AN ANATOMICAL STUDY OF THE PROPRIOSPINAL CONNECTIONS IN THE CAT

PROEFSCHRIFT

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Aan mijn ouders

This thesis is based in part on the following papers

1) Molenaar, I, Rustioni, A. Kuypers, H.G.J.M., *The location of cells of origin of fibers in the ventral and lateral funiculus of the cat's lumbosacral cord*, Brain Res. 78 (1974) 239-254.
2) Molenaar, I, Kuypers, H.G.J.M., *Cells of origin of propriospinal and ascending supraspinal fibers. A HRP study in cat and Rhesus monkey*. Submitted for publication in Brain Research.

CONTENTS.

Abbreviations in figures.

CC	column of Clarke
CN	cochlear nuclei
CR	restiform body
DF	dorsal funiculus
DH	dorsal horn
DLF	dorsolateral funiculus
DV	descending vestibular nucleus
IZ	intermediate zone
LF	lateral funiculus
LRF	lateral reticular formation
LTB	lateral tegmental bundles of Thomas
LV	lateral vestibular nucleus
ml	marginal layer of dorsal horn
mot	motoneuronal area
MRF	medial reticular formation
NCE	external cuneate nucleus
MV	medial vestibular nucleus
NGC	gracile and cuneate nuclei
NRL	lateral reticular nucleus
NR	retroambiguus nucleus
np	nucleus proprius of the dorsal horn
NTS	solitary nucleus and tract
OI	inferior olive
OS	superior olive
PD	pyramidal decussation
RN	raphe nuclei
sbc	spinal border cells
sg	substantia gelatinosa
Spin.V	spinal trigeminal complex
pc	pars caudalis
pi	pars interpolaris
po	pars oralis
VF	ventral funiculus

GENERAL INTRODUCTION.

In the spinal cord the neuronal cell bodies are located in the spinal gray matter, which may be subdivided into a dorsal horn, a ventral horn and an intermediate zone. Neurons in the dorsal horn give rise mainly to long ascending fibers, while the motoneurons of the ventral horn innervate the musculature of body and limbs. The intermediate zone harbours the majority of propriospinal neurons, which differ from other spinal neurons in that not only their cell bodies, but also their terminal axonal projections are located within the spinal gray matter.

The first indications of the functions of propriospinal neurons were provided by physiological studies, which demonstrated that neurons located entirely within the spinal cord are involved in the relay of impulses from supraspinal pathways to spinal motoneurons [123, 124, 125]. Such studies also indicated that propriospinal neurons are involved in the generation of patterned movements, which appeared to take place largely in the spinal cord itself [25, 65, 198, 199]. Anatomical studies extended the knowledge of the propriospinal system in demonstrating that propriospinal neurons form the main source of synapses on the spinal motoneurons and that the majority of the former neurons is located in the spinal intermediate zone [56, 210]. Anatomical observations also showed that the descending supraspinal pathways largely avoid the motoneuronal area and terminate preferentially in the intermediate zone [102, 105, 106, 155, 161, 204]. The distribution pattern of these fibers as well as that of the dorsal root afferents [187, 202, 203, 205] has been studied extensively. The spinal motoneuronal population has also been subjected to several investigations and it was found that the spinal motoneurons are somatotopically organized [15, 162, 166, 174, 175, 200, 206]. Little information, however, was available on the anatomical relationships between neurons in the intermediate zone and the spinal motoneurons. Therefore, an experimental neuro-anatomical research project was initiated by Kuypers [180, 207] with the aim to determine the distribution in the intermediate zone of neurons which project to different motoneuronal cell groups. The most recent study in this project will be described in the present thesis and deals with

the distribution in the lumbosacral intermediate zone of neurons which send their fibers to different parts of the lumbosacral ventral and lateral funiculi. This aspect of the organization of the spinal gray was studied in kittens with the aid of the retrograde degeneration technique and relates to a previous antegrade degeneration study [180]. In this study the terminal distribution in the motoneuronal cell groups of fibers traveling in different parts of the lumbosacral ventral and lateral funiculi was studied with the antegrade fiber degeneration technique. The combined results of these two studies will indicate the distribution of neurons in the lumbosacral intermediate zone, which project to different lumbosacral motoneuronal cell groups.

Since the retrograde degeneration technique has the drawback that chromatolytic changes become less pronounced after axotomy at increasing distances from the parent cell bodies, [40,119] the cells of origin of funicular fibers could be identified at relatively short distances only. Therefore, later, an attempt was made to complement the data obtained with the retrograde degeneration technique by utilizing the retrograde axonal transport of horseradish peroxidase [28, 95,96,97,107,111,112]. With the aid of the latter technique the location of the cells of origin of long and short propriospinal fibers and of fibers ascending to supraspinal levels was approximated in both cat and monkey.

In order to place the findings of these two studies in their proper perspective the anatomy of the spinal cord in cat and monkey first will be reviewed.

Chapter I: *Review of the anatomy of the spinal cord and the spinobulbar transition.*

1. the spinal white matter
2. the spinal gray matter
3. the transition from the spinal cord into the medulla oblongata

REVIEW OF THE ANATOMY OF THE SPINAL CORD AND THE SPINOBULBAR TRANSITION.

In a spinal cross-section the centrally located gray matter, containing the spinal neurons, can be distinguished from the surrounding white matter, which is composed of ascending and descending spinal fibers.

1. *The spinal white matter.*

The spinal white matter is usually divided in dorsal, ventral and lateral funiculi, such that the dorsal funiculi are separated from the lateral funiculi by the dorsal root entrance zone. The border between the lateral and ventral funiculi is less distinct, but corresponds roughly to the area where the ventral roots traverse the white matter (fig. 1B).

It has been described already by Cajal [34] that the parts of the funiculi bordering the gray matter contain mainly short propriospinal fibers, which arise from different parts of the spinal gray. Many of these fibers bifurcate in the funiculi in ascending and descending branches which give off collaterals during their funicular trajectory and then terminate in the gray matter at rather short distances from their origin. The more peripheral parts of the funiculi contain longer propriospinal fibers and fibers ascending and descending to and from supraspinal centers. The dorsal funiculi in all species harbour the majority of the primary dorsal root afferents which ascend to the dorsal column nuclei in the medulla oblongata, while the ventral and lateral funiculi harbour the long propriospinal fibers and the fibers which interconnect the spinal cord and other supraspinal centers. According to Oscarsson's physiological findings,[159] the ventral and lateral funiculi differ in that the dorsal part of the lateral funiculus contains uncrossed long ascending tracts, while the ventral part of the lateral funiculus and the ventral funiculus contain crossed long ascending pathways.

Van Beusekom [220] studied the fiber composition of the cat's ventral and lateral funiculi in normal and experimental material by means of the Häggqvist technique. He found a similar fiber arrangement as described above, such that short propriospinal fibers are located

in the deepest portions of these funiculi, while long fibers are located more peripherally. This author further emphasized the extensive intermingling of different pathways and advocated to speak of fiber systems rather than of tracts.

In studies of the monkey's spinal cord Tower, Bodian and Howe[215] isolated lumbosacral segments by transections of the cord immediately rostral and caudal to the lumbosacral enlargement. They found that, after a survival of two weeks, normal fibers in these segments were present throughout the white matter, but were concentrated in the deepest parts of the funiculi. The majority of these normal fibers was thin and unmyelinated and most likely represents short propriospinal fibers. A very dense concentration of thin surviving fibers was found medial and lateral to the tip of the dorsal horn, which area corresponds to Lissauer's tract. In addition some thick longitudinal fibers were present close fo the gray matter, especially in the deep one third of the ventral funiculus and in the area of the so-called spinal processus reticularis, at the border between the dorsal part of the lateral funiculus and the gray matter. The authors stated that these fibers might ascend to the brainstem, but that their location close to the spinal gray matter suggests an additional function in the intrinsic cord mechanisms.

The findings in the human spinal cord, mainly obtained from pathological material, have been reviewed by Nathan and Smith [149,150] and these auhors concluded that also in man the shortest fibers are located closest to the gray matter. They emphasized the concentration of very short intrinsic spinal fibers in Lissauer's tract, especially in its lateral parts, a finding which has also been reported for cat[209] and monkey[215].

2. The spinal gray matter.

According to Cajal [34] each half of the spinal gray matter can be divided in a dorsal horn, with its head, neck and base, a ventral horn, containing the spinal motoneurons and an intermediate zone, which is the area between the dorsal and ventral horns and contains the majority of the propriospinal neurons. Within these areas this author distinguished several nuclei (fig.1A), but mentioned that they cannot always easily be delineated. In his extensive studies of Golgi-material

obtained from animals of different species and varying ages, Cajal [34] described already in 1909 the cytoarchitecture of the spinal gray matter and most of his classical description is still valid. In more recent studies of the spinal cytoarchitecture Rexed [171,172,173] proposed the division of the spinal gray matter in laminae which follow each other from dorsal to ventral and extend throughout the length of the spinal cord (fig.1B). Although his studies dealt mainly with cat's spinal cord the author stated that "the structure of the spinal cord is similar in all higher animals so far as principles and important traits are concerned"[171]. After Rexed's description of these laminae the spinal architecture, as revealed by Golgi-material has

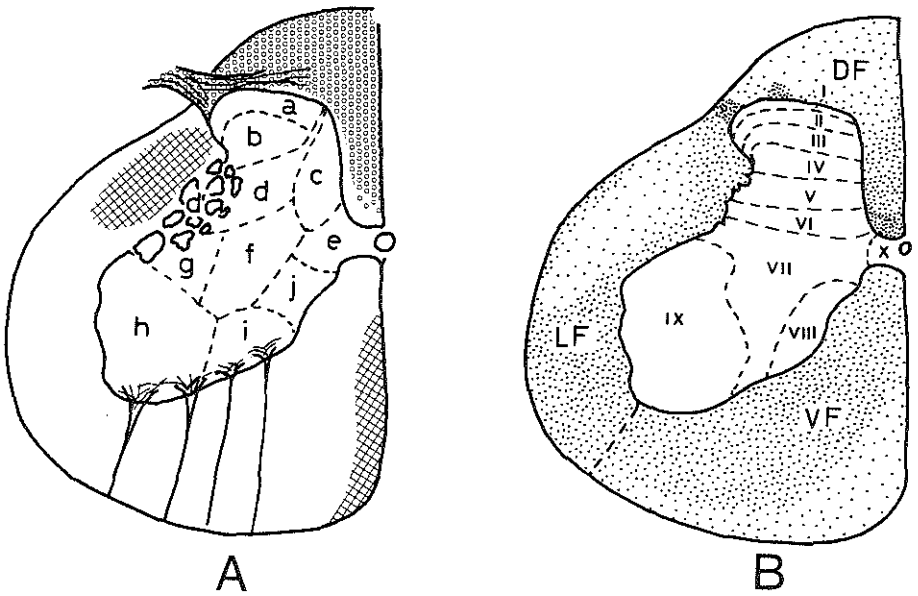

Fig.1A. The various nuclei in the spinal gray described by Cajal. a) substance de Rolando, b) tête de la corne postérieure, c) noyau basilaire interne, d) noyau basilaire externe, d') noyau interstitiëlle, e) substance grise ou gelatineuse centrale, f) noyau gris intermediaire, g) noyau du cordon antero-lateral, h) noyau moteur externe, i) noyau moteur interne, j) noyau gris commissural. Voies pyramidale ( ) et sensitive ( ).

Fig.1B. Laminae of Rexed (see text) in the spinal gray and distribution of propriospinal fibers in the spinal funiculi after Tower, Bodian and Howe (see text).

been studied by various authors, among others by Scheibel and Scheibel,[186,191] Szentagothai[209,211] and by Rexed.[171,172,173] Matsushita[136,137] and Mannen[133] especially investigated the trajectory of the axons of the spinal neurons. The data obtained by these different authors are largely in keeping with each other and Cajal's observations and the following description of the spinal cytoarchitecture is essentially based on a combination of these results.

The head of the dorsal horn is composed of the marginal layer (Rexed's[171,172,173] lamina I), the substantia gelatinosa (lamina II) and the nucleus proprius of the dorsal horn (lamina IV). Lamina III forms a transition between laminae II and IV and is by some authors considered as part of the substantia gelatinosa[186,209] and by others as part of the n.proprius.[171,172,205] Lamina I consists of cells of different sizes the cell bodies of which as well as their dendritic trees are usually flattened along the border of the gray matter.[34,171, 173,186,209,211] Occasionally large neurons are found in the white matter, especially lateral to the dorsal horn and at its apex.[34,171, 173] The cells in lamina II are small and densely packed, while those in lamina III are somewhat larger and more loosely arranged.[34,171,172, 173,209,211] The dendritic orientation of the cells in laminae II and III is predominantly longitudinal, i.e. parallel to the long axis of the cord.[34,186,295,211] Lamina IV consists of neurons of different sizes and contains the largest neurons in the dorsal horn.[34,171,172, 186,209,211] The dendrites of the large lamina IV neurons have a rather wide mediolateral extent and tend to be oriented perpendicular to the long axis of the cord.[34,186,206,211] Some of the dendrites of these large elements are directed dorsally and penetrate into the substantia gelatinosa.[34,186,205,209,211]

The afferent input to the dorsal horn is largely derived from dorsal root fibers the distribution of which will be described separately. Most of the axons of dorsal horn neurons enter the dorsal funiculus or the dorsal part of the lateral funiculus[133,136,137,173, 186] (Cajal's "faisceau de la corne postérieure") and some pass to the contralateral side.[34,133,136,186] Axons of the small cells of the substantia gelatinosa enter Lissauer's tract,[34,86,208,209] but some travel longitudinally within the substantia gelatinosa.[34,209] Accor-

ding to Szentágothai [208,209] some of the axons of dorsal horn neurons which travel in the dorsal and dorsolateral funiculi ascend or descend over short distances (1 to 4 segments) and then reenter the gray matter, especially the dorsal horn. In addition to short intraspinal connections long ascending fibers arise from the dorsal horn. Ha and Liu [66] demonstrated chromatolytic changes in the large lamina IV neurons of the cat's lumbosacral dorsal horn following cervical and thoracic hemisections. They concluded that these cells give rise to the spinocervical tract, a pathway which ascend to the lateral cervical nucleus. This nucleus is located lateral to the dorsal horn in the upper two cervical segments [89,219] and like the dorsal column nuclei sends its fibers to the contralateral thalamus.[14,147] Ha and Liu based their conclusion on the finding that degenerated fibers were present in the lateral cervical nucleus after destruction of dorsal horn neurons. Such a destruction, however, seems hardly possible without destroying axons as well cell bodies. Morin, Schwartz and O'Leary [148] searched for the cells of origin of the spinothalamic tract, which pathway is supposed to arise from the dorsal horn and to ascend contralaterally in the ventral part of the lateral funiculus.[15,162] Following cervical and thoracic ventrolateral cordotomies in cats and Rhesus monkeys they found chromatolytic neurons not only in lamina IV, but also in lamina I of the contralateral lumbosacral dorsal horn. Morin et al. also studied the terminal distribution of the fibers in the ventrolateral funiculus by means of the Marchi method. However, after ventrolateral cordotomies they found only few degenerating fibers in the thalami of the monkeys and hardly any in the cats, which is in keeping with Van Beusekom's findings [220] in the cat. Mehler et al., [142] on the other hand, applied the Nauta-technique and demonstrated anterogradely degenerating fiber bundles in the thalamus after cervical and thoracic anterolateral cordotomies in monkey. Following lesions in the dorsal horn in cat Szentágothai remained unable to demonstrate degenerating fibers in the contralateral ventrolateral cord (disc.ref. 159). Hence he supposed a more ventral origin of spinothalamic fibers. Thus, anatomically the existence of long ascending fibers arising from the lumbosacral dorsal horn could be established, but their site of termination could not be demonstrated convincingly. However, more recent,

physiological findings in Rhesus monkey indicate that the cells of origin of the spinothalamic tract as well as those of the spinocervical tract are located in the lumbar dorsal horn (Trevino, Coulter, Willis [217]; Albe-Fessard, Levante, Lamour [4,117]; Bryan, Coulter, Willis [26]). It has also been established physiologically that in the lumbosacral segments of the cat's spinal cord the cells of origin of the spinocervical tract are located in the dorsal horn (Bryan, Trevino, Coulter and Willis [27]), but those of the spinothalamic tract appeared to be situated mainly in the ventromedial part of the intermediate zone (Trevino, Maunz, Bryan and Willis [218]). In the cervical segments of the cat, on the other hand, Dilly, Wall and Webster [49] identified spinothalamic neurons in laminae V and VI and one such neuron in lamina I.

The neck and base of the dorsal horn correspond to Rexed's laminae V and VI, respectively. These laminae, however, are considered as part of the intermediate zone, which seems to be justified by the axonal projections of neurons in these laminae as well as by the transverse orientation of their dendrites (see below).

The ventral horn may be defined as that part of the gray matter that lies ventral to a line passing from the central canal laterally. The ventral horn thus includes laminae VIII and IX and the ventral part of lamina VII. Laminae VII and VIII contain neurons of different sizes which send their fibers to the ventral and lateral funiculi. These laminae will therefore be regarded as part of the intermediate zone, although they are located in the ventral horn. Lamina IX, on the other hand, is composed of spinal motoneurons, among which are the largest neurons in the spinal cord. The axons of these neurons traverse the white matter and converge into the ventral roots which innervate the striated muscles of body and limbs. Physiological observations [167,168] suggested the presence of recurrent collaterals from ventral root fibers, by demonstrating inhibition among motoneurons during antidromic stimulation of ventral roots. Such collaterals have been found in Golgi-material by Cajal [34], Testa [212] and the Scheibels [184,191] and were recently demonstrated with the aid of intracellular horseradish peroxidase injection by Cullheim and Kellerth.[42]

The spinal motoneuronal population may be divided in a medial motoneuronal cell group, which innervates by way of the dorsal ramus of

the spinal nerve the muscles along the vertebral column and a lateral motoneuronal cell group, which innervates by way of the ventral ramus the remainder of the musculature of the body and that of the limbs.[15, 162, 172, 173] At thoracic levels the medial and lateral group are fused into one, while the medial group is absent at L6 and L7. This division is in keeping with the findings by Sprague,[200] who demonstrated that in the thoracic cord of the monkey the neurons supplying the dorsal and ventral rami of the spinal nerve are not spatially separated. In the lumbar cord, on the other hand, a clear separation appeared to exist, such that the dorsal rami were found to be derived exclusively from motoneurons along the ventromedial border of the gray matter, which cell group corresponds to the medial motoneuronal cell group. The organization within the spinal motoneuronal cell pool was extensively studied by Romanes,[174, 175] especially in the lumbosacral cord of the cat. In this region the author identified 8 different longitudinal columns of large motoneurons (columns 1 to 6 and 3' and 3'') and one group of small motoneurons (column Y). The latter group, which is present in the sacral segments only, appeared to give rise to the pudendal nerve. In addition, a group of neurons was found in the segments L4 and L5 (column X), which neurons, although resembling motoneurons, did not respond to section of any peripheral nerve in the lumbosacral plexus. These neurons are presumably identical to the "spinal border cells" described by Cooper and Sherrington [37] (see below). A possible somatotopic organization of spinal motoneurons was studied by Sterling and Kuypers [206] in the brachial cord of the cat, by Reed [166] in the brachial cord of the monkey and by Romanes [174] in the lumbosacral cord of the cat. Their findings confirmed earlier findings [15, 162] and showed that in the cervical (C4 to T1) and lumbosacral (L3 to S1) enlargements the lateral motoneuronal cell group can be subdivided into several nuclei, innervating different groups of muscles of the fore- and hindlimbs, respectively (fig.2). The motoneurons which innervate the girdle and proximal extremity muscles were found to be located ventromedial to those innervating the distal extremity muscles and the small hand and foot muscles. Moreover, in the brachial cord the motoneurons innervating physiological flexors were found dorsal to those innervating the corresponding physiological extensors. In the lumbo-

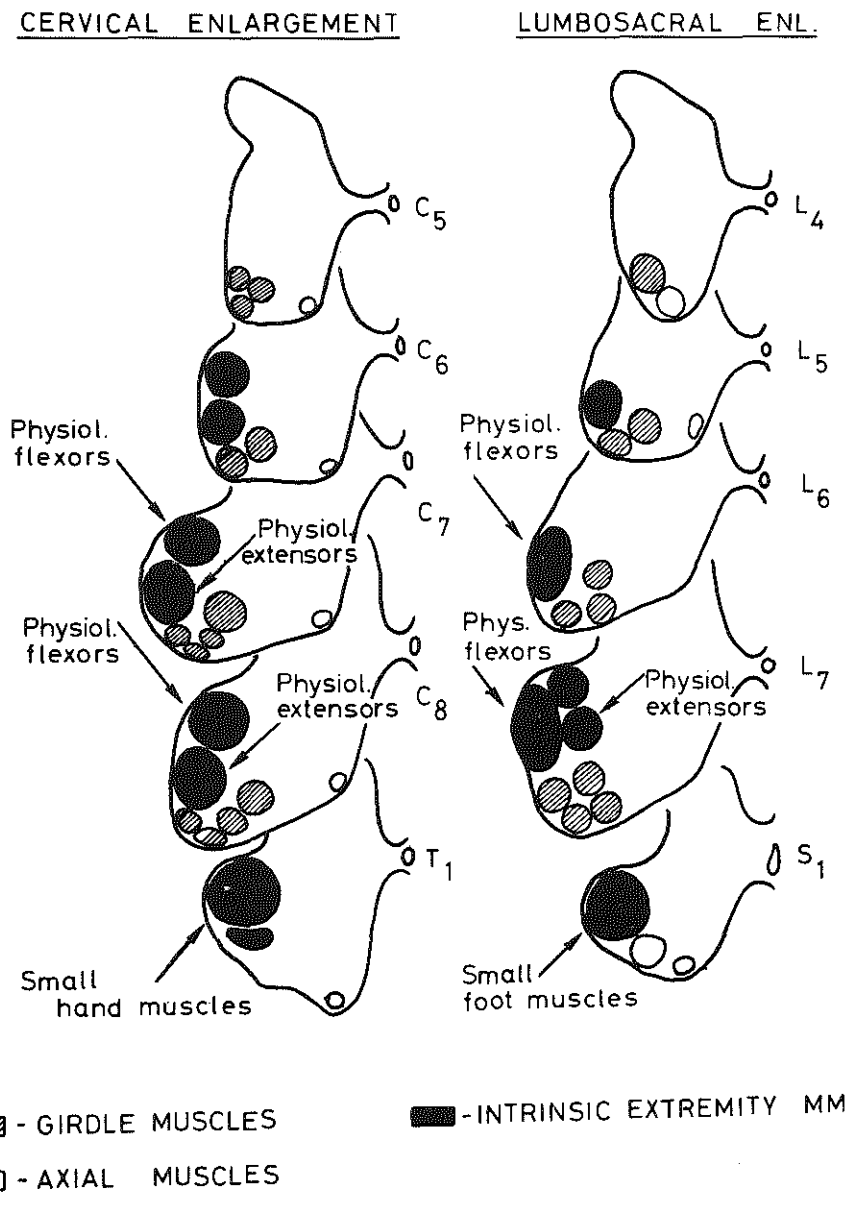

Fig.2. Organization of the motoneuronal cell groups in the cervical and lumbosacral enlargements. (From: Kuypers, H.G.J.M., The anatomical organization of the descending pathways and their contributions to motor control especially in primates, in "New Developments in EMG and clinical neurophysiology", Ed. J.E. Desmedt, S. Karger A.G. Basel)

sacral cord on the other hand the flexor motoneurons appeared to be located lateral rather than dorsal to the extensor motoneurons.

The arrangement of the motoneuronal dendrites contrasts with the organization of their cell bodies in that both the transverse and the longitudinal dendrites from neurons in the different nuclei intermingle. The presence of longitudinally oriented dendrites, corresponding to Cajal's [34] "dendrites verticaux", was emphasized by the Scheibels, [188] by Sterling and Kuypers [206] and by Szentágothai.[211] The distribution of longitudinally oriented dendrites in the ventral horn of the cat was studied quantitatively by Dekker, Lawrence and Kuypers. [47] The results of the latter authors indicate that in the spinal enlargements the longitudinal dendrites are almost entirely limited to the motoneuronal area, but that outside the enlargements such dendrites are distributed throughout the ventral horn. In a series of papers the Scheibels reported first the organization of the longitudinal dendrites in bundles, each of which consisting of dendrites of motoneurons from different groups. [188] Subsequently they related the postnatal development of such bundles in the cervical and lumbosacral enlargements to the appearance of integrated movements in fore- and hindlimbs, respectively.[189,190] In an electromicroscopic study Matthews, Willis and Williams [140] confirmed the existence of longitudinal dendrite bundles and occasionally found that the plasma membranes of the adjacent dendrites were in close apposition. However, in only few of these cases the opposed membranes showed detectable specializations, while synaptic vesicles were never present.

According to Gelfan's findings [56] the bulk of the terminals present on the motoneurons is located on their dendrites and is derived from propriospinal fibers (cf. also ref.141,210). Szentágothai [210] studied the morphology of the propriospinal synapses on spinal motoneurons. He demonstrated that the terminal arborizations of the propriospinal fibers on spinal motoneurons are of two different types, i.e. a) the straight type, with a very extended field of arborization, but a very small number of terminals contacting the same neuron and b) the grape-like arborization, which terminates densely on the soma of one or a few neighbouring motoneurons. Unfortunately, Szentágothai remained unable to find differences in the location of the cells of origin of

the propriospinal fibers which give rise to these two different types of terminal arborizations.

The spinal intermediate zone may be defined as the area corresponding to Rexed's laminae V to VIII and encompasses several of the cell aggregations described by Cajal [34] (fig.1A,B). Thus, the lateral part of lamina V and to some extent of lamina VI, which are penetrated by many longitudinal fiber bundles correspond to Cajal's "noyau interstitiël", which is also called "spinal processus reticularis". The central and medial parts of laminae V and VI correspond roughly to his "noyaux basilaire interne" and "externe", respectively. More ventrally in the intermediate zone Cajal distinguished the "noyau du cordon antéro-lateral" and the "noyau gris intermediaire", which are located in the lateral and central parts of lamina VII, respectively, as well as the "noyau gris commissural", which roughly coincides with the area occupied by lamina VIII in the intumescences. The part of the gray matter surrounding the central canal, i.e. Rexed's lamina X, corresponds to Cajal's "substance grise ou gelatineuse central". Not all of these nuclei and laminae described in the intermediate zone can be readily distinguished, because small, medium sized and rather large neurons are intermingled in this zone. Two distinct nuclei which are present in the thoracic cord should be mentioned, however. One is the column of Clarke, located dorsolateral to the central canal and the other is the intermediolateral nucleus or lateral horn, which extends laterally from lamina VII into the lateral funiculus. These two nuclei have in common that the dendrites of their neurons show a strong longitudinal orientation.[211] The cells in the column of Clarke are large to medium sized and their axons form the dorsal spinocerebellar tract.[132] The neurons in the intermediolateral nucleus are medium sized and their axons leave the spinal cord as the preganglionic fibers of the sympathetic nervous system.[15]

The heterogenous population of neurons of different sizes that occupies the bulk of the intermediate zone has mainly transversely oriented dendrites.[34,185,186,207,211] This orientation is in sharp contrast to the longitudinal dendritic orientation in the dorsal horn as well as to the pronounced longitudinal dendritic bundles of the motoneurons. The transverse dendrites of the neurons in the spinal

processus reticularis are frequently arranged around the longitudinal fiber bundles present in this area. Szentágothai [211] emphasized the arrangement of the dendrites in the central part of the intermediate zone along the surface of a virtual cylinder which extends longitudinally throughout the length of the spinal cord. The axons of neurons in the intermediate zone proceed into the funiculi, where they often bifurcate into an ascending and a descending branch.[34] Most of the intermediate zone neurons send their axons to the ipsilateral ventral and lateral funiculi, but contralateral projections also exist.[34,133,136,137] The latter arise particularly from the large neurons in the spinal processus reticularis [34,137,137] and in the ventromedial part of the intermediate zone.[34,136,137,184,191,208] Some of the neurons in the medial parts of laminae V and VI send their axons to the dorsal funiculus.[34,136] Moreover, one neuron may send different axonal branches or collaterals to different funiculi.[34,133,136,137,184,191]

The externospinal input to the intermediate zone, which is mainly derived from dorsal root afferents and from descending pathways will be dealt with later. On the basis of their terminal distributions the efferent projections from the intermediate zone can be divided into supraspinal and intraspinal projections. This division, however, is not very strict, because fibers ascending to supraspinal centers may give off spinal collaterals, thus establishing intraspinal as well as supraspinal connections.

The following long ascending pathways arising from the intermediate zone have been described in the literature.

1) The dorsal spinocerebellar tract. This system has since long been known to arise especially from the column of Clarke and ascends in the dorsal part of the ipsilateral lateral funiculus (Mann).[132]

2) The ventral spinocerebellar tract (VSCT), which ascends contralaterally in the ventral part of the lateral funiculus. This pathway arises presumably from the "spinal border cells", which were first described by Cooper and Sherrington in 1940.[37] These neurons are located in the lateral part of the ventral horn of the lumbar segments, especially from L4 to L6, and resemble motoneurons. In the experiments of Cooper and Sherrington in the Rhesus monkey these cells showed chromatolytic changes after contralateral thoracic and cervical hemisections, which

led the authors to the conclusion that these elements differ from motoneurons. They suggested a relation of these neurons to Gower's tract, a system that was already known to ascend contralaterally in the ventrolateral funiculus. The findings of Cooper and Sherrington were confirmed in the monkey by Morin et al. [148] and by Sprague [201] and in the cat by Morin et al. [148] and by Ha and Liu.[67] However, chromatolytic changes in spinal border cells could be evoked by cerebellar lesions in monkey only. In cat the cerebellar projection of such neurons was demonstrated by Hubbard and Oscarsson,[76] with the aid of physiological techniques. These authors found that neurons belonging to the VSCT are located in the lateral part of the ventral horn, corresponding to the spinal border cell area of Cooper and Sherrington, but in addition in the lateral part of the base of the dorsal horn. Burke, Lundberg and Weight [29] demonstrated the cerebellar projection of cells in the lateral part of the ventral horn in L3 to L6 and identified these cells histologically as spinal border cells. Their findings further indicate that the vast majority of the spinal border cells contribute fibers to the VSCT. Jankowska and Lindström [81] succeeded in the intracellular injection of Procian Yellow in the cell bodies of physiologically identified VSCT neurons. The combined anatomical and physiological findings of the latter authors demonstrate that spinal border cells as well as the more dorsally and medially located neurons described by Hubbard and Oscarsson contribute fibers to the VSCT and that the two groups of neurons differ in their afferent input.

3) The possible existence of *spinothalamic fibers* arising from the intermediate zone in the cat has already been discussed in relation to the dorsal horn. (see above)

4) Other long ascending fibers, such as spinoreticular fibers (cf. Van Beusekom;[220]; Mehler et al., [142]; Nauta and Kuypers [152]) may arise from the intermediate zone, as was suggested by physiological observations (Levante et al., [116]; Albe-Fessard et al.,[4]; Fields et al., [54,55]). These physiological findings indicate that the cells of origin of spinoreticular fibers in the cat are located in the ventromedial part of the intermediate zone. However, their cell bodies seem to be scattered among those of the propriospinal neurons and are morphologi-

cally indistinguishable from the latter.

Intraspinal projections arising from the intermediate zone are directed to the spinal motoneurons and to the intermediate zone. The existence of such projections has been described already by Cajal [34] and has later been confirmed by others e.g. the Scheibels [191] and Matsushita,[136,137] largely on the basis of Golgi-material. However, in such material the axonal trajectory of intermediate zone neurons usually could not be followed further than the funiculi and the axon could only occasionally be visualized from its origin to its termination. The development of the modern silver impregnation techniques which selectively visualize degenerating axons and axonterminals provided the opportunity to study the terminal distribution of fibers traveling in different parts of the spinal funiculi. The retrograde cell degeneration technique, on the other hand, appeared to be useful for the identification of the cells of origin of such fibers.

Szentágothai [208] applied the antegrade fiber degeneration technique in an attempt to determine the terminal distribution of the fibers of neurons in different parts of the gray matter. However, his electrolytic lesions were only designated as being located in the dorsal or ventral horns or in the intermediate zone without any documentation. Moreover, the electrode tracks must additionally have destroyed part of the white matter. Sprague [200] used the retrograde cell degeneration technique to determine indirectly the location of propriospinal neurons in the thoracic and lumbar ventral horn of the Rhesus monkey. He regarded as propriospinal neurons all those neurons which were left intact after section of the ventral roots. Such neurons appeared to be scattered throughout the ventral horn, but concentrated outside the motoneuronal areas.

A first attempt to determine the possible topical relationships between propriospinal neurons and spinal motoneurons was made by Sterling and Kuypers [207] in the brachial cord of the cat. Combining data obtained in antegrade and retrograde degeneration studies they inferred the existence of the following relationships. Cells in the lateral parts of laminae V to VII project preferentially to the dorsolateral part of the lateral motoneuronal cell group (motoneurons to intrinsic flexor muscles of the limbs), while cells in the central part

of lamina VII project preferentially to the medial parts of this cell group (intrinsic extensor motoneurons and girdle motoneurons). Neurons in the medial part of lamina VII and in lamina VIII project mainly to the medial motoneuronal cell group (axial motoneurons). Moreover, projections to the motoneurons innervating limb musculature are derived mainly from neurons in the brachial cord of the ipsilateral side, while those to motoneurons innervating axial muscles are derived from both sides and have a wider segmental origin. The findings of Sterling and Kuypers further indicate that homologous areas of laminae V to VIII are interconnected throughout the brachial cord.

The terminal distribution of long ascending and descending propriospinal fibers was studied in the cat by Giovanelli and Kuypers [58] and by Matsushita and Ueyama [139] by means of the antegrade fiber degeneration technique. Both long ascending and descending propriospinal fibers were found to terminate mainly in the ventromedial part of the intermediate zone, largely avoiding the motoneuronal areas. Giovanelli and Kuypers emphasized the coincidence of the termination area of the long propriospinal fibers with that of the reticulospinal fibers (cf. Chapter II).

3. The transition from the spinal cord into the medulla oblongata.

When proceeding from the upper cervical cord into the lower medulla oblongata the clearcut separation between the centrally located gray matter and the surrounding white matter which is found throughout the spinal cord gradually subsides. Nonetheless, many of the neuronal and fiber systems of the spinal cord can be followed into the medulla oblongata (fig.3) and the subdivision of the gray matter in dorsal and ventral horns and an intermediate zone still holds for low medullary levels. Thus, the spinal dorsal horn continues into the spinal trigeminal complex, which at these levels also comprises a cell group comparable to the n.proprius, the substantia gelatinosa and the marginal layer. The spinal ventral horn and the intermediate zone continue into the low medullary ventral gray. However, the fiber bundles which at spinal levels occupy the deepest portion of the dorsolateral funiculus penetrate into the gray matter. Thus, at the level of the pyramidal decussation they appear as longitudinal fiber bundles

entirely located in the lateral part of the ventral gray, parallel to its lateral border.[106] In addition many decussating corticospinal fibers traverse the gray matter during their trajectory from the pyramids to the contralateral lateral funiculus. Further, the ventral border of the gray matter becomes rather vague and at levels rostral to the pyramidal decussation neurons and fibers intermingle to form the medullary reticular formation. The population of interneurons which at spinal levels occupies the intermediate zone is at these levels, i.e. rostral to the pyramidal decussation, represented by the neurons in the reticular formation, while the motoneurons are grouped into the motor nuclei of the cranial nerves, which form the homologeus of the spinal motoneuronal cell groups.

At the spinobulbar junction the dorsal funiculi contain still many of the primary dorsal root afferents, but in addition harbour the dorsal column nuclei, i.e. the medially located gracile nucleus and the more laterally located cuneate nucleus. At levels rostral to the obex these nuclei, which form the termination area of the dorsal root fibers become located in the area dorsomedial to the spinal V complex. Golgi-material [34,109] revealed that at the most caudal levels the bases of both nuclei contain triangular, multipolar and fusiform neurons, with long radiating dendrites, while the more dorsal parts of the nuclei are occupied by large neurons with bushy dendrites, which neurons are often arranged in clusters. The rostral parts of the nuclei contain a similar type of neurons as that found at their bases, i.e. triangular, multipolar and fusiform cells with long radiating dendrites, and contain only very few cell clusters. The most rostral part of the cuneate nucleus becomes adjoined medially by the medial and inferior vestibular nuclei. Further rostrally the latter nuclei are accompanied and later replaced by the lateral and superior vestibular nuclei which form the most rostral part of the vestibular complex.

Analyses of the fiber systems at the spinobulbar junction in normal and experimental material indicate that the long fiber tracts which occupy the peripheral parts of the ventral and lateral funiculi continue uninterruptedly into the peripheral parts of the medulla oblongata (fig.3). [31,32,106,220] Thus, the long ascending spinal fibers which are located most peripherally in the lateral and ventro-

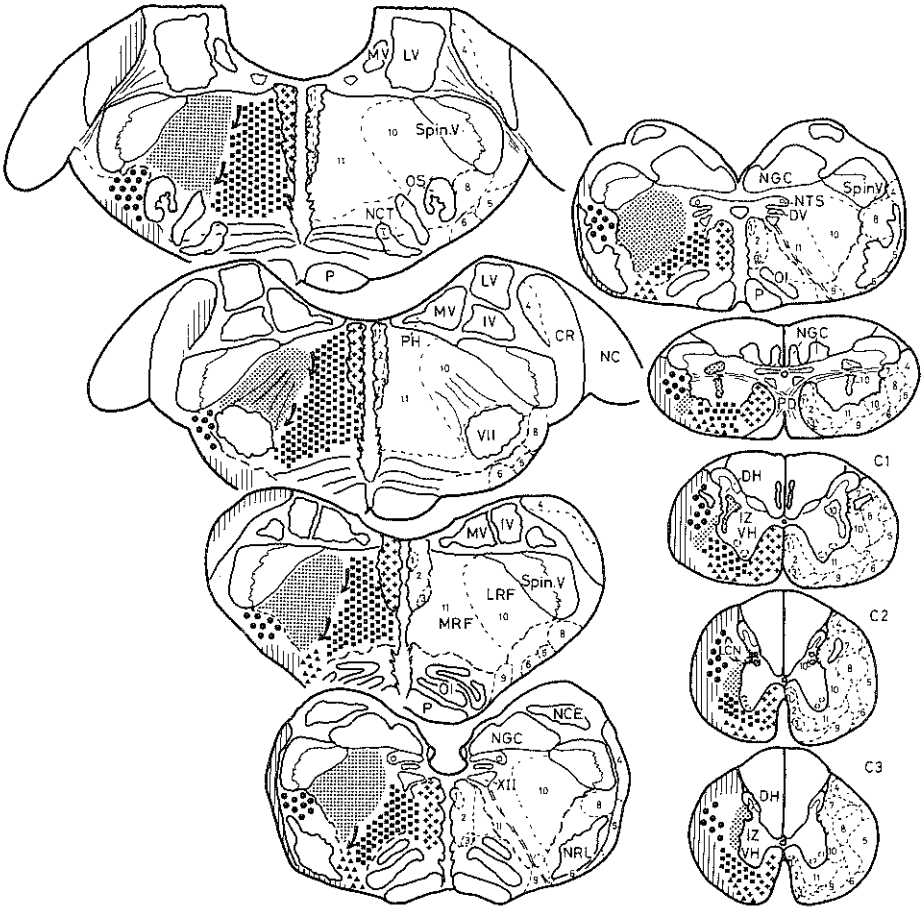
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Fig.3. The transition from the spinal cord into the medulla oblongata (see text). Long ascending pathways (||||||||||), lateral reticular and lateral propriospinal bundles (⁘⁘), medial reticular and medial propriospinal bundles (▪▪), lateral vestibulospinal tract (▲▲), medial longitudinal fasciculus (+++ +++), lateral descending brainstem pathways (●●● ●●●). 1) interstitiospinal tract, 2) medial longitudinal fasciculus, 3) tectospinal tract, 4) dorsal spinocerebellar tract, 5) ventral spinocerebellar tract, 6) spinoreticular tract, 7) corticospinal tract, 8) rubrospinal tract, 9) lateral vestibulospinal tract, 10) lateral part of reticular formation (=lateral tegmental field of Berman [10]), 11) medial part of reticular formation (=medial tegmental field of Berman [10]).

lateral spinal funiculi ascend mainly through the ventrolateral part of the medulla oblongata. A certain proportion of the constituent fibers enter the inferior cerebellar peduncle. The long descending systems, which are located medial and ventromedial to the ascending fibers, maintain this position during their descent through the ventrolateral and ventral parts of the medulla oblongata and the lateral and ventrolateral spinal funiculi while the fibers which descend in the medial longitudinal fasciculus continue into the spinal ventral funiculus at least in the cervical and thoracic cord. Finally, it should be mentioned that the fiber bundles which occupy the deepest parts of the ventral and lateral spinal funiculi and represent propriospinal fibers continue into the fiber bundles present in the medial and lateral parts of the medullary reticular formation, respectively.[106]

The anatomical data just reviewed thus indicate that the structural pattern which exists in the spinal cord exists in a slightly modified form also in the medulla oblongata. A similar conclusion has been drawn by Lloyd [123] on the basis of the physiological observations.

Chapter II: *Intrinsic spinal mechanisms and external input to the spinal cord*

1. intrinsic spinal mechanisms
2. dorsal roots
3. descending supraspinal pathways

INTRINSIC SPINAL MECHANISMS AND EXTERNAL INPUT TO THE SPINAL CORD.

1. Intrinsic spinal mechanisms.

Physiological observations [25,61,65,198,199,227] have indicated that the spinal cord itself can generate several patterned movements of the body and limbs. The complexity of the movements which can be elicited in the spinal animal may be exemplified by the coordinated movements of fore- and hindlimbs in quadrupedal stepping.[61,146,158] These movements require not only alternating contractions of flexor and extensor muscles in each of the limbs, but necessitate in addition a coordination of the movements executed by the individual limbs.

In view of anatomical data [56,141,210] which indicate that the major input to the spinal motoneurons is derived from propriospinal neurons, it may be assumed that the generation of "spinal movements" is largely based on the relationships between these two groups of neurons. This assumption is supported by the physiological finding [227] that selective destruction of lumbosacral interneurons abolishes the stepping movements of the hindlimbs which can be elicited in low spinal, deafferented animals. Physiological observations [146,158,199] further suggest that the coordination of simultaneous movements in fore- and hindlimbs is largely effectuated by long propriospinal fibers, interconnecting the spinal enlargements. However, according to both physiological [83,84,123,125,145,146] and anatomical [58,139] findings the long propriospinal connections with spinal motoneurons are established primarily by way of short propriospinal neurons.

Under normal circumstances, however, the intrinsic spinal mechanisms, described above, do not operate independently, but are under continuous control of external input, i.e. from the periphery (dorsal roots) and from supraspinal levels (long descending pathways). The dorsal roots convey somatosensory information from the periphery to the spinal cord at segmental levels, while the long descending pathways are concerned primarily with the regulation of spinal activities throughout the length of the spinal cord.

2. Dorsal roots.

Upon entering the spinal cord the dorsal root fibers penetrate

the dorsal funiculus, where part of them turns rostrally and ascends uninterruptedly to the medulla oblongata, while the remainder is distributed to the spinal gray. Thin unmyelinated fibers of the incoming dorsal roots turn laterally and enter the medial part of Lissauer's tract, where they ascend or descend over short distances and then enter the gray matter to be distributed to the substantia gelatinosa (lamina II).[170,203,205,209] However, the majority of the dorsal root fibers which terminate in the spinal gray enter the dorsal horn from its dorsal and medial aspects in the segment of their entry and the rostrally and caudally adjoining segments (fig.4A).[203,205] Within the dorsal horn the dorsal root fibers run mainly longitudinally and terminate especially in laminae I, III and IV.[80,186,203,205,210] More ventrally these fibers assume a dorsoventral orientation, when they traverse the base of the dorsal horn and the intermediate zone to reach the motoneuronal area.[170,187,203,205] During this trajectory the dorsal root fibers give off terminal branches to the central and medial parts of laminae V and VI and to lamina VII, including the spinal border cell area. In addition, in the thoracic cord primary afferent fibers enter the column of Clarke, where they run longitudinally, i.e. parallel to the main dendritic orientation in this nucleus.[170,210,211] According to Sterling and Kuypers[205] the dorsal root fibers have a more longitudinal orientation within the motoneuronal area than in the intermediate zone, but this was denied by the Scheibels.[187] The terminal distribution of dorsal root fibers in the spinal motoneuronal cell groups is largely restricted to the segment of their entry and the immediately adjoining segments, while that to the dorsal horn and the intermediate zone extends some segments further rostrally and caudally.[80,170,202,203,205]

The distribution of the dorsal root fibers in the spinal gray thus indicates that these fibers establish connections with neurons of long ascending pathways (dorsal horn, column of Clarke and spinal border cells) as well as with propriospinal neurons (intermediate zone) and spinal motoneurons. In the dorsal horn the distribution area of the dorsal root fibers appears to overlap with that of the corticospinal fibers from the primary sensory cortex (see below). However, the Scheibels[185,186] suggested that the inputs from these two systems

reach the neuronal somata through different dendrites, such that the dorsal root afferents terminate largely on the dorsomedially oriented dendrites of lamina IV neurons and on the medially oriented dendrites of neurons in laminae V and VI, while the cortical afferents terminate preferentially on the ventrolaterally oriented dendrites of lamina IV neurons and on the lateral dendrites of neurons in laminae V and VI.

The dorsal root fibers which do not terminate in the spinal gray ascend through the dorsal funiculi to the dorsal column nuclei in the medulla oblongata. The fibers from the most caudal dorsal roots travel most medially in the dorsal funiculus and terminate in the most medial part of the gracile nucleus.[69,109,181] Fibers from progressively more rostral levels are located progressively more laterally in the dorsal funiculus and their termination areas shift to progressively more lateral parts of the dorsal column nuclei, i.e. from the lateral part of the gracile nucleus to the medial and lateral parts of the cuneate nucleus.[87,109,181] Within the dorsal column nuclei the primary dorsal root afferents are distributed especially to the areas containing cell clusters (cf. Chapter I.3), which receive only few cortical afferents.[109] A somewhat comparable organization is displayed by the primary afferents of the trigeminal nerve, which carries the sensory information from the face. Part of the incoming fibers of this nerve project to the pontine main sensory nucleus,[44,88] which histologically resembles the dorsal column nuclei in this respect that this nucleus also contains cell clusters.[44,109] The descending primary afferent fibers travel in the spinal trigeminal tract and terminate especially in its nucleus caudalis,[44,88] which, as pointed out above (Chapter I.3), represents the rostral continuation of the spinal dorsal horn.

3. Descending supraspinal pathways.

Long pathways which descend to the spinal cord arise from the cerebral cortex and from several brainstem nuclei. Anterograde degeneration findings indicate that the vast majority of these descending fibers terminate in the intermediate zone, but physiological observations suggest that some may also terminate on spinal motoneurons (see below). The preferential terminal distribution in the intermediate zone and presumably also in the motoneuronal cell groups differs

in the fibers of the various systems.

The distribution of *corticospinal fibers* appeared to vary in different species, with regard to both its rostrocaudal extent and its preferential termination area.[33,68,149,192] In this paragraph the distribution of such fibers will be described for cat and monkey, since these two species have been used in the experiments described in this thesis. Anatomical studies, among others by Nyberg-Hansen [155,156] in the cat and by Kuypers in the monkey [102,105] have shown that the majority of the corticospinal fibers is derived from the primary sensori-motor cortex. This cortical area comprises the pericruciate cortex in the cat and the pericentral cortex in the monkey. Its long efferent fibers descend in the pyramidal tract, which for its major part decussates at the level of the spinobulbar junction, while a small part of its constituent fibers descends ipsilaterally, i.e. in the ventral funiculus. During their descent through the medulla oblongata the pyramidal fibers in both species send terminal branches to the lateral reticular nucleus and the medullary tegmentum as well as to the spinal V complex and the dorsal column nuclei.[23,36,100,101,102,109,122] Throughout the spinal cord the crossed corticospinal fibers descend in the dorsal part of the lateral funiculus, from where they enter the gray matter. The terminal distribution area of the corticospinal fibers appeared to be somewhat different in cat and monkey. Thus, in the cat the distribution area of these fibers comprises the n.proprius of the dorsal horn and its base (Rexed's laminae IV to VI) and the dorsolateral part of the intermediate zone (lateral part of lamina VII).[36,102,122,155,156,161,185,186] In the monkey the distribution area is more widespread and in addition involves the medial part of the intermediate zone on both sides.[102,122] Moreover, in monkey [99,100,102,105,122] and also in man,[99,192] direct corticomotoneuronal connections exist which are established especially with motoneurons in the dorsolateral spinal motoneuronal cell group and with cranial motoneurons. More detailed studies [36,100,101,102,122,155,156] of the cortical projections revealed a difference in the efferent projections from the primary motor and the primary sensory cortex (fig.4B), which comprise respectively the pre- and postcruciate gyri in cat and the pre- and post central gyri in monkey. Thus, the primary motor cortex

projects preferentially to the lateral parts of the base of the dorsal horn (lateral parts of laminae V and VI) and the dorsolateral part of the intermediate zone (lateral parts of lamina VII). In the monkey fibers from the precentral gyrus are also distributed to the cranial and spinal motoneurons and the medial part of the intermediate zone. The terminal distribution area of fibers from the primary sensory cortex comprises the n.proprius of the dorsal horn (lamina IV) and the medial part of its base (medial parts of laminae V and VI) as well as the spinal V complex. Fibers to the dorsal column nuclei arise from the entire sensorimotor cortex.[12,35,100,102,109,226] Their terminal distribution is densest in those parts of the nuclei which contain multipolar cells with long radiating dendrites, which cells are not arranged in clusters.[109]

The subcorticospinal pathways arise from several cell groups in the brainstem. According to Kuypers [99,105,106] these pathways may be divided into a lateral and a ventromedial system on the basis of their terminal distribution.

The fibers of the *lateral group* arise mainly from the n.ruber and descend contralaterally through the ventrolateral part of the medullary tegmentum to the spinal dorsolateral funiculus.[52,105,106,144,155,156,161,204] In the medulla oblongata the rubrospinal tract distributes fibers to the lateral medullary tegmentum, the lateral reticular nucleus and the dorsal column nuclei.[31,38,52,106,144] According to Edwards' autoradiography findings [52] in cat, some rubral fibers are also distributed to the pars caudalis of the spinal V complex, especially to its base. In both cat and monkey rubral projections have been demonstrated to the facial nucleus.[31,38,52,106,144] Throughout the spinal cord lateral descending brainstem fibers terminate preferentially in the area comprising the lateral part of the base of the dorsal horn and the dorsolateral part of the intermediate zone, i.e. the lateral parts of laminae V to VII (fig.4C).[52,105,106,144,155,161,192,204]

The ventromedial subcorticospinal system is composed mainly of vestibulospinal, reticulospinal, tectospinal and interstitiospinal fibers.[31,99,105,106,204] The vestibulospinal fibers originate in the lateral and medial vestibular nuclei, of which the former gives rise

to the lateral vestibulospinal tract and the latter to the medial and the crossed vestibulospinal tracts.[19,21,31,161,163,204] The long descending reticulospinal fibers arise especially from the medial parts of the pontine and medullary reticular formation.[20,106,155,161,204,214] The tectospinal fibers arise from the superior colliculus, while the interstitiospinal fibers have their origin in the mesencephalic interstitial nucleus of Cajal.[106,155,161] The fibers of the ventromedial subcorticospinal system pass through the ventromedial and medial parts of the medulla oblongata, where some are distributed to the medial tegmentum.[31,32,106,204] Further caudally the descending fibers enter the ventrolateral and ventral spinal funiculi, and descend throughout the spinal cord. However, the medial and crossed vestibulospinal fibers as well as the testospinal fibers presumably do not descend beyond thoracic levels.[19,155,161,204] The preferential terminal distribution area of the medial brainstem fibers in the spinal cord encompasses the medial and central parts of the intermediate zone (lamina VIII and the medial and central parts of lamina VII), to some extent bilaterally.[105,106,155,161,204] Within this area the vestibulospinal fibers terminate most ventromedially, while the reticulospinal fibers terminate somewhat more dorsolaterally (fig.4C).

Physiological studies support the anatomical findings and demonstrate that many of the descending supraspinal fibers are distributed to propriospinal neurons.[7,8,74,77,79,92,123,124,164,165] However, contrary to the anatomical findings, physiological observations indicate that descending brainstem fibers also establish direct connections with spinal motoneurons [']. Direct motoneuronal connections have

[']) This discrepancy may be explained by the presence of long motoneuronal dendrites which are not confined to the motoneuronal area, but penetrate into the intermediate zone. Such a dendritic termination of brainstem fibers on spinal motoneurons is also supported by some of the physiological characteristics of the connections (cf.ref. 50,195).

been demonstrated in both cat and monkey for reticulospinal and vestibulospinal fibers.[62,63,64,127,194,195,228,229] Rubromotoneuronal connections seem to be more pronounced in monkey than in cat.[72,194,195,196] Physiological findings further indicate that the respective supraspinal pathways exert different influences on motoneurons of functionally different groups of muscles, both monosynaptically and polysynaptically. Thus, the corticospinal tract and the rubrospinal tract, (i.e. the lateral brainstem system) appeared to facilitate especially flexor motoneurons and inhibit extensor motoneurons.[72,78,79,92,131] Moreover, especially in monkey, these two pathways seem to act primarily on motoneurons of distal muscles.[194,195,196] By contrast, the vestibulospinal pathway has been shown to facilitate preferentially extensor motoneurons,[62,63,75,127,131,163,183,228] in particular those of knee and ankle extensors,[63,158,163,195,228] and neck [228] and back [229] motoneurons, while reticulospinal fibers reportedly facilitate both flexor [61,183,195,228] and extensor [183,228] motoneurons. In monkey, both the vestibulospinal and the reticulospinal pathways, i.e. the ventromedial brainstem system, were found to influence especially proximal muscles.[194,195]

Behavioural studies in cat and monkey[1,2,16,99,103,104,113,114,115,121] provided further evidence for the functional differences between the corticospinal and the lateral and ventromedial subcorticospinal pathways by analyzing the motor deficits occurring after selective interruption of one of these systems. Such studies revealed that the ventromedial brainstem system is concerned primarily with the steering of proximal motor activity and is especially involved in posture and movements of the whole limb. The lateral brainstem system and the corticospinal tract, on the other hand, appeared to steer individual movements of the limbs, especially of their distal parts. Moreover, in animals with direct corticomotoneuronal connections the corticospinal tract also seems to provide the capacity to execute fractionated movements as exemplified by individual finger movements.

The anatomical and physiological observations, described above, thus indicate that the descending supraspinal pathwaysexert their influence primarily by way of propriospinal neurons. These neurons also receive primary afferent input, which may explain the control of

the descending pathway on spinal reflexes.[51,73,128,129] Further, the selective influence displayed by the respective pathways on the spinal motoneuronal population suggests some kind of topical organization at propriospinal level. The existence of such an organization has been indicated already by some physiological [7,11] and anatomical[207] observations and is further favored by some of the findings described in this thesis.

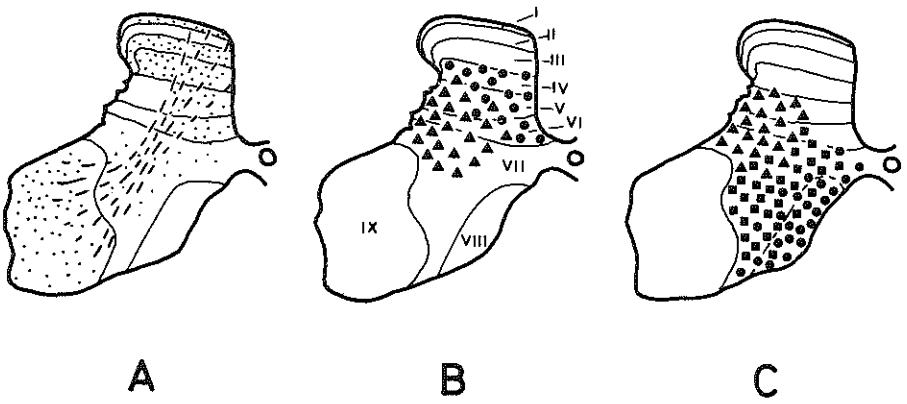

Fig.4. Afferent fibers to the spinal gray in the cat (see text). A) Dorsal root afferents, B) Corticospinal fibers, from primary motor (▲▲▲) and primary sensory (●●●) cortex, C) Subcorticospinal pathways, rubrospinal (▲▲▲), reticulospinal (■■■) and vestibulospinal (●●●).

Chapter III: *Techniques and material used in the experiments*

1. the retrograde cell degeneration technique
2. the horseradish peroxidase retrograde axonal transport technique
3. material used in the experiments
   -spinal lesions
   -spinal and supraspinal HRP-injections

TECHNIQUES AND MATERIAL USED IN THE EXPERIMENTS.

As pointed out in the introduction the present study deals mainly with the organization of the long and short propriospinal fibers. The location of the cells of origin of these fibers was studied both by means of the retrograde cell degeneration technique and by means of the horseradish peroxidase retrograde axonal transport technique.

1. The retrograde cell degeneration technique.

The retrograde cell degeneration technique is based on the occurrence of characteristic changes in the neuronal cell body after section of its axon. The most consistent features of the cell reaction, as described by Nissl (1892,1894),[153,154] are chromatolysis, i.e. lysis of Nissl bodies, cell swelling and nuclear eccentricity. Such cell changes reportedly [17,18,119] are most pronounced in young animals though not necessarily newborn, and especially in motoneurons. However, chromatolytic changes have also been observed in neurons located entirely within the central nervous system [17,18,120,214].

Since Nissl's descriptions, the phenomenon of the retrograde cell degeneration after axotomy has been widely used as a neuroanatomical tool in order to determine the cells of origin of a given fiber system. Nonetheless, the precise mechanism of the perikaryal responses to axotomy is still not precisely understood, despite rather extensive research (review: Liebermann, 1970) [119]. Yet, both light and electron-microscopic observations point to an increased protein synthesis after axotomy, which suggests that the chromatolytic cell changes reflect a regenerative rather than a degenerative process. Further, it became evident that the severity of the cell reaction is less pronounced either after axotomy at a large distance from the cell body or when many collaterals are left intact [40,119]. This forms at the same time one of the limitations of the technique, since this makes it virtually impossible to identify all the cells of origin of long fiber connections, especially when many axoncollaterals are given off. The technique can therefore be used only to determine the location of the cells of origin of certain fiber connections and cannot give valuable information about their absolute numbers.

In the present experiments the retrograde cell degeneration

technique has been applied to determine the distribution of the neurons in the lumbosacral intermediate zone which send their fibers to different parts of the lumbosacral ventral and lateral funiculi. For this purpose small lesions were made in different parts of these funiculi and the location of chromatolytic neurons was studied.

2. *The horseradish peroxidase retrograde axonal transport technique.*

With the aid of the enzyme horseradish peroxidase (HRP) the cells of origin of fiber connections in the nervous system can be identified in the following way. When HRP is applied to a fiber system it is taken up by axonterminals and transported retrogradely to their parent cell bodies [28,95,96,97,107,111,112,151]. In these neurons HRP can be visualized histochemically according to Graham and Karnovsky,[60] by letting the enzyme catalyze the oxidation of 3,3'-diamino-benzidine which yields a darkbrown reaction product at the site of enzymatic activity.

Several observations had pointed to the occurrence of a centripetal axonal flow (rev.: Lasek, 1970) [110]. In accordance with these findings Kristensson (1970) [94] demonstrated the uptake and retrograde axonal transport of exogenous proteins to the neuronal somata. In their first experiments this author and his coworkers injected albumin labeled with Evans blue [94,95] into different muscles and later they also used HRP [95,96,97]. They were able to demonstrate that these proteins accumulate in the corresponding motoneurons in the central nervous system. However, the results which they obtained in young animals were much more striking than those in adult ones. After these reports of retrograde labeling of neurons with HRP, several authors tested the applicability of this method to different neuronal systems. Successively, the use of HRP to identify the cells of origin of fiber connections within the central nervous system was established in young [107,111] and adult animals [28,107,112,151,197]. Some authors mentioned in addition the presence of brown stained fibers arising from the injection site, which probably reflects HRP transport by axons [107,130, 151,169,197]

In the reports mentioned above it was generally assumed that retrograde transport and subsequent labeling of neuronal cell bodies

resulted from HRP uptake by axonterminals. However, more recently, Kristensson and Olsson [96] described the retrograde labeling of neurons in the facial nucleus of the mouse following application of HRP to the cut or crushed facial nerve, while DeVito et al. [48] reported comparable results after HRP-application to the cat vagal nerve in cat and monkey. These findings thus provide strong evidence for axonal uptake and transport of HRP by interrupted axons in peripheral nerves. Some of our own preliminary observations (cf. also ref. 108) suggest that the same applies to axons of neurons located entirely within the central nervous system.

In the present experiments an attempt was made to label neurons of propriospinal and supraspinal fibers preferentially by way of retrograde transport of HRP after its uptake by damaged axons. For this purpose large unilateral injections were made in both the white and the gray matter at different spinal and supraspinal levels, in such a fashion that a great many axons was damaged by the needle penetrations.

3. Material used in the experiments.

Spinal lesions.

In the experiments in which the cells of origin of the propriospinal fibers in the different funiculi of the lumbosacral cord were studied by means of the retrograde degeneration technique spinal lesions were made in 6 weeks old kittens. In order to differentiate the cells of origin of the propriospinal fibers from those of the fibers which ascend beyond the lumbosacral cord in 7 such animals the spinal cord was hemisected between L1 and C2. In 58 other kittens different portions of the ventral and lateral funiculi were interrupted between L4 and S1, by means of a small hook. The lateral funicular lesions were made via a laminectomy, while the ventral funicular lesions were made via a hole drilled through the body of a vertebra or through the intervertebral disc.

The animals survived the operation for a period between 2 and 20 days. However, the majority of the animals was sacrificed after 5 to 10 days. After this period the animals were deeply anaesthetized with Nembutal and perfused with 10% buffered formaldehyde. All lumbosacral segments (L3 to S1) were then embedded in celloidin and cut serially

into transverse sections of 40 μ thickness. All sections were stained with cresylviolet and scanned for chromatolytic neurons.

A neuron was considered chromatolytic when the cell body was swollen, the nucleus occupied an eccentric position and the Nissl bodies were either absent or greatly diminished in quantity and density.

Out of the 7 cases with hemisections only 4 were studied in detail (fig.5), because in the other 3 cases, i.e. those with hemisections at

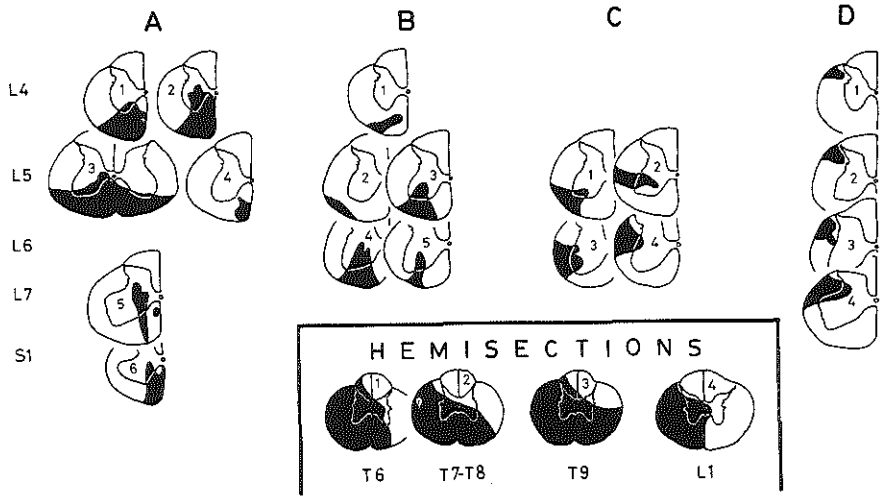

Fig.5. Semidiagrammatic representation of location and extent of the small funicular lesions (case of groups A to D) and of the hemisections (cases of group H) described in text. Numbers 1 to 6 refer to cases A1, A2 etc. (see text for explanation).

upper thoracic and cervical levels only a very limited number of chromatolytic neurons occurred in the lumbosacral segments. Out of the 58 cases with small funicular lesions 19 were studied in detail (fig.5). The others were discarded because either the lesions were too large or

charting of chromatolytic neurons was difficult, due to profuse glial reaction or meaningless because of pronounced cell loss.

In all lumbosacral segments containing chromatolytic neurons the location of such neurons was charted in every other section with the aid of an X-Y-plotter which by means of transducers was attached to the microscope stage. Chromatolytic neurons in the motoneuronal area (lamina IX) were disregarded, since no distinction could be made between motoneurons and interneurons in this area. Charts of 24 or 36 consecutive sections were combined to one.

Spinal and supraspinal HRP injections.

In the second series of experiments an attempt was made to complement the retrograde degeneration data by using the HRP retrograde axonal transport technique.

In a group of 8 cats (SSp) the cells of origin of the various spinal fibers which ascend to supraspinal levels were identified by injecting HRP in the brainstem at different levels and at C1. In one cat (SSp1) HRP was injected unilaterally at pontobulbar levels, in two cats (SSp2,3) in the medial bulbar tegmentum and in two other cats (SSp4,5) in the dorsal column nuclei. In the latter two animals five days prior to these injections the ipsilateral lateral and ventral funiculi had been transected at C2. In three cats (SSp6,7,8) unilateral injections were made at C1.

In a group of ten cats (Sp) the intrinsic spinal connections were studied. In these animals unilateral HRP injections were made at different spinal levels, i.e. at T1 (Sp1,2,3), at T6 (Sp4,5) at L1 (Sp6,7,8) and at L6 (Sp9,10). In one additional animal (Sp11) injections were made at C4 and the labeled neurons were studied rostral to the injections.

In a group of four cats (SpTr) the spinal trajectory of the fibers from the various groups of spinal neurons was studied. In these cases different funiculi were transected unilaterally on the same side at two midthoracic levels one segment apart. Five days later HRP-injections were made in the segment between the transections on that same side. In cases SpTr1 and 2 the dorsal and dorsolateral funiculi were transected at T8 and T10 and at T6 and T8 respectively, while in

cases SpTr3 and 4 the ventral and ventrolateral funiculi were transected at T7 and T9 and at T6 and T8, respectively.

In order to compare the location of the cells of origin of the supraspinal and propriospinal fibers in cat and monkey, in two rhesus monkeys (SSpM1,2) injections were made unilaterally in the dorsal column nuclei, in two others (SSpM3,4) at C1 and in a third one (SpM1) at T7.

In all animals, but especially in those with spinal injections, an attempt was made to have the needle penetrations damage a great many axons in the funiculi. For this purpose three to four transverse rows of narrowly spaced needle penetrations were made and every 0.25 mm along each needle penetration 0.2 µl of 30% HRP was deposited, i.e. about 30 µl in each case [108]. In the case with pontobulbar injections (SSp1) five needle penetrations were made in the P3 stereotactic transverse plane. In the same way as in the spinal injections 30% HRP was deposited at many places along these needle penetrations (in toto about 60 µl). The injections in the medial bulbar tegmentum (SSp2,3) were made by way of oblique needle penetrations at 4 different levels between the P6 and P11 transverse stereotactic planes (in toto about 20 µl). The injections in the dorsal column nuclei (SSp4,5) were made by longitudinal needle penetrations parallel to the dorsal surface of the caudal medulla oblongata (in toto about 20 µl).

All the animals, after having survived the injections for three days, were deeply anaesthetized with Nembutal and perfused with dextran followed by a mixture of 0.5% paraformaldehyde and 2.5% glutaraldehyde. The medulla oblongata and spinal cord were removed and the spinal cord was cut into segments. In all cases the segments C1 to T1,T4,T7,T10, T13 (in monkeys T12) and L3 to S1 were processed. They were stored overnight in 30% sucrose in cacodylate buffer at 4°C. The following day these segments as well as the medulla oblongata were cut transversely into frozen sections 40 µ thick, which were incubated according to Graham and Karnovsky.[60] In cases SpTr 1 to 4 and SSp2,3 the segments with the funicular transections were cut transversely into 40 µ celloidin sections and were stained with cresylviolet.

The material was studied under brightfield and darkfield illumination and charts were made of the location of retrogradely labeled

neurons with the aid of an X-Y-plotter. In the spinal cord 12 sections of each segment were charted and the charts were combined to one. In one cat from each group with injections at the same spinal level and in the one cat with C4-injections the location of retrogradely labeled neurons in the medulla oblongata was also studied.

Chapter IV: *Results*

1. the distribution in the lumbosacral intermediate zone of chromatolytic neurons after ventral and lateral funicular transections
   A. Spinal hemisections
   B. Small lesions of the ventral and lateral funiculi
2. the spinal distribution of retrogradely labeled neurons after spinal and supraspinal HRP-injections
   A. Local findings at the injection site
   B. Injections at C1 and brainstem levels
   C. Injections in the thoracic and lumbar cord
   D. Injections at midthoracic levels preceded by funicular transections
   E. Injections at C1 and T7 and in the dorsal column nuclei in monkey
   F. Interrelationships between the labeled neurons in the upper cervical cord and the medulla oblongata
3. Addendum. The distribution in the brachial intermediate zone of neurons which send their fibers to different parts of the low cervical lateral motoneuronal cell group.

1. THE DISTRIBUTION IN THE LUMBOSACRAL INTERMEDIATE ZONE OF CHROMATOLYTIC NEURONS AFTER VENTRAL AND LATERAL FUNICULAR TRANSECTIONS.

A. Spinal hemisections.

In order to identify the neurons in the lumbosacral cord which send their fibers rostrally beyond the lumbar cord, in 7 kittens hemisections were made at L1 (H4,fig.5) and at different thoracic (H3 at T9, H2 at T7T8 and H1 at T6;fig.5) and cervical levels (3 cases; not represented in fig.5).

The *hemisection at L1* (case H4) spared the dorsal funiculus, but interrupted the ventral and lateral funiculi completely without involving the contralateral side (cf.fig.6). *Ipsilateral* to the lesion chromatolytic cells were present in the column of Clarke from L1 to L4 and in the dorsal horn, mainly in lamina IV and in the medial parts of laminae V and VI from L3 to S1 (fig.7A). In the intermediate zone chromatolytic neurons were concentrated in the medial part of lamina VII and in lamina VIII in L2 and L3, but rapidly diminished in number at more caudal levels and were absent below L5. *Contralateral* to the lesion chromatolytic cells were present in the dorsal horn and intermediate zone, but none in the column of Clarke. In the contralateral dorsal horn the chromatolytic neurons were less numerous than in the ipsilateral one and were located in lamina IV as well as in laminae V and VI. In the contralateral intermediate zone large chromatolytic cells were found centrally (fig.7D) and laterally (fig.7C) from L2 throughout L6. The cells located laterally will be referred to as spinal border cells. Retrogradely affected cells were also present in the medial part of the contralateral intermediate zone throughout the lumbosacral cord. They were concentrated in lamina VIII and the adjoining part of lamina VII and were most numerous in the segments L5 to S1. However, especially in L6 to S1, these cells were not much swollen and did not display a pronounced eccentricity of the nucleus. Yet, they showed a definite lysis of the Nissl bodies which made them look very different from the surrounding cells and those in the corresponding area on the other side (fig.7B). On this basis these cells were also regarded as retrogradely affected.

In the cases H1-H3 with *large thoracic lesions* the distributions of the chromatolytic cells were similar to that observed after hemi-

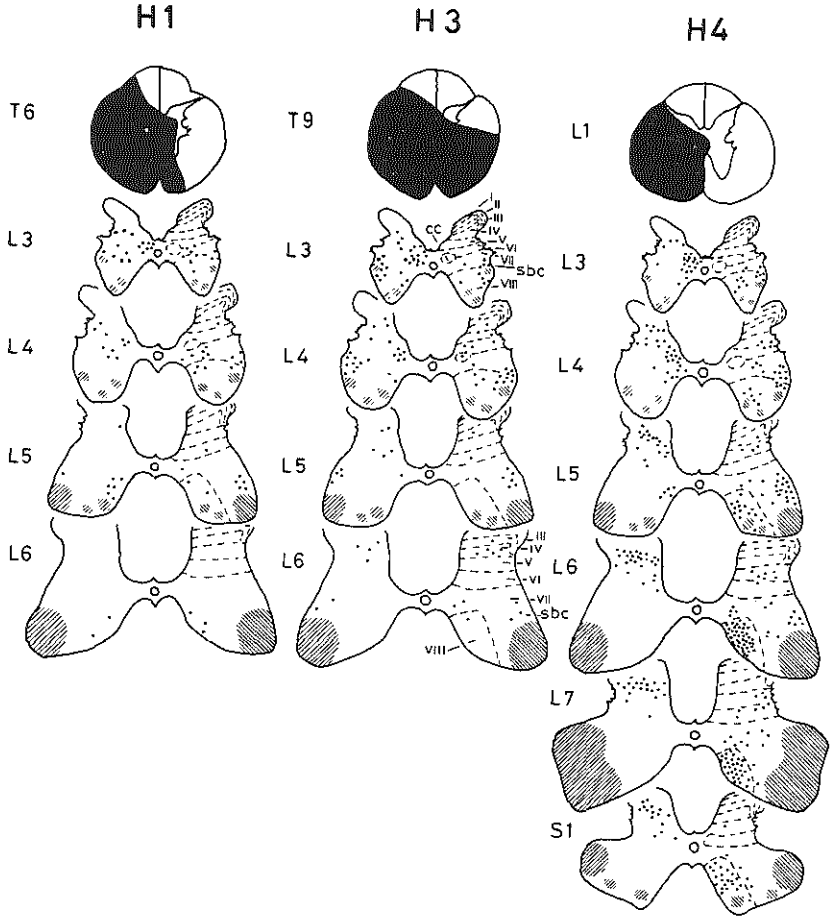

Fig.6. Semidiagrammatic representation of the distribution of chromatolytic neurons in lumbosacral cord of cases H1,H3 and H4 with hemisections or large spinal lesions at T6,T9 and L1. Each level represents the composite of the plots of 36 consecutive sections. Motoneuronal cell groups are shaded. Note the concentration of chromatolytic cells ipsilaterally in the column of Clarke and the dorsal horn and contralaterally in the lateral part of lamina VII, in lamina VIII and the medial part of lamina VII and in the dorsal horn.

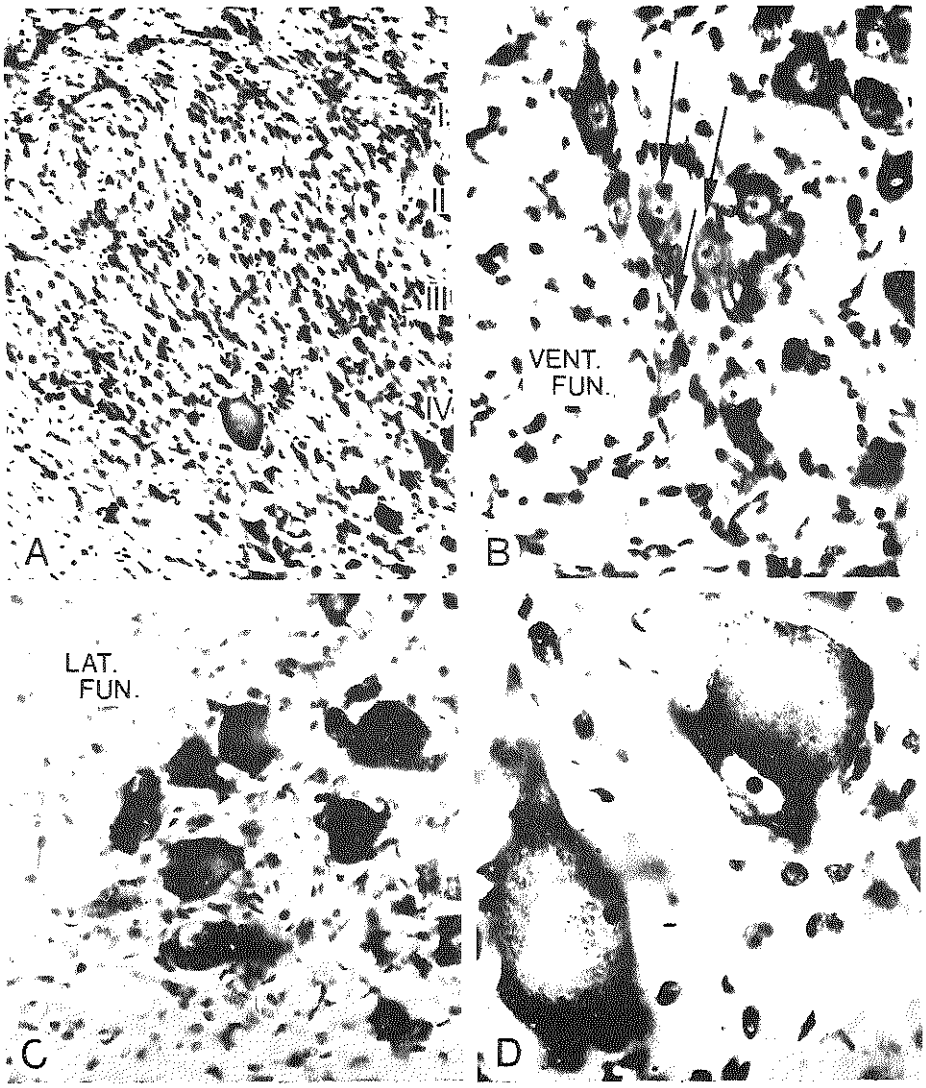

Fig.7. Photomicrographs of chromatolytic neurons following hemisection at L1 (case H4,cf, fig.6). A. Neuron in lamina IV of ipsilateral dorsal horn at L6 (magn.235x); B. Several neurons with lysis of Nissl bodies in contralateral lamina VIII at L6 (magn.510x); C. Chromato-

lytic neurons in lateral parts of contralateral intermediate zone (area of spinal border cells) at L4 (magn.400x). D. Large chromatolytic neurons in contralateral intermediate zone at L4 (magn.875x). LAT FUN., lateral funiculus; VENT FUN., ventral funiculus; arrows indicate chromatolytic neurons. (Republished from Brain Res., 78, 1974, 239-254).

section at L1 (fig.6). For example, chromatolytic cells were present in the ipsilateral column of Clarke and, especially following transection at T9, also in the contralateral spinal border cell area in L2 to L5. However, few retrogradely affected cells were present in the dorsal horns and none were present in lamina VIII. Moreover, no chromatolytic neurons were found caudal to L6.

In the three cases with *hemisections at cervical levels* only a limited number of chromatolytic neurons was present at lumbosacral levels, which were located mainly in the ipsilateral dorsal horn, in the ipsilateral column of Clarke and in the contralateral spinal border cell area.

Summary of the findings in group H. The findings in the cases of group H show that after unilateral transection of the ventral and lateral funiculi at or above L1 the bulk of the chromatolytic neurons in the lumbosacral cord is located ipsilaterally in the column of Clarke and in lamina IV as well as contralaterally in the area of the spinal border cells and in lamina VIII, while virtually no chromatolytic neurons are present in laminae V to VII on either side.

B. Small lesions of the ventral and lateral funiculi.

In order to identify the cells of origin of short ascending and descending propriospinal fibers in different parts of the lumbosacral ventral and lateral funiculi, in 58 kittens small parts of these funiculi were transected between L4 and S1. The 19 cases studied in detail (cf. Chapter III.3) are subdivided into 4 groups according to the locations of the lesions (fig.5).

Group A consists of 6 cases with lesions of the ventral funiculus

including its medial portion at L4 (A1,A2), L5 (A3,A4), L7 (A5) and S1 (A6). Group B consists of 5 cases with lesions laterally in the ventral funiculus at L4 (B1), L5 (B2,B3) and L6 (B4,B5). Group C consists of 4 cases with lesions of the ventral two-thirds of the lateral funiculus at L5 (C1,C2) and L6 (C3,C4), while group D consists of 4 cases with lesions of the dorsal one-third of the lateral funiculus at L4 (D1), L5 (D2), L6 (D3) and L7 (D4).

In all these cases chromatolytic cells were present in the ipsilateral intermediate zone and were concentrated in the segments adjoining the lesions. In the cases of groups A and B chromatolytic cells were also present in the contralateral intermediate zone.

Among the cases of *group A* with ventral funicular lesions chromatolytic cells were most numerous in case A1 in which the lesion at L4 was strictly unilateral (fig.8). *Ipsilateral* to the lesion, chromatolytic cells were present in the intermediate zone from L3 to L6. The bulk of these cells was located in laminae VII and VIII, while relatively few cells were present in laminae V and VI. Caudal to the lesion some chromatolytic cells were also present in lamina IV of the ipsilateral dorsal horn from L5 to S1. *Contralateral* to the lesion chromatolytic cells were distributed differently. Rostral to the lesion, in L3 and L4 they were present mainly in the medial parts of the intermediate zone, i.e. in lamina VIII and the adjoining parts of lamina VII. However, at the level of the lesion and caudal to it they were present in the medial as well as in the lateral parts of the intermediate zone and in the dorsal horn. Chromatolytic cells in the medial part of the intermediate zone caudal to the lesion were present from L5 to S1. Below L6 the majority of these cells seemed to correspond to the retrogradely affected neurons observed in this area (lamina VIII and the adjoining part of lamina VII) following contralateral hemisection at L1. The chromatolytic cells in the lateral part of the intermediate zone were present from L5 to L6 while those in the dorsal horn were present from L5 to L7. These two groups of chromatolytic neurons in turn seem to be identical with the chromatolytic spinal border cells and dorsal horn cells observed following contralateral hemisection at L1.

In case A2 in which the lesion at L4 involved mainly the medial

portion of the ventral funiculus as well as the ventral horn (fig.8) most of the chromatolytic neurons in the *ipsilateral* intermediate zone

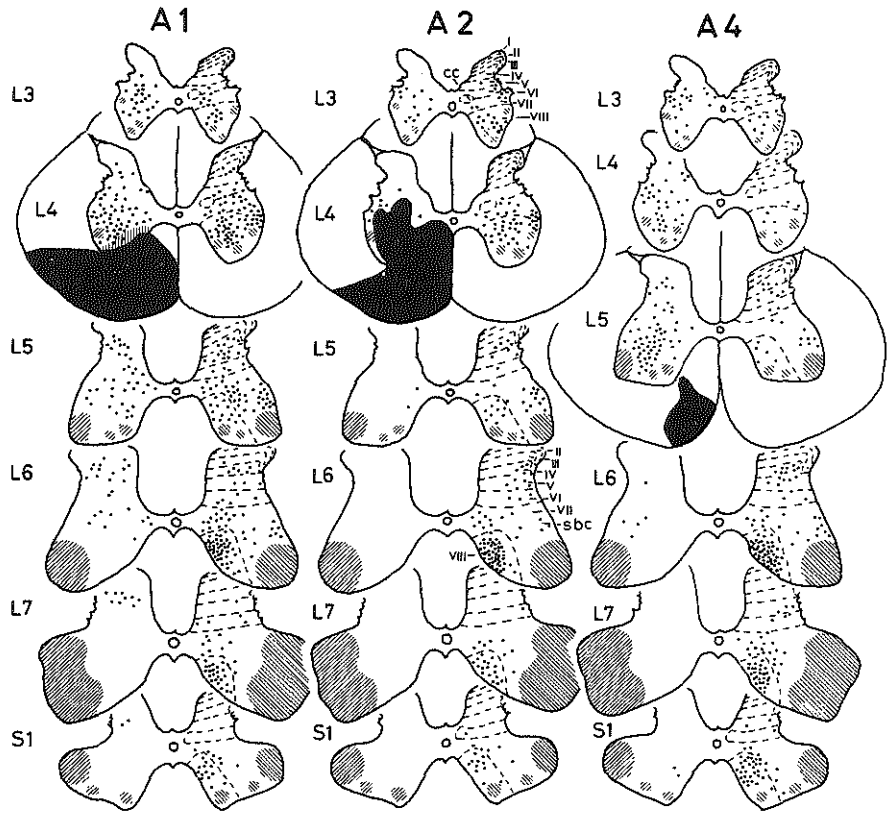

Fig.8. Semidiagrammatic representation of the distribution of chromatolytic neurons in cases A1, A2 and A4 with lesions of the ventral funiculus. Each level represents the composite of the plots of 24 consecutive sections. Motoneuronal cell groups are shaded. Note that ipsilaterally, immediately above and below the lesion, chromatolytic neurons are concentrated in the medial and central parts of lamina VII and in lamina VIII and that the distribution at more caudal levels resembles that found following hemisection at L1 (fig.6).

were present throughout the medial and central parts of lamina VII in the same way as in case A1. *Contralaterally* chromatolytic neurons were also distributed as in case A1. A similar ipsilateral and contralateral distribution occurred even in case A4 (fig.8) with a small lesion of the ventromedial part of the ventral funiculus at L5.

In case A3, with a bilateral lesion of the ventral funiculus at L5 (fig.5) the distribution of the chromatolytic cells rostral and caudal to the lesion corresponded on either side to the combined ipsilateral and contralateral distributions observed in case A1.

In cases A5 and A6 the lesions involved the medial portions of the ventral funiculus and the adjoining part of the ventral horn at L7 and S1, respectively. In these cases very few chromatolytic cells were present ipsilateral to the lesion and were located mainly in the medial part of the intermediate zone at L7 and S1, respectively. Contralateral to the lesion, however, many retrogradely affected cells occurred mainly in the medial part of lamina VII and in lamina VIII immediately rostral and caudal to the lesion.

Summary of the findings in group A. The findings in the cases of group A show that after transection of the ventral funiculus the bulk of the chromatolytic neurons in the ipsilateral intermediate zone is located in the central and medial parts of lamina VII and in lamina VIII, while the bulk of the chromatolytic neurons in the contralateral intermediate zone is located in lamina VIII and the dorsally adjoining part of lamina VII.

Group B consists of 5 cases in which the lesions primarily involved the lateral part of the ventral funiculus and the ventral part of the lateral funiculus (fig.5). However, in cases B1 and B4 the lesions extended more medially than in the others and encroached upon the medial part of the ventral funiculus. The distribution of chromatolytic cells in the cases of this group was similar to that in cases of group A. For example, in the *ipsilateral* intermediate zone chromatolytic cells were present only in the segments adjoining the lesion and were located mainly in the medial and central parts of lamina VII (fig.9). In the *contralateral* intermediate zone chromatolytic cells were present in the medial part of lamina VII and in lamina VIII caudal

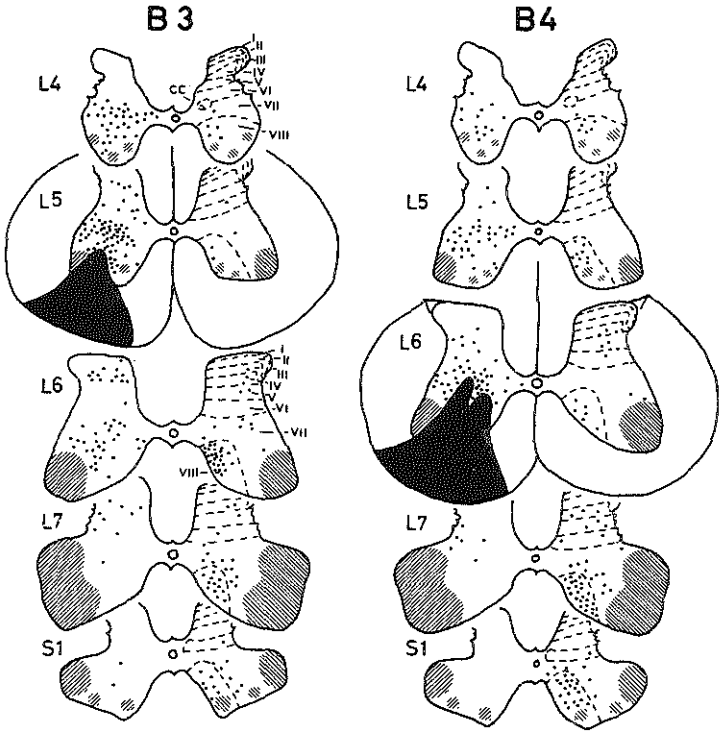

Fig.9. Semidiagrammatic representation of the distribution of chromatolytic neurons in cases B3 and B4 with lesions of the lateral part of the ventral funiculus. Each level represents the composite of the plots of 24 consecutive sections. Motoneuronal cell groups are shaded. Note that immediately above and below the lesion chromatolytic neurons are present mainly ipsilaterally and are concentrated in the medial and central parts of lamina VII. At caudal lumbosacral levels the distribution resembles that found after hemisection at L1 without the accumulation of cells in the lateral part of the intermediate zone.

to the lesion. However, in comparison to the findings in group A, only few chromatolytic neurons were present in the medial part of the contralateral intermediate zone rostral to the lesion. In addition, caudal to the lesion a very few chromatolytic cells were present in the lateral part of the contralateral intermediate zone, including the

area of the spinal border cells. Chromatolytic cells were found in this lateral area only in cases B1 and B5 and were restricted to the level of the lesion.

In all the cases of group B some chromatolytic cells were also found in the ipsilateral dorsal horn caudal to the lesion, mainly in lamina IV. In the contralateral dorsal horn chromatolytic cells were located mainly in laminae V and VI. Chromatolytic neurons in these contralateral laminae were present especially in cases B1 and B4 in which the lesions encroached upon the medial portion of the ventral funiculus (fig. 9).

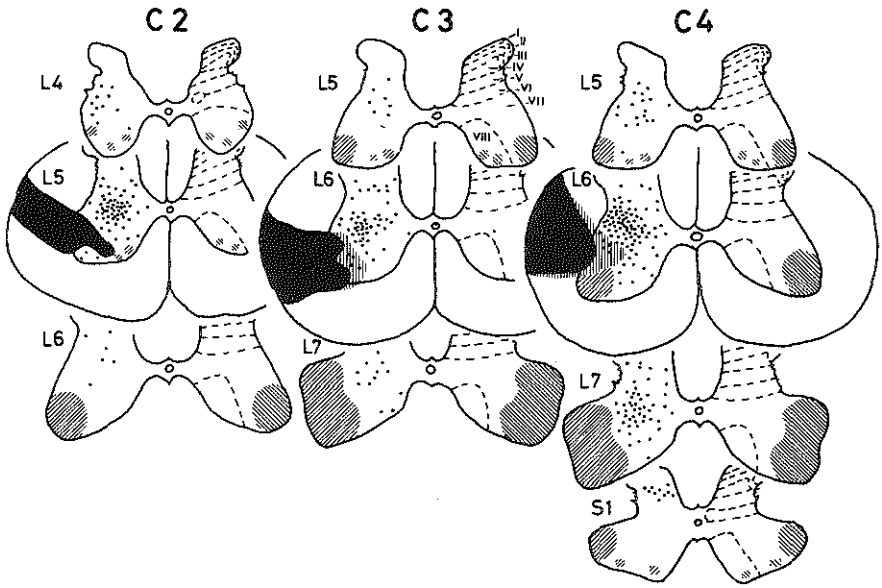

Fig. 10. Semidiagrammatic representation of the distribution of chromatolytic neurons in cases C2, C3, C4 with lesions of ventral and intermediate parts of lateral funiculus. Each level represents a composite of the plots of 24 consecutive sections. Motoneuronal cell groups are shaded. Note that the chromatolytic cells are concentrated in the ipsilateral intermediate zone and are present almost exclusively immediately above and below the lesion.

Summary of the findings in group B. The findings in the cases of group B show that after transection of the lateral part of the ventral funiculus the distribution of chromatolytic neurons is similar to that after transection of its medial part (group A). Thus, the bulk of the chromatolytic neurons is located ipsilaterally in the central and medial parts of lamina VII and in lamina VIII and contralaterally in lamina VIII and the dorsally adjoining part of lamina VII. However, after transection of the lateral part of the ventral funiculus the chromatolytic neurons in the contralateral intermediate zone tend to be less numerous than after transection of the medial part of this funiculus, especially rostral to the transection.

In the cases of *groups C and D*, with lesions of the lateral funiculus, the chromatolytic neurons showed a different distribution pattern as compared to those in the cases of groups A and B.

Group C. In the cases of this group the lesions involved mainly the ventral two-thirds of the lateral funiculus, sparing its dorsal one-third. In all these cases the bulk of the chromatolytic cells in the intermediate zone was located in the central part of lamina VII ipsilaterally (fig.10). In case C4 in which the lesion at L6 encroached upon the dorsal portion of the lateral funiculus many chromatolytic cells were also present in the lateral parts of laminae VII to V (Fig.11; compare cases of group D) and in laminae IV of the ipsilateral dorsal horn caudal to the lesion from L6 to S1 (fig.10).

Group D. In the cases of this group the lesions involved mainly the dorsal portion of the lateral funiculus. The findings in the cases of this group were similar to those in group C in that the chromatolytic neurons in the intermediate zone were present mainly ipsilaterally (except in case D2, in which such neurons were present in the intermediate zone on both sides). However, the chromatolytic cells in the cases of group D were especially concentrated in the lateral parts of laminae VII, VI and V (fig.12). In cases D3 and D4 with dorsal lateral funicular lesions at L6 and L7 respectively, chromatolytic neurons were present also in lamina IV of the ipsilateral dorsal horn caudal to the lesions.

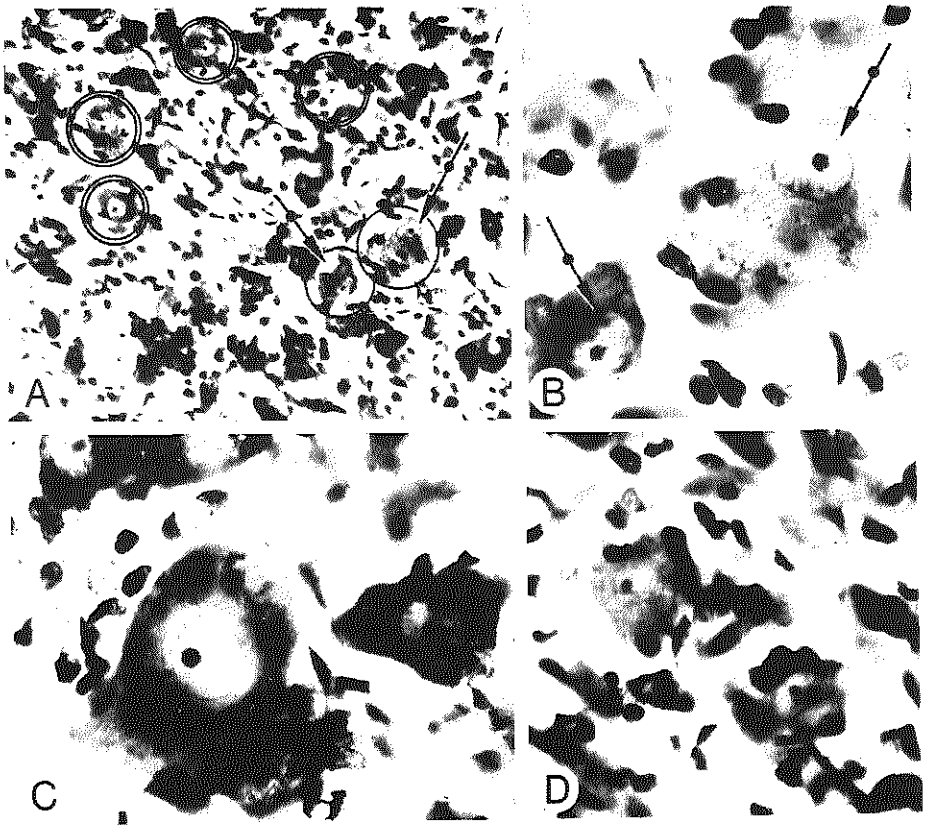

Fig.11. Photomicrographs of chromatolytic neurons in the lateral part of the intermediate zone at L6 of case C4 with lateral funicular lesion at L6 (cf. fig.10). Two of the encircled chromatolytic neurons indicated by arrows in A (magn.355x) are shown in detail in B (magn. 1140x). C and D show other chromatolytic neurons (magn. ± 1100x). (Republished from Brain Res., 78, 1974, 239-254).

Summary of the findings in groups C and D. The findings in the cases of groups C and D show that after transection of the lateral funiculus chromatolytic neurons are almost exclusively present in the ipsilateral intermediate zone. After transection of the ventral two-thirds of this funiculus (group C) chromatolytic neurons are located especially in the central part of the ipsilateral lamina VII, while after transection of the dorsal one-third of the lateral funiculus (group D) the chromatolytic neurons tend to be located somewhat more dorsally, i.e. in the lateral parts of the ipsilateral laminae V to VII.

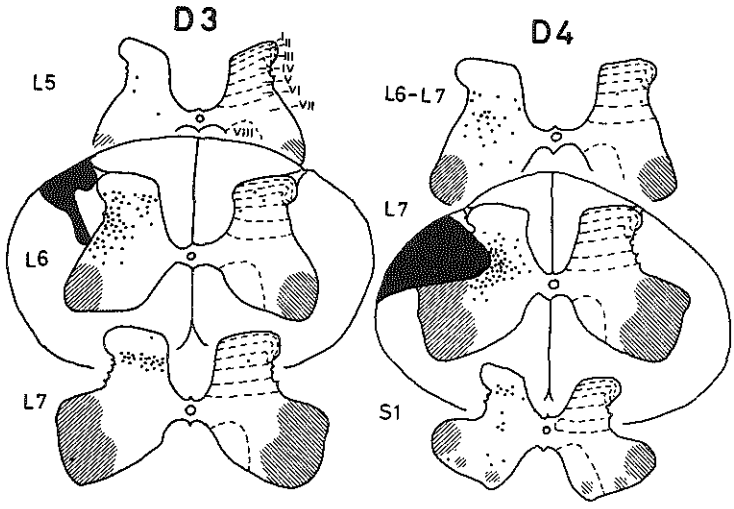

Fig.12. Semidiagrammatic representation of the distribution of chromatolytic neurons in cases D3 and D4 after lesions of the dorsal parts of the lateral funiculus. Each level represents composite of the plots of 24 consecutive sections. Motoneuronal cell groups are shaded. Note that the chromatolytic neurons are concentrated in lateral parts of laminae VII, VI and V ipsilaterally.

Conclusion. In this chapter a group of experiments has been described in which an attempt was made to determine the cells of origin of fibers in the lumbosacral ventral and lateral funiculi by means of the retrograde degeneration technique. The findings in these experiments indicate that ascending fibers are derived mainly from cells in laminae IV and VIII as well as from cells in the column of Clarke and the spinal border cell area. The findings further indicate that short propriospinal fibers are derived mainly from cells in the intermediate zone. The bulk of these fibers in the ventral funiculus and ventral part of the lateral funiculus is derived from the medial and central parts of the ipsilateral lamina VII. However, some fibers in the medial part of the ventral funiculus are also derived from the contralateral lamina VIII, while the fibers in the dorsal part of the lateral funiculus are derived mainly from the lateral parts of the ipsilateral laminae VII, VI and V.

2. THE SPINAL DISTRIBUTION OF RETROGRADELY LABELED NEURONS AFTER SPINAL AND SUPRASPINAL HRP-INJECTIONS.

In the experiments described in this chapter an attempt was made to complement the data obtained by means of the retrograde degeneration technique (Chapter II.1) by studying the distribution of retrogradely labeled neurons after HRP-injections at different spinal and supraspinal levels. The local findings at the injection sites will be described first and then the distributions of the labeled neurons in the various cases will be reported.

A. Local findings at the injection site.

In all cases with spinal HRP-injections the local findings at the injection sites were essentially similar. In these cases the needle tracks which were surrounded by HRP reaction products involved both the white and the gray matter (fig.19B). In all cases the needle tracks in the ventral and lateral funiculi were restricted to one side, but in some cases they involved the dorsal funiculi on both sides. Thus, in all cases HRP reaction products in the ventral and lateral funiculi were present only unilaterally, but in the dorsal funiculi they were in some cases present bilaterally. In the sections immediately rostral and caudal to the injections brown stained fibers were present in the funiculi, which fibers were distributed according to the same pattern as the accumulations of HRP reactionproducts at the injection sites and occurred in the ventral and lateral funiculi unilaterally, but in the dorsal funiculi in some cases bilaterally (fig.19B). In addition, some brown stained fibers frequently could be traced from the ventral funiculus on the injected side to the medial part of the ventral funiculus on the other side. Further, at the injection site, HRP reaction products were also present in the gray matter on the non-injected side, which in addition contained some diffusely brown stained neurons as well as retrogradely labeled neurons with HRP-positive granules.

In the cases with brainstem injections the needle tracks were also generally restricted to one side and in the cases in which injections were made in the medial bulbar tegmentum and in the dorsal column nuclei the needle tracks were largely restricted to these re-

spective areas. However, in the case with pontobulbar injections some of the needle tracks also involved the contralateral side. In all cases a dense accumulation of HRP reaction products was present in the area immediately surrounding the needle tracks and some diffuse HRP reaction products occurred in the adjoining parts of the reticular formation. Comparable to the findings after spinal injections, some brown stained fibers occurred in the medullary white matter immediately caudal to the injections. In the cases with dorsal column nuclear injections such fibers were located almost exclusively in the ipsilateral dorsal funiculi, while after tegmental injections they were located mainly in the area of the medullary ventral and lateral funiculi. Finally, after tegmental injections brown stained fibers were distributed to the reticular formation on both sides.

B. Injections at C1 and brainstem levels.

As a first step an attempt was made to determine the location of spinal neurons which give rise to fibers which ascend to supraspinal and suprabulbar levels. Since the HRP transport method is much more sensitive than the retrograde degeneration technique the neurons of supraspinal fibers could be identified throughout the spinal cord not only after injections at C1, but also after injections at pontobulbar levels. Therefore, unilateral injections were made at C1 (cases SSp6, 7,8) as well as the level of the pontomedullary junction (SSp1).

In the three cases with *C1-injections* the needle penetrations did not involve the dorsal funiculus on the other side. The distribution of the retrogradely labeled neurons in the spinal cord was roughly the same in all three cases and is exemplified by the findings in case SSp6 (fig.13). Throughout the length of the spinal cord labeled neurons were present bilaterally in the dorsal gray and mainly contralaterally in the medial part of the ventral gray. Labeled neurons were also present in the ipsilateral column of Clarke from T4 to L4 and in the contralateral area of the spinal border cells from L3 to L6. Further, a dense accumulation of labeled neurons was present in the intermediate zone, but mainly in the cervical segments.

The labeled neurons in the dorsal gray were distributed as follows. A limited number of labeled neurons was present bilaterally in Rexed's

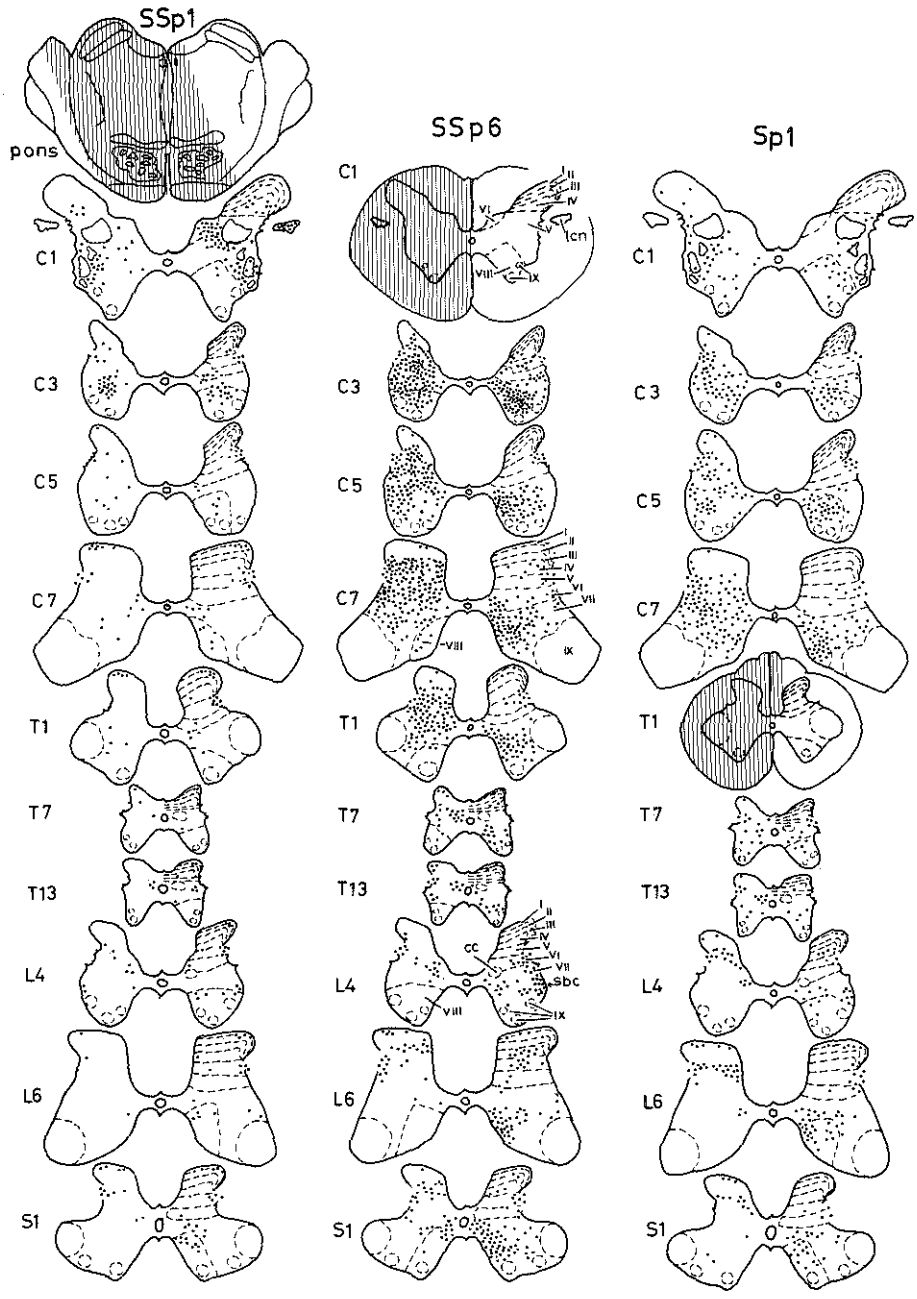
SSp1
pons
C1
C3
C5
C7
T1
T7
T13
L4
L6
S1
SSp6
C1
I
II
III
IV
VI
Icn
VIII
IX
C3
C5
I
II
III
IV
V
VI
VII
C7
VIII
IX
T1
T7
T13
I
II
III
IV
V
VI
VII
cc
Sbc
L4
VIII
IX
L6
S1
Sp1
C1
C3
C5
C7
T1
T7
T13
L4
L6
S1

Fig.13. Semidiagrammatic representation of the spinal distribution of labeled neurons after pontobulbar injections (case SSp1), after C1-injections (case SSp6) and after T1-injections (case Sp1). Each level represents the composite of the plots of 12 sections. The shaded areas indicate the extents of the injections. Note the similarity in the distributions in the dorsal and ventral gray caudal to the injections in the three cases and the presence of labeled neurons in the medial part of the ventral gray rostral to the T1-injections. Note also that a dense accumulation of labeled neurons is present in the intermediate zone in the segments adjoining the C1- and T1-injections.

lamina I and many were present mainly ipsilaterally in lamina IV and the medial parts of lamina V and VI (fig.s 13,15A). Further, large labeled neurons were present bilaterally in the most lateral reticulated parts of laminae V and VI at the border with the dorsolateral funiculus. The labeled dendrites of these neurons were distributed between the fiber bundles of the deep portion of this funiculus (fig. 15A). The labeled neurons in the contralateral ventral gray were distributed throughout the spinal cord and were concentrated in lamina VIII and the dorsally adjoining part of lamina VII. In addition, some widely scattered large labeled neurons occurred in lamina VII throughout the spinal cord, especially contralaterally.

The dense accumulation of labeled neurons in the intermediate zone occurred mainly in the cervical cord, but extended in diminishing density into the upper thoracic segments. These neurons in the intermediate zone were situated in the lateral parts of laminae V to VII as well as in the central and medial part of lamina VII. However, the former group of neurons was present mainly ipsilaterally and was restricted to the cervical cord, while the latter was present bilaterally and extended into the upper thoracic segments.

In the case with *pontobulbar injections* (SSp1, fig.13) the needle tracks surrounded by HRP-reaction products involved the inferior colliculus, the cerebellar peduncles, the pontine and upper medullary tegmentum as well as the nuclei of the lateral lemniscus and the pontine gray on one side and the medial portion of the pontine and upper medullary tegmentum on the other side. The spinal distribution of labeled neurons in this case resembled that observed after C1-injections, but labeled neurons were far less numerous. Throughout the spinal cord they were present bilaterally in the dorsal gray and mainly contralaterally in the medial part of the ventral gray. However, in contrast to the findings after C1-injections the labeled neurons in the dorsal gray were present only in lamina I and the lateral reticulated parts of laminae V and VI bilaterally, while none occurred in lamina IV and the medial parts of laminae V and VI. The labeled neurons in the contralateral ventral gray were situated in lamina VIII and the dorsally adjoining part of lamina VII. In the upper cervical cord this group of labeled neurons shifted somewhat laterally and became

located in the lateral part of the ventral gray at the border between laminae VII and VIII [1]). In addition, some labeled neurons were present in the ipsilateral column of Clarke from T13 to L3 and in the contralateral spinal border cell area from L3 to L6. Some labeled neurons were also present in the intermediate zone, but in contrast to the findings after C1-injections they were largely restricted to the cervical segments and were located mainly in the central and medial parts of lamina VII on both sides. In C2 to C4 these neurons were concentrated in a column in the central part of the intermediate zone at the border between laminae VII and VIII.

The groups of labeled neurons in the upper cervical cord on both sides could be traced rostrally into the medulla oblongata. At the spinobulbar transition they were situated in the ventral gray around the ventral tegmental bundles of Thomas.[118] Further rostrally this population of neurons continued on both sides into the lateral bulbar reticular formation (lateral tegmental field of Berman [10]). Some labeled neurons were also present bilaterally in the medial bulbar reticular formation and the vestibular complex as well as, mainly contralaterally, in the lateral cervical nucleus, the gracile and cuneate nuclei and the spinal V complex.

The lack of labeling of neurons in lamina IV and in the medial parts of laminae V and VI of the ipsilateral dorsal gray and the relatively limited number of labeled neurons in the medial part of the contralateral ventral gray after injections in the pons and the upper medulla oblongata suggests that the labeling of many neurons in these areas after C1-injections resulted from HRP-transport through spinal fibers to the caudal medulla oblongata. It seems likely that neurons in these two areas send fibers to the dorsal column nuclei [163,164,169] and the medial reticular formation [45,46] respectively.

[1]) This shift may be related to the presence of motoneuronal cell groups in the medial part of the upper cervical ventral gray.[134,137]

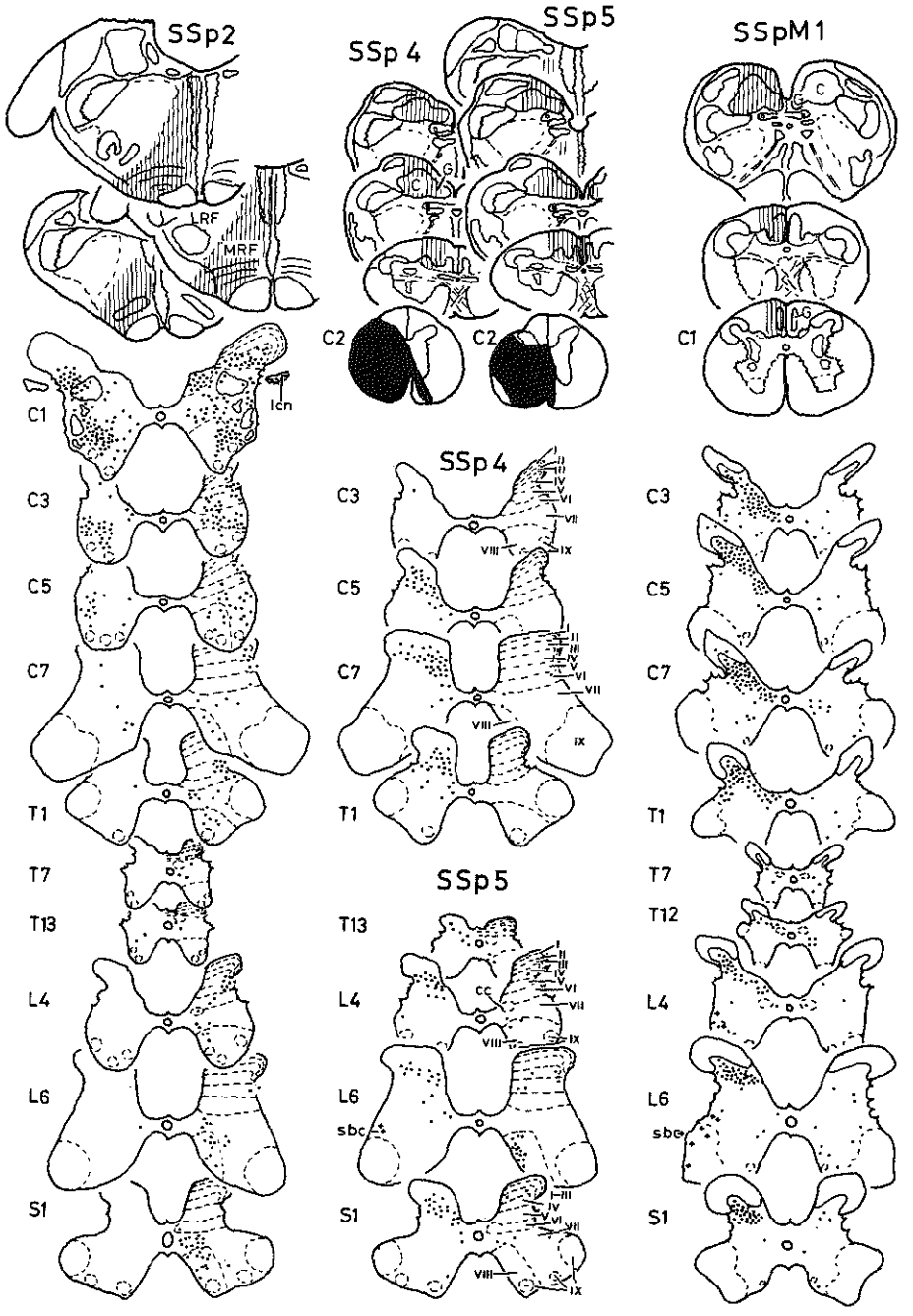
SSp2
LRF
MRF
C1
C3
C5
C7
T1
T7
T13
L4
L6
S1
lcn
SSp 4
SSp5
C2
C2
SSp 4
C3
C5
C7
T1
SSp5
T13
L4
L6
sbc
S1
SSpM1
C1
C3
C5
C7
T1
T7
T12
L4
L6
sbc
S1

Fig.14. Semidiagrammatic representation of the spinal distributions of labeled neurons after medial bulbar tegmental injections in cat (SSp2) and after dorsal column nuclear injections in cat (SSp4,5) and monkey (SSpM2). Each level represents the composite of the plots of 12 sections. The shaded areas indicate the extents of the injections and the black areas those of the funicular transections. Note that after unilateral medial tegmental injections the majority of the labeled neurons is present in the contralateral ventral gray, while after unilateral dorsal column nuclear injections it is present in the ipsilateral dorsal gray.

Therefore, in two cases (SSp2,3) injections were made in the medial bulbar tegmentum and in two others in the dorsal column nuclei (SSp4,5). In the latter two cases the ipsilateral ventral and lateral funiculi were transected at C2 five days prior to the injections, which transection was aimed at restricting the HRP-transport to the dorsal funiculi.

In the two cats with *medial bulbar tegmental injections* (SSp2,3) the findings were roughly the same and are exemplified by those in case SSp2 (fig.14). In this case the needle tracks surrounded by HRP-reaction products were entirely limited to one side and involved the nuclei of the inferior olivary complex as well as the medial bulbar tegmentum, the medial longitudinal fasciculus and the medial lemniscus. Throughout the spinal cord labeled neurons were present in the medial part of the contralateral ventral gray, i.e. in lamina VIII and the dorsally adjoining part of lamina VII. Labeled neurons were also present contralaterally in the lateral reticulated parts of laminae V and VI (fig.15B), but they were sparse in this area at low lumbar and sacral levels. In addition, a dense accumulation of labeled neurons occurred in the intermediate zone of the upper six cervical segments. These neurons in the intermediate zone were situated mainly in the central and medial parts of lamina VII on both sides. At the level of the spinobulbar transition many labeled neurons were also present contralaterally in the lateral cervical nucleus and in the gracile and cuneate nuclei.

In the two cases with *injections in the dorsal column nuclei* (SSp4,5) the needle penetrations surrounded by HRP-reaction products were present unilaterally in the cuneate nucleus, especially in its central and medial parts (fig.14). In case SSp5 the needle penetrations in addition involved the gracile nucleus on the same side and at levels caudal to the obex also on the other side. Moreover, in this case some HRP-reaction products were present in the most dorsal part of the medial tegmental field on the injected side (cf. fig.14). The transections at C2 in both cases interrupted the ventral and lateral funiculi on the injected side, but spared the dorsal funiculi. However, in case SSp4 the lesion slightly involved the dorsal funiculus on the injected side, while that in case SSp5

spared the most superficial part of the ipsilateral ventrolateral funiculus (cf.fig.14).

The distribution of labeled neurons in these two cases was very similar, but was entirely different from that observed after medial tegmental injections (cases SSp2,3). In cases SSp4 and SSp5 the great majority of labeled neurons occurred in the ipsilateral dorsal gray, where they were situated in lamina IV and the medial parts of laminae V and VI. In case SSp5 this population of neurons in the dorsal gray extended throughout the spinal cord. However, in case SSp5, in which the injections involved mainly the cuneate nucleus the labeled neurons in the ipsilateral dorsal gray were most numerous from C5 to T1, while only few were present in this area at lumbosacral levels. In addition, in case SSp5 some labeled neurons were present in lamina VIII of the contralateral ventral gray, which seems to be due to HRP-transport through spinoreticular fibers.

Summary of the findings after C1- and brainstem injections. The findings in the above described cases show that after C1- and pontobulbar injections the bulk of the labeled neurons is located in the column of Clarke and the spinal border cell area as well as throughout the spinal cord in the dorsal gray and the medial part of the ventral gray. After unilateral injections in the dorsal column nuclei labeled neurons occur almost exclusively in the ipsilateral dorsal gray, while after unilateral injections in the medial medullary tegmentum they occur predominantly in the medial part of the contralateral ventral gray.

C. Injections in the thoracic and lumbar cord.

In the next group of experiments the location of the cells of origin of propriospinal fibers was approximated by studying the distribution of labeled neurons throughout the spinal cord after thoracic and lumbar injections.

In these cases with injections in the thoracic cord (cases Sp1 to 5) and in the lumbar cord (Sp6 to 10) the labeled neurons were distributed according to the following general pattern. *Caudal to the injections* the distributions resembled those after C1-injections. Thus, labeled neurons occurred in the ipsilateral column of Clarke and in the

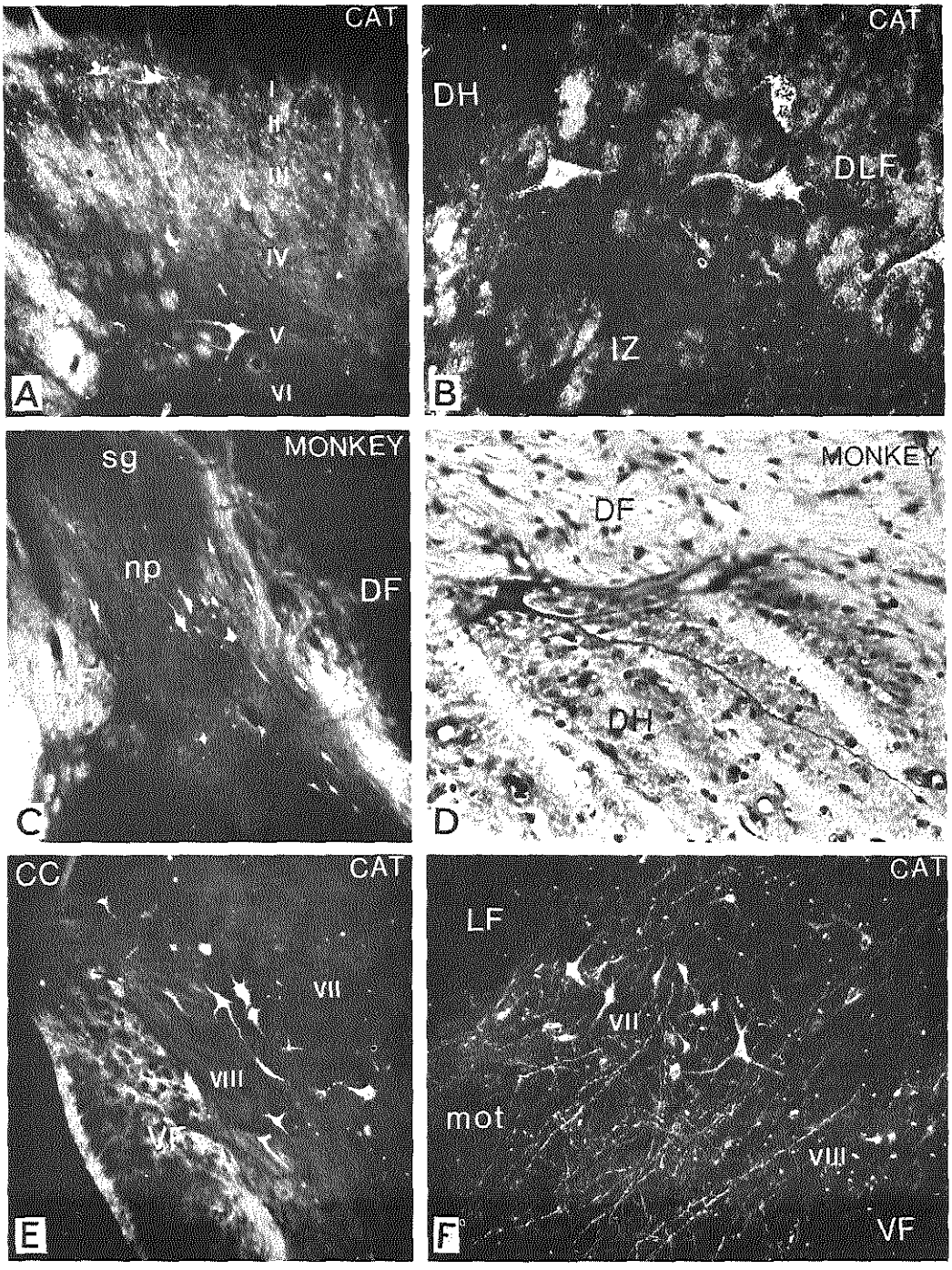
CAT
I
II
III
IV
V
VI
A
CAT
DH
DLF
IZ
B
sg
MONKEY
np
DF
C
MONKEY
DF
DH
D
CC
CAT
VII
VIII
VF
E
CAT
LF
VII
mot
VIII
VF
F

Fig.15. Photomicrographs of labeled neurons of supraspinal (A to C) and of propriospinal fibers (D to F). A L6 dorsal gray in cat after ipsilateral C1-injections (case, SSp6, magn. 50x), B C4 processus reticularis in cat after contralateral medial bulbar tegmental injections (case SSp2, magn. 175x), C C6 dorsal gray in monkey after ipsilateral dorsal column nuclear injections (case SSpM2, magn. 50x), D labeled lamina I neuron in monkey at S1 after contralateral T7-injections (case SpM, magn. 110x counterstained with cresylviolet, brightfield illumination) E C6 ventral gray in cat after contralateral T6-injections (case Sp4, magn. 50x, CC: central canal), F L5 intermediate zone in cat after ipsilateral L6-injections (case Sp10, magn. 50x). Note the presence of antegradely HRP transporting fibers.

contralateral spinal border cell area. They were also present in the dorsal gray, i.e. in lamina I and in the lateral reticulated parts of laminae V and VI bilaterally and in lamina IV and the medial parts of laminae V and VI mainly ipsilaterally. Further, labeled neurons were concentrated in the medial part of the contralateral ventral gray, i.e. in lamina VIII and the dorsally adjoining part of lamina VII and some large neurons were scattered throughout the contralateral intermediate zone. Some labeled neurons were also present in the ipsilateral lamina VIII, but only in the 12 to 15 segments caudal to the injections.

Rostral to the injections labeled neurons were also present in the dorsal gray and the medial part of the ventral gray throughout the spinal cord. In the dorsal gray the labeled neurons were located in lamina I, but in contrast to those caudal to the injections, they were situated mainly ipsilaterally. Moreover, labeled neurons were present bilaterally in the lateral reticulated parts of laminae V and VI. A limited number of labeled neurons was also present ipsilaterally in lamina IV and the medial parts of laminae V and VI, but they occurred only in 5 to 6 segments immediately rostral to the injections. The labeled neurons in the contralateral ventral gray rostral to the injections were concentrated in lamina VIII and the dorsally adjoining part of lamina VII (fig.15E) and in the same way as after pontobulbar injections shifted laterally in the upper cervical cord. In all cases, rostral to the injections, labeled neurons were also present ipsilaterally in lamina VIII and the dorsally adjoining part of lamina VII.

In the segments rostrally and caudally adjoining the injections a massive accumulation of labeled neurons was present in the intermediate zone. In the segments close to the injections the labeled neurons were situated in the lateral parts of laminae V to VII ipsilaterally and in the central and medial parts of lamina VII bilaterally. Further rostrally and caudally the labeled neurons in the former area rapidly diminished in number, but the group of labeled neurons in the latter area continued over somewhat longer distances. However, in this respect it should be noted that the two groups of labeled neurons in the intermediate zone are less easy to distinguish in the thoracic cord, where the area comparable to the lateral parts of laminae V to VII of the cervical and lumbar segments seems relatively small.

The upper thoracic injections (T1) in cases Sp1,2,3 produced roughly the same results, which are exemplified by those in case Sp1 (fig.13). In this case the injections were almost entirely unilateral, but in addition slightly involved the contralateral dorsal funiculus (fig.17B).

The labeled neurons were distributed according to the general pattern described above and those in the ipsilateral lamina IV and the medial parts of laminae V and VI rostral to the injections were present up to C4. The dense accumulation of labeled neurons in the lateral parts of laminae V to VII of the ipsilateral intermediate zone extended rostrally to C4 and caudally to midthoracic levels. On the other hand, the bilateral group of neurons in the central and medial parts of lamina VII extended throughout the cervical and thoracic cord.

The midthoracic injections (T6) in cases Sp4,5 gave virtually the same results, which are exemplified by those in case Sp4 (fig.16). In this case the needle tracks surrounded by HRP-reaction products were largely restricted to one side, but spared the most medial part of the ventral funiculus, while involving also the dorsal funiculus of the other side.

The labeled neurons were distributed according to the general pattern described above, but probably due to the massive bilateral injections in the dorsal funiculi, those in lamina IV and the medial parts of laminae V and VI were present bilaterally, both rostral and caudal to the injected segment. Rostral to the injections the labeled neurons in these laminae were present up to C5. The dense accumulation of labeled neurons in the lateral parts of the ipsilateral laminae V to VII of the intermediate zone extended rostrally throughout the thoracic segments and caudally into the upper lumbar segments. The bilateral group of labeled neurons in the central and medial parts of lamina VII extended rostrally into the upper cervical and caudally into the low lumbar cord.

The upper lumbar injections (L1) in cases Sp6,7,8 produced roughly the same results which are exemplified by the findings in case Sp6 (fig.16). In this case the needle penetrations surrounded by HRP-reaction products were restricted to the lateral and ventral funiculi on one side, but involved the dorsal funiculi on both sides.

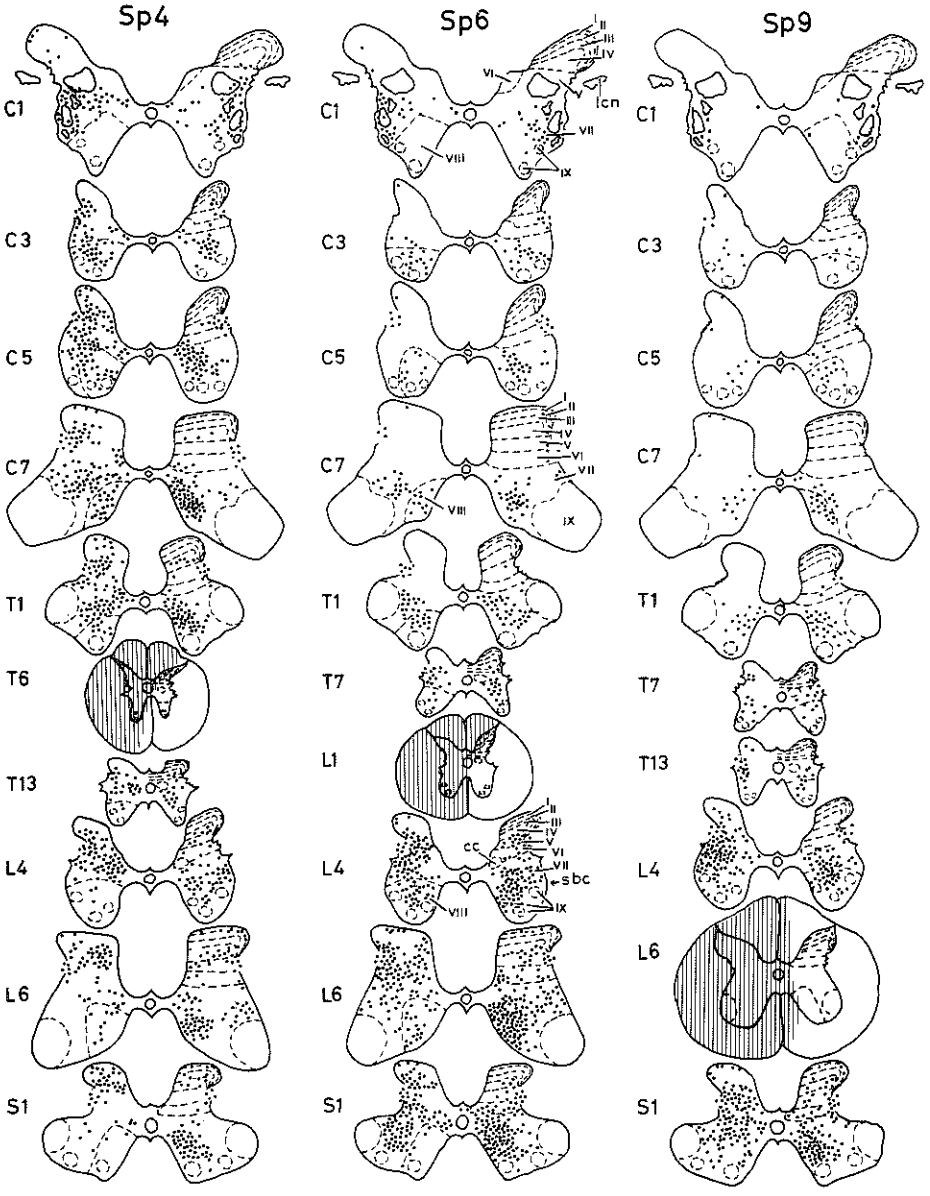
Sp4
Sp6
Sp9
C1
C3
C5
C7
T1
T6
T7
T13
L1
L4
L6
S1
I
II
III
IV
V
VI
VII
VIII
IX
lcn
cc
sbc

Fig.16. Semidiagrammatic representations of the spinal distributions of labeled neurons after injections in T6 (case Sp4), in L1 (case Sp6) and in L6 (case Sp9). Each level represents the composite of the plots of 12 sections. The shaded areas indicate the extents of the injections. Note the presence of labeled neurons in the medial part of the ventral gray throughout the spinal cord and the dense accumulation of labeled neurons in the intermediate zone in the segments adjoining the injections.

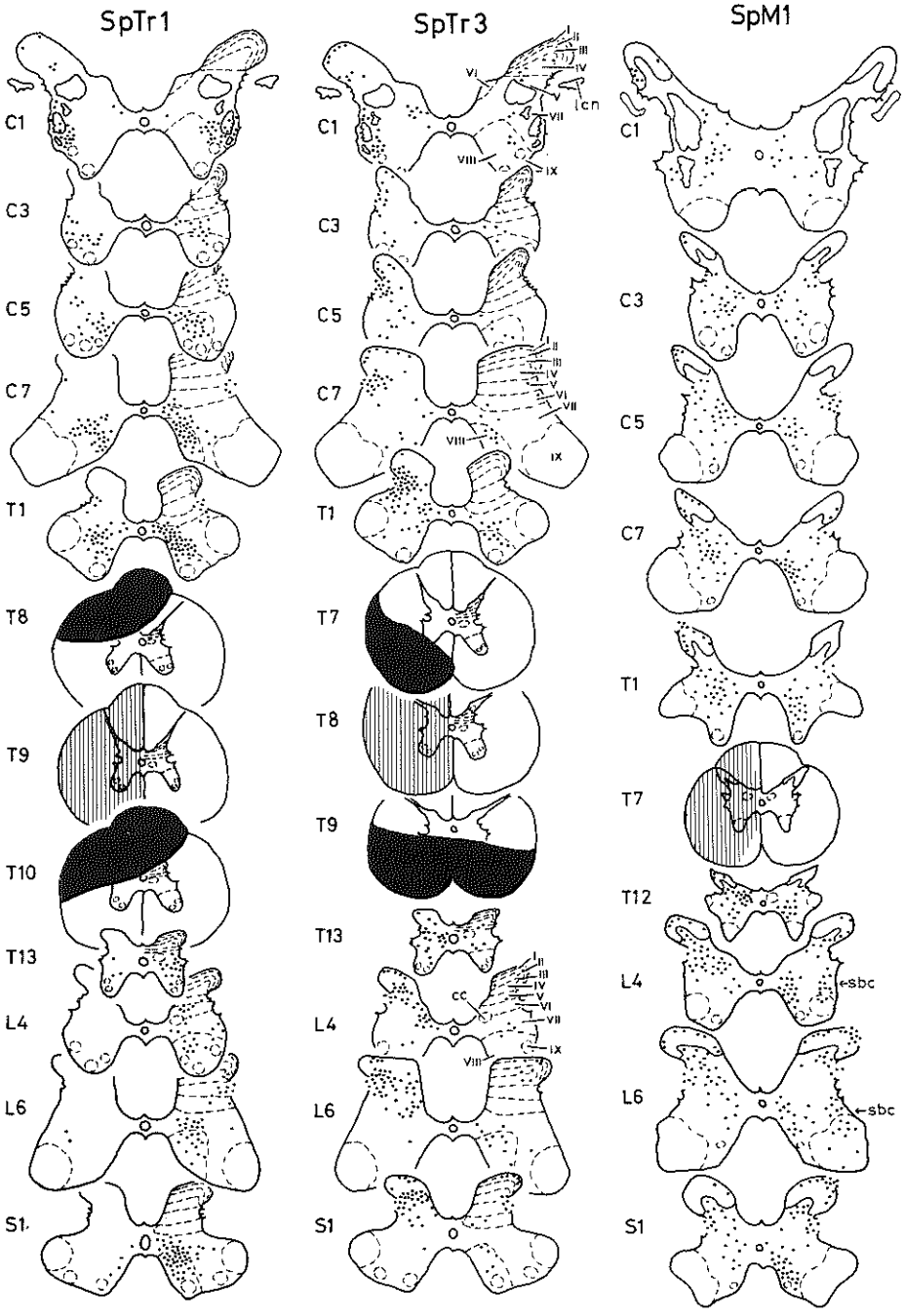
SpTr1
SpTr3
SpM1
C1
C3
C5
C7
T1
T7
T8
T9
T10
T12
T13
L4
L6
S1
I
II
III
IV
V
VI
VII
VIII
IX
I cn
cc
sbc

Fig.17. Semidiagrammatic representations of spinal distributions of labeled neurons after midthoracic injections preceded by funicular transections (case SpTr1,3) and after T7-injections in monkey (case SpM1). Each level represents the composite of the plots of 12 sections. The shaded areas indicate the extents of the injections and the black areas those of the funicular transections. Note that after dorsal and dorsolateral funicular transections (case SpTr1) labeled neurons occur predominantly in the ventral gray, while after ventral and ventrolateral funicular transections (case SpTr3) they occur predominantly in the dorsal gray.

additionally involved these same funiculi on the other side.

The distributions of the labeled neurons in these two cases (SpTr1,3) were roughly complementary. In case SpTr1, with the dorsal and dorsolateral funicular transections, the vast majority of the labeled neurons was located in the ventral gray, while in case SpTr3, with the ventral and ventrolateral funicular transections, it was situated in the dorsal gray, including the column of Clarke. Thus, in the first case (SpTr1) many labeled neurons were present in lamina VIII and the dorsally adjoining part of lamina VII. In the same way as in case Sp4 they were distributed caudal to the injections mainly contralaterally, but rostral to the injections bilaterally. Some labeled neurons were also present in the lateral reticulated parts of laminae V and VI, i.e. caudal to the injections contralaterally, but rostral to them to some extent bilaterally. In the second case (SpTr3) many labeled neurons were present in the dorsal gray, which were distributed in roughly the same way as after T6-injections without funicular transections. Thus, caudal to the injections they were present in lamina I bilaterally and in lamina IV and the medial parts of laminae V and VI mainly ipsilaterally, while rostral to the injections they were present in lamina I ipsilaterally. Further, some labeled neurons also occurred in the lateral reticulated parts of laminae V and VI throughout the spinal cord, mainly ipsilaterally. However, probably due to the fact that the transection rostral to the injections spared the dorsomedial part of the ventral funiculus, some labeled neurons were present in the contralateral lamina VIII of the upper thoracic and cervical cord. A few also occurred in these laminae in the lumbosacral cord.

In the two other cases (SpTr2,4) the transections of the dorsal and dorsolateral funiculi (SpTr2) and of the ventral and ventrolateral funiculi (SpTr4) slightly differed from those in SpTr1 and SpTr3 and the same was true for the distribution of the labeled neurons. In case SpTr2 both the rostral and the caudal transection was restricted to the dorsal and dorsolateral funiculus and in contrast to case SpTr2 did not involve the dorsal part of the ventrolateral funiculus. The labeled neurons were distributed in roughly the same way as in case SpTr1, except for the fact that also those in the lateral reticulated parts of laminae V and VI caudal to the injections tended to be distributed bi-

laterally. Further, many labeled spinal border cells occurred contralaterally, which were sparse in case SpTr1. In case SpTr4 the medial part of the ventral funiculus caudal to the injections was spared, in contrast to the situation in case SpTr3 described above, in which this part of the ventral funiculus was spared rostral to the injections. In case SpTr4 several labeled neurons were present in the contralateral lamina VIII especially caudal to the injections.

In all four cases a dense accumulation of labeled neurons was present in the intermediate zone of a limited number of segments rostral and caudal to the injections. In cases SpTr1 and SpTr2 with dorsal and dorsolateral funicular transections the neurons in the intermediate zone of the low cervical and upper lumbar segments were concentrated in the central and medial parts of lamina VII on both sides and in the lateral parts of the contralateral laminae V and VI of the lumbar cord (cf.cases Sp6 to 10). In contrast, in cases SpTr3 and SpTr4 with ventral and ventrolateral funicular transections the labeled neurons were concentrated in the lateral parts of the ipsilateral laminae V to VII at low cervical and upper lumbar levels.

Summary of the findings after midthoracic injections preceded by funicular transections. The findings in the above described cases show that after midthoracic injections preceded by transections of either the dorsal or the ventral half of the spinal white matter immediately rostral and caudal to the injected segment labeled neurons are distributed differently. Thus, after dorsal transections the bulk of the labeled neurons throughout the spinal cord is located in the medial part of the ventral gray, while after ventral transections it is located in the dorsal gray. The bulk of the labeled neurons in the intermediate zone of the segments adjoining the injections tends to be located in the central and medial parts of lamina VII after dorsal transections and in the lateral parts of laminae V to VII after ventral transections.

E. Injections at C1 and T7 and in the dorsal column nuclei in monkey.

In the preceding groups of HRP-experiments the locations of the cells of origin of ascending supraspinal and of propriospinal fibers were studied in cat. In the next group of experiments the cells of ori-

gin of such fibers were studied in a few monkeys in which HRP-injections were made at C1, in the dorsal column nuclei and at T7.

In the two rhesus monkeys with *HRP-injections at C1* (cases SSpM3,4) and in the one monkey with *injections at T7* (case SpM1) the needle penetrations surrounded by HRP-reaction products involved the funiculi on the injected side, and in case SSpM4 they also involved the medial parts of the dorsal and ventral funiculi of the other side. In case SpM1 with the T7-injections the needle penetrations were limited to one side, but spared the most medial parts of the dorsal and ventral funiculi on that side.

The distribution of labeled neurons in these cases resembled those observed in the cats with injections at corresponding levels (cases SSp4 to 6, Sp4,5). Thus, in all three monkeys labeled neurons were present caudal to the injections in the ipsilateral column of Clarke and the contralateral spinal border cell area. The distribution of the latter cells slightly differed from that in the cat, such that at L5 and L6 some of them in the monkeys were located within the lateral motoneuronal cell group and along its border (fig.2, 17,18) as described earlier (cf. ref.s 37,201). Further, throughout the spinal cord caudal to the injections labeled neurons occurred bilaterally in the dorsal gray and mainly contralaterally in the medial part of the ventral gray as well as scattered throughout the contralateral intermediate zone.

The labeled neurons in the dorsal gray of the monkeys were located in the same laminae as in the cat (fig.15D,18). They were present bilaterally in the marginal layer of the dorsal horn (lamina I) and in the lateral reticulated parts of its base (lateral reticulated parts of laminae V and VI). However, in contrast to the findings in the cats the labeled neurons in the n.proprius of the dorsal horn (lamina IV) and in the medial parts of its base (medial parts of laminae V and VI) in the monkey were present bilaterally. These neurons tended to be more numerous ipsilaterally at cervical levels, but contralaterally at lumbar levels. Moreover, at low lumbar levels the neurons in the medial part of the base of the dorsal horn were sparse. After T7-injections (case SpM1, fig.17) labeled neurons were also present in the dorsal gray throughout the spinal cord rostral to the injections, where they were

situated ipsilaterally in the marginal layer of the dorsal horn and bilaterally in the lateral reticulated part of its base. In the upper thoracic and low cervical cord some labeled neurons were also present ipsilaterally in the n.proprius of the dorsal horn and the medial part of its base.

In all three monkeys the labeled neurons in the contralateral ventral gray caudal to the injections were located in the area corresponding to lamina VIII and the dorsally adjoining part of lamina VII in cat (fig.18). However, ipsilaterally a limited number of labeled neurons also occurred in this area, but only in the 12 to 15 segments caudal to the injections. Labeled neurons were also present in the medial part of the ventral gray rostral to the injections, where they were distributed to some extent bilaterally.

In the three monkeys, as in the cats, a dense accumulation of labeled neurons occurred in the intermediate zone of a restricted portion of the spinal cord close to the injections. These neurons were located mainly ipsilaterally in the lateral part of the intermediate zone (lateral parts of laminae V to VII) and bilaterally in its central part (central and medial parts of lamina VII). After C1-injections the former group of neurons extended through the cervical cord, while the latter group continued into the upper thoracic segments. In the case with the T7-injections (SpM1, fig.17) the group of labeled neurons in the lateral part of the intermediate zone seemed to extent throughout the thoracic cord, but the group of neurons in the central parts of the intermediate zone, which was present on both sides extended into the upper cervical and low lumbar levels.

In the two monkeys with *dorsal column nuclear injections* (SSpM1, 2) the results were roughly the same and are exemplified by those in case SSpM2 (fig.14,15C). In this case the needle penetrations surrounded by HRP-reaction products were entirely limited to one side and involved the gracile and cuneate nuclei as well as the dorsal funiculus from the level of the obex caudally into upper C1. Similar to the findings in cat (cases SSp4,5) the vast majority of labeled neurons was located ipsilaterally in the n.proprius of the dorsal horn and in the medial part of its base throughout the spinal cord, but at low lumbar levels those in the medial part of the base of the dorsal horn were relatively

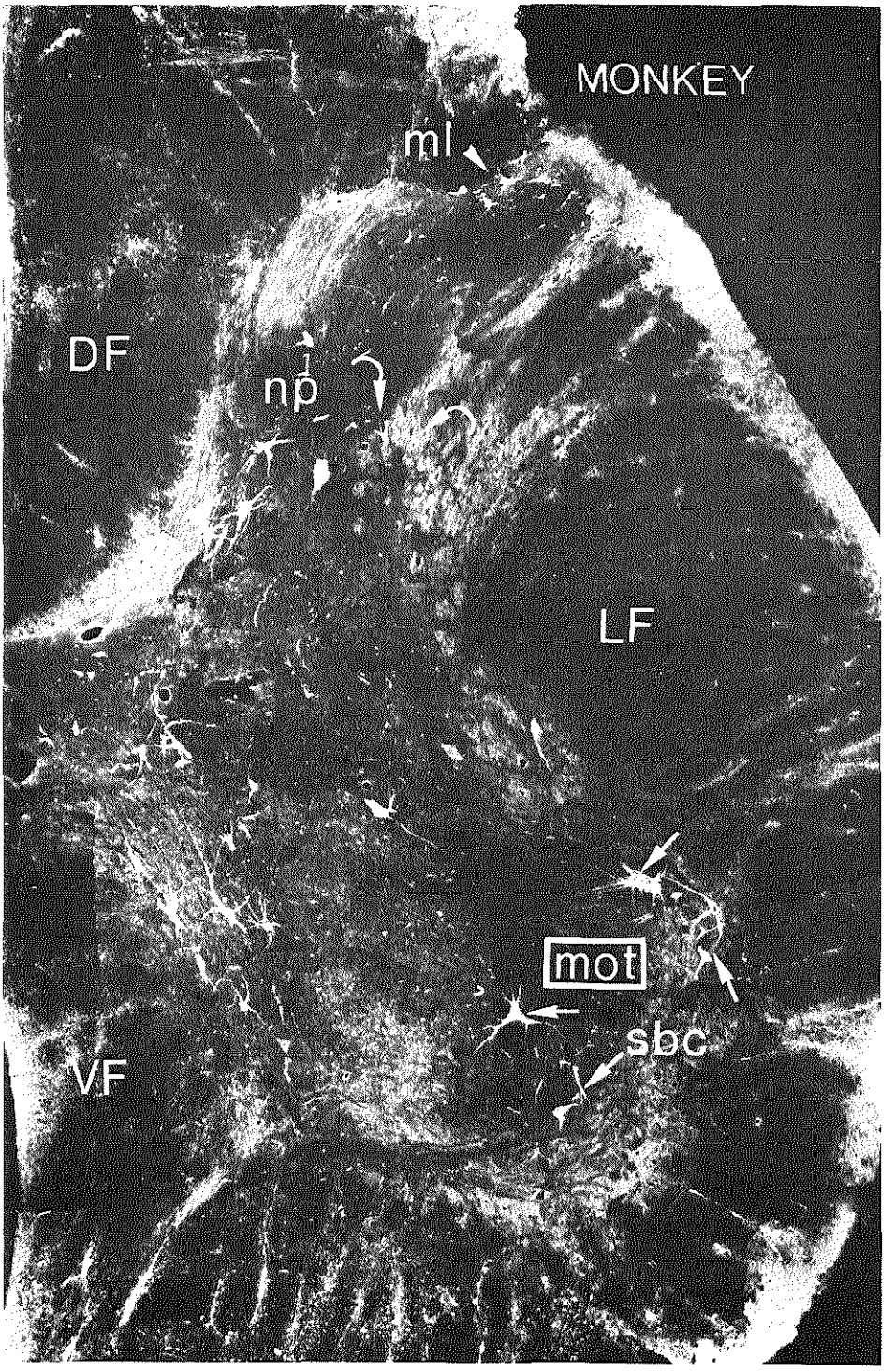
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Fig.18. Photomicrograph of labeled neurons of supraspinal fibers in monkey; L6 spinal gray after contralateral C1-injections (case SSpM3, magn. 47x). Arrows indicate labeled spinal border cells and curved arrows labeled neurons in spinal processus reticularis.

sparse. Few labeled neurons also occurred in the medial part of the ventral gray throughout the spinal cord, mainly contralaterally. Moreover, especially at L5, some labeled spinal border cells were found which, however, were located ipsilateral to the injections. Some such neurons were also observed in the ipsilateral ventral gray in the cats with dorsal column nuclear injections (SSp4,5), but in comparison to those in the monkey, labeled spinal border cells were much less numerous in cat. This may indicate that the fibers from these neurons travel through the funiculi interrupted at C2, but may also reflect an interspecies difference. However, the limited number of labeled spinal border cells in a third cat with dorsal column nuclear injections, which were not preceded by a funicular transection, seems to favor the latter explanation (cf. also ref.s. 178,179).

Summary of the findings in the monkey. The findings in the above described cases show that the distributions of labeled neurons after spinal and brainstem injections in monkey are roughly similar to those observed in cat. Thus, after C1-injections the bulk of the labeled neurons is located in the column of Clarke and the spinal border cell area and throughout the spinal cord in the dorsal gray and the medial part of the ventral gray. After unilateral dorsal column nuclear injections labeled neurons occur almost exclusively in the ipsilateral dorsal gray. After T7-injections the labeled neurons throughout the spinal cord caudal to the injections are distributed as after C1-injections, while throughout the spinal cord rostral to the injections the bulk of the labeled neurons is located in the dorsal gray and the medial part of the ventral gray. Similar to the findings in the cat a dense accumulation of labeled neurons occurs in the intermediate zone of the segments adjoining the injections.

F. Interrelationships between the labeled neurons in the upper cervical cord and the medulla oblongata.

As has been pointed out above (Chapter II.3) the spinal neuronal cell groups continue from the spinal cord into the lower brainstem. It is therefore meaningfull to describe briefly the distributions of labeled neurons in the lower brainstem of some of the cats with different spinal injections and to relate the distributions to those of

the labeled neurons in the spinal cord.

In all cats with spinal injections the population of labeled neurons in the spinal cord could be followed into the medulla oblongata as exemplified by the findings, after Th-injections (case Sp1,fig.19A). Thus, the labeled neurons at C1 in this case were located mainly in the ventral and ventrolateral parts of the ventral gray around the ventral components of the lateral tegmental bundles of Thomas [118] on both sides. Around the level of the pyramidal decussation, the population of labeled neurons in the ipsilateral ventral gray became largely restricted to a small group along the ventrolateral margin of the ventral gray, while that on the contralateral side largely disappeared. On this side instead many labeled neurons appeared in the retroambiguus nucleus. The group of labeled neurons in the ipsilateral ventral gray continued rostrally into the low medullary area dorsomedial to the lateral reticular nucleus, i.e. lateral to the ventral portion of the intramedullary hypoglossal root fibers. At the level of the obex this group of scattered neurons became accompanied medially by an increasing population of labeled neurons in the medial tegmental field and the raphe nucleus. At the level of the rostral pole of the inferior olive the population in the medial tegmentum extended ventrolaterally into the area C1 of the catecholaminergic neurons (Hökfelt et al. [70]). The labeling of contralateral retroambiguus neurons continued up to the level of the obex, while more rostrally some dispersed large labeled neurons were present in a corresponding area, i.e. between the spinal V complex and the facial nucleus. Some labeled neurons were also present within the confines of the former cell group. Around the obex labeled neurons also occurred in the contralateral solitary nucleus and in the lateral reticular formation, where they tended to be grouped in a line between the solitary and retroambiguus nuclei. In addition labeled neurons were present bilaterally in the medial and descending vestibular nuclei and mainly ipsilaterally in the lateral vestibular nucleus. In the caudal medulla oblongata labeled neurons were present in the ipsilateral dorsal column nuclei. After Th-injections they were concentrated in the gracile nucleus, where they were located in the base of the nucleus and in its rostral part (cf. fig.19C).

After midthoracic and lumbar injections labeled neurons occurred

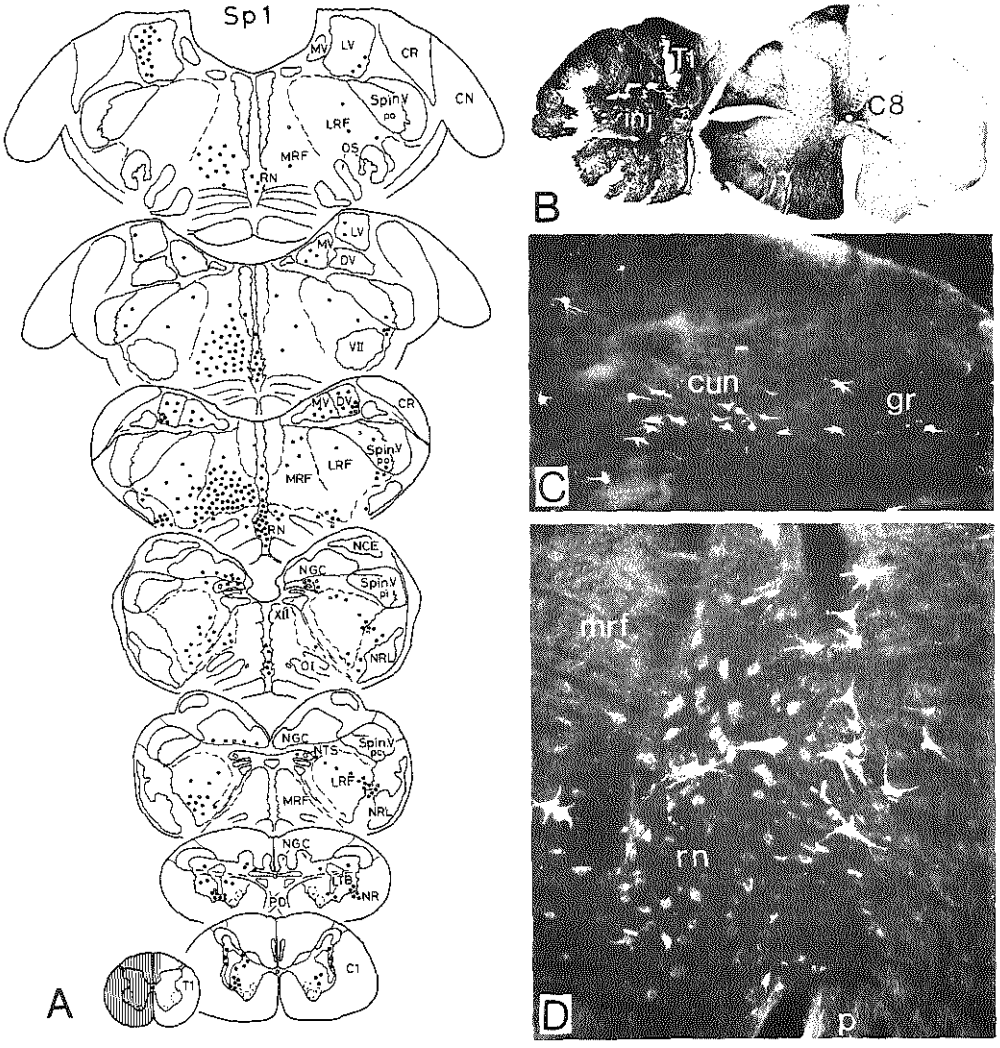
Sp1
MV
LV
CR
CN
Spin.V po
LRF
MRF
OS
RN
DV
VII
NCE
NGC
Spin.V pr
XII
OL
NRL
NTS
LTB
NR
PO
C1
T1
A
T1
inj
C8
B
cun
gr
C
mrf
rn
p
D

Fig.19. A) Semidiagrammatic representation of the distribution of labeled neurons in the medulla oblongata and the spinobulbar junction in cat after unilateral T1-injections (case Sp1). Note that the population of labeled neurons in the upper cervical ventral gray continues into the medulla oblongata in the area ventrolateral to the hypoglossal root fibers. Note also the presence of labeled neurons in the ipsilaterally gracile and cuneate nuclei (NGC).
B) Photomicrographs of injection site at T1 (left) and of caudally adjoining segment (C8, right) in cat (Sp1, magn. 5x). Note the accumulation of HRP reaction products in the white and gray matter at T1 and the brown stained fibers in the funiculi at C8.
C) Photomicrograph of labeled neurons in the bases of the gracile and cuneate nuclei of the cat after ipsilateral T6-injections (case Sp4, magn. 40x).
D) Photomicrograph of labeled neurons in raphe nucleus of cat after L1-injections (case Sp6, magn. 75x).

in most of the above brainstem cell groups (fig.s 19C,D), but none were present in the spinal V complex. Further, after lumbar injections the labeled neurons in the contralateral retroambiguus nucleus tended to become concentrated in its caudal part.

Upper cervical injections (C1,C4) resulted in the additional labeling of neurons in some other cell groups. Thus, caudal to the obex many labeled neurons were present in the medial part of the lateral tegmental field bilaterally and in its lateral part mainly ipsilaterally. These lateral tegmental neurons were especially numerous after C1-injections, but some were also present after C4-injections. After C1-injections labeled neurons also occurred in the spinal V complex, where they were located in the pars caudalis, including the marginal layer, mainly ipsilaterally and in the pars interpolaris and the pars oralis bilaterally.

After the midthoracic injections combined with dorsal and dorsolateral funicular transections (cases SpTr1,2) virtually no labeled neurons occurred in the dorsal column nuclei. On the other hand, after complete ventral and ventrolateral funicular transections (case SpTr4) virtually no labeled neurons occurred in the medial tegmental field, the raphe nuclei and the caudal medullary ventral gray and only very few were present in the vestibular, solitary and retroambiguus nuclei.

Summary of the findings in the brainstem. The findings in the above described cases show that after thoracic and lumbar injections the bulk of the labeled neurons in the medulla oblongata is located in the medial tegmental field, in the raphe nuclei and in the vestibular nuclei as well as in the retroambiguus and solitary nuclei. Some labeled neurons are also present in the dorsal column nuclei. After upper cervical injections labeled neurons additionally occur in the lateral tegmental field of the medulla oblongata, i.e. bilaterally in its medial part and mainly ipsilaterally in its lateral part.

Conclusion. In this chapter a group of experiments has been described in which the HRP retrograde axonal transport technique has been applied in order to determine the location of the cells of origin of fibers ascending to supraspinal levels, of ascending and descending proprio-

spinal fibers, and of descending fibers from the medulla oblongata. The findings in these cases show that in both cat and monkey long fibers which ascend to supraspinal levels arise from the column of Clarke and the spinal border cell area as well as from the dorsal gray and the medial part of the ventral gray. Some of the neurons in the dorsal gray appeared to project to the dorsal column nuclei, which nuclei were found to distribute fibers back to the spinal cord. Neurons in the medial part of the ventral gray appeared to give rise to fibers which ascend to the lower medulla oblongata as well as to long propriospinal fibers. In contrast, neurons in the intermediate zone were found to give rise to relatively short propriospinal fibers, of which those from the central part of the intermediate zone are distributed bilaterally and those from its lateral part mainly ipsilaterally. Similarly, in the medulla oblongata, neurons in the medial tegmental field were found to give rise to long descending bulbospinal fibers, while those in the lateral tegmental field appeared to give rise to mainly short bulbospinal fibers to the upper cervical cord.

The findings after transections of the different funiculi above and below the injected segment indicate that the fibers from neurons in the dorsal gray and in the lateral part of the intermediate zone as well as the descending fibers from the dorsal column nuclei travel preferentially through the dorsal half of the white matter, while those from neurons in the ventral gray and the central part of the intermediate zone travel preferentially through the ventral half of the white matter.

made in the way described above. In one group of cats (MiA) the injections involved both the dorsal and the ventral part of the lateral motoneuronal cell group at C6 (2 cases),C7 (1 case) and C8 (4 cases). In a second group of cats (MiB) they involved mainly the dorsal part of the lateral motoneuronal cell group at C6 (1 case), and C8 (4 cases) and in a third group of cats (MiC) they involved mainly its ventral part at C6 (2 cases),C7 (1 case) and C8 (4 cases). After a survival of two days the animals were perfused with a 0.5% paraformaldehyde-2.5% glutaraldehyde mixture and the segments C1 to T2 and T4 were processed as described above (chapter III.3). In all cases the injection site plus the micropipette track was studied and the location of retrogradely labeled neurons was charted in all sections of the segments C3 to T2 and T4 and in some cases also of the segments C1 and C2. The charts of each segment were combined to one.

The HRP-reaction products were generally restricted to the lateral motoneuronal cell group, but in some cases they also involved the adjoining part of the ventral or lateral funiculus. In the injected area an accumulation of HRP reaction products occurred, while large evenly brown stained neurons were present at the level of the micropipette penetration and 1 to 2 mm rostral and caudal to it. From the injected part of the motoneuronal area brown stained fibers of large caliber entered the ventral root bundles, while brown stained fibers of small caliber passed radially into the intermediate zone. In cases in which the injections additionally involved the funiculi such thin brown stained fibers were also distributed from the injected funiculi into the lateral motoneuronal cell group. In these cases the fibers from the ventral funiculus were distributed especially to the ventral part of the lateral motoneuronal cell group while those from the dorsolateral funiculus were especially distributed to its dorsal part, in accordance with the anterograde degeneration findings [207].

The distribution of the retrogradely labeled neurons was in all cases largely restricted to the brachial cord (C3 to T2), where they were situated almost exclusively in the intermediate zone (fig.21). Further, the distribution of retrogradely labeled neurons seemed to be largely independent of the funicular trajectory of the pipette, traversing either the ventral or the dorsolateral funiculus. This is based on the

finding that in the cases in which HRP was deposited in roughly the same portion of the ventral horn and the immediately adjoining funiculi the retrogradely labeled neurons displayed a similar distribution, no matter whether the pipette had passed through the ventral or through the dorsolateral funiculus.

In the 7 cases of *group MiA* HRP was deposited in both the dorsal and the ventral part of the lateral motoneuronal cell group and in one of these cases some HRP was also deposited in the ventrolateral funiculus. The bulk of the labeled neurons in these cases occurred ipsilaterally in the lateral parts of laminae V and VI, excluding their lateral reticulated parts as well as in lamina VII, while some labeled neurons were present contralaterally in lamina VIII. In the cases of *groups MiB and MiC* in which the injections involved mainly the dorsal and the ventral parts of the lateral motoneuronal cell groups respectively, different distributions occurred. In the 5 cases of *group MiB* HRP was deposited in the dorsal part of the lateral motoneuronal cell group and in at least two of these cases some HRP reaction products were also present in the dorsolateral funiculus. In these cases the bulk of the labeled neurons occurred ipsilaterally in the lateral parts of laminae V to VII and some were present in the central and medial parts of lamina VII. In the 7 cases of *group MiC*, on the other hand, HRP was deposited in the ventral part of the lateral motoneuronal cell group and in four of them some HRP reaction products were additionally present in the adjoining part of the ventral funiculus. In these cases the bulk of the labeled neurons was present in the central and medial parts of the ipsilateral lamina VII and some labeled neurons were also present in the contralateral lamina VIII.

These findings suggest that the fibers which are distributed to the low cervical lateral motoneuronal cell group are derived especially from neurons in the brachial intermediate zone. The finding that injections of HRP in the different parts of the lateral motoneuronal cell group result in the labeling of neurons in different parts of the intermediate zone suggests that these various cell populations distribute their fibers to different parts of the lateral motoneuronal cell group. However, the labeling of neurons in the intermediate zone in several cases may also have occurred due to uptake and transport of HRP from

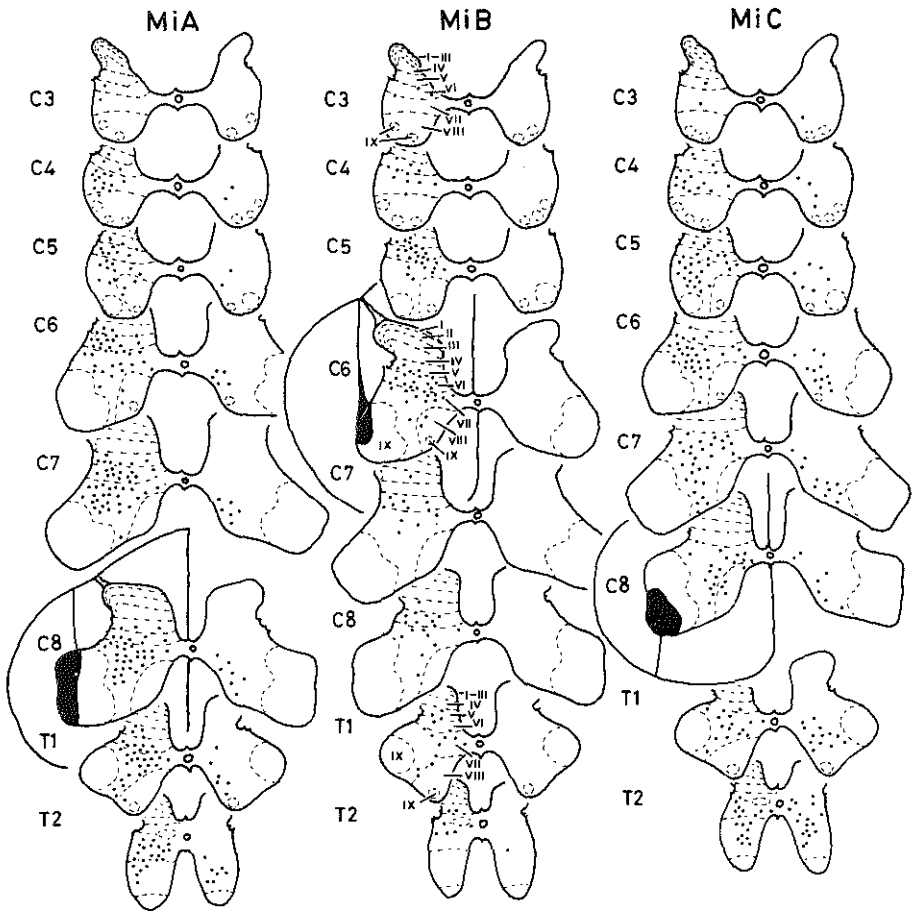

Fig.21. Semidiagrammatic representations of the distributions of the labeled neurons in the brachial cord after small HRP-injections in the dorsal and ventral part of the lateral motoneuronal cell group at C8 (MiA), in its dorsal part at C6 (MiB) and in its ventral part at C8 (MiC). Each level represents the composite of the plots of all sections of the respective segment. The black areas indicate the injection sites and the micropipette tracks. Note that the majority of the labeled neurons is located in the intermediate zone of the segments adjoining the injection. Note also the differences in the distributions of labeled neurons after injections in the dorsal and ventral parts of the lateral motoneuronal cell group.

the deep parts of the adjoining funiculi, which contained in these cases some HRP reaction products. This is an important consideration since in one case with a microinjection of HRP in the ventral funiculus labeled neurons were also present in the intermediate zone, mainly in its ventral part. However, the bulk of the fibers in the deep parts of the ventral and ventrolateral funiculi which surround the ventral horn is distributed to the neighbouring groups of motoneurons [180,207]. As a consequence the bulk of the fibers in the deep parts of the funiculi which in some cases contained HRP reaction products tend to be destined for the motoneurons in the injected part of the lateral motoneuronal cell group. In view of this, the present findings strongly suggest that the cells in the dorsolateral and the ventromedial parts of the intermediate zone distribute their fibers preferentially to the dorsolateral and ventromedial parts of the lateral motoneuronal cell group, respectively.

Chapter V: *Discussion*

1. techniques
2. ascending supraspinal fibers
3. long and short propriospinal fibers
4. short propriospinal fibers to different motoneuronal cell groups
   a. in the lumbosacral cord
   b. in the brachial cord
5. medullospinal fibers

DISCUSSION.

From the present results, obtained both by means of the HRP retrograde axonal transport technique and by means of the retrograde cell degeneration technique, the location of the cells of origin of the following groups of fibers can be approximated.

- Ascending supraspinal fibers (HRP-injections at C1 and at supraspinal levels).

- Long and short propriospinal fibers (HRP-injections at different spinal levels).

- Short propriospinal fibers to different motoneuronal cell groups

a) in the lumbosacral cord (present retrograde degeneration findings combined with previous anterograde degeneration findings [180]).

b) in the brachial cord (micro-injections of HRP).

- Medullospinal fibers (HRP-injections at different spinal levels).

Before discussing the distribution of these various groups of neurons, however, some aspects of the different techniques should be considered.

1. Techniques.

In applying *the retrograde degeneration technique* an attempt was made to minimize the limitations of this technique (cf.Chapter III.1) in the following way. In the first place, in order to obtain a maximal reaction, [17,18,119] kittens of 5 to 6 weeks of age have been used throughout the experiments. Further, only cases without definite cell loss or marked gliosis have been studied in detail. Finally, only neurons which displayed classic retrograde changes or pronounced lysis of Nissl bodies have been taken into account, which presumably excludes neurons showing atrophic changes due to interruption of their afferent fibers.[39] It may therefore be assumed that the chromatolytic neurons which were studied in the present cases represent cells of origin of fibers which travel in the lumbosacral ventral and lateral funiculi.

Horseradish peroxidase may be transported retrogradely after uptake by axonterminals[28,95,96,97,107,111,112] or by damaged axons.[48,96,108] In the present experiments (excluding those described in Chapter IV.3) an attempt was made to label neurons preferentially by way of HRP uptake through damaged axons. The large unilateral HRP-injections

which were for this purpose made into both the white and the gray matter resulted in the labeling of many neurons throughout the spinal cord and medulla oblongata, which neurons consistently showed different ipsilateral and contralateral distributions. The labeled neurons are therefore regarded to give rise to fibers which either pass through or terminate in the injected area. This makes the results directly comparable to those obtained with the retrograde degeneration technique. Further, the fact that injections combined with more or less complementary funicular transections (group SpTr) resulted in more or less complementary distributions of labeled neurons was taken as an indication that no HRP-transport occurred through the transected parts of the funiculi.

The *micro-injections of HRP* in the motoneuronal area (Chapter IV.3) resulted in the labeling of a limited number of neurons relatively close to the injections. These neurons probably give rise to fibers which terminate in the motoneuronal area and the results are therefore comparable to the combined anterograde and retrograde degeneration findings (cf. General introduction).

2. *Ascending supraspinal fibers.*

Cells of origin. The distribution of labeled neurons after HRP-injections at C1 indicates that in the cat fibers ascending to supraspinal levels are derived mainly from neurons in Clarke's column, in the spinal border cell area, in the dorsal gray and in the medial part of the ventral gray as well as from neurons dispersed in the intermediate zone (fig.22). The findings after C1-injections in the monkey suggest that a similar arrangement exists in this animal.

The distribution of labeled neurons after C1-injections also indicates that the fibers from the dorsal gray which are distributed to supraspinal levels in both cat and monkey arise mainly from neurons in laminae I and IV, in the medial parts of laminae V and VI as well as in the lateral reticulated parts of these two laminae. The fibers from the ventral gray which are distributed to supraspinal levels appeared in both species to come mainly from neurons in lamina VIII and the dorsally adjoining part of lamina VII. Further, in both species the fibers from the column of Clarke appeared to ascend mainly ipsilaterally, those from

lamina I and the lateral reticulated parts of laminae V and VI bilaterally and those from lamina VIII and the dorsally adjoining part of lamina VII as well as from the spinal border cells mainly contralaterally. However, the fibers from lamina IV and the medial parts of laminae V and VI were found to behave differently in the two species, such that in cat they ascend predominantly ipsilaterally, but in monkey bilaterally.

As pointed out earlier (Chapter III.1) chromatolytic changes are very difficult to detect after axotomy at large distance from the cell body.[40,119] Correspondingly, after hemisection at upper cervical levels virtually no chromatolytic neurons were present in the lumbosacral segments, but after hemisections at T6,T7-T8,T9 and L1 they did occur. The distributions of the chromatolytic neurons in these cases are in keeping with the distribution of HRP labeled neurons after injections at C1, except for the fact that none of the neurons in lamina I of the dorsal gray displayed pronounced chromatolytic changes. Yet, after hemisection at L1 in a few neurons in this lamina on both sides some lysis of Nissl bodies seemed to have occurred.

Terminal distribution. The present data provide some information concerning the differences in the distribution of the supraspinal fibers from the various groups of spinal neurons. Thus, the distribution of the labeled neurons after pontobulbar injections as compared to those after C1-injections shows that many neurons in Clarke's column and in the spinal border cell area as well as neurons in lamina I and in the lateral reticulated parts of laminae V and VI distribute their supraspinal fibers to the upper medulla oblongata or beyond. Neurons in lamina VIII were also found to distribute some supraspinal fibers to these levels, but appeared to distribute the bulk of their supraspinal fibers to the lower medulla oblongata. The absence of labeled neurons in lamina IV and the medial parts of laminae V and VI after pontobulbar injections versus their presence after C1-injections indicates that the long ascending fibers from these neurons are mainly distributed to either the lower medulla oblongata or to C1 or both.

In respect to *the long ascending fibers from Clarke's column and the spinal border cell area* the present findings are in keeping with earlier anatomical [37,67,132,201] and physiological [76,81,132] findings

which demonstrated that these neurons distribute fibers to the cerebellum, the former ipsilaterally and the latter bilaterally (cf.Chapter I.2).

The long ascending fibers from neurons in lamina IV in both cat and monkey presumably project in part to the ipsilateral lateral cervical nucleus [24,26,27,41,66] (cf.Chapter I.2). According to earlier anatomical [3,216] and physiological [4,217] findings some lamina IV neurons in monkey, but not in cat, also contribute fibers to the contralateral spinothalamic tract (cf.Chapter I.2). This may explain the presence of labeled lamina IV neurons in the contralateral dorsal horn after unilateral C1-injections in monkey, which were absent after unilateral C1-injections in cat.

In view of the present findings (cases SSp4,5 and SSpM1,2) many neurons in lamina IV and the medial parts of laminae V and VI in both cat and monkey distribute fibers to the ipsilateral dorsal column nuclei, (cf.ref.'s 178,179) at least in part by way of the dorsal funiculus (cases SSp4,5).[179] A comparison of the distributions of labeled neurons in cases SSp4 and SSp5 suggests that neurons in the lumbosacral dorsal gray project mainly to the ipsilateral gracile nucleus, while those in the cervical dorsal gray project mainly to the ipsilateral cuneate nucleus. The fibers from these neurons in all likelihood are identical to the non-primary afferents from the lumbosacral and cervical cord which ascend by way of the dorsal and dorsolateral funiculi to the ipsilateral gracile and cuneate nuclei, respectively.[5,46,59,157 176,177,182]

In view of the existence of a pronounced projection from neurons in lamina IV and the medial parts of laminae V and VI to the dorsal column nuclei it is of interest to note that according to the present findings these nuclei also contain neurons which distribute fibers back to the spinal cord '). These neurons appeared to be located especially

') During the revision of this manuscript a paper was published by H. Burton and D. Loewy (J.Comp.Neurol. 173,1977,pp.773-792), in which the distributions of labeled neurons in the dorsal column nuclei after spinal HRP-injections were reported. The findings of these authors are essentially similar to those of the present study.

in the bases of the dorsal column nuclei and in their rostral parts, which areas also receive the bulk of the ascending non-primary afferents, mentioned above, as well as fibers from the contralateral sensorimotor cortex (cf.Chapter I.2).[102,109] The descending fibers from the dorsal column nuclei appeared to travel through the same area as the ascending spinal projections, i.e. through either the dorsal or the dorsolateral funiculi or both (cases of group SpTr;cf.ref.45). Moreover, in the same way as the ascending projections, the descending projections were found to be topically organized, since the present findings show that the cells in the area of the gracile nucleus project to the lumbosacral cord, while those in the cuneate nucleus project to the cervical and upper thoracic cord.

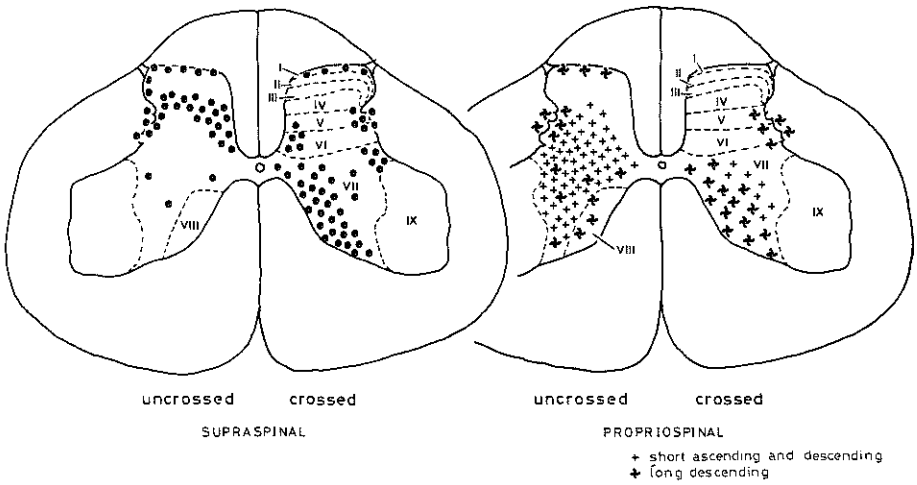

Fig.22. Diagrams summarizing the location of neurons of ascending supraspinal fibers and of long descending (+) and short ascending and descending (++) propriospinal fibers. Note that the neurons in lamina VIII and the dorsally adjoining part of lamina VII as well as those in the lateral reticulated parts of laminae V and VI and in lamina I give rise to both supraspinal and long descending propriospinal fibers. Neurons in these areas may also give rise to long ascending propriospinal fibers (see text).

The conclusion that *long ascending fibers from neurons in lamina I, in the lateral reticulated parts of laminae V and VI and in lamina VIII* are distributed to the upper medulla oblongata or beyond is in keeping with the anatomical[3,216] and physiological[4,49,98,117,217,218] findings that in both cat and monkey neurons in these areas contribute fibers to the spinothalamic tract, mainly contralaterally (cf.Chapter I.2).

The bulk of the supraspinal fibers from neurons in lamina VIII, however, is presumably distributed to the medial bulbar reticular formation (cases SSp2,3);[4,54,55,116] while at least some of the contralaterally distributed supraspinal fibers from neurons in the lateral reticulated parts of laminae V and VI pass through or terminate in the medial medullary tegmentum (cases SSp2,3).[54]

The funicular trajectories of the supraspinal fibers arising from the various groups of spinal neurons appeared to be different. Thus, according to the HRP-findings in group SpTr the ipsilaterally ascending fibers from the column of Clarke, from lamina IV and the medial parts of laminae V and VI as well from the lateral reticulated parts of laminae V and VI travel mainly through the dorsal half of the white matter. In contrast, the contralaterally ascending fibers from the spinal border cells, from lamina VIII and the dorsally adjoining part of lamina VII and some of those from the lateral reticulated parts of laminae V and VI travel through the ventral half of the white matter. This arrangement is reminiscent of the physiological findings of Oscarsson,[159] who demonstrated that the ventral and ventrolateral funiculi contain mainly contralaterally ascending spinal fibers, while the dorsolateral funiculus contains mainly ipsilaterally ascending ones.

Summary. The various anatomical and physiological data discussed above thus indicate that neurons in lamina I, in the lateral reticulated parts of laminae V and VI and in lamina VIII establish direct connections with the contralateral thalamus, while in the monkey neurons in lamina IV also establish such direct thalamic connections. In cat, on the other hand, many neurons in lamina IV appeared to project indirectly to the contralateral thalamus, i.e. by way of the ipsilateral lateral cervical nucleus and the crossed medial lemniscus,

which projection reportedly is less pronounced in higher animals, including monkey.[89,157,219] Moreover, in both cat and monkey neurons in lamina IV appeared to give rise to ascending fibers to the dorsal column nuclei, which nuclei distribute fibers to the contralateral thalamus as well as back to the spinal cord. Finally, at least in cat, neurons in lamina VIII were found to distribute fibers to the medial medullary reticular formation, which area is known to give rise to ascending fibers to the thalamus[20,152] as well as to descending fibers to the spinal cord.[20,108,214]

3. Neurons of long and short propriospinal fibers.

Cells of origin. The distributions of labeled neurons in the spinal gray after thoracic and lumbar HRP-injections (group Sp) as compared to those after C1-injections indicate that many neurons in laminae V to VIII and some neurons in lamina I give rise to propriospinal fibers (fig.22). A similar organization appeared to exist in the monkey (case SpM1, cf. ref. 30). The findings also indicate that neurons in the lateral parts of laminae V and VI and in lamina VII distribute their fibers only over relatively short distances, while those in lamina VIII and the dorsally adjoining part of lamina VII distribute them throughout the length of the spinal cord. This is in keeping with the distributions of chromatolytic neurons in the lumbosacral cord after hemisections at upper lumbar and thoracic levels (group H) and after partial transections of the lumbosacral ventral and lateral funiculi (groups A to D).

Long propriospinal fibers. Neurons in lamina VIII and the dorsally adjoining part of lamina VII apparently form the main source of the longest *descending* propriospinal fibers which travel throughout the length of the spinal cord (cases Sp9,10). Many of these fibers are distributed contralaterally, but some are also distributed ipsilaterally. A very limited number of long descending propriospinal fibers appeared to come also from neurons in lamina I and in the lateral reticulated parts of laminae V and VI. The fibers from the former neurons are distributed ipsilaterally, but those from the latter bilaterally. Neurons in all the above laminae presumably also give rise to long *ascending* propriospinal fibers. This, however, could not be demonstrated

convincingly, since their cells of origin could not be distinguished from those of ascending supraspinal fibers. Yet, it could be demonstrated that from lamina VIII and the dorsally adjoining part of lamina VII ipsilaterally ascending propriospinal fibers arise, which ascend over a distance of 12 to 15 segments (cases Sp1 to 5).

Short propriospinal fibers. Neurons in the lateral parts of laminae V to VII, excluding those in the lateral reticulated parts of laminae V and VI, appeared to give rise mainly to short propriospinal fibers which generally do not extend further rostrally and caudally than six to eight segments. These fibers appeared to be distributed mainly ipsilaterally, but in the lumbosacral cord some are also distributed contralaterally (cases Sp6 to 10, cases of groups A and B with small funicular lesions).[43] Some short propriospinal fibers appeared to be derived also from neurons in lamina IV, but for the same reason as above, only the descending ones could be demonstrated convincingly.

Propriospinal fibers of intermediate length. Neurons in the central and medial parts of lamina VII appeared to give rise to propriospinal fibers of intermediate length, the longest components of which travel rostrally and caudally over a distance of 12 to 15 segments and are distributed to some extent bilaterally. However, the trajectory of these fibers seems to be somewhat longer when they pass through the thoracic cord, since after L1-injections (cases Sp6 to 8) some neurons were also labeled in the medial part of lamina VII in the low cervical cord.

The funicular trajectories of the propriospinal fibers from the various groups of spinal neurons appeared to be different. Thus, the findings in the cases of group SpTr indicate that the long propriospinal fibers from neurons in lamina VIII and the dorsally adjoining part of lamina VII travel mainly through the area comprising the ventral funiculus and the ventral part of the lateral funiculus, which also harbour some of the contralaterally distributed fibers from the lateral parts of the lumbosacral laminae V and VI (cf. also cases of groups A and B). The findings in group SpTr also suggest that the long propriospinal fibers from neurons in the lateral reticulated parts of laminae V and VI travel preferentially through the intermediate portion of the lateral funiculus, in which area the contralaterally

distributed fibers tend to follow a more ventrally located trajectory than the ipsilaterally distributed ones. The findings in group SpTr and in groups A to D (small transections of the ventral and lateral lumbosacral funiculi) further indicate that the short ipsilaterally distributed propriospinal fibers from the lateral parts of laminae V to VII travel preferentially through the dorsal half of the white matter, presumably mainly through the dorsal half of the lateral funiculus.[34,43,133,136,137,191] Short propriospinal fibers from the central and medial parts of lamina VII appeared to travel preferentially through the intermediate and ventral parts of the lateral funiculus and the lateral part of the ventral funiculus, while the medial part of the ventral funiculus presumably harbours short propriospinal fibers from the contralateral lamina VIII. These conclusions are in general in agreement with previous observations concerning the preferential distribution of axons from cells in different portions of the intermediate zone.[34,43,91,133,136,137,184,191,207,208]

The terminal distributions of the different groups of propriospinal fibers may be inferred from a comparison of the present data with earlier Golgi[34,133,136,137,184,191] and anterograde degeneration findings.[58,138,139,180,207] Such a comparison strongly suggests that the long propriospinal fibers from neurons in lamina VIII and the dorsally adjoining part of lamina VII are distributed bilaterally to the medial parts of the ventral gray throughout the spinal cord.[58,139] Short propriospinal fibers from laminae V to VII and presumably also from lamina VIII appeared to be distributed to the intermediate zone and the motoneuronal cell groups.[138,139,180,207] The distribution to the motoneuronal cell groups is largely restricted to the immediately adjoining segments, while that to the intermediate zone extends over somewhat longer distances.[138,139,141,180,207]

A comparison with physiological findings. The present anatomical conclusions in general are supported by physiological findings. These findings indicate that in the enlargements the monosynaptic input to the motoneurons is derived primarily from *short propriospinal fibers*, which originate in the intermediate zone[7,11,77,78,82,83,125] of 3 to 4 adjoining segments.[93,123,221] Further, physiological findings indicate that the *long descending propriospinal fibers* from the cervical

to the lumbar cord, which are activated from forelimb nerves, establish connections mainly with neurons in the medial part of the ventral gray,[83,125] which is in keeping with the inferred terminal distribution of these fibers. Correspondingly, the long propriospinal fibers influence lumbosacral motoneurons primarily polysynaptically[6,83,84,125,126,193] and their monosynaptic input is weak.[83] According to physiological studies the long descending propriospinal fibers from the cervical cord influence especially ipsilateral lumbosacral motoneurons,[125,193] (cf. also 6,83,84,126) although some contralateral influence is also present.[193] This primarily ipsilateral influence may be exerted by way of long descending propriospinal fibers from neurons in the medial part of the ipsilateral cervical ventral gray (cases Sp6 to 10), but may also be brought about through double-crossing by way of neurons in the medial part of the contralateral ventral gray.[125] Physiological findings further indicate that the long descending propriospinal fibers which establish monosynaptic connections with lumbosacral motoneurons travel preferentially through the area comprising the ventral part of the lateral funiculus and the lateral part of the ventral funiculus[83] (cf. also 221). A comparison with the present findings therefore suggests that at least some of these fibers arise from neurons in the central and medial parts of the low cervical lamina VII, which neurons were found to give rise to fibers which descend to the lumbar cord (cases Sp 6 to 8) by way of the area comprising the ventral funiculus and the ventral part of the lateral funiculus (cf. cases SpTr3,4). The *long ascending propriospinal fibers* from the lumbar to the cervical cord probably behave in much the same fashion and influence the cervical motoneurons polysynaptically.[57,135,145] However, some lumbar and low thoracic fibers which travel through the ventral and lateral funiculi[145] also establish direct connections with cervical motoneurons of the pectoral muscles.[58,139,145] The present findings suggest that these fibers are derived primarily from neurons in the ipsilateral and contralateral lamina VIII and adjoining parts of lamina VII (cases Sp1 to 3).

4. Propriospinal fibers to the motoneurons.

a. In the lumbosacral cord. The preferential motoneuronal pro-

jections from neurons in different parts of the intermediate zone may be approximated by combining the present retrograde degeneration findings (Chapter IV.I) with earlier anterograde degeneration findings in the lumbosacral cord [180] (fig.23). The latter findings indicate that fibers in the medial part of the ventral funiculus are distributed preferentially to motoneurons which innervate axial muscles, while the fibers in the lateral part of the ventral funiculus are distributed preferentially to motoneurons which innervate girdle and thigh muscles. The fibers in the dorsal part of the lateral funiculus are distributed mainly to the motoneurons of the long plantar flexors of the toes and small muscles of the foot, while the fibers to the dorsiflexors of the ankle and of the toes are located more ventrally in the lateral funi-

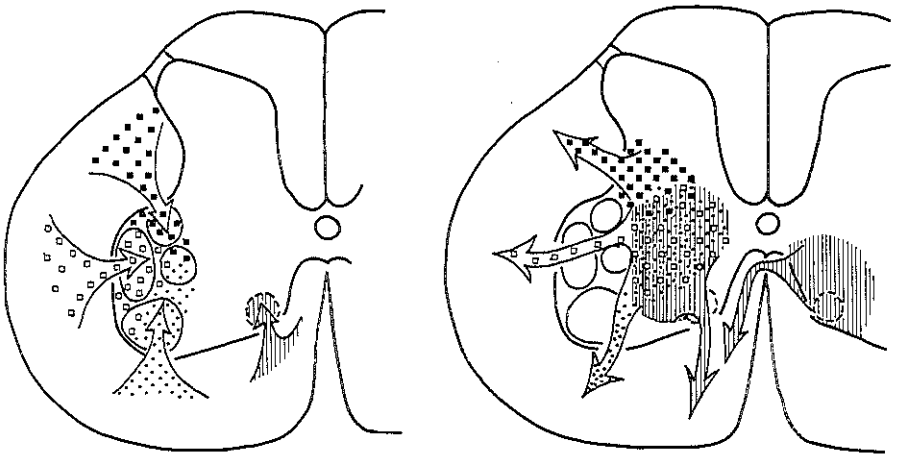

Fig.23. Diagram on the left shows preferential distribution of fibers in the different parts of ventral and lateral funiculi to the different motoneuronal cell groups of the lumbosacral ventral horn (cf.Rustioni et al. 1968). Diagram on the right shows differential location of cells in the lumbosacral intermediate zone which send their fibers into the different parts of the ventral and lateral funiculi. Note that the medial part of the ventral funiculus receives fibers from cells in both the ipsilateral and the contralateral intermediate zone.

culus. A combination of these findings with the present retrograde degeneration findings (groups A to D) suggests the following arrangement. Cells in lamina VIII and adjoining parts of lamina VII which send short propriospinal fibers contralaterally to the medial part of the ventral funiculus, may establish connections with contralateral motoneurons of axial muscles. Cells in the medial and central parts of lamina VII and in the adjoining part of lamina VIII which send fibers ipsilaterally to the intermediate and ventral parts of the lateral funiculus and to the lateral part of the ventral funiculus establish widespread connections with ipsilateral motoneurons. These connections are established mainly with motoneurons of axial, girdle and thigh muscles though to a lesser extent also with those of distal extremity muscles. However, cells in the dorsolateral part of lamina VII and in the lateral parts of laminae V and VI which send their fibers ipsilaterally to the dorsal part of the lateral funiculus, form the main source of the propriospinal fibers to the motoneurons of the latter muscles.

b. In the brachial cord. The findings after small HRP-injections in the cervical motoneuronal area (groups MiA,MiB,MiC) suggest that in the brachial cord a similar arrangement exists as in the lumbosacral cord. Thus, the dorsal part of the lateral motoneuronal cell group, which innervates distal extremity muscles, receives mainly ipsilateral propriospinal projections from neurons in the lateral parts of laminae V to VII. The ventral part of the lateral motoneuronal cell group, on the other hand, which innervates proximal extremity muscles, receives short propriospinal projections mainly from neurons in the central and medial parts of the ipsilateral lamina VII and some from neurons in lamina VIII on both sides. These conclusions are in keeping with those previously drawn from a combination of anterograde and retrograde degeneration findings in the brachial cord.[207]

A comparison with physiological findings. In respect to a somatotopic organization of propriospinal projections to the motoneuronal cell groups only few physiological data are available. The group of interneurons which mediate the disynaptic reciprocal inhibition from group Ia muscle afferents to motoneurons innervating antagonistic muscles was extensively studied by Jankowska et al.[82,85,86] The Ia-

inhibitory interneurons mediating the reciprocal inhibition from the knee flexor quadriceps to the knee flexors posterior biceps and semitendinosus muscles appeared to be located especially in the area dorsomedial to the low lumbar motoneuronal cell groups.[82] The morphology of these neurons was visualized by intracellular Procion Yellow injections and these cells were described as medium sized, with rather long dendrites projecting in all directions in the transverse plane.[82] A similar type of neurons was frequently labeled in the present cases in the proximity of the motoneuronal cell groups at levels close to the injections (compare plates 1 and 2 in ref.82 with Fig.15F of the present study). The axons of these interneurons were found to travel in the ventral part of the lateral funiculus and the lateral part of the ventral funiculus,[85] which is in keeping with the present findings concerning the axonal trajectories of neurons in the central part of lamina VII. However, the central position in lamina VII of these Ia-inhibitory interneurons which project to the posterior biceps and semitendinosus muscles[82,85,86] has been regarded as arguing against a somatotopical organization of propriospinal projections to the spinal motoneuronal cell groups. Yet, within the large motoneuronal complex of the ventral horn as it exists in L7 the target motoneurons of these interneurons occupy an intermediate position (cf. ref. 174). According to the arrangement suggested above it is therefore not unexpected to find that the bulk of these interneurons is also located in an intermediate position, i.e. in the central part of lamina VII. The bulk of the interneurons impinging on truly distal motoneurons may be expected to be located in the lateral portion of the intermediate zone. Such a location has been shown physiologically for the interneurons projecting to the peroneus motoneurons,[11] which innervate distal hindlimb muscles as well as for cervical interneurons mediating pyramidal activity to motoneurons of distal forelimb muscles.[7] A comparison of the latter findings with those of Jankowska's group suggests that the Ia-inhibitory interneurons to such motoneurons would be located most ventrally in this portion of the intermediate zone, i.e. close to the motoneuronal cell groups.

Relationships between the descending supraspinal pathways and the cells of origin of propriospinal fibers. As was pointed out above

(Chapter II.3) the neurons in the cat's intermediate zone form the main recipients of the descending supraspinal pathways, while these neurons in turn form the main source of afferent input to the spinal motoneurons. It is therefore of interest to compare the distributions in the intermediate zone of the various descending pathways with the differential projections from neurons in the intermediate zone to the motoneuronal cell groups, inferred above. The termination areas of the various descending pathways overlap in the dorsolateral part of lamina VII (cf.Chapter II.3).[99,103,104,105,106,155,161] However, the termination areas of the interstitiospinal, vestibulospinal and reticulospinal tracts additionally involve lamina VIII and the dorsally adjoining part of lamina VII, while those of the corticospinal and the rubrospinal tracts additionally involve the lateral parts of laminae V to VII. In view of the proposed arrangement of the propriospinal projections to the motoneuronal cell groups the former pathways, which correspond to the medial subcorticospinal system (cf.Chapter II.3), would act primarily on proximal extremity and girdle muscles, by way of neurons in the medial part of the intermediate zone. The latter group of pathways, which corresponds to the corticospinal and lateral subcorticospinal system, on the other hand, would act primarily on motoneurons of distal extremity muscles by way of interneurons in the dorsolateral part of the intermediate zone. These conclusions are in keeping with several functional observations, particularly those obtained in freely moving animals,[103,104,114,115,121] which indicate that the medial subcorticospinal pathways are concerned primarily with the steering of body and integrated limb-body movements, while the corticospinal and the lateral subcorticospinal pathways are mainly concerned with steering movements of the limbs, especially of their distal parts (cf.Chapter II.3).

According to physiological observations the long propriospinal fibers are especially concerned with the coordination of fore- and hindlimbs during locomotion.[61,145,146,158] The terminal distribution area of these fibers appeared to coincide with that of the medial descending brainstem pathways, especially with that of the reticulospinal fibers (cf. ref. 58). It is therefore of interest to note that physiological findings suggest that the reticulospinal fibers activate

the long ascending propriospinal fibers.[9] Such findings also indicate that the reticulospinal as well as the vestibulospinal fibers strongly influence the locomotor performance, while only a minor influence is derived from rubrospinal fibers[158] (cf. also ref.'s 1,2). These observations further support Lloyd's[123] conclusion that the reticulospinal and long propriospinal fibers are closely interrelated. In the following section of this chapter the anatomical interrelationships between the cells of origin of propriospinal and of reticulospinal fibers, will be discussed further.

5. Neurons of medullospinal fibers.

In the present study the distribution of labeled neurons in the medulla oblongata after the various spinal injections were especially studied in order to compare the organization of the cell population in the lower medulla oblongata with that in the spinal cord. The present findings indicate that some similarities exist in both areas, especially in respect to the medullary reticular formation on the one hand, and the spinal intermediate zone on the other. For example, in the spinal cord the longest propriospinal fibers appeared to be derived from neurons in the medial part of the intermediate zone and in the medulla oblongata the longest descending reticulospinal fibers appeared to be derived mainly from neurons in the medial tegmental field.[20,108,214] Further, in both areas the more laterally located neurons were found to give rise to relatively short fibers. In the spinal cord these fibers, including the short spinobulbar fibers (cases SSp1 and SSp6) are derived mainly from neurons in the lateral and central parts of the intermediate zone. In the medulla oblongata the short bulbospinal fibers appeared to be derived mainly from neurons in the lateral tegmental field of Berman[10] and appeared to be distributed caudally to the upper five cervical segments (cases SSp6 and Sp11). Moreover, the distribution pattern of these short bulbospinal fibers confirms to that of the short fibers in the spinal cord, such that those from the lateral part of the lateral tegmental field tend to be distributed mainly ipsilaterally, while those from the medial part tend to be distributed bilaterally (cf. ref. 71).

The present findings in the medulla oblongata further confirm

earlier anatomical and physiological findings which indicate that long descending fibers also arise from the raphe[13,22,108] and vestibular nuclei,[19,108,160] from the solitary[108,213,223,224,225] and retroambiguus[108,143,223] nuclei as well as from a linear group of neurons in the lateral tegmental field. The fibers from the latter three groups of neurons descend mainly contralaterally throughout the length of the spinal cord. The terminal distribution area of these fibers could not be demonstrated with the present technique. Yet, physiological[90,143,223,224,225] observations indicate that these fibers are also involved in the supraspinal control of spinal movements, in particular respiratory movements.

SUMMARY AND CONCLUSIONS.

In the present study an attempt has been made to clarify the anatomical organization of the propriospinal system and especially of the propriospinal projections to the spinal motoneurons. The cells of origin of the propriospinal fibers are located in the spinal gray, which consists of a dorsal horn, a ventral horn and an intermediate zone. From the literature (Chapters I and II) it was already known that neurons in the dorsal gray give rise mainly to long ascending pathways, while the ventral horn contains the spinal motoneurons which are somatotopically organized in roughly the following way. In the lateral motoneuronal cell group motoneurons of distal extremity muscles are located dorsally to those of proximal extremity and of girdle muscles, while the medial motoneuronal cell group contains motoneurons of axial muscles. The neurons in the intermediate zone form the main source of the propriospinal fibers and in turn are the main recipients of the corticospinal and of the descending brainstem pathways. According to Kuypers the descending brainstem pathways may be divided in a medial and a lateral system on the basis of their terminal distribution areas. In cat the lateral brainstem pathways as well as the corticospinal tract terminate preferentially in the dorsolateral part of the intermediate zone and are concerned primarily with the steering of movements of the limbs, in particular of their distal parts. The medial pathways terminate preferentially in the ventromedial part of the intermediate zone and are concerned primarily with the steering of body and integrated limb-body movements.

In light of the above mentioned data an attempt has been made to determine the distribution in the intermediate zone of the cells of origin of long and short propriospinal fibers, including those of fibers projecting to the spinal motoneurons. In order to differentiate the cells of origin of propriospinal fibers from those of long ascending fibers the location of the latter neurons was studied first by means of the retrograde cell degeneration technique and the HRP-retrograde axonal transport technique (Chapter III). With these techniques the following experiments have been conducted.

In kittens the distribution in the lumbosacral cord of neurons of long ascending fibers and of fibers in different parts of the ventral

and lateral funiculi was approximated by studying the distribution of chromatolytic neurons after hemisections at or above L1 and after small transections of the lumbosacral ventral and lateral funiculi, respectively (Chapter IV.1). In cats and Rhesus monkeys the cells of origin of propriospinal fibers and of fibers ascending to supraspinal levels were identified by studying the spinal distribution of retrogradely labeled neurons after HRP-injections into both the white and the gray matter at different spinal levels, in the pons, in the dorsal column nuclei and in the medial bulbar tegmentum (Chapter IV.2 A,B,C, E). Further, the funicular trajectories of the various groups of fibers were approximated by means of midthoracic HRP-injections combined with funicular transections immediately above and below the injections (Chapter IV.2D). Finally, the distribution of cells of origin of descending fibers from the medulla oblongata was studied after spinal HRP-injections in cat (Chapter IV.2F).

In an additional group of experiments an attempt was made to determine the distribution in the brachial intermediate zone of neurons which project to different parts of the low cervical lateral motoneuronal cell group (Chapter IV.3). For this purpose micro-injections of HRP were made into different parts of this motoneuronal cell group and the distribution of retrogradely labeled neurons was studied in the brachial cord.

The results obtained in the various experiments lead to the following conclusions.

1) Ascending supraspinal fibers are derived mainly from neurons in Clarke's column, in the spinal border cell area, in the dorsal gray and the medial part of the ventral gray. Neurons in lamina IV and the medial parts of laminae V and VI of the dorsal gray send fibers to the ipsilateral dorsal column nuclei, which in turn give rise to fibers to the spinal cord. Neurons in lamina VIII and the dorsally adjoining part of lamina VII of the ventral gray give rise to fibers to the medial part of the bulbar reticular formation.

2) Propriospinal fibers arise mainly from neurons in the intermediate zone (laminae V to VIII). Long propriospinal fibers which travel throughout the spinal cord and are distributed primarily contralaterally come mainly from lamina VIII and the adjoining parts of lamina VII.

This area presumably also gives rise to contralaterally distributed short propriospinal fibers. Neurons in the lateral parts of laminae V to VII give rise almost exclusively to short ipsilaterally distributed propriospinal fibers, while neurons in the central and medial parts of lamina VII give rise to bilaterally distributed propriospinal fibers of intermediate length. The present retrograde degeneration findings combined with earlier anterograde degeneration findings in the lumbosacral cord[180] suggest the existence of the following organization. Neurons in the lateral parts of laminae V to VII project preferentially to ipsilateral motoneurons of distal extremity muscles. Neurons in the central and medial parts of lamina VII project preferentially to ipsilateral motoneurons of proximal extremity muscles and of girdle muscles. Neurons in lamina VIII and the dorsally adjoining part of lamina VII project preferentially to contralateral motoneurons of axial and to some extent of girdle muscles. In view of the present findings after small HRP-injections in the cervical motoneuronal area a similar arrangement seems to exist in the brachial cord. This organization would be quite compatible with Kuypers' concept concerning the functional differences between the various descending pathways.

3) Medullospinal fibers which descend throughout the length of the spinal cord arise from the vestibular complex, the raphe nuclei, the retroambiguus and solitary nuclei and from the medial tegmental field of the medullary reticular formation. Neurons in the lateral tegmental field give rise to short bulbospinal fibers to the upper cervical cord. The bulbospinal fibers from the lateral part of the lateral tegmental field are distributed mainly ipsilaterally, but those from the medial part of the lateral tegmental field bilaterally. The present findings in the medulla oblongata support the view that the structural pattern which exists in the spinal cord also exists, in a slightly modified form, in the medulla oblongata.

SAMENVATTING EN CONCLUSIES.

Het onderzoek beschreven in dit proefschrift had vooral ten doel verder inzicht te verkrijgen in de organisatie van het propriospinale systeem, vooral van de propriospinale projecties naar de spinale motoneuronen. De oorsprongscellen van deze vezels zijn gelegen in het spinale grijs, dat bestaat uit een dorsale hoorn, een ventrale hoorn en een intermediaire zone. Uit litteratuur gegevens (hoofdstukken I en II) was het reeds bekend dat neuronen in de dorsale hoorn vooral oorsprongscellen zijn van lange ascenderende banen, terwijl de ventrale hoorn de spinale motoneuronen bevat, die de volgende somatotopische organisatie tonen. In de laterale motoneuronale cel groep zijn de motoneuronen van distale extremiteits spieren dorsaal gelegen van die van proximale extremiteits spieren en gordel spieren, terwijl de mediale motoneuronale cel groep gevormd wordt door motoneuronen van axiale spieren. De neuronen in de intermediaire zone zijn de voornaamste bron van de propriospinale vezels en ontvangen op hun beurt het grootste deel van de afferenten van de descenderende supraspinale banen. Volgens het concept van Kuijpers kunnen de descenderende hersenstam banen op basis van hun eindigingsgebied onderverdeeld worden in een mediaal en een lateraal systeem. In de kat eindigen zowel de laterale hersenstam banen als de corticospinale baan vooral in het dorsolaterale deel van de intermediaire zone en zijn vooral betrokken bij de regulatie van bewegingen van de ledematen, in het bijzonder van hun distale delen. De mediale banen eindigen vooral in het ventromediale deel van de intermediaire zone en zijn vooral betrokken bij de regulatie van bewegingen van het gehele lichaam en van geïntegreerde bewegingen van lichaam en ledematen.

In het licht van deze gegevens is getracht om vast te stellen waar de oorsprongscellen van lange en korte propriospinale vezels in de intermediaire zone gelegen zijn, met inbegrip van de oorsprongscellen van vezels die naar de motoneuronen projecteren. Ten einde de oorsprongscellen van propriospinale vezels te onderscheiden van die van lange ascenderende vezels is eerst de localisatie van de laatst genoemde groep neuronen bestudeerd. Voor deze doeleinden zijn twee technieken gebruikt (hoofdstuk III), te weten de retrograde cel degeneratie techniek en de techniek gebaseerd op het retrograde axonale

transport van "horseradish peroxidase" (HRP). Met behulp van deze technieken zijn de volgende experimenten uitgevoerd.

De localisatie van oorsprongscellen van lange ascenderende banen en van vezels in verschillende delen van de lumbosacrale ventrale en laterale funiculi werd bestudeerd in het lumbosacrale ruggemerg van jonge katten, door middel van hemisecties t.h.v. L1 of verder rostraal en d.m.v. lesies in verschillende delen van de lumbosacrale ventrale en laterale funiculi. (hoofdstuk IV.1). De oorsprongscellen van propriospinale en van lange ascenderende vezels werden geïdentificeerd in de kat en de aap door de distributie van retrograad "gelabelde" cellen te bestuderen na injectie van HRP op verschillende niveaus in het ruggemerg, in de pons, in het mediale deel van de reticulaire formatie van de medulla oblongata en in de achterstrengkernen (hoofdstuk IV.2 A,B,C, E). Verder werd het funiculaire verloop van de verschillende groepen vezels bepaald door midthoracale HRP-injecties te combineren met doorsnijdingen van de funiculi direct rostraal en caudaal van het geïnjiceerde niveau (hoofdstuk IV.2D). Tenslotte werd de distributie van oorsprongscellen van descenderende vezels van de medulla oblongata naar het ruggemerg in de kat bestudeerd m.b.v. spinale HRP-injecties (hoofdstuk IV.2F).

In een laatste groep experimenten (hoofdstuk IV.3) werd getracht vast te stellen in welke delen van de brachiale intermediaire zone de oorsprongscellen gelegen zijn van vezels die naar verschillende delen van de laag cervicale laterale motoneuronale cel groep projecteren (hoofdstuk IV.3). Voor dit doel werden micro-injecties van HRP gemaakt in verschillende delen van deze motoneuronale cel groep en de distributie van retrograad "gelabelde" cellen werd bestudeerd in het brachiale ruggemerg.

De resultaten die verkregen werden in de verschillende experimenten leiden tot de volgende conclusies.

1) Lange ascenderende banen ontstaan vooral in de zuil van Clarke, in het gebied van de "spinal border cells", in de dorsale hoorn en in het mediale deel van de ventrale hoorn. De vezels van de neuronen in lamina IV en de mediale delen van laminae V en VI van het dorsale grijs projecteren ten dele naar de achterstrengkernen, welke op hun beurt vezels naar het ruggemerg projecteren. Neuronen in lamina VIII en in het

dorsaal aangrenzende deel van lamina VII projecteren vezels naar het mediale deel van de reticulaire formatie van de medulla oblongata.
2) Propriospinale vezels, ontstaan vooral in de intermediaire zone (laminae V tot VIII). Lange propriospinale vezels die vooral contralateraal door het gehele ruggemerg gedistribueerd worden komen vooral van lamina VIII en de aangrenzende delen van lamina VII. In dit gebied ontstaan waarschijnlijk eveneens korte propriospinale vezels. Neuronen in de laterale delen van laminae V tot VII distribueren hun vezels voornamelijk ipsilateraal over korte afstand, terwijl bilateraal gedistribueerde vezels van intermediaire lengte ontstaan in de centrale en mediale delen van laminae VII. Op grond van een combinatie van de huidige retrograde degeneratie gegevens met eerdere anterograde degeneratie gegevens in het lumbosacrale ruggemerg[180] mag het bestaan van de volgende organisatie aangenomen worden. Neuronen in de laterale delen van laminae V tot VII projecteren vooral naar ipsilaterale motoneuronen van distale extremiteits spieren. Neuronen in de centrale en mediale delen van lamina VII projecteren vooral naar ipsilaterale motoneuronen van proximale extremiteits spieren en van gordel spieren. Neuronen in lamina VIII en de aangrenzende delen van lamina VII projecteren vooral naar contralaterale motoneuronen van axiale spieren en in zekere mate naar die van gordel spieren. Op grond van de huidige gegevens verkregen na micro-injecties in de cervicale laterale motoneuronale cel groep lijkt een vergelijkbare organisatie te bestaan in de bovenste intumescentie. Deze organisatie van de propriospinale projecties naar verschillende motoneuronale cel groepen past goed in Kuijpers' concept betreffende de functionele verschillen tussen de groepen van descenderende supraspinale banen.
3) Medullospinale vezels die door de gehele lengte van het ruggemerg gedistribueerd worden ontstaan vooral in het vestibulair complex, de raphe kernen, de nuclei retroambiguus en solitarius en het mediale tegmentaal veld van de medulla oblongata. Neuronen in het laterale tegmentaal veld distribueren vooral korte bulbospinale vezels naar de bovenste cervicale segmenten. De bulbospinale vezels van het laterale deel van het laterale tegmentaal veld projecteren vooral ipsilateraal, maar die van het mediale deel van het laterale tegmentaal veld bilateraal. De huidige gegevens verkregen in de medulla oblongata geven

verdere aanwijzingen dat het structurele patroon dat bestaat in het ruggemerg ook voorkomt in de medulla oblongata, zij het in een enigszins gewijzigde vorm.

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CURRICULUM VITAE.

De schrijfster van dit proefschrift werd op 27 juli 1950 in Den Haag geboren. Na de opleiding gymnasium B aan het Libanon Lyceum te Rotterdam volgde in 1969 de medische studie aan de Erasmus Universiteit te Rotterdam. In het 3e jaar van deze studie werd een keuzepraktikum gedaan op de afdeling neuro-anatomie van deze Universiteit. Tijdens dit keuzepraktikum werd een aanvang gemaakt met het onderzoek naar oorsprongscellen van propriospinale vezels, beschreven in dit proefschrift. In de daaropvolgende jaren werd dit onderzoek voortgezet in het kader van een studentassistentschap. Na het doctoraalexamen Geneeskunde in 1974 volgde een aanstelling als wetenschappelijk medewerkster op de afdeling neuro-anatomie, welke eindigde in het voorjaar van 1977. In deze jaren werd het onderzoek, beschreven in dit proefschrift, afgerond en werd bovendien onderwijs gegeven in de anatomie van hoofd en hals en in de neuro-anatomie.