Motor-Sensory Cortex-Corticospinal System and Developing Locomotion and Placing in Rats

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ABSTRACT Normal and abnormal development of movement in the rat were studied by investigating the growth and organization of the motor-sensory cortex-corticospinal tract system (MSC-CST) and the functional and morphologic effects of ablating the MSC or quadrants of it at different ages. Major growth of the MSC outflow, the CST, in the brain stem and rostral cord occurred in the second and third weeks postnatally, coinciding approximately with the normal mid-third week transition from infantile to mature locomotion. Ablation of the MSC at birth revealed that while the MSC-CST was not essential for ordinary locomotion on flat terrain, its presence hastened normal development of this kind of movement, and that it was absolutely essential for locomotion on difficult terrain. The MSC quadrants showed quite different, and in some domains mutually exclusive, CST projection patterns to forebrain, diencephalon, brain stem, and spinal destinations (determined by Fink-Heimer-Nauta fiber degeneration studies). Ablation of some quadrants produced distinctive syndromes of disordered movement: the posterolateral quadrant related to active grasping in positioning limbs, while the posteromedial quadrant related to tactile motor-sensory positioning of limbs. Thus in addition to the classic somatotopic organization of the MSC, there was another kind of organization into regions concerned with components of integrated movement of a number of parts of the body. Several forms of aberrant circuitry developed after MSC ablations in infants, but their possible roles in functional adaptation remain to be determined.

Young mammals, including man, have been said to fare better functionally after nervous system injury than adults. It has become increasingly plain, however, that no such generalization is possible. The embryo, infant, and adult respond very differently to injuries. The young mammal sometimes shows a capacity for repair and compensation that the adult lacks, but the outcome of a reaction to injury or alteration of development at a particular age depends on many complex factors, and only rarely is it remarkably successful. In the early mammalian embryo at stages of the neural folds or the beginning of formation of the forebrain, destruction of large numbers of primitive cells, as many as half of the cells in the embryo, may be followed by restitution and formation of an apparently normal organism from the residual primitive cells. Such success is the exception; the rule in almost all other stages is that the effects of destruction outweigh those of restitution, and malformation, or even death, results (Hicks, '54; Hicks et al., '57; Hicks and D'Amato, '66). A common response to nervous system injury in fetal and infant life is growth of axons from their normal sites into zones of partial injury, as in the cortex and basal ganglia of infants surviving severe perinatal asphyxia, or into regions not normally innervated, as the meninges in fetal brain injury (Hicks et al., '59). This aberrant exploratory growth is chaotic and malformative in these situations, but in some other circumstances the aberrant growth has seemed more orderly, as when axons follow pathways left vacant by failure of normal fibers to fill them. When normal optic tract fibers were prevented from reaching the superior colliculus, aberrant

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fibers from the other tract entered the void (Schneider, '73), and when one corticospinal tract was prevented from forming, the other contributed fibers to the empty course (Hicks and D'Amato, '70, '73a; Leong and Lund, '73). Removal of the innervation of the hippocampus from the ipsilateral entorhinal cortex in the young rat was followed by aberrant innervation from the contralateral entorhinal cortex, and it was electrophysiologically functional (Steward et al., '73). Such examples of plasticity have suggested that young brains might have a more general capacity for developmental reorganization that would account for restitution of function after injury, as well as for some forms of abnormal functional development. In fact, little is known about how much this kind of plasticity may operate in developmental adjustments, or even whether it is a significant mechanism. In those uncommon instances of individuals who develop seemingly "impossible brains" but make rather remarkable adjustments, the mechanisms involved in their adaptations are largely beyond present knowledge: for example, persons who developed almost no cerebellum (Boyd, '70) or hippocampal fornix system (Nathan and Smith, '50), or who had a diseased cerebral hemisphere nearly completely removed surgically in infancy (White, '61), were able to function very much as though these parts were not missing. Even in the much more common circumstance where an abnormally developed brain is associated with neurologic or mental deficit, understanding of the mechanisms of altered function is usually only very general. Thus it is important to learn everything possible about the responses to adversity of the developing nervous system.

Our laboratory has been engaged in a series of experimental studies to find out more about the mechanisms that determine the relative balances of incapacity and adaptability that follow early injury and malformation of the nervous system (Hicks, '54; Hicks et al., 57; Hicks et al., '62; Falk and D'Amato, '62; Fowler et al., '62; Hicks et al., '64; D'Amato and Hicks, '65; Hicks et al., '69; Hicks and D'Amato, '74b). In experiments which led to the present work (Hicks and D'Amato, '70), we compared the reactions of the nervous system and the capacities for functional adaptation of newborn and mature rats after hemispherectomy or ablation of the motor-sensory cortex (MSC). The salient features were these. Removal of one or both MSC's, or removal of nearly all of one cerebral hemisphere (hemispherectomy) in the mature rat promptly abolished certain tactile placing reflexes, as they are commonly tested, in limbs contralateral to the lesions. Locomotor placing and some limb positioning responses were also lost or impaired: that is, the feet, and even the limbs, opposite the lesions were allowed to slip off edges of a broad track, and the animal could be positioned sometimes so that the limbs were left briefly in these unusual positions. This latter transient "paresis" notwithstanding, the animals were not paralyzed in the usual sense; their locomotion on flat level surfaces and jumping from one platform to another resembled the normal. Visual placing was undisturbed in animals with MSC ablated. Hemispherectomized rats (whose optic nerves were intact) placed neither tactually nor visually alone on the side opposite the lesion, but if the animals could see the ledge and touch it at the same time with the forefoot, placing occurred.

When hemispherectomy or unilateral MSC ablation was performed at birth, there was no effect on tactile placing — which had been present normally from about the end of the first week — until around the 17th day, when the response ceased permanently contralateral to the lesion. The animals then resembled those operated on at maturity in most ways, a finding in agreement with observations of C. M. Brooks ('33, '40) on the functional effects of MSC ablations in infant and mature rats. It was, coincidently, around the 17th day that locomotion in the rat normally underwent a rapid developmental transition from infantile crawling to the adult rhythmic pattern of walking and running. Some preliminary studies which formed the beginning of the present work (Hicks and D'Amato, '73b) showed another paradox: if both MSC's were removed at birth, no impairment of tactile placing responses developed, although animals so treated had other locomotor problems. To make the matter more complex, if the remaining

MSC was removed after the age of 17 days in a rat whose MSC was ablated unilaterally at birth, it did not restore the placing deficit caused by the operation at birth. Rather, the animal had now lost its tactile placing bilaterally.

The loss of placing after unilateral ablation of the MSC at birth, the rapid transition from infantile to mature locomotion, and the difference in effects of unilateral and bilateral ablation at birth that developed in mid-third week raised questions about what special developmental events were going on then and what neural systems were involved. Earlier observations by others, and beginning neuroanatomic studies of the corticospinal tract (CST), in our own animals, suggested the MSC-CST system as a place to begin investigation. Barron ('34) and Liddell and Phillips ('44) had shown that section of the CST in the medulla of rats and cats abolished tactile placing and positioning responses of the limbs, feet, and digits, complementing Bard's ('34) study of the cortical dependence of these activities. We were able to show with appropriate fiber degeneration studies, that after hemispherectomy or unilateral MSC ablation in newborn rats, but not after the operations were done in mature rats, a tiny uncrossed CST developed in the medulla and spinal cord (Hicks and D'Amato, '70, '73a,b). It seemed to follow precisely, in miniature, the course of the tract that was prevented from forming by MSC ablation in infancy. Slow motion movies showed that animals operated on at maturity had a slight impairment of stride and of extending the forefoot digits in locomotion, but those operated on at birth were spared. Searching for evidence of plasticity in the infant to explain differences between adult and infant reactions, we speculated that the little aberrant tract might have compensated in a minor way for the missing normal tract (Hicks and D'Amato, '70).

The CST, or pyramidal tract, was once regarded as a direct pathway from neurons in the motor cortex to motor neurons in the brain stem and spinal cord by which the cortex commanded voluntary movements. This notion gave way before a growing body of observations in a number of laboratory mammals and man to a larger concept of the organization of motor systems and one in which the MSC and its outflow, the CST, were major components (Paillard, '60; Zimmerman et al., '64; Bucy, '66; Phillips, '66; Scheibel and Scheibel, '66; Wall, '67; Lawrence and Kuypers, '68; Brodal, '68; Evarts and Thach, '69; Brooks, '69; Eccles, '69; Phillips, '69; Beck and Chambers, '70; Wall, '70; Brooks and Stoney '71; Kemp and Powell, '71; Wiesendanger, '72; Merton, '72; Castro, '72; Matthews, '72; Porter, '73; Henneman et al., '74; Stein, '74). Outlining this organization briefly, the ultimate effector of a large part of behavior, the musculoskeletal system, was controlled locally by segmental spinal cord circuits (and their cranial counterparts). Sensory input from muscles, joints, tendons, and integumentary structures reached motor neurons which in turn controlled the muscles. Though these local closed circuits represented the basic unit control mechanisms for movement, and though some of their reflex activities, like the muscle-stretch reflex, had a quality of autonomy, they were linked complexly for integrated patterns of function. Walking involved not just limbs, but the trunk and head, and vocalization not just the oral parts, but the coordination of the whole respiratory mechanism. Superimposed on and interlocked with with the integrated segmental circuits were several elaborate motor mechanisms or systems concerned with movement: the brain stem reticular formations, the basal ganglia, certain midbrain thalamic, and subthalamic centers, the vestibular centers and cerebellum. They assured continuity and progression of patterned movement, coordinated its execution and oriented it in relation to gravity and space. The MSC, a region of cortex variously represented in mammals, projected directly or indirectly to these systems, to many parts of the thalamus, posterior column nuclei and other medullary nuclei, and to interneurons of the segmental spinal circuits. Its action in mammals below primates was said to be almost exclusively on interneurons and sensory systems concerned with movement; in primates some CST axons also synapsed on spinal motor neurons themselves. The MSC received feedback from all of its targets through

afferent systems and had means to regulate the feedback itself. A large, although imprecisely known, part of the outflow of the MSC, projections to basal ganglia, thalamus, pons, red nucleus, and reticular formation for example, had come to be regarded as collaterals of fibers destined for more caudal stations, such as those coursing in the pyramids in the medulla and the CST in the cord. Hence the concept of the CST or pyramidal tract system came to be that it was essentially the outflow of the MSC, with axons extending from cortex to spinal cord, giving off collaterals along the way. ("Non-pyramidal" and "extra-pyramidal" were variously used for MSC efferents that did not travel in the CST or for efferent systems arising from targets of the CST, such as basal ganglia.) Against this background, the MSC-CST system has continued to be regarded by some as the chief controller, the commander, of movement. However there are many enigmas about its anatomy and functions, such as whether it is really the initiator, integrator and the seat of programs for movement, or less grandly a steerer, facilitator and adjustor in difficult circumstances, for those elaborate subcortical mechanisms concerned with movement, mentioned earlier.

The nervous system is an integrated mechanism; separating out its functions and the neural mechanisms underlying them is artificial. Nevertheless much of our information about the nervous system has come from taking it apart or observing the effects of deficits produced by experiment, development, disease or injury; this study has taken that approach. It had several aims. One was to find parallels and possible correlations between growth of the CST and developing motor function. Another was to define the projections of the CST from different parts of the MSC. A third was to describe aberrant CST growth and other developmental alterations related to MSC injury in infancy as possible indicators of plasticity in developing brain. A fourth was to compare the functional effects of ablating regions of the MSC in infant and mature rats. The overall purpose was to find out as much as possible about the MSC-CST's role in locomotor development, the structural-functional organization of the MSC-CST in relation to movement, and to compare the capacity of infant and mature rats to compensate for loss of parts of the MSC. Brief preliminary reports of certain parts of the work have been published (Hicks and D'Amato, '73a,b, '74a,b,c).

MATERIALS AND METHODS

General statement

Black "Irish" rats, described later, were the subjects. Anatomic studies were made of the developing and mature CST by conventional histology and by the Fink-Heimer-Nauta method (FHN) for degenerating axons (Heimer, '70). In the latter, selected parts of the cortex were ablated surgically in rats of different ages and the courses of the degenerating axons of the nerve cell bodies removed by the ablation were observed. The distribution of the CST projections from various parts of the cortex at maturity was plotted and to some extent the development of the ramifications was observed. The method was also used to study the origin and growth of the small aberrant CST that formed after infant MSC ablation, and the age at which it could be elicited. Supplemental methods were used to check the validity of the FHN method in these experiments: parts of the CST were mapped by demonstration of axonal transport of incorporated tritiated amino acids using autoradiography, and Alzheimer-Mann chrome-mordant stains helped establish optimal intervals after cortical ablations for demonstrating degenerated axons. Photography of whole brains from autopsies of experimental and normal rats and further histologic examination of some of them served to delineate the ablations, demonstrate histologic features of them and establish anatomic coordinates for the MSC at different ages. We have already published earlier accounts of some aspects of the pre- and postnatal morphogenesis and cytodifferentiation of the rat cortex (Hicks et al., '59; Hicks et al., '62; D'Amato and Hicks, '65; Hicks and D'Amato, '68).

Behavioral studies of developing motor function were selected from a battery of motor, visual, learning and other tests which we had used and described in detail

earlier (Hicks et al., '69; Hicks and D'Amato, '70, '74b). They included observations of locomotion on a flat track or narrow pathways and the testing of placing reactions. A visual discrimination test using a Lashley jumping stand (Lashley, '30) was applied to some of the rats with MSC's bilaterally ablated at birth. Animals were observed from birth and begun on the tasks at about two weeks of age, reinforcement being the opportunity to explore and be handled (Hicks and D'Amato '70, '74b). Slow motion movies recorded excerpts of the developing and mature behavior.

Cortical ablations, for functional study or the FHN method, were done surgically under a microscope with the rats anesthesized. Their purpose was to explore possible relations between the anatomy of the MSC-CST and the functional deficits produced by ablation of the regions at different ages. Most ablations for functional studies were done at birth, three weeks or two months of age.

Animals

The rats, black with white feet (Irish), were the F_1 cross between albino females of Wistar origin, brother-sister mated about 60–70 generations, and black-selfed non-agouti males also brother-sister mated for 50–60 generations. They were members of a closed colony, kept in clear plastic or wire cages at about 25°C with variable humidity and common fluorescent lighting from 7 A.M. to 11 P.M. They were fed Purina brand pellets for rats and water ad lib. Their maintenance, care and the conduct of experiments conformed to standards set by the USPHS and this University's Animal Care Facility. Litters usually had 7 to 10 members. Rats were called newborn during the first day after birth; infancy extended from birth to early in the third week; and the juvenile period followed to about 7 or 8 weeks when the capability to reproduce appeared, heralding adulthood. We use mature in several contexts: for example, the mature pattern of locomotion appeared around the 17th day; reproductive maturity appeared around two months. Rats 21 days to two months old were collectively called mature when certain general comparisons of their brain development and motor function were being made with those of infants. Three weeks old was 21 days; two months old ranged from the end of the 7th to the 10th week.

Anatomic studies

Definitions of MSC and CST. The MSC and CST are concepts based on anatomic, physiologic and behavioral studies into which new information is continuously incorporated. Some attributes of the MSC and CST were mentioned in the beginning of the article. Our working definition of the adult rat's MSC was the isocortex of the frontal region from its junction with the cingular cortex frontomedially and dorsomedially to the rhinal fissure laterally and non-isocortex inferofrontally. The posterior border was defined by a coronal plane about 3 mm caudal to the bregma and other coordinates given later. Ablation of the whole MSC, thus defined, resulted in degeneration of all fibers in the CST as observed in the medullary pyramid and the spinal cord by axon degeneration studies. Ablations of quadrants of the MSC, defined later, yielded characteristic patterns of fiber degeneration in the medullary pyramid and spinal cord, but a series of small lesions to determine the exact borders of the MSC laterally, medially, and frontally was not done. A few of these borders have been investigated by Krieg ('46) in relation to his histologic parcellation of the rat's cortex, and by Leonard ('69) in FHN studies of projections of the cortex. We did determine, however, with a number of lesions, that the posterior border of the MSC is about 3 mm caudal to the bregma dorsally, because, as will be described in the RESULTS, the posterior part of the MSC dorsally is the only part that projects to the spinal cord, and it abuts on "visual" cortex that projects along with the CST as far as the pons. The MSC, as defined here, included the topographic areas of motor-sensory representation of the rats' body determined earlier by Woolsey and associates (Woolsey, '52) and more recently by Hall and Lindholm ('74), who used elicitation of movements by electrical stimulation of points on the cortex and cortical potentials evoked by stimulating parts of the body surface to prepare their cortical maps.

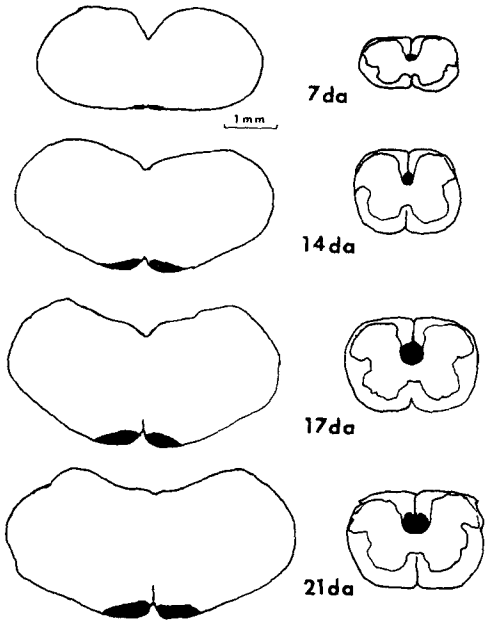

Fig. 1 Growth of the medulla and cervical spinal cord in the rat from birth to 21 days, represented in outline tracings of frontal histologic sections from a series of successively older rats. The increasing cross sectional area of the CST in the medullary pyramid and dorsal funiculus of the cord is shown in relation to other regions that were also growing.

Coronal (frontal) sections of rat brains for histologic study and determination of landmarks of the MSC were approximately in the following frame of reference. In the 2-month-old rat, the long axis through the brain was considered horizontal when the bregma was 1 mm lower than the lambda, the head tilting slightly more forward than that in several published atlases. A coronal section (perpendicular to the horizontal long axis) through the bregma passed about 1.5 mm rostral to the optic chiasm. Another coronal section 3 mm caudal to the bregma passed through the hippocampal formation and rostral parts of the habenula, and included ventrally the caudal extreme of the entopeduncular nucleus. It passed just caudal to the globus pallidus. The brain, like other tissues, grows in a complexly irregular manner. From birth the forebrain and cerebellum grew relatively enormously, the diencephalon much less. By increments of cell numbers up to about the end of the first postnatal week and growth of individual cells, the mantle expanded rostrally, dorsally, and especially caudally, reaching almost maximum size at three weeks. The gross differences between the rat's brain at three weeks and two months were not great, as reflected in several measures. There was almost no increase in the distance from bregma to lambda between these ages; there was a slight increase in the dorsoventral thickness of the forebrain and a little widening and some lengthening of the brain stem and cerebellum. Measures reflecting earlier growth indicated some problems in making comparable ablations at different ages. With the bregma a millimeter lower than lambda, coronal sections through the bregma passed less than a millimeter rostral to the chiasm at birth. From about one week to two months this distance remained about 1.5 mm. Between birth and three weeks, the distance from nasion to bregma increased from about 3.5 mm to 5 or 5.5 mm at maximum, but the dimension from bregma to lambda grew from about 4 or 5 mm in the first week to 7.5 or 8 mm by two weeks, increasing no more after that. The great mantle growth, then, was during about the first two weeks after birth. We set the caudal border of the MSC at about 3 mm in rats three weeks to two months old, used a slightly smaller distance at two weeks and set the distance at 1.5 mm at birth. Coronal sections at the bregma and at the designated caudal border of MSC from two weeks to two months presented similar topographic relations histologically, but these planes in younger rats were difficult to compare. The mushrooming mantle with its increments of cells to the cortex and striatum during the first week (Hicks and D'Amato, '68) made the relation of the cortex to deeper structures a changing one. However, ablation of the MSC, as designated at birth, prevented formation of the CST as seen in the medullary pyramids and spinal cord.

To determine the CST projections from various parts of the MSC and the functional effects of partial ablations, we divided the MSC into quadrants. This was done because there was only limited correlation between topographical representa-

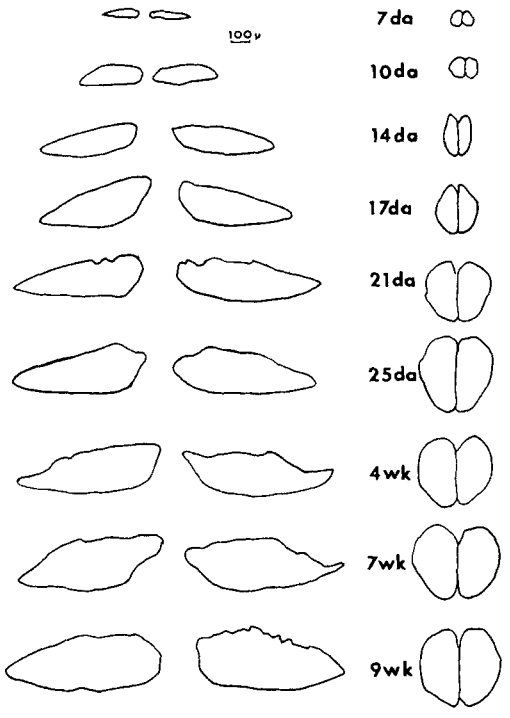

Fig. 2 Growth of the CST in the medullary pyramids and spinal cord in the rat from birth to adulthood from the same material represented in figure 1.

tion of the rat's body in the cortex mapped by neurophysiologic methods, division of the region into histologically distinct areas, and our own earlier findings about functional deficits following partial MSC ablations. Quartering a curved area that had a linear posterior border but whose rostral portion, the frontal pole, was a tapered convexity was an approximation. In mature rats, the posterior border was defined by the line on the MSC made by a coronal plane passing 3 mm caudal to the bregma. A line dividing the MSC into anterior and posterior halves was defined by another coronal plane passing about 1.5 mm rostral to the bregma. A third line defined by the passage of a horizontal plane divided the MSC into lateral and medial halves. Intersection of this line with those of the coronal planes occurred about 6 mm from the medial and lateral borders of the MSC given earlier. The quadrants thus defined by these planes were anteromedial (AM), posteromedial (PM), anterolateral (AL) and posterolateral (PL), and they are diagrammed in figure 3.

Histologic studies to show the growth of the CST. The principal purpose of these was to show graphically the growth in size (cross section) of the CST and related structures during postnatal life and to observe some other cellular aspects of the MSC-CST system. The following material was used. A reference series of brains, from our Irish rats 1 to 7 days old, 10, 14, 17, 21 and 25 days old, 4, 5 and 6 weeks old, and 2, 3, 6 and 9 months old were fixed in Bouin's fluid with 10% formalin), serially sectioned frontally and sagittally, and stained usually with luxol fast blue and cresyl violet. First and 8th cervical, 4th and 8th thoracic, 1st and 4th lumbar, and sacral levels of spinal cord from the same animals were prepared comparably. The formalin-fixed brain stem was serially frozen-sectioned frontally at 15 or 20 μ in normal Irish rats 4, 7, 10, 14, 17, 21 days, and two months old and stained with hematoxylin or pyridine silver carbonate. A modified Golgi stain was applied to blocks of the forebrain, including the MSC, and to the brain stem and spinal cord at some of these stages also.

Ablation-fiber degeneration studies of the growth and origins of the CST from different parts of the MSC

Fink-Heimer-Nauta (FHN) stain. When nerve cell bodies are destroyed their axons die and usually become argyrophilic, and the FHN stain blackens them selectively in histologic sections (Heimer, '70). However, the argyrophilia varies in the time of its first appearance, maximum development and persistence depending on several factors, including size of the axons, distance from their cell bodies, individual characteristics of a particular tract, and especially the age of the animal. Van Crevel and Verhaart ('67) showed that the axons in the cat's CST, in the spinal cord, became argyrophilic at different rates because they were of different diameters. Assessment of the number of fibers in the tract by this staining reaction, they claimed, would require examinations at two or more inter-

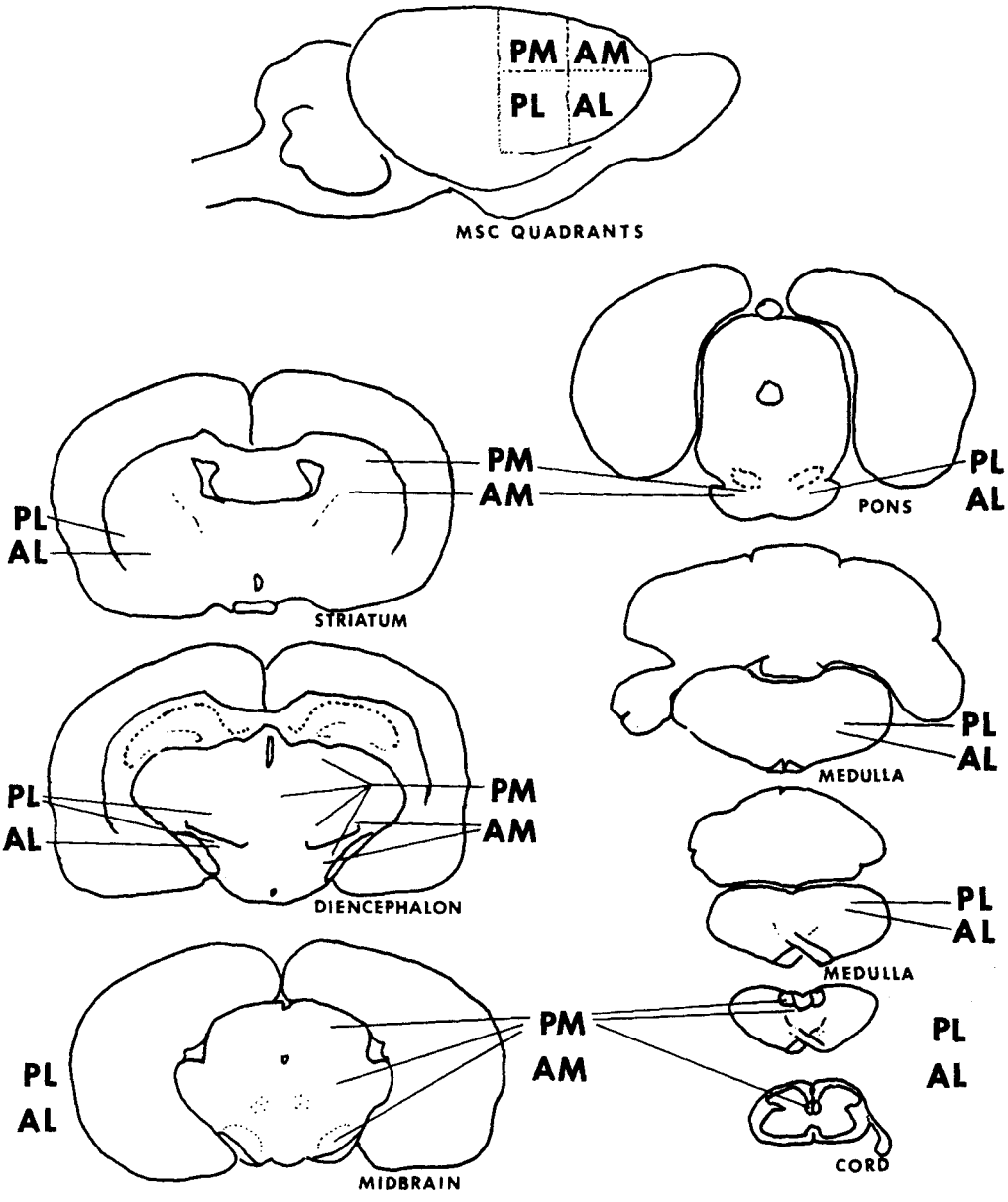

Fig. 3 Diagrams indicating the quadrants of the MSC and regions to which there were substantial projections from them. Where the abbreviations of the quadrants have no lines, projections from them at that level were absent or relatively minor.

vals after cortical ablation to obtain a nearly true count.

In destroying the MSC by ablation to trace the outflow of its axons, our aim was to demonstrate the more peripheral ramifications of the CST optimally rather than determine the number of fibers in the main tract. Trials and errors showed that fibers in the main trunk of the rat's CST in the spinal cord and caudal medulla became argyrophilic at a fairly uniform rate. The optimal interval for demonstrating the

ramifications was shorter than the interval necessary for the appearance of degeneration of virtually all fibers present in the main tract, but they were close enough that the main tract could be studied adequately for our purposes. The time of optimal argyrophilia after ablation of one whole MSC varied greatly with age as the following indicates. In newborn rats, 12 to 16 hours after ablation, the FHN stain demonstrated the main tract, which was unmyelinated and consisted of few fibers and virtually no ramifications as seen in the medulla and spinal cord. After an interval of 24 hours, argyrophilia was no longer evident, and after a couple of days there was no trace of the tract. Progressive dissolution of the fibers, and growth of the animal that stretched out the fiber remnants, had diluted the tract beyond detection; remaining interstitial elements provided no clues that the tract had been there. This contrasted with the persistence of argyrophilic remnants of degenerated fibers, some of which were also stainable with luxol fast blue, as long as 16 months after ablations in adult rats (Hicks and D'Amato, '70). Staining properties were about the same during the first week as at birth. Twenty-four hours was used to show the main tract and ramifications from age 9 to 17 days, and after ablations from age 9 days onward persistence of argyrophilic remnants of degenerated fibers for long periods became noticeable. Between 36 and 40 hours was optimal to show ramifications in rats 21 days old, based on a good many observations; 24 hours yielded scant staining, and by 48 hours fine ramifications stained less. Few animals were studied at 4 or 5 weeks of age, but optimal time increased to 48 to 72 hours. For animals around two months old the optimal interval was 4 to 5 days after ablation; trials increasing the interval by 24 hours from 2 to 9 days showed that visibility of the ramifications fell off as the intervals increased beyond 4 or 5 days, although useful information could still be obtained after longer intervals. At all ages, the cross sectional area of the main tract had been reduced considerably by the degenerative process in the axons by the time the interval for optimal viewing had been reached.

The FHN staining procedure was adjusted to color the degenerated fibers maximally and also to color a good many normal fibers. Recognition of the degenerated fibers rested on a clear contrast between normal axons in continuity and irregularly segmented or beaded degenerating axons, best seen, of course, when a length of fiber was observed. Most brains were sectioned frontally, a few sagittally. In studies of the spinal cord (of mature animals) some samples were sectioned frontally and sagittally. Generally, the brain or cord was divided into convenient blocks and serially frozen sectioned, collecting the sections serially in five jars. Sections in one or more jars were stained as needed. The cord was usually examined at two cervical and thoracic levels, and lumbar and sacral levels.

Eighty-four rats were included in the present FHN study, and others done earlier in first studies of the aberrant uncrossed CST tract and infant CST development provided complementary information. Usually blocks of the whole brain up to the lesion, and sometimes beyond, were cut and stained. The few sagittally sectioned brains (ablation of the whole MSC) were serially sectioned virtually completely and stained. In some instances, those in the infant studies for example, the spinal cord and caudal medulla only were examined.

Methods to check the FHN procedure. A modification by Van Crevel and Verhaart ('67) of the Alzheimer-Mann stain after prolonged chrome fixation distinguishes normal myelinated fibers from those undergoing Wallerian degeneration. It was applied to frontal sections of the medulla and spinal cord in rats 3, 5, 7, 9, or 30 days after one MSC had been ablated at about age two months, and showed that almost all of the fibers had degenerated by five days and that essentially all had degenerated by 7 and 9 days. Counts of fibers, to determine whether any disappeared altogether in the intervals after an ablation, were not done. The Alzheimer-Mann method was superior to the FHN stain in demonstrating virtually all the fibers in fine detail in cross-sections of the main tracts, but was of little value for the ramifications.

Introduction of tritiated proline or isoleucine, labeled precursors of protein, into

the MSC's of infant and adult rats demonstrated fibers of the CST by slow axonal transport of the incorporated label in autoradiographs (Hicks and D'Amato, '71). It indicated the main course of the CST in adult, newborn, and 3- and 5-day old rats. There was precise correspondence with findings by conventional histologic and FHN methods in delineating the main tracts, but the procedure was of no value for outlining the fine ramifications of the CST. The distances traversed by the labeled material in the CST at different ages, as determined by killing animals at intervals after the intracerebral injection, is noted briefly in RESULTS.

Studies of the CST projections of the MSC and their development

There were three groups of experiments: those determining the CST projections from the MSC as a whole, from its quadrants, and in circumstances relating to the development of the miniature uncrossed "plastic" tract. Fewer data were gathered in stages before two weeks than later.

CST projections from whole MSC and their development. MSC ablation followed by the FHN stain was done at 1 day (newborn), 3, 5, 7, 14, 21, and 25 days, 4 and 6 weeks, and 2 and 3 months. Except at 4 and 6 weeks, two or more animals were studied at each age. Some older animals, up to 16 month of age, had been studied previously (Hicks and D'Amato, '70).

CST projections from the MSC quadrants. These were usually determined by ablating one of the quadrants unilaterally in rats three weeks or two months old. Two different quadrants, one on each side, were ablated in a couple of animals, providing a comparison of projections in the same circumstances in one specimen. Quadrant studies of infant rats were not done, but some indirect information on the matter was obtained in the following.

Time and place of origin of the miniature aberrant uncrossed CST from the MSC. To determine when the miniature tract appeared at medullary levels, unilateral MSC ablation was done at birth; then the other MSC was ablated 7, 9, 14, or 17 days of age and the FHN method carried out. To determine at what ages the aberrant growth could be elicited, the initial ablation of one MSC was done at 3, 5, 9, or 14 days of age and then at 21 days the other MSC was ablated and the FHN method applied. To find out which MSC quadrants contributed to the little tract, and whether the aberrant tract fibers pursued courses and destinations correspond-to those of their normal counterparts, the MSC on one side was removed in rats at birth, and then at three weeks or two months of age one of the quadrants of the other remaining MSC was ablated, and the FHN procedure applied. We also did the converse experiment, ablating one of the quadrants at birth, then removing the whole opposite MSC at maturity.

Studies of cortical alterations adjacent to MSC ablations in newborns

The isocortex of the rat at birth was immature; neurons in its outer layers were only beginning to differentiate, and many had yet to arrive on their migratory paths. Virtually no glia had immigrated into this region of the brain, and many afferent axons would enter the cortex later (D'Amato and Hicks, '65; Hicks and D'Amato, '68). The capillaries of the cortex were still differentiating (Caley and Maxwell, '71). Against this background, we sought for (1) changes in the cytoarchitectural differentiation or transformation of cortical neurons that might occur in the cortex adjoining the site of infant ablation, and (2) possible sources of aberrant CST axons other than those forming the aberrant tract already mentioned. In the first, histologic examination of the sites of MSC ablations was made. In the second, ablation of dorsal occipital cortex in mature animals that had had both MSC's removed at birth was followed by the FHN procedure, to see whether this region formed aberrant CST fibers, which it normally did not.

Methods of operating on animals, consequences to the young brain and errors in making ablations

Ablation of MSC. As previously described in detail (Hicks and D'Amato, '70), with the animal under ether anesthesia and viewed with a dissecting microscope,

the cerebral cortex was aspirated through dulled 30 to 40 gauge hyodermic needles. Access was through a scalp incision and a skull opening made by turning a bone flap. Scalp incisions were closed with sutures. Infants were operated on at room temperature and returned to their mothers a couple of hours later, when they resumed nursing. More mature animals recovered equally quickly from the acute effects of anesthesia. Mortality from operations has been a few percent and infection almost nil.

Ablations were done after the measurements necessary for the whole MSC or its quadrants were marked on the exposed skull. At the conclusion of the experiments, whether for FHN study or behavioral studies, the brain was removed by autopsy, fixed in formol-saline (10% formalin in 8.1% NaCl) and photographed on all sides, with a millimeter ruler, to show the position and extent of the lesions. Outline drawings of the brains magnified $\times 3$ were traced from the photographs (color transparencies). In animals used for functional studies, principal reliance was put on the gross appearance of the lesions, but microscopic frontal sections were also prepared of some of the brains to examine the margins, extent of the lesions, and remote degenerative effects, especially in animals operated on in infancy. Several examples of the ablations are shown in Plate 1.

Consequences of operations on the newborn infant brain. Histologic reaction to injury was different in the early infant rat brain from the adult, as the present and earlier studies showed. Proliferation of vascular tissue elements and leukocytic and phagocytic responses were much less in the infant. Astrocytic gliosis did not follow single injuries such as incision or ablation: at birth where glia were present they were relatively unreactive, and in the isocortex, as noted before, very few had yet arrived. The response of nerve cells to direct injury varied in different circumstances. If the cortex was cut with a very thin knife, a few cells were killed and disappeared, and there was little visible evidence of damage later on. If a remnant of the mantle was left after an operation relatively isolated but with adequate blood supply, it continued to grow in a limited way. In other situations, nerve cells were much more vulnerable to injury than those in adults. Transneuronal degeneration with cell death developed fairly rapidly in some sites. Retrograde degeneration of thalamic neurons whose axons had been cut in ablation of the MSC or visual cortex, for example, was fulminant, with visible evidence of necrosis of these cells in less than a day and virtual disappearance of the cell bodies in less than three days. The cell loss was reflected in permanent architectural distortions of the corresponding thalamic and other regions. Thus in some circumstances the consequences of ablation of cortex or other region in the infant was much more severe and far-reaching than in the adult. Bilateral removal of the MSC in infants resulted in corresponding loss of thalamic volume and there was both apparent and real reduction of the occipital regions, due to gradual gross displacements of parts of the brain, disappearance of axonal projections, retrograde and transneuronal neuron deaths, and perhaps secondary trophic effects that are yet to be defined.

Errors in making ablations. There were variations from the ideal in ablating the cortex. In the newborn, especially, the lesions usually encroached considerably on the white matter, and sometimes extended to the lateral ventricle. In plate 1, figures 3, 6, and 7, the ventricle is visible partly because it was encroached upon at operation and partly because the thin residual membrane enclosing it was torn at autopsy. Sometimes, as in bilateral MSC ablations in newborns, small cortical remnants were left, which grew up relatively isolated and only scantly connected to adjacent brain. Skull openings were made smaller than the intended area of ablation to avoid damage to the adjacent brain or blood vessels, and lateral quadrants were approached by relatively small openings to spare the musculature and bones of the lateral part of the head and face. Generally the ablations included much or most of the quadrant intended. The inferomedial region of the frontal pole tended to escape ablation, and lateral quadrants did not always reach quite to the rhinal fissure. Lesions in animals killed within one to five

days for FHN studies, being fresh and not yet having undergone shrinkage and collapse, usually resembled the quadrant intended, but lesions of much longer standing that had undergone these changes appeared relatively smaller. We discuss these variations further in the RESULTS as each group of animals is considered.

The variable encroachment on the white matter beneath the sites of cortical ablation involved passing fibers. The degenerating fibers that this added to what were properly the efferent fibers of the ablated cortex certainly confused the picture close to the ablation, but consistency of results among animals in the more distal projections indicated that this was not a substantial spoiling factor for the objectives of the study.

Methods for examining locomotor functions and limb placing and positioning responses

Background of previous experiments. In previous experiments with rats with cortical ablations, hemispherectomy, cerebellectomy or malformations of the brain or retina induced at birth, we used a number of methods, some of our own devising, for examining developing neurological functions and behavior. They were begun at the time of birth and were carried through until mature life, being adapted to the changing characteristics and capabilities of the animal as it grew up. Included were elements of a neurological examination applicable to a rat, tests of visuomotor function, visual pattern discrimination, locomotor function and coordination. Related to the last two were observations of the animals jumping variable distances and directions from one small platform to another stationary or moving platform, climbing, and walking and running on a level board track or on horizontal ladders with cross rungs or longitudinal rungs. There were also tests of tactile and visual placing reactions, and observations of natural use of placing and grasping responses in traversing elevated narrow pathways. Slow motion movies recorded representative excerpts of many of these activities.

Reinforcements for the animals' behavior from the middle of the third week on for several weeks or more were the opportunity to explore and perform the tasks, and being handled. Jumping from one platform to another, learning to discriminate visual patterns such as upright versus inverted triangles on a Lashley apparatus and running along elevated narrow paths required no other reinforcement in the first weeks (Hicks and D'Amato, '69, '70, '74b).

It was against this background and from this array of examinations that the principally used tests in the present experiments were selected: locomotion on a broad flat track, locomotion on narrow pathways, and examinations of tactile placing.

Chronology of some developing motor functions and other behavior against which abnormalities were measured. When the rats were born between 22 and 23 days of gestation they promptly directed their (motor) behavior to nursing by crawling, rooting, struggling and fighting, if necessary, to that end. They were handled almost daily from birth through juvenile life, then usually on a less frequent schedule. Tactile placing, described later, could be elicited from around the end of the first week, being hard to separate from spontaneous movements before then. There was a rapid transition from the immature to the mature pattern of locomotion in the third week, usually during the 17th day, as noted in the beginnning of the article. Eyes opened around the end of the second week, and the rats became increasingly exploratory from that time, beginning to move along tracks, narrow paths, platforms, or whatever was presented to them to explore. By 17 or 18 days they began to run up and down a board track and by three weeks they were able to jump 20 cm from one platform to another. If they had been introduced to a Lashley visual pattern discrimination apparatus toward the end of the third week, they could be approaching errorless performances by four weeks of age and attaining them soon thereafter (Hicks and D'Amato, '70, '74b).

The immature gait at the beginning of the third week was an awkward combination of crawling with the belly on the ground and walking with legs extended as in mature locomotion. The rat positioned its feet poorly on edges, compared with a

more mature animal, allowing hind limbs to dangle briefly over the edge of a track. In contrast, mature locomotion was characterized by a rhythmic cycle of movements of the four limbs, and the feet were positioned in coordinated sequence. The head and tail were held steady, and the trunk movements related to limb positions were precise. This propulsion was adjusted to a walk or a run, to making turns, and being brought to a stop gradually or abruptly. Like many other mammals, the rat in slow motion movies appeared to move smoothly and gracefully (Gray, '68). A distinctive characteristic of motion of the forelimbs as seen in the movies was a horizontal foreward thrust of the limb, preceding placing it on the ground, in which the foot was extended, toes spread and extended, and as the foot was brought down, outer toe and ball of the foot touched ground an instant before the rest of the contacting surface of the foot. Impairment of this thrust, alluded to in the beginning of the article in connection with MSC ablations and hemispherectomy, was associated with a slightly shorter stride, but did not seem to diminish speed.

During locomotion on a flat level board track (3 m long, 15 cm wide, curved on a 2.2 m radius for movies and marked at 10 cm intervals), the feet of the normal rat older than 17 days virtually never slipped as much as a toenail over the edge, and if the animal was held with its feet over an edge it retrieved them with alacrity and force if necessary, to a normally placed position. With increasing age and body size, the basic pattern of locomotion remained the same. At five or six weeks, rats began to gallop on rare occasions, using a different sequence of limb positions, but we did not study this activity. Normal rats two months and older, that had been introduced to the various activities that have been described, continued to run actively, easily, and precisely on a track or along narrow paths, though with a normal range of errors on the latter as we describe next.

Narrow pathways were elevated about 25 cm from ground, horizontal, about 90 cm long, and there were three: two (round) wood dowels, 7 mm in diameter, approximated side by side; a narrow strip of wood, rectangular in cross section, 12 mm wide and 20 mm high; and a large (round) wood dowel, 23 mm in diameter. Normal mature rats could walk or run on these with ease, positioning their feet, limbs, and other parts of the body with precision and grace. Such an animal is seen traversing the round dowels in figure 4A. Yet the paths were difficult enough that an animal seldom traversed the whole length without error, and fairly frequently a foot or a limb slipped off. Rarely one nearly fell off. After slips, the limbs and feet were retrieved quickly and repositioned by very rapid, precisely directed searching, grasping, and placing movements. If an animal nearly fell off, its scrambling was accurate and usually rapidly effective in regaining a normal upright posture and resuming locomotion. When rats were introduced to these narrow paths at about two weeks of age, they were extremely clumsy and let their limbs dangle over the edges of the path. They improved rapidly, aided by the normal mid-week transition to mature locomotor mechanisms and further daily experience. In all experiments, foam cushions protected the animals from possible harm if they fell anywhere at all, and also avoided possible aversive effects of falls on exploratory expression of their curiosity.

A naive rat three weeks to two months old, introduced to these narrow paths, stumbled and slipped and could scarcely negotiate them at first, but with experience of a couple to several sessions could usually do very well from then on. We elected to avoid this kind of variability in learning and accept another: all the rats in these experiments (except one animal) were run on the program described, beginning at about two weeks of age regardless of whether they were operated on at 1 day, 3 weeks, or 2 months.

Tactile placing could be tested several ways. "Lateral tactile placing" was the most reliable and reproducible. Touching the forefoot to the vertical side of a ledge, such as the board track, while holding the animal in a normal upright position with one or both hands resulted in instant raising of the touched foot and placing it accurately on the top of the ledge. The eye was shielded, to prevent visual placing, by the experimenter's finger, or by a jersey cloth sheath over the head to which the

animals had become accustomed from infancy. Indeed, this mask which covered the vibrissae and eyes tended to heighten placing responsiveness to touch, and to stepping if it was tested. The stimulus in lateral tactile placing was probably displacement of hairs and skin touch. It wasn't necessary to press the foot or limb and passively move the joints against the ledge to get the response in normal animals. Touching the dorsum of the forefeet or the toes to a ledge in a forward direction elicited placing but it was a little used maneuver because it was not abolished and sometimes only variably impaired by MSC ablations. Lateral tactile placing of the hind feet was regularly tried but normal rats often gave no response this way to touch or stronger contact with a ledge. Chin and whisker placing were not usually tested. Visual placing was regularly examined by allowing the animal to see the ledge, platform, or track with its eye on the side of the forelimb whose placing was to be tested. Normally the animal turned its head slightly toward the ledge and put its foot on it. Earlier studies showed that in some instances when an animal did not tactually or visually place, say on its left side, it would nevertheless turn and place with the right forefoot if the ledge could be seen by the right eye. Circumstances leading to this response did not develop in the present experiments.

Some of the animals with MSC's bilaterally removed at birth were also tested on visually guided jumping procedures and visual pattern discriminations on the Lashley apparatus, already mentioned (Lashley, '30; Hicks and D'Amato, '70, '74b). These experiments were of interest especially in respect to the initiation of movement and carrying through a discriminative learning procedure involving movement in the absence of an MSC-CST. They are included in the RESULTS.

In all these activities, but especially locomotion on the track and narrow pathways, slow motion movies (64 frames per second) frequently revealed details the eye could not see.

Assessing abnormal locomotor function and limb placing and positioning responses. The patterns of disordered movement that we categorized were the empirical result of observing rats with a variety of cortical ablations performing on the broad flat track, narrow pathways, while having placing responses tested, and in other circumstances. It is appropriate to anticipate some aspects of the results here to explain how we assessed abnormal motor-sensory functions.

On the flat track we compared locomotion on the flat surface by an experimental subject with that of littermate normals, looking for deviations from the normal extension of the forefeet and digits, placing and positioning the feet on the track and overall rhythmic smoothness of movement. At the edges of the track we looked for degrees of slippage of the fore and hind feet and limbs off the edge of the track. This impairment ranged from just letting the toes slip over slightly with quick retrieval to letting the feet or sometimes much of the limb slip off. We tested whether the affected limbs would be allowed to dangle briefly over the edge in unnatural repose if the animal were gently positioned motionless that way. We dubbed this slippage of the feet off the edge of a flat track during walking and running, "loss of locomo-

Fig. 4 Tracings of rats in movies to represent some of the characteristics of motor-sensory behavioral alterations that resulted from ablating the MSC or its quadrants. Their brains, removed some time after the movies, are shown in plate 1. A. Normal rat seven weeks old positioning its feet precisely as it traverses a narrow path of two small dowels. B. A rat whose MSC's were removed bilaterally at birth running virtually normally on a flat broad track at the age of two months. Its brain removed at seven months appears in plate 1, figure 2. C. A rat six weeks old that had its right MSC ablated at birth. The whole left forelimb and left hind toe have slipped off the edge of a broad flat track. The animal's brain is shown in plate 1, figure 3. D. A rat three months old, both of whose PM quadrants of the MSC were ablated about three weeks earlier. Though tactile placing was retained, the feet and limbs slipped off edges of narrow paths, as the left hind limb demonstrates here. The animal's brain appears in plate 1, figure 4. E. A rat five weeks old whose PL quadrant of the right MSC was ablated at birth, applying its left feet in slipshod manner to a narrow path, unable to grasp and hold on well. Its brain appears in plate 1, figure 5. F. Littermate rats a month old whose PM and PL quadrants of the MSC were ablated on both sides at birth. They show great difficulty negotiating a narrow path of two narrow dowels, grasping almost aimlessly and holding on poorly. Their brains are shown in plate 1, figures 6, 7.

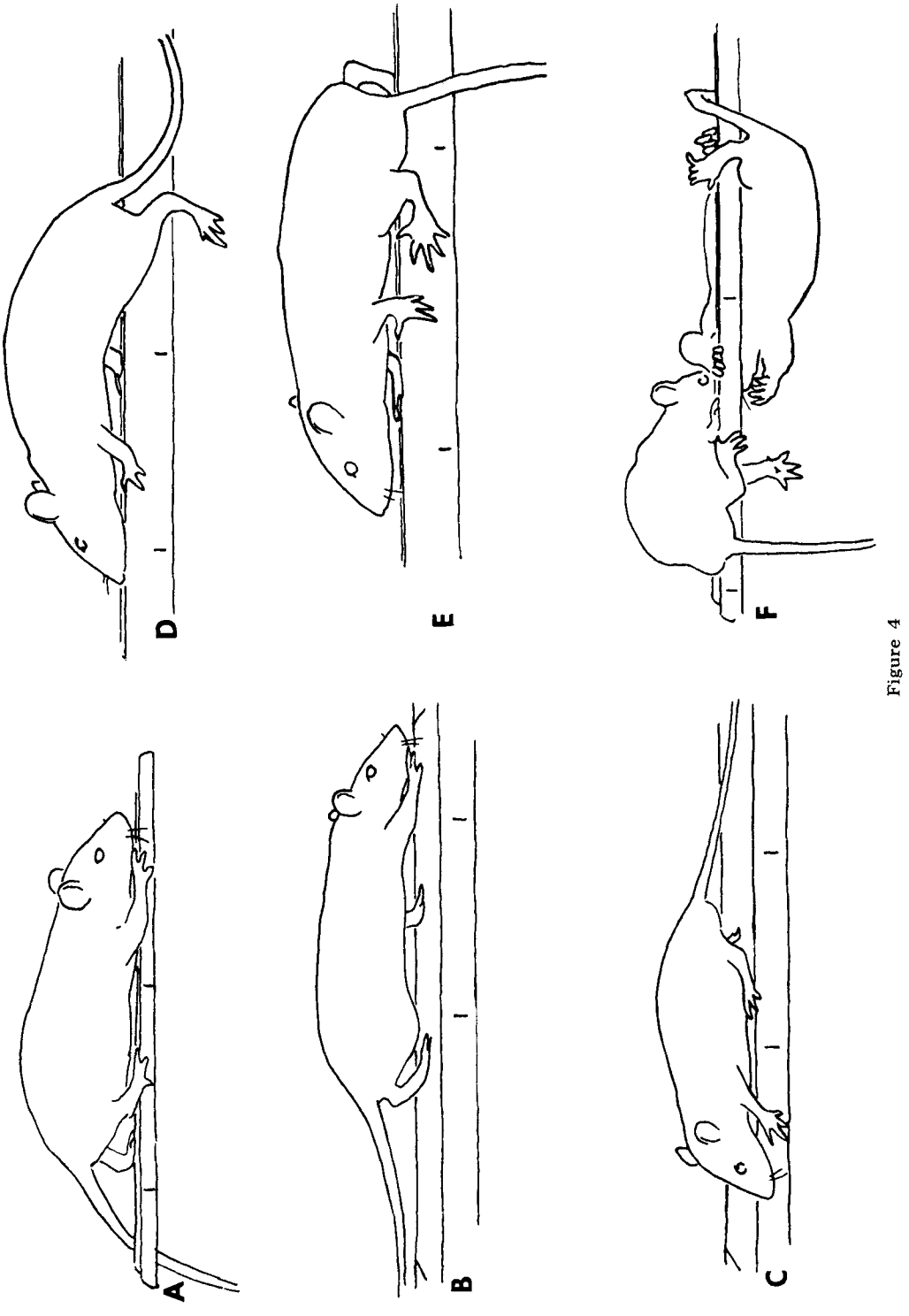

Figure 4

tor placing" and the unnatural positions of the limbs "dangling."

On the narrow paths, we learned to look for two patterns of abnormality. One was a defect in which the feet slipped off the edges or sides of the narrow paths, resembling the slipping off of the edges of the flat track; that is, a form of impaired locomotor placing. It was especially noticeable on the rectangular strip, which sometimes revealed the defect when it was not evident on the flat track. The other deficit was an inability to grasp the paths securely during locomotion, especially the small dowels and rectangular strip, and having not grasped well, a further serious defect in directing the feet back to the path. In this deficiency the animal's dislodged feet grasped blindly at the other foot or the animal's own face, or whatever part of the path it contacted. A mild version of this defect was a slipshod positioning of the foot on the path, sometimes as often as each step, in contrast to the normal, relatively uniform positioning pattern which was rapidly and smoothly adaptive to almost any contour encountered. As will be seen in the RESULTS, in their simplest expressions, the slipping or loss of locomotor placing was associated with unilateral ablation of the posteromedial quadrant (PM), and a relatively mild version of the grasping deficiency with ablation of the posterolateral quadrant (PL).

In animals with cortical ablations whose lateral tactile forefoot placing was tested, we classed the responses as normal, absent, or impaired, and described the impaired response when appropriate. Normal was the immediate, fast, accurate response following just touching the foot to the ledge. Absent was no response, even to pressing the limb slightly against the side of the ledge or platform. Impaired meant a deviation from the fast, accurate, almost invariably executed normal response. Impaired was generally expressed in one of two ways: a slight delay in initiating the response and performing it more slowly than normal — sluggish — or simply responding only occasionally and usually sluggishly. Another abnormal placing response, recently observed after certain ablations, was a hyperactive one in which touching the feet laterally to a ledge resulted in an instantaneous placing movement which considerably overshot the mark, occasionally wildly. Visual placing was classed as present or not. Lateral tactile placing of the hind limbs was tested and at times, when it was present, it was a useful maneuver as shown in the RESULTS. Absent or impaired lateral tactile placing, allowing the feet to slip off the edge of the broad track, and allowing them to slip off a narrow path were not entirely equivalent abnormalities: for example, rats with MSC's bilaterally ablated at birth placed tactually normally, and they never let feet slip off the edge of a flat track, yet they got into considerable trouble on the narrow paths.

Testing placing reactions was done by applying the stimulus about 5 to 10 times as necessary as part of each session when locomotion on a track and traversing narrow pathways were being observed.

RESULTS

Postnatal development of the CST

Normal growth of the main trunk of the CST. It has been known for a long time that the rat has one of the largest corticospinal tracts in proportion to brain size of any mammal; it forms the medullary pyramids as in many other mammals, crosses completely in the major caudal medullary decussation and continues in the ventral part of the *posterior* funiculus the length of the spinal cord (Ranson, '13; Barron, '34; Barnard and Woolsey, '56).

At the time of birth, a small number of CST axons had reached the caudal medulla, decussated there and entered the ventral part of the dorsal funiculus of the cervical spinal cord for a few segments. These pilot fibers, studied by MSC ablation and FHN stain (and by axonal flow of tritiated proline or isoleucine injected into the MSC) grew as far as the mid-thoracic region by three days and to about the level of the first lumbar vertebra by the fifth day. Allowing for the animal's body growth in this early period, a rough estimate of the growth rate of the axons was somewhat less than a centimeter a day.

At the end of the first week, the pyramids in the mid-portion of the medulla were still relatively tiny, dorsoventrally

flattened structures as seen in paraffin-embedded, dye or silver stained frontal and sagittal sections. By ten days they had enlarged considerably, and between 10 and 14 days they roughly doubled their cross section, and roughly doubled it again between 14 and 17 days. Between 17 and 21 days this rate of increase in cross section diminished, and fell off considerably by 25 days. The enlarging cross section was essentially the result of an increase in numbers of axons, a surge of growth of CST fibers caudalward through the medulla during the second week and into the middle of the third. Increasing diameter of axis cylinders, growth of interstitial elements and myelination in this period contributed very little to the expanding cross section compared to increased numbers of axons. Myelination in the CST lagged considerably behind that of most other tracts in the medulla and cord. It was still progressing actively between 21 and 25 days, and the tract was still contrastingly less stained by luxol fast blue at three weeks than were neighboring ones.

The surge of growth of the fibers through the spinal cord followed a later schedule. The increase in size of the CST in the cervical cord was greatest from 10 to 25 days. At 14 days there were little more than pilot fibers in the lumbar region, but by 21 days the tract here had grown a great deal.

Rostrally at the level where the CST fibers in the peduncle gathered into a more circumscribed bundle in the rostral pons, a more advanced time schedule of growth could be recognized. By the end of the first week the cross section was approaching mature size and there was not much increment between then and 21 days.

These observations on CST growth were approximations based on the several kinds of material and they provide orders of magnitude of steps in its growth. In figure 1 an overall view of growth of the pyramids in the medulla and the CST in the spinal cord in the infant and early juvenile period is shown. These outline tracings of microscopic sections of paraffin-embedded material described earlier emphasize that other parts of the nervous system, such as the white matter of the spinal cord, were also growing in this period. Figure 2 shows tracings of the pyramids and CST from the same material over a more extensive period. The continuing increase in size of the tract after about the first month was attributed mainly to growth of myelin and interstitial cells (Bernstein, '66).

The histologic autoradiographic studies of slow axonal flow after injections of tritiated amino acids of high specific activity into the MSC of newborn and adult rats were of interest to the logistics of growing cells. Examination of various levels of the brain and spinal cord in a series of animals killed at daily intervals after the radioactive compounds were injected showed that the label incorporated by CST neurons was transported along their axons in the CST at a rate of around 1 cm a day in both mature and infant animals. In three days, for example, the label had reached the caudal brain stem of the adult, but in the very much smaller infant rat, now four days old, it had virtually caught up with tips of the growing axons in the spinal cord CST (Hicks and D'Amato, '71).

Ramifications of the CST and their growth

The mature picture. FHN stains of the brains of rats of various ages killed at appropriate intervals after the total surgical removal of one MSC showed the following general projections at maturity. There was a fairly abundant outflow of fine fibers into the caudate-putamen from the fascicles of corticofugal fibers, more from the rostral than the caudal quadrants. Numerous degenerated fibers extended to the posterior cortex dorsally and into the cingulum, and they crossed in the corpus callosum to the opposite cortex. There was abundant projection to many parts of the thalamus, pretectal and subthalamic regions, but not to the hypothalamus. The midbrain colliculi, tegmentum and the substantia nigra received fibers. The pons received an abundant component and a few fibers entered the midline and regional reticular formation at this level. As it became condensed into the pyramidal tract of the medulla, the CST gave off some fibers, mostly to the opposite rostral reticular formation just caudal to the level of the trapezoid body, and more posteriorly formed the major

caudal medullary decussation. The caudal decussation of fibers, which were virtually 100% crossed, formed three major components: those to the caudal medullary reticular formation and caudal spinal trigeminal nuclei, those to the posterior column nuclei and those forming the CST of the spinal cord. The latter tract ran exclusively in the base of the dorsal funiculus to the end of the cord.

The projections to the caudate and putamen appeared as fine reduced silver grains fairly evenly distributed in the neuropil between the corticofugal fascicles. They also involved the nucleus accumbens. A few larger individual fibers represented by beaded strings of grains could be seen. There were grains in the neuropil of the globus pallidus away from the passing fascicles. In the internal capsule in frontal sections, the MSC outflow occupied intermittent large areas somewhat more concentrated medially, taking an increasingly more medial position as the peduncles were approached.

Fibers to the thalamus and subthalamic regions were abundant, sweeping into most of the ventrobasal complex in fascicles and forming a fairly dense bed of terminations in places. Fewer fibers entered the dorsal and lateral regions, and the geniculates were essentially spared unless the visual and auditory cortex regions had been encroached upon as occurred in a couple of animals. The anterior dorsal (large cell) nucleus of the thalamus was sharply spared while regions around it received fibers. Probably the heaviest concentration of terminations was throughout the parafascicular nucleus along the habenulointerpeduncular tract.

Geographically related to this heavy projection, seen best in whole brain sagittal sections, were dense projections to the zona incerta, field of Forel, rostral half of the subthalamic body and a region rostral to the red nucleus, probably corresponding to the rostral part of the interstitial nucleus of Cajal. Fibers entered these subthalamic regions by two routes, one by rostral-caudal inflow of corticofugal fiber bundles of the internal capsule as it approached the level of the peduncle, and the other by a dense right angle influx from the peduncle itself, the radiation of Forel, coursing just rostral to the substantia nigra (Gurdjian, '27). Extension of fibers across the midline to contralateral thalamic and subthalamic centers was extremely sparse (Rinvik, '68).

Somewhat continuous with these subthalamic influxes were bundles and ill-defined fibers coursing to the central pretectal regions, deep gray layer of the superior colliculus and to the ventral lateral and generally central tegmental regions of the midbrain. Many seemed to parallel the incerta-tectal and incerta-tegmental fibers. From the caudal internal capsule and peduncle, fiber bundles coursed into the substantia nigra, more in the reticulated part. Some probably passed through and central to the adjacent ventral gray of the midbrain. Virtually no degenerated fibers were seen in the large-cell part of the red nucleus, though they were abundant dorsolaterally around it, where the long dendrites of its large cells may extend. Some fibers entered the zone of small cells of the rostral part of the red nucleus. As the fibers gathered to form the more condensed and circumscribed CST in the pons, many more fibers departed to the ipsilateral adjacent pontine nuclei ventrally, fewer to the reticular formation dorsally and medially.

Beginning about the level of the trapezoid bodies and cochlear nuclei and extending nearly to the rostral level of the XII nerve nucleus, fibers again took off in substantial numbers, in planes at right angles to the brain stem's long axis, to travel principally across the midline to the opposite reticular formation, mostly dorsolaterally, few ventrally. Some also entered the region of the oral trigeminal nucleus. A good many fibers from this minor "rostral decussation" also ascended throughout the median raphe nearly to the floor of the fourth ventricle, and a very few coursed into the ipsilateral reticular formation. No further excursions of fibers from the pyramids occurred until the rostral beginning of the major caudal pyramidal decussation in the medulla. These decussating fibers, after they crossed the midline, ran in great abundance into the reticular formation, medially and laterally, at levels throughout the longitudinal extent of the decussation, to the caudal trigeminal nucleus and nearby

substantia gelatinosa, the cuneate and gracile nuclei, and the caudal part of the commissural nucleus just ventral to gracile nucleus (Torvik, '56). And, of course, a large component continued caudalward to form the CST in the spinal cord. In the reticular formation the fibers were abundant in the gray matter, but some also joined the longitudinal fiber fascicles there and followed them at least short distances caudalward and perhaps rostralward, as seen in sagittal sections. No degenerating fibers entered the XII nerve nucleus. The cross section of the CST in the spinal cord was about half that of the pyramid, indicating that a very large proportion of fibers to the medulla were not collaterals of fibers continuing in the spinal cord. This parcelling of the CST was further borne out in the study of the outflow of the MSC quadrants described later.

In the spinal cord, fibers left the main tract to enter the ipsilateral adjacent medial gray matter of the posterior horns. While many appeared to turn off at right angles to the long axis of the cord, as was so often the case in the brain stem, longitudinal horizontal and sagittal sections showed that many fibers took off at a much smaller angle and coursed for some distance, gradually entering the gray. We could not make a good estimate of the distance, only that it could be up to several hundred microns.

Growth of ramifications. FHN studies in animals younger than two weeks were scant except for recording the growth of the first pilot fibers along the CST in the spinal cord, as noted. By 14 days the mature pattern was fairly well developed as far as it could be revealed by the FHN method. There were several substantial changes in the third week, the period when mature locomotion was assumed and the paradoxical placing responses mentioned at the beginning showed up. It was difficult to detect an increase in ramifications in the striatum and diencephalon after two weeks, but the following were real. There was an increase in profusion of fine fibers in the pons between 14 and 21 days, a difference between 14 and 17 days not being certain. In the caudal medulla at 14 and 17 days, there was a dense infiltrate of fibers extending from the decussating bundles into the medial and mid-reticular zone, but virtually none more laterally. By 21 days fibers had extended in great numbers to the lateral limits of the reticular formation and the trigeminal zones. There was a coincidence, at least, between this change and the increasing number of longitudinal fiber bundles, described earlier in dye stained sections. The CST in the spinal cord showed growth between 14 and 25 days. There were very few CST fibers in the rostral lumbar region at 14 days, but growth to nearly the full complement had occurred between 17 and 25 days. Between 17 and 21 days the fibers exiting from the spinal CST into the adjacent posterior horn gray matter increased substantially as seen in horizontal and frontal (cross) sections of thoracic cord.

It appeared that there were more fibers in the reticular formation of the caudal medulla at two months than three weeks, but modest differences in fiber density were difficult to be sure of in such situations. Single animals were studied at 3.5, 4 and 5 weeks, but differences between them and animals three weeks old were not certain in any respect.

Distribution of CST fibers from different MSC quadrants

Each quadrant was ablated in an animal three weeks and two months old. Additional information came from animals in which two different quadrants were removed, one on each side, and from those animals from which a quadrant was ablated on one side at three weeks or two months following removal of the MSC on the other side at birth, to demonstrate the sources of aberrant CST fibers. PL was represented three times, the others four.

The quadrants showed some quite striking differences in their projections and revealed that the CST was not a uniform system of corticospinal fibers from the MSC with collaterals given off to stations along the way, as is often depicted in current diagrams of the CST. Principal features of the quadrant projections are summarized in figure 3, and an example of projections from PL and PM is given in plate 2, figures 11, 12, 13.

PM gave off some fibers to the adjacent striatum. PM fibers accounted for the ex-

tensive longitudinal projections in the cingulum and to caudal cortex mentioned in the account of the whole MSC ablations. Fibers from PM first gathered into the dorsal medial border of the internal capsule, then into large separate bundles more caudally, and then to the medial half of the cerebral peduncle. Projections to the thalamus, subthalamic regions, pretectal and midbrain structures, and pons were qualitatively similar in distribution to those described for the MSC as a whole, but those to the midbrain and pons seemed less dense than those from the MSC altogether. The projections in the medulla were to the cuneate, gracile, and commissural nuclei. Very few or almost no fibers projected to the reticular formations or raphe regions, except in one of the four animals in which a fair number of fibers ran into the reticular formation intermittently in the more caudal medulla. The number was in no way comparable to those arising from PL. PM was the only source of the spinal CST; some fibers from the other quadrants extended to the junction of the most caudal part of the posterior column nuclei and beginning of the spinal cord, apparently ending in those nuclei and possibly the nucleus basalis and dorsal commissural nucleus at the medullary-spinal junction (Torvik, '56).

AM gave off fairly numerous fine fibers to the striatum from the fascicles it sent through it to the internal capsule. AM fibers first ran in bundles in the middle of the internal capsule but soon moved to the medial extreme of the peduncle, holding medially in the pons and medullary pyramid. Considerable numbers of fibers ran to the thalamus and subthalamic regions as in the case of ablation of the whole MSC. Fibers to stations in the midbrain were rare. Ramifications to the pontine nuclei were principally caudal and medial. Fibers coursed through the entire extent of the major caudal medullary decussation, but they were few in number. A few went to the gracile and cuneate nuclei and to gray regions immediately lateral and inferior to them. A very few went to the medial reticular formation there, but virtually none extended into the more lateral reticular formation. A few fibers reached the rostral junction of the cervical spinal cord with the medulla as noted above. Thus AM was not a big contributor to the more caudal reaches of the CST, sending more fibers to rostral targets, the regionally adjacent basal ganglia, thalamus and subthalamus, and some to limited parts of the pons.

PL and AL were similar in their caudal projections, their major terminations being to the more caudal medullary reticular formation, medial and lateral, and caudal trigeminal nucleus. They were the source of the "minor rostral medullary decussation" to the opposite reticular formation, sending fibers also to the trigeminal complex at that level and to the median raphe. They sent virtually nothing to the poserior column nuclei and spinal cord, except the few fibers at the medullary-spinal junction already mentioned. Rostrally AL fibers were central and medial in the capsule, extending medially to the zona incerta and most ventral part of the thalamus, few to the substantia nigra and pons, and none to other midbrain stations. PL probably sent more fibers to the ventral basal thalamic complex than AL. In the animals with both PL and PM lesions, the distribution of bundles of their projections in the internal capsule were complementary, and the influx into the thalamus from PM carried further and more dorsally into the ventral thalamus. PM was essentially the source of the fibers to the more central parts of the thalamus, the parafascicular and dorsal projections.

Growth of aberrant uncrossed CST and other axons following unilateral MSC ablation in infancy

Time and place of origin. When this little tract, as seen in the medulla and cord, was first observed (Hicks and D'Amato, '70), it appeared as miniature bundles and individual fibers that took off from the major caudal medullary decussation of the CST before crossing the midline. The fibers distributed themselves to the reticular formation, trigeminal region, posterior column nuclei and spinal cord like the normal. It wasn't known at the time whether they were unusual collaterals from local medullary fibers or originated some other way. By removing the remaining MSC in a series of animals at

successive intervals after the contralateral MSC had been removed at birth, and using the FHN procedure, it was shown that the aberrant tract did not appear in the medulla until mid-third week. It was difficult to prove that these aberrant fibers were not unusual collaterals sprouting from local fibers. However, their origin from the whole longitudinal extent of the decussation and from the fascicles of decussating fibers before they crossed (plate 3, figs. 14, 15), and their growth schedule that coincided with that of the normally crossing fibers, led us to believe that they had developed normally from the MSC except for their aberrant course. Other aberrant fibers described later seemed to be of a similar nature.

When one whole MSC was removed at birth and then one of the quadrants, AL, AM, or PM, was removed at three weeks or two months, the FHN method showed that the resulting aberrant fiber growth corresponded precisely to the normal distribution of the particular quadrant ablated. For example, when PM was ablated as the second operation at age three weeks or two months, the small cohort of aberrant fibers that developed had gone to the ipsilateral posterior column nuclei and spinal cord, not to other ipsilateral sites. Removal of AL at the second operation showed that the aberrant CST components had gone to ipsilateral sites peculiar to the projections of AL, for example the reticular formation both rostral and caudal in the medulla. Removal of AM revealed that some fibers entering the ipsilateral ventrobasal complex continued across the midline to the opposite thalamic ventrobasal complex (which had undergone considerable degeneration after its corresponding MSC was removed at birth). An exact course of these fibers, in relation to interthalamic commissures, for example, was not determined. Some additional fibers also crossed in the posterior commissure, but their origins and destinations were not recognized either.

When we did the converse experiment, removing AL, AM, or PM at birth, then removing the remaining contralateral (whole) MSC at three weeks, the results were in line with those just outlined, but with scantier aberrant fiber growth response than might have been expected. Because AM and AL operations at birth were sometimes difficult to do with precision, and in this case the AM ablation was suboptimal, the scanty response might be ascribed to the ablations. The PM and, as it turned out, AL ablations, however, seemed quite adequate; and some other explanation for the scant response may be necessary, such as that small lesions at birth were disproportionately less stimulating to aberrant fiber growth than larger ones.

Age at which aberrant CST growth could be elicited. The MSC was unilaterally ablated in rats 3, 5, 7, 9 or 14 days old, then the remaining contralateral MSC was wholly ablated at three weeks and the FHN procedure done. The aberrant fiber growth response as seen in the medulla was judged to be about as great when ablation occurred at 3 or 5 days, less at 7, and just detectable at 9, when some residual argyrophilic degenerated fibers partly obscured the picture. After ablation at 14 days, there were enough residual argyrophilic fiber remnants at the time of the second operation, 21 days, to obscure aberrant fibers that might have formed. In somewhat similar experiments others have shown a similar fall-off of aberrant fiber production (Leong and Lund, '73).

Other forms of aberrant growth following MSC ablation at birth

Possible CST fibers from posterior isocortex. Ablations were made in the posterior (visual) cortex of rats several months old whose MSC's had been ablated bilaterally at birth, and essentially the same ablations were done in littermate normal controls. Three rats with MSC's ablated and two controls have been investigated so far. The posterior cortical ablations, approximately 4 × 4 mm, with sides parallel to the brain's long axis, were placed in the mid-dorsal cortex of the controls. One lesion was brought to 3.5 mm caudal to the bregma and the other to 4 mm. As nearly as possible, corresponding lesions were made in the animals operated on at birth, using both lambda and bregma as references. The lesions were separated from the posterior borders of the ablations made at birth by a thin margin of intact

"posterior" cortex. One of the (four) control lesions closest to the MSC yielded a very few degenerated fibers in the corresponding medullary pyramid and major caudal decussation. One lesion in each of the animals with MSC's ablated at birth also yielded a few degenerated fibers along the "empty" course of the CST in the medulla. The latter results, though not impressive, were taken to indicate a slight degree of aberrant CST fiber growth, and more experiments are in progress.

The PM quadrant of the MSC just rostral to the visual (occipital cortex) was a major source of CST fibers in the medullary pyramid. As has long been known (Nauta and Bucher, '54), and our own experiments showed, the cortex just caudal to PM was a source of fibers that coursed as far as the pons in the lateral part of the internal capsule and the peduncle in the company of fibers attributed to the MSC. In further searches for the origins of aberrant "CST" fibers from occipital cortex, horizontal rather than coronal sections of the hemispheres may be more revealing.

Neuron transformations and aberrant fiber growth in cortex adjacent to ablations of MSC at birth. In a couple of dozen rats subjected to various subtotal removals of the MSC on one or both sides at birth in earlier experiments two manifestations of aberrant development occurred regularly in the vertex cortex medial to the ablations. One was that what would normally have become the most medial part of the MSC differentiated instead into cingular cortex continuous with the normal cingular cortex. The other was the ingrowth of an excessive number of fibers into layer 1 of this aberrant cortex as well as the normal cingular cortex. These are demonstrated in plate 3, figures 16, 17. The cingular cortex has a distinctive appearance, the relative condensation of small neurons in the outer part of layer 2 being one feature; our designation of the aberrant cortex as "cingular" was based on the cytoarchitectural appearance in dye stained sections. Golgi and silver stains have not yet enlarged our information about this cortex. Because the excess fibers in layer 1 appeared to run longitudinally, delicate coronal surgical incisions of the mantle were made rostral and caudal to the site of partial MSC ablations in newborn rats to see if the fibers developed from the rostral and caudal parts of the forebrain. The aberrant fibers grew just as densely as without the incisions. The source of the fibers will be sought in other experiments.

Functional effects of ablating MSC and its quadrants at different ages

Unilateral ablation of the whole MSC. Comparisons of the effects of unilateral MSC ablation done at birth, three weeks and two months showed that there were some differences in the degree of impairment of locomotor and tactile placing and associated disorders of movement among them. In the rat two months old (adult) the operation produced immediate loss of lateral tactile placing and locomotor placing. The toes and feet repeatedly slipped over the edge of the broad track when they contacted it during locomotion, but usually were retrieved quickly each time. If the animal was positioned carefully with feet or limbs over the edge of the track, however, these members were often left hanging passively in the unnatural position for a few moments, then retrieved when further movement was to be initiated, or when the animal was disturbed. Walking or running on the flat appeared normal, except that in some animals the normal horizontal forward thrust of the forefoot and spreading of the digits prior to bringing the foot to the ground in the cycle of running movements was a little depressed compared with normal littermates. This was a difficult distinction to make, however, because stride usually was not shortened and there was variation among the normals. On the narrow pathways, the deficiency showed as slipping of the fore and hind feet opposite the lesion in the manner seen on the edge of the broad track, but retrieval was usually quick, and there seemed to be little problem in directing the grasping actions of the feet. This was somewhat surprising because as we show later grasping was affected when certain more limited parts of the MSC (involving the posterolateral quadrants, PL) were ablated.

The animals operated on at birth were

different in that while lateral tactile placing was lost (in the third week), locomotor placing was less impaired than in animals operated on at three weeks or two months. The animals let affected toes and feet slip over an edge (fig. 4C), but not as much as the animals operated on later. A particularly noticeable difference was that it was virtually impossible to position the animal operated on at birth so that its affected feet would be allowed to dangle over an edge. There was little difference between animals operated on at three weeks and two months, but it was harder to position the three weeks-operated subject so that its limbs would dangle than the one operated on at two months.

Bilateral ablation of whole MSC at birth. Rats with both MSC's ablated at birth (13 animals) were characterized as follows. Examined when they were several weeks old, they typically showed normal brisk and accurate lateral tactile placing with the forelimbs, placed visually normally, never let even a toe slip off the edge of the broad track, and walked and ran essentially normally on the flat (fig. 4B). In running, the forward thrust, spreading of digits, and positioning of the forefeet on the ground was either normal or slightly depressed in respect to the horizontal thrust. This impairment, if it was real, was minor; it was looked for because it had characterized the gait of animals in earlier experiments (Hicks and D'Amato, '70). On the narrow paths, these animals showed marked clumsiness in contrast to their performance on the flat surface: their feet and limbs, the hind limbs especially, slipped off the edges, or sides, and were retrieved with difficulty. The limbs dangled at times and to some extent the feet were poorly directed in grasping to restore their positions on the paths. This latter component of the animals' disorder was not as distinctive a feature as it was in some other animals described later.

The developmental events leading up to this state were significant. In mid-third week, rats with MSC's bilaterally ablated at birth did not at once assume the characteristics of mature locomotion, either as ordinarily carried out on the flat surface, or on the narrow paths. They continued to move very much like infants, on the flat, sometimes backing up a little, turning clumsily, and frequently seeming unable momentarily to start forward movement. This all gradually improved a great deal in the following weeks, locomotion on the flat becoming nearly normal, though some animals never ran as fast as normals and occasionally hesitated in starting forward motion. The few animals that were tested on jumping either were never able to jump from one platform to another or only did so after a good many weeks. In attempting to jump, they moved back and forth along the edge of the jumping platform, leaning outward and straining as though to jump, sometimes falling off in the effort, occasionally backing off the platform. Despite the clumsiness in circumstances other than flat surfaces, several animals were introduced to the Lashley visual discrimination apparatus just before age three weeks, and allowed to approach and choose the doorways from a closely placed "jumping platform." They carried through the program, which included learning to discriminate vertical from horizontal stripes, and upright from inverted triangles. Of the four tested this way, three attained criterion of 20 consecutive errorless trials in one session, and a fourth after many sessions found a plateau of about two errors in 40 consecutive trials in a session. This animal was also tested on reversal of the stripe patterns three times, which it learned though more slowly than normals. The visual ability in these animals was not unexpected, perhaps, because adult rats with extensive cortical ablations have demonstrated it, as others have shown.

In attempting to assess what the MSC does for the rat these findings were of interest to us. In sum, an MSC was essential for locomotion on irregular terrain, but not ordinary locomotion on a flat surface; it assured the rapid normal maturation of locomotion, but without it ordinary locomotion developed slowly; perhaps most interesting, the MSC was not essential for learning tasks involving sequences of movements to accomplish them, although without an MSC they were done clumsily.

Bilateral ablation of whole MSC at three weeks and two months. For a couple of days after the operation, animals with

these lesions were helpless on a narrow path, all four limbs dangling over the edges; on the broad flat track they sometimes fell over the side as the affected limbs slipped over the edge, but walked fairly well on the flat surface. Within days, locomotion on the flat surface closely resembled normal, but the feet on both sides slipped off the edges like the affected limbs in unilateral MSC ablation. On narrow paths, after the initial virtual helplessness postoperatively, the feet and limbs repeatedly slipped off the edges bilaterally. They were retrieved repeatedly but at times left dangling momentarily. This appeared like the tactual locomotor placing defect expressed on the edges of the broader flat track. With time and repeated trials the animals improved their performance considerably. In retrieving and replacing the limbs and feet, groping and grasping in a misdirected way was not a noticeable characteristic.

There was no appreciable difference between rats operated on at three weeks and two months; they stood equally in contrast to the animals with bilateral MSC ablations at birth.

Functional effects of ablating various quadrants of MSC, singly and in combinations. Unilateral and bilateral ablation of single quadrants or of two quadrants at different ages presented a large number of possible experiments. Earlier studies (Hicks and D'Amato, '70) had suggested that partial ablation of the more posterior part of the MSC might affect placing more seriously than removal of the whole MSC, while ablation of the more rostral parts had little effect on movement. We have just noted the differences in effects of ablating the MSC bilaterally at birth and maturity. Without other precedents to go on we began a systematic study of quadrant ablations, but unexpected results early led us to pursue leads as they arose, accounting for the seemingly disparate choice of ablations. Before describing the results in detail, which include some that are still exploratory, it will help if we summarize some high points and major findings first.

Unilateral ablation of the posteromedial quadrant (PM) at birth or maturity resulted in contralateral loss of tactile and locomotor placing, the loss characteristically appearing in mid-third week in those operated on at birth. When the lesion was made bilaterally, tactile placing was variably impaired or normal; the feet did not slip off the edge of the broad track, but regularly did on the narrow paths (fig. 4D).

Ablation of the posterolateral quadrant (PL) produced a quite different picture. The principal finding when it was done unilaterally, bilaterally, and in combinations with ablations of other quadrants was to impair positioning of the feet and limbs by grasping on the narrow paths (fig. 4E,F). Ablation of PL unilaterally or bilaterally did not affect tactile or locomotor placing. Unilateral ablation of PL alone did not impair locomotion on narrow paths seriously; the affected feet, especially hind feet, being applied in slipshod fashion. Ablation of PL in combination with other quadrants made the expression of the grasping disorder more obvious and often extremely severe.

Combined ablation of PL and PM on both sides at birth produced a particularly severe impairment of locomotion on narrow paths, predominantly a defect of grasping to hold on and replace the feet on narrow paths (fig. 4F), but slipping and dangling suggested an effect also of the PM ablation. However, tactile placing and locomotor placing on the broad track were not abolished; indeed, lateral tactile placing in both hind and forelimbs in some animals was hyperactive, the limb being raised high and overshooting the mark in the response. One of these animals did not place visually until about six weeks of age, when it became normal in this respect. It was the only animal in all of the present experiments to show the defective visual response. The one animal with PL-PM lesions made at maturity resembled the others on the narrow paths, but tactile and locomotor placing were abolished.

Ablation of either of the anterior quadrants (AL, AM) unilaterally or bilaterally at birth or maturity did not affect placing or locomotion.

Other combinations of lesions such as AL with PL and AM with PM did not differ fundamentally in their effects from what might have been expected on the basis of distinctive PL or PM effects. However, there was a suggestion that adding AM to

PM or AL to PL ablations intensified the effects expected from the PM or PL effects. The numbers of animals and the inherent variables in the experiments make more experiments necessary to confirm this possibility.

Thus, ablations of PM and PL produced distinctive impairments of positioning the feet and limbs during movement, the syndromes could be modified by the presence of other ablations, and the effects of unilateral lesions could be modified by making the lesions bilateral.

Ablations of posteromedial quadrant (PM). Ablation of this quadrant was performed unilaterally in two rats at birth, two at three weeks, and one at two months. Loss of locomotor placing in the limbs contralateral to the lesion developed at once in the mature rats, and in the third week in the infants. It was manifested as slippage, as described, on the edges of the broad and narrow tracks. All but two rats developed loss of tactile placing in the opposite forelimb; in those two, one operated on at birth, the other at three weeks, the placing was impaired. In one of these, three weeks old, the lesion was placed farther rostral than intended, sparing the posterior part of PM. The lesion in the other appeared well placed.

Bilateral removal of PM was done in three newborn rats, three rats three weeks old, and one rat two months old. Tactile placing and locomotor placing on the flat track were variably affected. Those operated on at birth showed normal placing in the third week, then tactile placing began to vary from day to day, being absent on one side, or impaired. Finally after several weeks, tactile placing was present in both forelimbs, but hyperactive on one side in one animal. Locomotor placing was never impaired on the flat track, but the animals' feet, especially hind feet, slipped off the edges of the narrow (rectangular) path from late third week onward. The rats operated on at three weeks showed similarly altered placing responses, variably impaired and in one hyperactive on one side. All slipped bilaterally on the edges of the narrow paths, but not of the flat track. The rat two months old did not lose tactile or locomotor placing, but slipped on the narrow paths.

Visual placing was not affected in any of the animals.

The bilateral lesions in those operated on at birth or two months were well placed in PM. Those in two of the animals three weeks old that had impaired tactile placing were placed a little more rostral than was intended, especially on one side, encroaching on AM; but the other was well placed.

Ablations of posterolateral quadrant (PL). Ablation of this quadrant unilaterally was performed at birth in two rats, and in two rats at three weeks. The lesion had no measurable effect on tactile or locomotor placing. In three animals it slightly impaired grasping to position the feet and hold on securely to the narrow paths in the limbs opposite the lesion, appearing in those operated on at birth late in the third week. The affected feet were applied irregularly and in slipshod fashion. The lesions in these three animals were well placed in PL. The fourth rat, operated on at three weks, showed transient impairment of tactile placing opposite the lesion, which disappeared in a day or two. It had slight impairment of grasping on narrow paths as just described. Its lesion was more rostral than intended, encroaching a good deal on AL and sparing the caudal part of PL.

The PL quadrant included somatic sensory area 2 which in somatotopic maps represented both sides of the body. One of the animals operated on at birth showed some impaired application of the feet on the ipsilateral side as well as on the contralateral side of narrow paths, but it was hard to be sure that the events on that side might not be chance errors.

Bilateral ablations of PL were performed in two newborn rats. Impaired grasping maneuvers of the feet necessary to position them and hold on in negotiating the narrow paths developed in the third week. Because the functional effect was bilateral, locomotion on these paths was more noticeably impaired than in the unilateral PL ablations. There was no impairment of locomotor placing on the flat track. Tactile placing was not only present but in one animal the response of one forelimb was hyperactive. Touching the foot to a ledge

elicted an instant placing reflex that overshot the mark.

Visual placing was not affected in any of the PL animals.

Ablating PM on one side and PL on the other in the same rat. Bilateral symmetrical removal of some quadrants indicated that they influenced each other in ways we presently know little about. The only cases in which bilateral ablations of a different quadrant on each side were made were for FHN studies, and they included two rats, three weeks and two months old, in which PM was ablated on one side, PL on the other. Though we tested placing and locomotion in most of our FHN rats, the time interval, usually 36 hours to five days, was considered too short for most observations because transient disturbances of placing and locomotion sometimes occurred postoperatively. In the two PL-PM rats, short term as they were, the effects of ablating each of the quadrants could be seen in one animal simultaneously, and added support to the emphasis we have been giving to the difference between them. Opposite the PM lesion, placing was lost in the forelimb, and both hind and forelimbs slipped off the edge of a track or the narrow rectangular and dowel paths. The affected limb dangled at times but could be retrieved onto the path. Opposite the PL lesion there was no slipping of feet and limbs and placing was normal and brisk. On the narrow paths the affected feet, especially the hind foot, could not hold on well and searching-grasping movements to restore the feet's position were awkward and misplaced.

Ablations of anteromedial quadrant (AM). AM was ablated unilaterally in one newborn and four rats three weeks old. Tactile and locomotor placing, traversing narrow paths, grasping to hold onto the latter and locomotion on the flat were not impaired. In two of those operated on at three weeks, there was transient sluggishness of forelimb tactile placing for about a week after the operations. One rat was operated on bilaterally at three weeks and showed transient sluggishness of forelimb tactile placing and bilateral slipping of the feet on narrow paths for several days, then the responses became normal. Locomotion on the flat track was unremarkable.

All of the AM animals showed normal visual placing.

Ablations of anterolateral quadrant (AL). This quadrant was removed in three rats three weeks old and had no effect on locomotion or locomotor, tactile, or visual placing. (Animals with unilateral ablation of AL at birth were included in the FHN studies of the aberrant uncrossed CST. They, like still other animals in earlier studies with ablations of various parts of the rostral quadrants, did not show abnormal locomotion or placing.)

Ablations of posteromedial (PM) combined with posterolateral (PL) quadrants. Removal of PM and PL on one side was done in one newborn and one rat three weeks old. Tactile and locomotor placing were lost contralaterally at once in the mature rat and toward the end of the third week in the rat operated on at birth. Associated with these defects was difficulty in grasping to hold on to the narrow paths, especially the paired small dowels. As an affected foot, especially the hind foot, slipped its grasp, it groped and searched-grasped awkwardly to regain position.

PM and PL were ablated on both sides in five newborn rats and one rat two months old. All five animals ultimately walked and ran well on the flat track. Those operated on at birth, however, were hesitant and moved only a few steps at a time in the latter part of the third and during the fourth week, then improved. In this they were somewhat like rats with both MSC's wholly ablated at birth. The two month old rat moved slowly for a day or so postoperatively. It lost tactile and locomotor placing on both sides permanently. Those operated on at birth not only retained their tactile placing, which could be readily elicited in all four limbs, but in some instances the placing response was not only instantaneous, but hyperactive and overshot the mark, sometimes wildly. In one, both forelimbs responded hyperactively; in another, all four limbs were extremely hyperactive; in a third, one forelimb responded this way. The rat with all four limbs hyperactive in tactile placing did not place visually until it was about six weeks old. It simply ignored all opportunities to respond that way, then gradually acquired a normal visual response, turn-

ing its head slightly toward a ledge or track as it placed its forefoot on it simultaneously. All the other animals with PL-PM lesions placed visually.

All of the bilateral PM-PL rats had severe difficulty on the narrow paths, those operated on at birth showing this particularly from the end of the third week through the fourth week, when normal rats would have assumed adult locomotor patterns. The defect in all was expressed principally as a difficulty in holding on by grasping, and having lost hold, rather "blindly" searching-grasping to get hold again. Since tactile placing and locomotor placing on the edges of the flat track were not abolished in those operated on at birth, the only element of placing loss that we could identify in the presence of the severe grasp problem was a tendency also to let the feet and limbs dangle briefly. This dangling was not a feature of bilateral PL ablations alone. The animals operated on at birth behaved characteristically in the manner of young rats, persisting at crossing the narrow paths along with their normal littermates. Frequently they fell partially off the paths in the third and fourth weeks but gradually improved their performances considerably. But their feet, especially hind feet, continued to be applied imprecisely to the narrow paths, they held on with difficulty, and continued to grope in replacing their feet.

The rat operated on at two months resembled those operated on at birth, on the narrow paths. It was markedly incapacitated on the narrow paths after operation, having been negotiating them previously beginning at age two weeks. In the course of a couple of weeks after operation, performance improved to about the state of those operated on at birth. On the narrow paths it was difficult, as mentioned earlier, to recognize elements of placing loss in the presence of the bilateral grasping deficiency except for a tendency to dangle the hind feet momentarily.

The lesions in these animals were well placed in PL and PM, but showed some variation. No characteristic of the lesions in those with hyperactive placing was recognized, except that they may have extended slightly more rostral than the others, especially in the animal that was most hyperactive. This slight rostral extension of the lesions was also present in the rat operated on at three weeks, which lost its placing reactions.

Ablations of anterolateral (AL) combined with posterolateral (PL) quadrants. One rat two months old and two newborns received the AL-PL ablations bilaterally. All three retained tactile and locomotor placing, but the two infants developed hyperactive tactile placing, overshooting the mark with both forelimbs and placing briskly with hind limbs. The lesions all ablated PL on both sides well, but on the left side in one infant the most rostral part of AL was spared. The relatively tiny area comprising the extreme rostral lateral part of the frontal pole was spared in all, being almost inaccessible to aspiration in the relatively narrow craniotomies we elected to use in lateral quadrant ablations.

The 2-month old rat negotiated the narrow paths fairly well with little grasping problem. The infants learned to traverse these paths without losing hold very often, but slow motion movies showed that the application of the feet, especially the hind feet, in grasping the small dowels was consistently slipshod, the position of the feet and toes varying a good deal from step to step.

Ablation of anteromedial (AM) combined with posteromedial (PM) quadrants. One rat two months old was treated in this manner. It was seriously incapacitated just after the operation, almost unable to use its hind limbs, but quickly recovered and walked and ran well on the flat. Tactile placing with the forelimbs was at first abolished, then remained permanently impaired, being sluggish and intermittently elicited. The hind limbs, however, placed tactually. All limbs slipped off the narrow paths a good deal. Visual placing was present.

This ablation has not yet been done in infants.

DISCUSSION

In respect to the original aims and purpose of this work, the experiments established relationships between MSC-CST growth and developing "skilled" and ordinary movement, and they seemed to indicate, on the basis of ablations, that the

MSC-CST was organized regionally for special aspects of movement, not simply somatotopically. Removal of MSC quadrants resulted in characteristic motor-sensory syndromes, but these could be altered considerably by simultaneous ablation of other quadrants, and age influenced the functional effects of ablations. Infant brains responded to MSC ablations by forming aberrant circuitry, some of it orderly, such as miniature replacement of an unformed CST, but whether such plasticity affected function normally, abnormally, or not at all remains to be determined. We discuss certain aspects of these conclusions further.

Role of the MSC-CST in developing and mature motor function

Rats without MSC's could run and walk virtually normally on a flat surface — ordinary locomotion — but when extraordinary locomotion was called for, such as walking or running on difficult narrow pathways, these animals were severely handicapped. A major role of the MSC-CST, then, was to bring skill and refinement to basic motor performance. The initiation and carrying through of a motor performance was not totally cortically dependent however, because rats without MSC's could go through the program of learning visual pattern discrimination or locomotion on a series of pathways which involved sequences of learned movements. Despite their handicaps, they moved.

In the course of development, the MSC exercised an influence on the acquisition of ordinary locomotion and on tactile placing. The rat deprived of its MSC's at birth did not go through the normal rapid transition from infant to mature locomotion in mid-third week, but took much longer, up to several weeks, to make the transition from crawl-walking much like a baby to moving like an adult.

Although tactile placing developed whether the MSC was normally present or wholly removed at birth, when one MSC was removed at birth, it revealed that both MSC's were exerting an influence on placing in mid-third week. Since ablation of one MSC at birth was followed around 17 days by contralateral loss of placing, and bilateral ablation prevented it, we hypothesize that the remaining MSC must have exercised an influence on placing that came into play rapidly at this time. We incorporate these observations into a scheme shown in figure 5 to help depict the mid-third week placing paradox. The MSC's as they approached this stage of development were pictured as exercising a "facilitating" influence on the contralateral placing mechanisms, shown as black boxes, and an "inhibiting" influence on the ipsilateral placing mechanisms. (Facilitating and inhibiting are used in a descriptive, not neurophysiologic sense.) Normally the facilitating-inhibiting balance favored perpetuation of placing, but if one MSC was removed before the 17th day, placing was rapidly lost when that day was reached. The postulated ipsilateral inhibiting effect

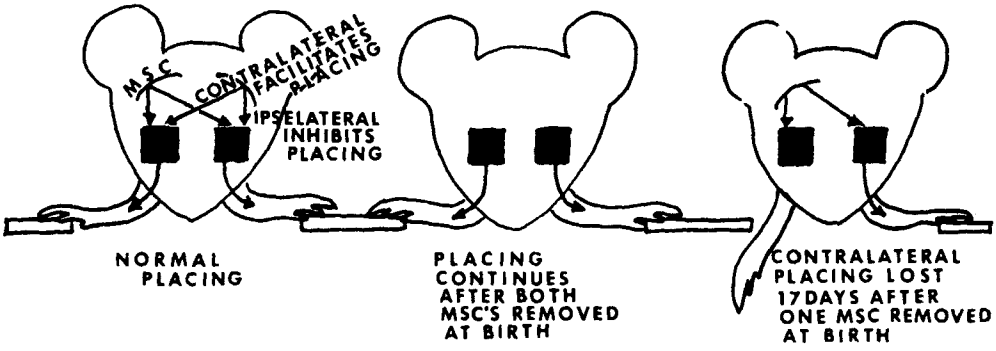

Fig. 5 Scheme depicting hypothetical relations between the MSC's and subcortical mechanisms involved in the paradoxical placing responses that followed ablations of the rat's MSC at birth. It is discussed in the text, page 28.

permanently turned off placing, but its action must have been quite transient, because removal of both MSC's after mid-third week, which abolished both of the hypothetical cortical inhibiting influences, still resulted in immediate placing loss on both sides.

The neural mechanisms involved remain unknown, although the PM ablation experiments indicated that that quadrant of the MSC was probably the cortical region principally involved.

Localizaion of function in the MSC

Localization of function in the nervous system can be illusory, especially in the cerebral cortex where neurophysiologic measures, surgical ablations and disease may provide different pictures. The pictures in turn may vary with the age of the subject studied.

Potentials evoked in the cortex by stimulating skin elements and other tissues over the body, and muscle contractions elicited by direct electrical stimulation of points in the cortex, have provided reproducible cortical maps of the body's "sensory" and "motor" representation in a number of mammals, including man (Woolsey, '52; Hall and Lindholm, '74). Other topographies have shown an organization of the MSC — or parts of it — into input-output motor units in the form of radially oriented columns of functionally related cortical neurons. The output members include pyramidal tract (CST) neurons whose effects are virtually channeled to single spinal motor units. A major part of the input to the MSC columns comes from regions of skin, joints, tendons, and muscles most closely related to movements involving those muscles being influenced by the CST cells (Brooks, '69; Henneman, '74). The wiring in this respect seems to be such that these inputs provide feed-back to the cortical output cells, so that a prime function of this kind of organization of the MSC is one of servoassistance to the spinal motor mechanisms (Matthews, '72).

These elegant measures reveal a precise, almost one-to-one, cortex-to-muscle-and-back somatotopic aspect of the nervous system, but the manner in which the cortical columns are organized to carry out integrated movement in the expression of behavior is obscure. The columns would have to be played upon like a vast keyboard, just as the spinal segmental units were, to accomplish this; but "who" plays the keyboard, perhaps a number of subcortical systems concerned with movement, isn't known (Paillard, '60).

The results of our experiments, in which we quite arbitrarily divided the MSC into quadrants, do not conform to a simply somatotopic organization of the MSC. Ablation of the PM quadrant affected tactual positioning and placing of contralateral fore and hind limb; on a strictly somatotopic basis it might have been expected to affect all aspects of movement of these limbs, perhaps predominantly the hind limb. Ablation of the PL quadrant affected grasping of the contralateral limbs, more noticeably perhaps the hind limb, but had no effect on the tactual aspects as they were tested. It might have been expected that the forelimb would be affected predominantly and that all aspects of movement would be impaired.

Had we tested motor functions of the head, eyes, jaws, and tongue as we did locomotor functions of the limbs, it might have revealed evidence of somatotopy in AL and AM quadrants. But it is the departures from somatotopy that we emphasize.

Equally inconsistent with a strictly somatotopic organization were the projections of the MSC quadrants. Those of PM and PL were not only different, but in considerable degree mutually exclusive in their destinations. PM, it will be recalled, was essentially the only quadrant that projected to the spinal cord, an observation in line with others not only in the rat (Valverde, '62), but in other mammals (Chambers and Liu, '57; Barnard and Woolsey, '56; Brodal, Marsala and Brodal, '67). That the MSC could appear to be organized somatotopically with point to point corticospinal connections on one hand, yet show regionally different kinds of function and anatomic projections on the other, presents an ambiguity that cannot be resolved simply on a basis of the methods that produced the two pictures. The two pictures don't have to be mutually exclusive, but certainly deserve study.

Limitations in determining MSC projections

Something approaching a complete picture of the MSC-CST system would require a combination of fine-structure and biochemical details correlated with neurophysiologic and meaningful behavioral studies, an attainment beyond reach. What was sought in these experiments was an approximation of some structural-functional relations.

The FHN and related methods gave a good picture of the course and regional destinations of fiber projections, but generally could not give an exact location of terminations of axons on cell bodies, axons, and dendrites. This inherent limitation was pointed to in our suggestion that the apparent paucity of CST endings in the large cell part of the red nucleus might be because they were forming synapses at some distance on those cells' long dendrites. Our Golgi preparations of the rat's spinal cord illustrated a similar problem emphasized by Valverde ('65) about the supposed lack of synapses on the large motor neurons in the ventral horns of mammals below the primates. The dendritic span of these cells was enormous, almost half the cross section of the spinal cord. For example, one cell extended one of its main dendrites through the white matter of the ventral funiculus almost to the medial margin of the spinal cord, another comparably far into the lateral white funiculus, and a third into the dorsal horn of gray matter to its medial zones where the CST fibers terminated. Like the large neurons in the brain stem reticular formation they reached into almost every corner of the region, making it very difficult to say what connected with what on anatomic grounds.

These uncertainties about the exact cellular sites of termination of the CST fibers do not diminish the more general usefulness of the FHN procedure, even with the relatively large lesions we used, in indicating regional sites, sometimes quite circumscribed, to which the CST fibers projected. Also some of the domains of the MSC quadrant projections were so different and mutually exclusive that extensively ranging dendrites were not the problem.

Formation of aberrant fiber systems and other transformations after cortical ablation at birth

The early infant rat cortex was not only immature (Hicks et al., '62, '69; D'Amato and Hicks, '65; Hicks and D'Amato, '68), but capable of pursuing alternate pathways of development. The tiny aberrant uncrossed CST that arose from the remaining MSC after unilateral MSC ablation at birth was an example of unusually orderly growth of axons in response to injury of the young brain. The change in direction of differentiation of the dorsomedial cortex from isocortex toward cingular cortex architecture, after ablation of part of the MSC at birth, emphasizes that the cortex at birth had neither received its full complement of immigrating young neurons destined for the superficial layers (Hicks and D'Amato, '68; Hicks et al., '59), nor committed the young neurons already arrived to a final course of differentiation. Nor had it received its full complement of afferent fibers.

It was these observations and a deviation in the development of the tactile placing pattern in two rats of the 13 from which we removed both MSC's at birth that led to the search for aberrant CST fibers arising in occipital (non-MSC) cortex in rats so treated. In brief, these two rats, among the first thus ablated, began to develop impaired tactile placing at about age two months, after having had quite normal placing. Placing was lost in one forelimb in one rat and impaired bilaterally in the other rat. Histologic examination showed small CST's in the animals' medullas, the most likely source being residual PM quadrant cortex missed in the ablations. Nonetheless, the possibility that these fibers represented delayed aberrant growth from occipital cortex, which disturbed the tactile placing balance, was considered. In the later FHN experiment reported here, the animals retained normal placing (they were 7 months old), but the finding of a few CST fibers, possibly from occipital cortex, has led us to continue the search for such aberrant fibers.

At the present time these various exhibitions of aberrant development simply confirm and extend what was said in the Introduction, that the infant brain has a

considerable capacity for remodeling its circuits and altering the course of its cytodifferentiation. That was a first step. It remains to devise ways to determine whether any of them have functional relevance.

Placing

In our earlier experiments (Hicks and D'Amato, '70), rats hemispherectomized at birth or maturity placed neither tactually nor visually with the forefoot and eye opposite the lesion. If a rat hemispherectomized on the right was allowed to see a ledge on the left with its left eye, to which its left forefoot was being touched, normal placing of that limb occurred. In rats with ablations limited to the MSC or its quadrants, visual placing was unimpaired except for a period of time in one rat from which PM and PL were ablated bilaterally at birth. The "dissociation" or independence of visual placing from defects of locomotion produced by MSC ablations was also shown in slow motion movies. At times an animal that was struggling clumsily along one of the narrow paths would turn its head to look at the neighboring parallel path several centimeters away, extend its forelimb to it, gracefully place its foot there, then cross over clumsily and resume its difficult way.

Transient restoration of tactile and visual placing, lost after cortical ablations in cats, has been effected by giving d-l-amphetamine (Meyer et al., '63), drawing attention to the possible role of aminergic neural systems in limb positioning and some locomotor functions. Amphetamine also transiently restored visual placing in rats, which had been lost after injection of 6-hydroxydopamine (6OHDA) into the lateral forebrain bundle at the anterolateral hypothalamic level (Sechzer et al., '73). The 6OHDA was thought to have selectively damaged adrenergic neurons or their axon terminals, which regenerated sufficiently after a period for their previous function in placing to be revealed by amphetamine. We gave 6OHDA parenterally to newborn rats to determine whether it affected the development of movement. It had no effect on visual or lateral tactile placing, but a defect of positioning the limbs in traversing the narrow paths developed toward the end of the third week, a little reminiscent of the grasping defect and slipping seen after bilateral PL and PM ablations. It has recently been suggested that the adrenergic neurons of the locus coeruleus exercise a trophic influence on the growth of neurons in the rat's cortex through their ramifying axon terminals (Maeda et al., '74). Should the effects of 6OHDA reveal a differential trophic influence of aminergic systems on growth of different parts of the cortex, the finding would help open a new area in the development of movement.

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PLATES

PLATE 1

EXPLANATION OF FIGURES

1 Brain (unfixed) of a normal rat, seven months old, littermate of the animal represented in 2.

2 Brain (unfixed) of a rat seven months old, both of whose MSC's were removed at birth. The animal is shown performing earlier in figure 4B.

3 Brain (fixed) of a rat seven weeks old whose right MSC was removed at birth. The animal is shown performing in figure 4C.

4 Brain (fixed) of a rat three months old whose PM quadrants of the MSC were ablated bilaterally at about two months. The animal is shown performing in figure 4D.

5 Brain (fixed) of a rat about two months old whose right PL quadrant of the MSC was removed at birth. The animal is shown performing in figure 4E.

6–7 Brains (fixed) of littermate rats about seven weeks old whose PM and PL quadrants of the MSC were removed bilaterally at birth. The animals are shown together performing in figure 4F.

8 Brain (fixed) of a rat 23 days old whose right PM quadrant of the MSC was removed at birth, then whose left MSC was removed for FHN study 36 hours before it was killed.

9–10 Brains (fixed) of rats two months and 23 days old whose left PM and right PL quadrants of the MSC were removed five days and 36 hours, respectively, before they were killed for FHN study. The FHN preparation from the 2-month old rat, figure 9, is represented in plate 2.

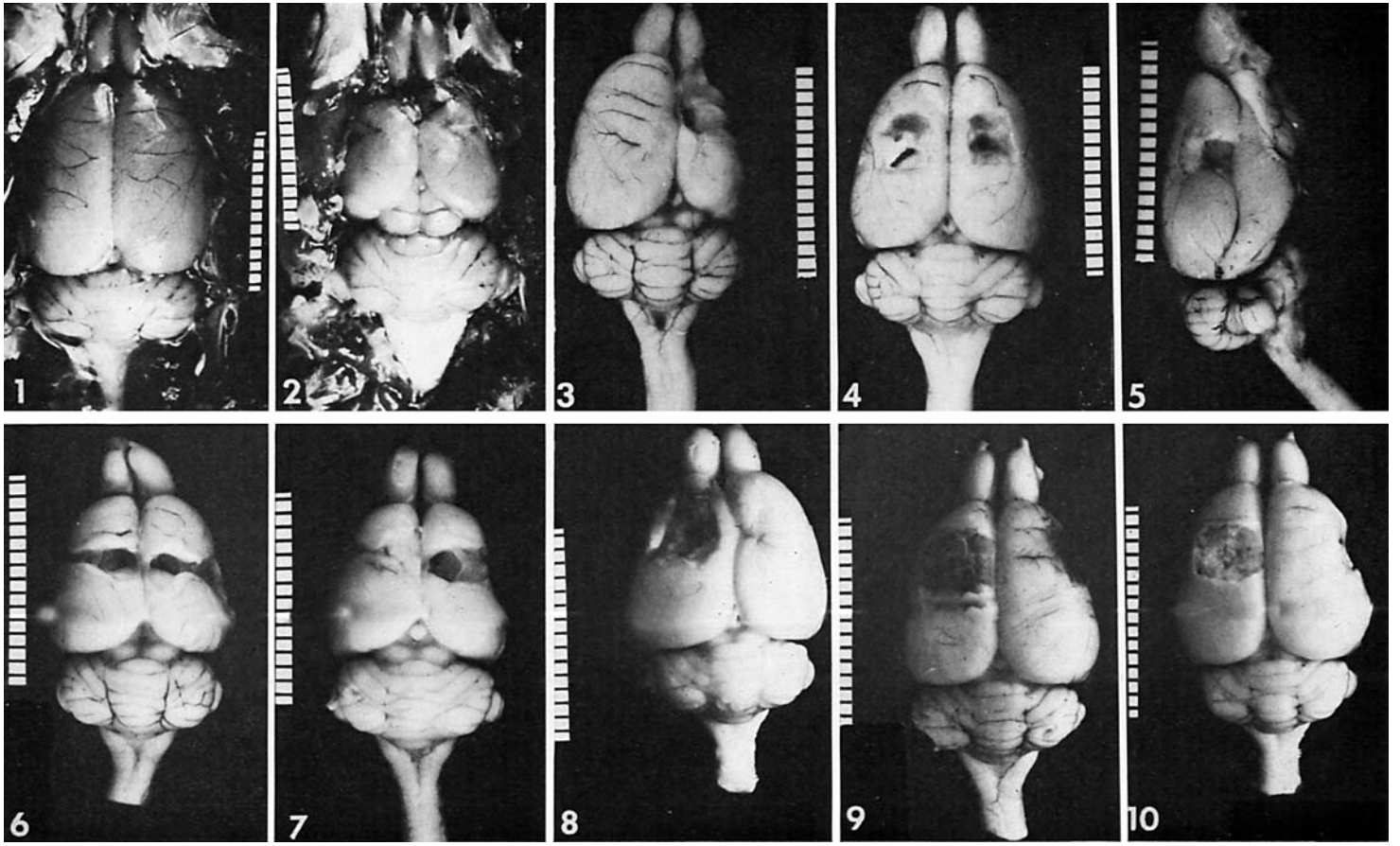
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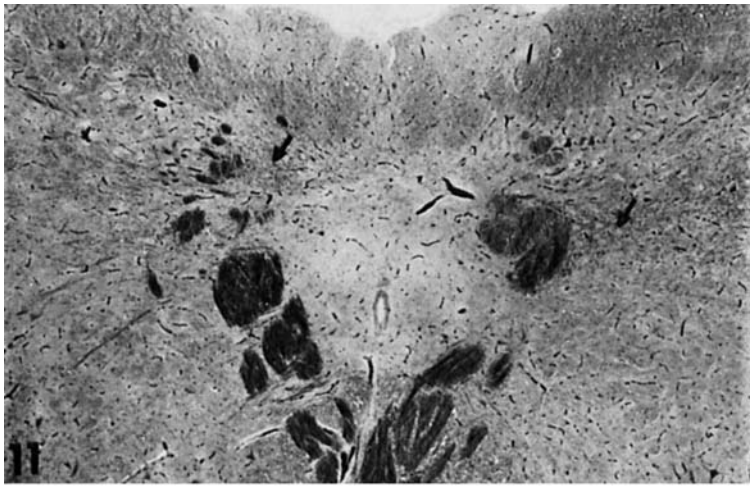
PLATE 2

EXPLANATION OF FIGURES

11 Frontal section of the central dorsal part of the medulla of a rat two months old showing the decussation of the CST. The PM and PL quadrants of the MSC of the rat were removed five days before the rat was killed (plate 1, fig. 9). The section is stained by the FHN method; the degenerated fibers from the ablated PM quadrant course upward to the left, and those from the PL quadrant to the right. The PM arm of the decussation has more degenerated fibers than PL. Many PM fibers terminated at this level in the region of the cuneate nucleus (left arrow), which is shown at higher magnification in figure 12. PL fibers coursed more laterally to the reticular formation and a representative region (right arrow) is shown at higher magnification in figure 13, FHN stain. × 50.

12 Higher magnification of the region indicated by the left arrow in figure 11, showing degenerated fibers especially in the region of the cuneate nucleus, FHN stain. × 300.

13 Higher magnification of the region indicated by the right arrow in figure 11, showing degenerated fibers coursing in the reticular formation, FHN stain. × 300.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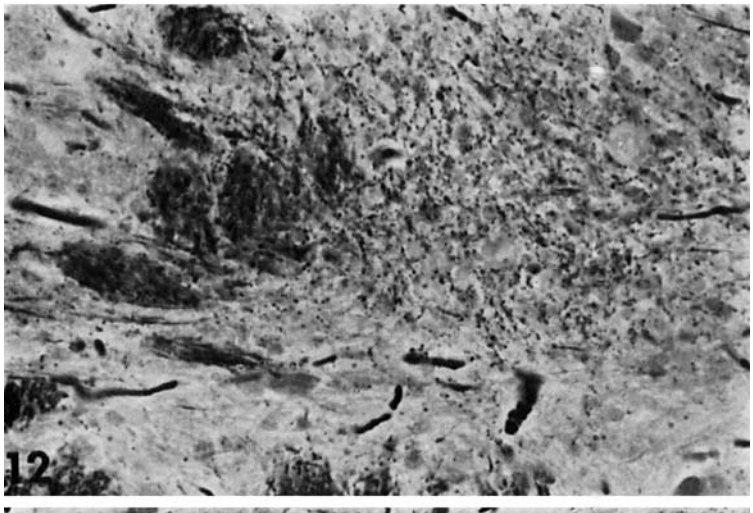
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PLATE 3

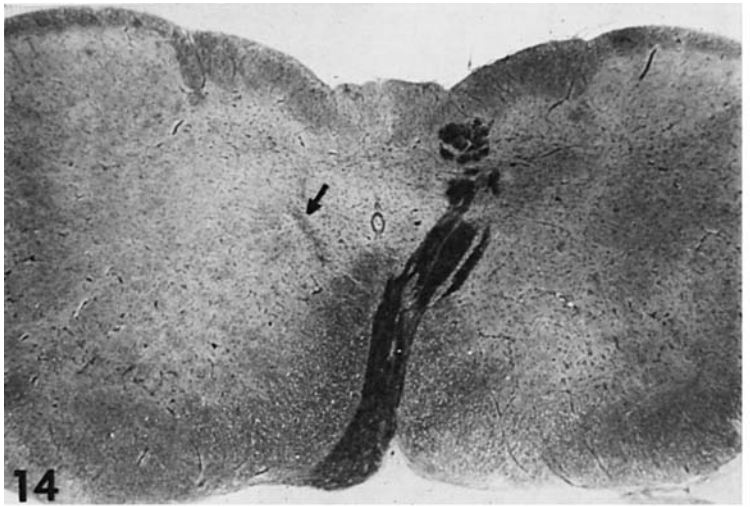
EXPLANATION OF FIGURES

14 Frontal section at low magnification of medulla of a rat that had one MSC removed at birth and the other at three weeks. The animal was killed seven days later for maximal demonstration of main tract CST fibers and sections stained by the FHN method. There was no residual CST on the side corresponding to the ablation at birth; the remaining CST is seen coursing from the pyramid on the left in the photomicrograph upward to the right. A small group of aberrant fibers (arrow) has taken off from the main tract near the midline to continue on the ipsilateral side, FHN stain. × 30.

15 The center of the photomicrograph in figure 14 is shown at higher magnification, the arrow designating the aberrant group of fibers. A substantial number of degenerated fibers may be seen coming off the main tract in the midline, FHN stain. × 120.

16 Frontal sections of the dorsal middle part of the brain of a rat five months old, part of whose MSC was ablated at birth. The depression of the cortex at far left represents the margin of the lesion. The left arrow indicates the abnormal dorsolateral extension of the concentrated layer of small neurons characteristic of layer 2 in cingular cortex. The right arrow indicates an excess of fibers in layer 1, better seen in figure 17. Luxol fast blue and cresyl violet. × 20.

17 Higher magnification of the upper center of figure 16, showing the extension of the cingular cortex architecture, left arrow, and the excess myelinated fibers in layer 1, right arrow. Luxol fast blue and cresyl violet. × 80.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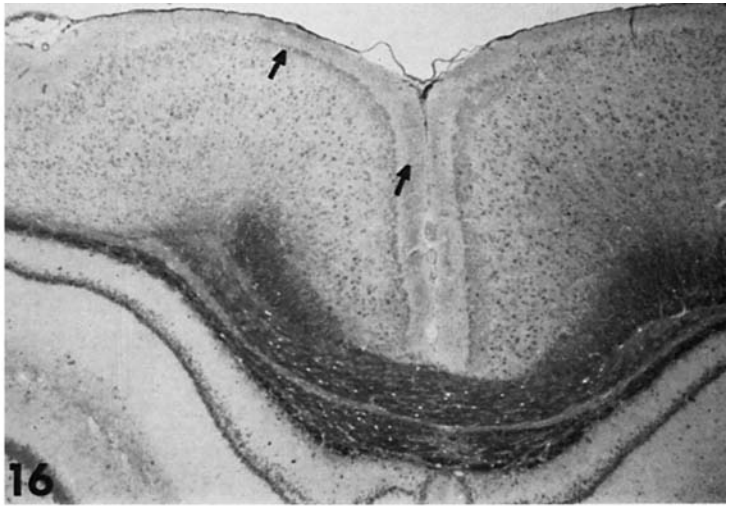
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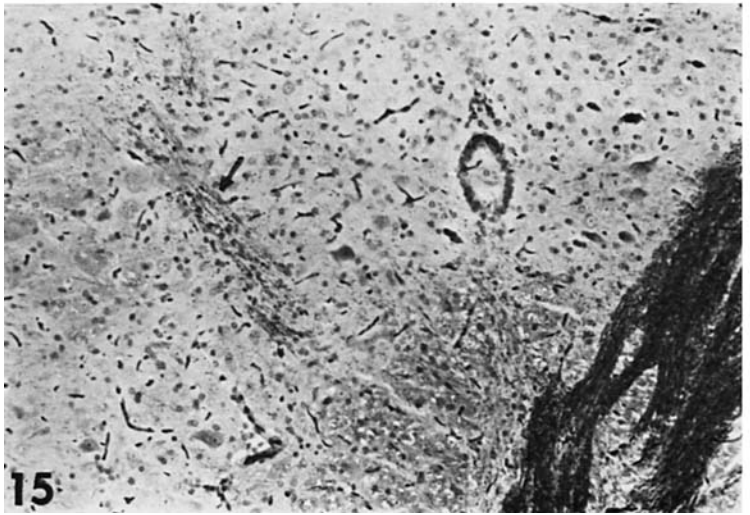
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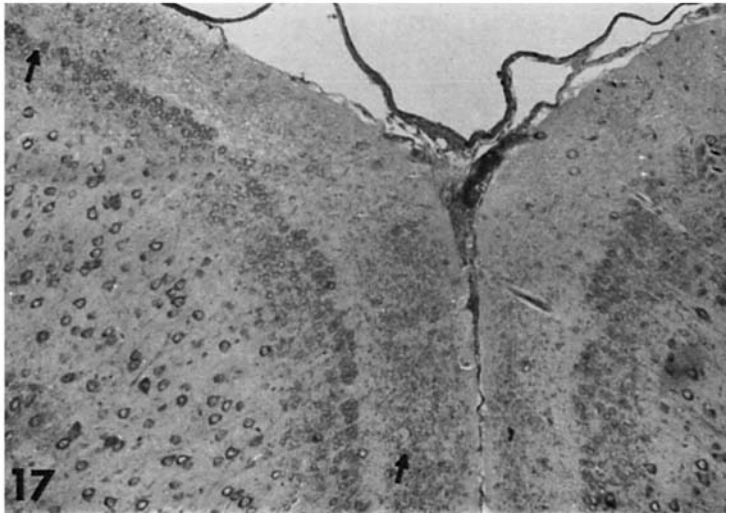
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