cat spinal cord, indicating a locus in the medial part of lamina V. Wall ('62) had found prolonged sinks to be limited to laminae II and III after the first 20 ms following an afferent volley, a finding difficult to reconcile with that of Eccles et al. The inhibitory effects found by Eccles et al. would correspond better with the inhibitory surround of lamina V cells described by Wall ('67a) and Hillman and Wall ('69) and the pronounced inhibition of such cells by descending tracts. Taub ('64) and Hongo et al. ('68), recording from the axons of lamina IV cells in the spinocervical tract found inhibitory effects from areas of skin near but not actually surrounding the receptive areas for excitation of such cells. Thus the build-up of neighboring inhibition has been traced back to the second sensory neurone. The inhibition associated with antidromic stimulation of dorsal columns was found by Hillman and Wall ('69) to be particularly intense, and not changed by

blocking descending tracts. Thus the largest root fibers must be involved in the Lissauer inhibitory system, as well as the smallest.

A recent investigation by Gregor and Zimmerman ('72) has shown cells activated by natural cutaneous stimulation of both A and C fibers to be scattered through laminae IV, V and VI of the dorsal horn. Of these a considerable proportion were monosynaptic for A fiber transmission. This finding, if confirmed, makes it unlikely that transmission from C fibers has a mechanism fundamentally different from that of A fibers. Cells activated directly by natural stimulation of C fibers have been found to have characteristics more closely resembling those activated by A fibers than was found by Wall. Such findings should not detract from the important representation of progressively greater numbers of primary afferents in single cells found by Wall ('67a) in the cells of laminae IV, V and VI respectively. All investigators report that cells responsive to C fibers in cutaneous nerves more frequently exhibited spontaneous discharge and prolonged tonic response to discrete stimuli than those responsive only to A fibers, but both types of cell exhibit surround inhibition. In the monkey dorsal horn, Wagman and Price ('69) found, in addition, that even the smallest receptive areas were larger than in the cat. The more rapidly conducting cutaneous fibers relayed directly into the dorsal column nuclei in the squirrel monkey, but all A and C fibers inhibited each other at spinal segmental level (Jänig, Schmidt and Zimmermann, '67) and, therefore, require a collateral mechanism for interaction at that level. Such reports do not support the proposed "gating" mechanism of C fibers. The long persistent reciprocal excitatory and inhibitory components would be a more logical mechanism for the dominance of common sensation by C fibers, synapsing directly with lamina IV cells, than the gating mechanism of Mendell and Wall ('64) and Melzack and Wall ('65).

Two distinct sensory mechanisms:

The first synapse and its tonic regulation

The crucial question is the nature of the

input to the small-celled component of the substantia gelatinosa. One of us (DD-B) has verified in sections of lumbar spinal cord of cat, dog and monkey stained by Ranson's pyridine silver method the enormous numbers of very fine non-medullated fibers that enter Lissauer's tract from the overlying dorsal root, as originally described by Ranson ('14), though denied by Wall ('62). Though these are clearly not the pathway for pain and temperature as maintained by Ranson and Billingsley ('16), they appear to us to be even more numerous than the preponderance of non-medullated fibers that make up the dorsal root found by Ranson and Davenport ('31) and by Gasser ('55). Recently Heimer and Wall ('68) and Réthelyi and Szentágothai ('69), using a sensitized Nauta method within four days of root section, have shown large numbers of very fine degenerating fibers moving laterally and terminating in all parts of laminae I and II near the entering root. The fine plexus illustrated by Cajal, particularly in the Babes Atlas (Cajal, 1895) appear to indicate that all sizes of dorsal root fiber contribute to this network. It is of particular interest that Van Gehuchten (1891) and Cajal (1892, 1899) illustrate collaterals of fibers in the entering nerve roots, passing directly to the substantia gelatinosa before the root fiber bifurcates (fig. 18A). Cajal frequently drew this dorsal root collateral, as well as the better known ventral root collateral in his diagrams of the reflex pathway (fig. 18B). The proportion of such root collaterals to substantia gelatinosa that arise from large fibers is unknown, for studies by the Golgi method were usually made in very young or newborn animals before the full development of collaterals has occurred. Nevertheless, such root collaterals with synapses in the small cells of the substantia near the point of entry could provide an input for the phenomena discussed in this paper. We would also draw attention to the atrophy of the corresponding portion of the substantia gelatinosa immediately related to the medial or lateral Lissauer lesion, as illustrated in our figures 15 and 16. The small cells of the substantia, each with extensive longitudinal synaptic nets, shown well by the Scheibels ('68), complete a

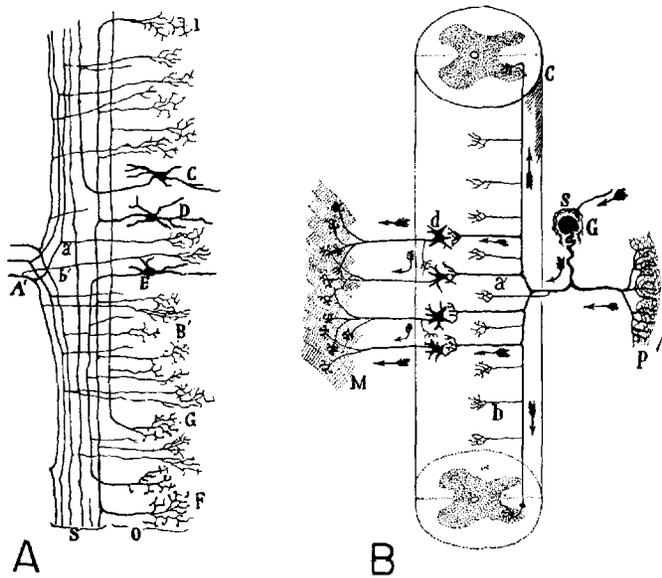


Fig 18 A. Dorsal root entry zone, spinal cord in chick embryo showing collaterals entering the dorsal horn, with one root collateral (b) arising before the division of entering large root fiber (Cajal, 1899). B. Cajal's scheme of the reflex arc showing both anterior and posterior root collaterals (Cajal, 1892, 1899).

linkage between the collaterals of entering root fibers at one level and the dorsal arborizations of lamina IV cells of the several neighboring segments. Such a system would be independent of, and lie across the first synapses of the primary sensory pathway, provided by the dorsal column collaterals curving up to entwine with the candelabra-like dorsal dendrites of lamina IV cells, an arrangement we have shown diagrammatically in figure 19. The dorsal column system of collaterals provides for simple spatial summation of all sizes of afferent fiber. The Lissauer system provides a tonic modulating substrate for all sensation.

The clear-cut and readily reproducible effect of strychnine in completely reversing the suppressor mechanism of the tract of Lissauer found in our own experiments implies that the inhibitory effect of the small cells of the substantia gelatinosa is post-synaptic on the second and probably also the third sensory neurones in the dorsal horn. There now appears to be no possibility that strychnine can reverse pre-synaptic inhibition in the spinal cord (Eccles, Schmidt and Willis, '63; Schmidt, '64; Curtis, '69). Post-synaptic inhibition

has been clearly demonstrated in the responses of lamina IV cells by Hongo et al. ('68). There is thus no obvious function at present known for the presynaptic depolarization so clearly demonstrated in the dorsal horn by a number of investigators since Barron and Matthews ('38). Recent anatomical studies of the substantia gelatinosa, nevertheless, show large numbers of axo-axonic (presynaptic) junctions in lamina III (Ralston, '68).

Our approach to the problem does not permit any conclusion as to the relative effects of large or small, rapidly or slowly conducting afferents as generators of the effects we have observed, for response to all types of stimulation have been affected similarly by facilitation or restriction. Facilitated responses can be easily precipitated by a few hairs of a camel hair brush. In the monkey there is no clear evidence of differential loss to touch or pinprick resulting from root lesions. In man differences in borderlines of loss of these modalities following thoracic root lesions is a zone of only a few millimeters in width, and a corresponding zone in the monkey would be difficult to detect. The wider extent of cutaneous loss to light touch and

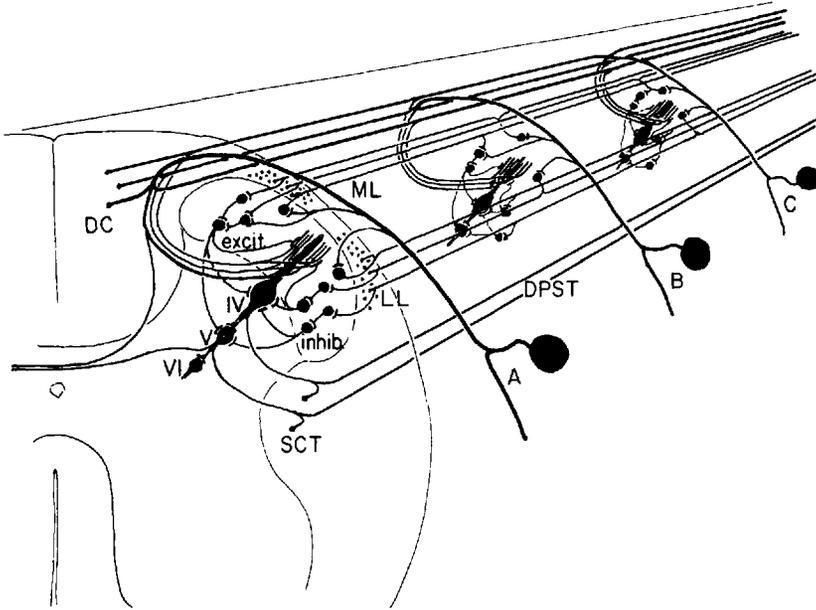


Fig. 19 A diagram to represent the first sensory synapse between the collaterals of the dorsal column prolongations of the dorsal roots (A, B, C), as shown by Cajal (1899), Szentágothai ('64) and the Scheibels ('68) curving dorsally into substantia gelatinosa to synapse with the candelabra of dendrites of lamina IV cells. Spatial summation is served by the overlap of collaterals of the different dorsal column (DC) fibers. In addition, finer collaterals of the entering dorsal root fibers (Cajal, 1899) synapse with small cells in lateral and medial substantia gelatinosa which contribute axons to the lateral (LL) and medial (ML) divisions of the tract of Lissauer. The Lissauer tract fibers give collaterals to the polysynaptic networks in the substantia gelatinosa of neighboring segments. It is postulated that the lateral polysynaptic networks converge on an inhibitory neurone (inhib.) with both pre- and post-synaptic inhibitory effect on laminae IV and V cells. Likewise the medial network (excit.) converges on an excitatory small neurone, activating laminae IV and V neurones with overlapping peripheral representation. Thus more distant neighboring afferents would have predominantly inhibitory surround effect. Both lamina IV and V neurones contribute to the ascending projection pathways such as spinocervical tract (SCT) of Gardner and Morin ('53) in the monkey, and the descending dorsal propriospinal tract (DPST) of Sherrington and Laslett ('03).

small changes in temperature resulting from lesions of peripheral nerve in man is much more obvious on the distal parts of the limbs, with related hyper-sensitivity of such borderline zones in peripheral nerve injury (Denny-Brown, '65). This disparity must partly be due to more extensive branching of C fibers in distal cutaneous nerves. We concluded that the hyper-sensitivity in this situation could be due to the loss of the more specific receptors which normally provide suppression of tonic C fiber activity reaching the dorsal horn, and which are present in greater density in the distal segments of the limbs. The postulation of an additional mechanism of "gating" type appears unnecessary.

*The momentum of tonic fringe effects;
a spinal mechanism for
sensory correlation*

The most remarkable finding in the present investigation is the long latency of full development of either inhibitory or excitatory equilibrium. There has been nothing in the many studies of the dorsal horn by intra- and extra-cellular recording to support the operation of transmitting agents or mechanisms that persist for as long as five to ten days. The longest recorded dorsal root potentials last only 200-300 ms. It was clear from our earlier paper (Kirk and Denny-Brown, '70) that the anatomical integrity of neighboring nerve roots facilitated the efficiency of conduction from the test root, without specific

stimulation of the neighboring skin segments. Even after section of three neighboring roots distal to their ganglia, their facilitatory influence was significant, and disappeared slowly in three to ten days following further section medial to the ganglia. One of us (Kirk, '73) has found that after section distal to the ganglion, the dorsal root cells, at first silent, begin to discharge spontaneously after the third day, and reach a steady state of slow, spontaneous discharge some five to ten days after distal section. Following proximal section of the roots, the interneurons of the substantia gelatinosa of the deafferented segment may be presumed also to recover a spontaneous discharge which continues to affect the synapses of the test root. In this circumstance an inhibitory effect, reversible by strychnine, becomes predominant. The presence of a continued background excitatory effect, however, can be demonstrated by section of the medial portion of the tract of Lissauer, which results in further restriction of the test dermatome, or its complete disappearance. We have to predicate that the neighboring deafferented segments contribute a spontaneous background fringe of both excitatory and inhibitory effect to the test synapse, independent of the well-known collaterals of dorsal column fibers passing to lamina III. Indeed, we have to postulate the presence of a continued equilibrium of neural activity representing the whole body surface throughout the substantia gelatinosa, in which the arrival of an impulse from any one point greatly lowers the threshold for the synapse of the axon involved and of the topographically related afferents, (i.e., arising in the same area of skin), while concurrently raising the threshold of all synapses representing surrounding skin. The predominance of inhibitory effects from neighboring cord segments would have an explanation in such an arrangement. The mechanism provides for a combination of temporal and spatial summation such as must be necessary for the type of integration of sequential directional information (as from a moving skin parasite) that is the adequate stimulus for the spinal scratch reflex (Sherrington, '06, Denny-Brown, '66). The intercalated neurone for the scratch reflex is evidently

a lamina IV cell with large axon descending in the dorsal propriospinal tract, as demonstrated by Sherrington and Laslett ('03) and shown as DPST in figure 19. The inhibitory effects observed by the electrophysiologists in lamina IV cells include some from the ipsilateral and contralateral extremities, which may account for the longer fine fibers in the lateral fasciculus proprius noted by Szentágothai ('64) and confirmed by our own observations.

The full expansion of the cutaneous dermatome obtained by section of the lateral segment of Lissauer's tract demonstrates the enormous overlap of nerve roots, and correspondingly of nerve fibers, in the skin. Sherrington (1898) had concluded that each skin point was innervated by at least three nerve roots. The present investigation shows that at least five nerve roots may contribute to the innervation of any point in the ventral segments of the trunk dermatomes (and distal segments in the limbs). If five or more disparate fibers contribute, as they must, to the threshold of sensation at any skin point, the central synapse for common sensation from that point would be the convergence of the endings of these fibers at a pre-ordained synapse on the lamina IV cell. It is the efficiency of this convergence at this first representation of that point that must underlie the facilitations or suppressions, enlargements or restrictions of the test dermatome. Thus we see that the most intense hyper-sensitivity results from section of the lateral segment of Lissauer's tract when the neighboring roots are intact, for the subliminal excitatory fringe should then be maximal.

It must not be forgotten that the test stimuli of the electrophysiologist form a very small part of the natural input of a structure as complex as the substantia gelatinosa. The enormous synaptic complexity of thousands of small neurones spontaneously active could be expected to give momentum without the need for some long-acting chemical transmitter. The arrival on lamina IV neurones of numbers of very small spontaneous IPSPs that would be expected to result from such an arrangement has already been recorded by Hongo et al. ('68). Indeed the rapid effect of strychnine in reversing the inhibitory

mechanism suggests that glycine, on which strychnine has its effect (Curtis, Duggan and Johnston, '71) is alone concerned. It would be of great interest to know the effect of bicuculline, the specific depressant of GABA transmission, on the isolated sensory dermatome, but this substance was not available until after our experiments were completed. Conversely, the action of barbituates in producing a progressive restriction in polysynaptic facilitation (Wall, '67b) with corresponding compression of the firing pattern of each lamina IV cell, demonstrates the type of prolonged loss of efficiency in transmission that limits the scope of short laboratory experiments on this problem.

Conclusions

The area of skin in the conscious macaque monkey from which responses to pin scratch can be obtained has been used as index of efficiency of the transmission of common sensation through the primary afferent pathway. The area is approximately equal for general response and for reflex effect. The observed changes indicate that the effectiveness of summation depends on the contribution of neighboring nerve roots with fibers derived from this same area of skin. As many as five roots innervate any skin point. The mechanism of summation includes not only the multiple collaterals from dorsal column fibers converging on lamina IV cells, a phasic system which contributes a short lasting DRP, but also a small-celled system with prolonged effects served by Lissauer's tract. Inhibitory effects, which appear to be part of the mechanism of inhibitory surround, relate to the lateral division of Lissauer's tract, with similar polysynaptic connections through small cells in substantia gelatinosa. The suppressive effects exert post-synaptic inhibition on the first and probably also the second synapse. Prolonged tonic excitation derived from fibers in neighboring roots that innervate this same receptive area and tonic inhibition from all other adjacent areas provide an essential fringe background equilibrium that is necessary for any sensory transmission. In the absence of input from neighboring skin, the spontaneous activity in the dorsal root ganglion cells and cells

of substantia gelatinosa can still contribute to the background equilibrium of excitation at the first synapse, for lesion of the tract of Lissauer still had some effect. The multitude of small cells composing the substantia gelatinosa and this multisynaptic net possess a remarkable momentum of background activity which can continue in some degree for five to ten days. The competitive effects in this equilibrium can account for the observed qualities of hyperesthesia without the necessity of any "gate" mechanism.

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